National Institute for Health and Care Excellence

Draft

Head Injury: assessment and early management (update)

[F] Evidence reviews for brain injury biomarkers and/or MRI for predicting post-concussion syndrome

NICE guideline <number>

Evidence reviews underpinning recommendations x to y and research recommendations in the NICE guideline

September 2022

Draft for Consultation

These evidence reviews were developed by the Guideline Development Team NGC

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1.1 Review question

- What is the prognostic accuracy of brain injury biomarkers and/or MRI for predicting post-concussion syndrome?
- What is the clinical and cost effectiveness of biomarkers and/or MRI when each is followed by the appropriate treatment for post-concussion syndrome to improve patient outcomes?

1.1.1 Introduction

Head injury is a common reason for presentation to the emergency department. Most injuries are classed as minor, and most patients make a full recovery. However, a significant number will go on to develop persistent and disabling symptoms including headaches, dizziness, cognitive difficulties and difficulty sleeping. This constellation of symptoms is known as post-concussion syndrome.

The ability to identify head injured patients most at risk of post-concussion syndrome would enable appropriate follow up and support to be put into place at any early stage. This would reduce the risk of the symptoms being unrecognised and becoming intractable and would improve health-related quality of life, which has been shown to be poor in this group of people.

The present reviews are investigating the prognostic accuracy of brain injury biomarkers and/or MRI for predicting post-concussion syndrome and the clinical and cost effectiveness of biomarkers and/or MRI when each is followed by the appropriate treatment for post-concussion syndrome to improve patient outcomes.

1.1.2 Summary of the protocol

For full details see the review protocols in Appendix A.

Table 1: PICO characteristics of review question – prognostic accuracy

Population	Inclusion: Infants, children and adult with suspected head injury • Strata: ○ Adults (aged ≥16 years) ○ Children and babies (aged 0 to <16 years) If data is available from studies report separately for children: 0-4 years, 5-15 years and > 15 years Mixed population studies will be included but downgraded for indirectness. Cut-off of 60% will be used for all age groups Exclusion: Adults and children (including babies infants under 1 year) with superficial injuries to the eye or face without suspected or confirmed head or brain injury.
Prognostic variables under consideration	**1. Biomarkers** <u>Blood biomarkers</u> - S100 calcium binding protein B (S100B)

	-Ubiquitin C-terminal Hydrolase-L1 (UCHL1) -Neuron Specific Enolase (NSE) -Brain-derived neurotrophic factor (BDNF) -Neurofilament light (NFL) - Neurofilament Heavy (NF-H) - αII-Spectrin breakdown products (SBDP) - Myelin basic protein (MBP) - glial fibrillary acidic protein (GFAP) <u>Salivary biomarkers</u> -salivary microRNAs (miRNAs) -Extracellular vesicles (EVs) -S100B <u>Urine biomarkers</u> -Extracellular vesicles (EVs) Biomarkers are used within 48 hrs of head injury. Measurements of biomarkers in CSF not relevant as usually only access to this in those with severe head injury, while most people with post-concussion syndrome have mild head injury (GCS 13-15) and lumbar puncture to analyse CSF biomarkers is not indicated here. **2. MRI** MRI to be left open for signs (and sequences) used to predict post-concussion syndrome. MRI is booked during acute presentation (it could be done 3 weeks to a month after injury) **3. Combination of MRI and blood/salivary biomarkers**
Reference standard	**Post-concussion syndrome confirmed by constellation of symptoms** • Range of symptoms including cognitive, physical, emotional and sleep related. Reference standard to include symptoms as reported in the studies. In adults, diagnosis of post-concussion syndrome is based on: 1. Glasgow Coma outcome scale (GOS) and GOSE (Glasgow Outcome Score Extended 2. Rivermead Post-Concussion Score 3. Other symptoms commonly used to define include: o Duration of post-traumatic amnesia o Abnormalities in cognition – most common include: Rey Auditory Verbal Learning Test (RAVLT), Trails Making Test Part A/B, WAIS IV Processing Speed Index, NIH Toolbox Cognitive Battery, CANTAB

	○ Patient reported outcomes - Quality of Life After Brain Injury – Overall Scale (QOLIBRI-OS) and SF-12/SF-36 ○ Markers of mental health problems - PTSD Checklist (PCL-5), Participant Health Questionnarie-9 (PHQ-9), Generalised Anxiety Disorder-7 (GAD-7), Brief Symptom Inventory (BSI), Hospital Anxiety and Depression Scale (HADS) ○ Scales of sleep disturbance and fatigue In children diagnosis is based on symptoms, The Rivermead Post-concussion Symptoms Questionnaire (RPQ) and acute stress response. <u>Post- concussion syndrome definition:</u> Post-concussion syndrome occurs when concussion symptoms last beyond the expected recovery period after the initial injury. The usual recovery period is weeks to months. These symptoms could be physical, cognitive, emotional or sleep related. This may include multiple physical symptoms such as headaches, dizziness, nausea, balance and co-ordination problems, changes in appetite, sleep, vision, and hearing; and cognitive and behavioural symptoms such as fatigue, anxiety, depression, irritability; problems with memory, concentration, and decision-making. In some people these symptoms may persist from 2 weeks to longer than 3 months post injury. GCS in such patients will be 14-15.
Outcome measures	Prognostic accuracy of listed prognostic factors for predicting post-concussion syndrome To be reported by test sensitivity/specificity For measurement of imprecision, clinical decision thresholds for sensitivity and specificity are set at 90% and 60%. Both sensitivity and specificity are considered to be of equal value. Sensitivity is important as at the moment treatment of post-concussion syndrome is symptom based so patients are not likely to be given treatments unless in need. If the specificity is too low there is the potential to harm many people who will delay their return to work/school/sport and become hypervigilant for symptoms, for example.
Study design	Prospective cohort studies Retrospective cohort studies will be included only if no sufficient prospective cohort studies are identified Systematic reviews and meta-analyses of the above

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2 **Table 2: PICO characteristics of review question – prognostic test and treat**

Population	Inclusion: Infants, children and adult with suspected head injury • Strata: ○ Adults (aged ≥16 years) ○ Children (aged ≥1 to <16 years) ○ Infants (aged <1 year) Mixed population studies will be included but downgraded for indirectness. Cut-off of 60% will be used for all age groups

	Exclusion: Adults, and children (including infants under 1 year) with superficial injuries to the eye or face without suspected or confirmed head or brain injury
Prognostic variables and subsequent treatment	**1. Biomarkers** Blood biomarkers - S100 calcium binding protein B (S100B) -Ubiquitin C-terminal Hydrolase-L1 (UCHL1) -Neuron Specific Enolase (NSE) -Brain-derived neurotrophic factor (BDNF) -Neurofilament light (NFL) - Neurofilament Heavy (NF-H) - αII-Spectrin breakdown products (SBDP) - Myelin basic protein (MBP) - glial fibrillary acidic protein (GFAP) Salivary biomarkers -salivary microRNAs (miRNAs) -Extracellular vesicles (EVs) -S100B Urine biomarkers -Extracellular vesicles (EVs) Biomarkers are used within 48 hrs of head injury. Measurements of biomarkers in CSF not relevant as usually only access to this in those with severe head injury, while most people with post-concussion syndrome have mild head injury (GCS 13-15) and lumbar puncture to analyse CSF biomarkers is not indicated here. **2. MRI** MRI to be left open for signs (and sequences) used to predict post-concussion syndrome. MRI is booked during acute presentation (it could be done 3 weeks to a month after injury) **3. Combination of MRI and blood/salivary biomarkers** Each test must be followed by an appropriate treatment for post-concussion syndrome after brain injury. Subsequent treatment to include but not limited to: • Neuropsychologist interventions e.g. CBT, coping strategies • multimodal therapy delivered by uni- or multi-disciplinary team. • physical therapy

	• sleep hygiene interventions including pharmacological treatment • fatigue management • vestibular rehabilitation • management of headache (including medications) • psychoeducation
Comparators	• To usual care (no testing with MRI/biomarkers) • To each other
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Quality of life - 3 months or more • Objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or extended GOS - at 3 months or more • Time to return to education/work/usual activities • Duration of post-concussion syndrome (to analyse 2 weeks to <3 months and 3 months and longer than 3 months separately)
Study design	• Randomised controlled trials (RCTs), systematic reviews of RCTs. • If no RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders, starting with prospective cohort studies. Key confounders (only include studies adjusting for all 3 confounders below): • Age • Gender • GCS or pupillary response at presentation Other confounding factors (to include studies even if they do not adjust for these factors) • Anxiety, depression • Sleep disorder • Gender • Extra cranial injury • Migraine • Previous concussion and or head injury • Learning disability (paediatric population) • atypical neuro development (paediatric population) • ADHD (paediatric population) • Autism Spectrum Disorder (ASD) (paediatric population) • Mechanism of injury
Subgroups	Subgroups that will be investigated if heterogeneity is present: • Older adults ○ older/frail adults who have suffered a fall

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Prognostic evidence

1.1.4.1 Included studies

Prognostic accuracy

A search was conducted for prospective cohort studies investigating the association of the following factors: blood biomarkers (see list provided in section 1.1.2 above), MRI observations or a combination of blood biomarkers and MRI observations, reporting the outcome of post-concussion syndrome in people with mild head injury (also termed mild traumatic brain injury; TBI; GCS 13-15). It was agreed in the protocol that if sufficient prospective cohort studies were not identified, retrospective cohort studies would also be included.

36 prospective cohort studies (from 37 papers) were included in the review, including one which had a prospective component as well as a retrospective component;[1-23, 25-38] these are summarised in Tables 3 and 4 below, reported separately for adults (27 prospective studies from 28 papers and 1 study with prospective and retrospective components) and children (8 prospective studies). Evidence from these studies is summarised in the clinical evidence summary below (Tables 5-33).

No relevant clinical studies investigating the effects of the following biomarkers were identified:

- In adults:
  - Blood biomarkers: neurofilament heavy (NF-H); and myelin basic protein (MBP)
  - Salivary biomarkers: extracellular vesicles; and S100 calcium-binding protein B (S100B)
  - Urine biomarkers: extracellular vesicles
  - Combination of MRI and blood/salivary biomarkers

- In children:
  - Blood biomarkers: ubiquitin C-terminal Hydrolase-L1 (UCH-L1); neuron specific enolase (NSE); brain-derived neurotrophic factor (BDNF); neurofilament light (NF-L); NF-H; αII-Spectrin breakdown products (SBDP); MBP; and glial fibrillary acidic protein (GFAP)
  - Salivary biomarkers: extracellular vesicles; and S100B
  - Urine biomarkers: extracellular vesicles
  - Combination of MRI and blood/salivary biomarkers

Population

Most of the included studies are studies focusing on those with mild TBI (GCS 13-15). Studies with mixed populations of varying severity of TBI (for example, mild-severe TBI) were included if at least 60% of the population had mild TBI or (if the proportion with each severity was not reported) the mean/median GCS score reported was consistent with mild TBI. These studies were however downgraded for indirectness if <75% of the population had mild TBI, as post-concussion syndrome is most relevant to those with mild TBI.

Prognostic factors

The way in which prognostic factors were analysed varied depending on the study. Some studies reported prognostic accuracy measures for biomarkers as a continuous variable, while others reported prognostic accuracy measures for a particular threshold of the

biomarker measured. In the case of MRI, data was often available for prognostic accuracy of particular findings on MRI in predicting outcome.

Reference standard/outcome

Various outcomes were accepted in terms of post-concussion syndrome. Many studies clearly reported post-concussion syndrome or symptoms as an outcome. Others only reported other outcomes that are often used in determining a post-concussion syndrome diagnosis, such as Glasgow Outcome Score (GOS) or Extended Glasgow Outcome Score (GOSE) or cognitive tests measuring specific cognitive abilities.

Outcomes measured using GOS or GOSE, cognitive testing and other measures such as post-traumatic stress disorder (PTSD), depression or individual symptoms (such as headache) were still extracted and analysed even if a post-concussion syndrome or symptom scale outcome was also reported in the paper as these are still useful ways of assessing possible post-concussion symptoms.

Outcome measures/statistical measures

As well as sensitivity and specificity listed in the protocol, other measures of prognostic accuracy [area under the curve (AUC), calibration measures and net reclassification index] were accepted if reported.

See also the study selection flow chart in Appendix A, study evidence tables in Appendix D and forest plots (where applicable) in Appendix E.

Prognostic test and treat

No studies matching the review protocol for the test and treat component of this review were identified, as none of the studies involved a comparison between two interventions/strategies involving the use of biomarkers.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix I including for the prognostic accuracy and prognostic test and treat components of this review.

1.1.5 Summary of studies included in the prognostic evidence

Table 3: Summary of studies included in the evidence review – adults

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
Blood biomarkers – S100B						
Bazarian 2006[4] N=96 Prospective Conducted in USA	Mild TBI of all ages with head CT scan and presenting within 4 h of injury GCS 13-15 to be included	S100B – continuous and thresholds	Post-concussion syndrome at 3 months (Rivermead Post-concussive Questionnaire) Score ≥5 considered to	AUC, sensitivity and specificity	Risk of bias: very serious Indirectness: serious – mixture of adults and children with proportion unclear	

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
	Age, mean (SD): 39.9 (19.5) years		have post-concussion syndrome AND Headache at 3 months			
Bazarian 2006[5] N=35 Prospective Conducted in USA	Adults or children presenting to ED within 6 h of mild TBI GCS: • 15, 94.3 % • 14, 5.7% Mean age 37.0 years (range 10-83 years)	S100B - continuous	Post-concussion syndrome (Rivermead Post-concussive Questionnaire) at 3 months Score ≥5 considered to have post-concussion syndrome	AUC, sensitivity and specificity	Risk of bias: very serious Indirectness: serious – mixture of adults and children with proportion unclear	
Herrmann 2001[9] N=29 or 39 Prospective Conducted in Germany	Adults (≥16 years) admitted to Department of Neurosurgery following TBI GCS at site of accident (median, range): • 13 (3-15) GCS at admission (median, range): • 15 (3-15) Median (range) age: • 29 (17-56) years for those analyse	S100B – continuous or threshold >140 ng/l, measured median 27 hours post-injury Blood also drawn at second and third day of admission (median 49.5 hours and median 80.0 hours post-injury, respectively), but results describe 'initial' serum	Neuropsychological assessment at 6 months Neuropsychological disorders present if performed <1 SD below (age-adjusted) normal data in at least three cognitive domains. Included the following components: • Global cognitive and behavioural screening • Memory/learning • Language • Visuoperception/construction	AUC, sensitivity and specificity	Risk of bias: very serious Indirectness – mixed severity and not limited to mild TBI (proportions unclear). Included as median value at site and on admission was consistent with mild TBI in those analysed at 6 months.	2-week time-point also reported but this time-point is less relevant to post-concussion syndrome

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
	d at 2 weeks • 27 (17-54) years for those analysed at 6 months	levels suggesting first time-point included	• Executive functions • Attentional performance • Psychomotor speed			
Lagerstedt 2020[17] N=49 Prospective Conducted in Finland	Adults (≥18 years) with TBI – reports result separately for mild subgroup GCS: 13-15 range in the mild subgroup Age, mean (SD): 44.1 (19.8) years	S100B – threshold 23.17 pg/ml	Complete recovery based on GOSE at >6 months GOSE 8 considered complete recovery and GOSE ≤7 considered incomplete recovery	Partial AUC, sensitivity and specificity	Risk of bias: none Indirectness: none	Mixed severity within the population but provides results for those with mild TBI separately. Threshold selected based on best threshold with a sensitivity 95-100%
Lee 2015[19] N=31 with mild TBI Prospective Conducted in Korea	People with mild TBI (GCS 13-15) GCS: mean, 14.5 Age: mean (range), 58.5 (19 to 84) years for the whole population including severe TBI	S100B – continuous (for AUC) or 27.01 ng/ml cut-off value (for sensitivity and specificity)	Poor outcome based on GOS at 3 months GOS 1-3 was considered poor outcome and GOS4-5 was considered good outcome	AUC, sensitivity and specificity	Risk of bias: very serious Indirectness: none	Includes mild and severe TBI, but in the methods section, results for prognostic accuracy said to be for the mild TBI group.
Posti 2020[27] N=137 (n=82 and n=55 in CT-positive and CT-negative groups)	Adults (≥18 years) with TBI with or without confirmed lesion on CT (separately for the two groups)	S100B – continuous/threshold	Two outcomes based on GOSE scores at 4-16 months • Unfavourable outcome (GOSE 1-4) • Incomplete recovery	AUC, sensitivity and specificity	Risk of bias: very serious Indirectness: mixed TBI severity with proportion with mild TBI unclear, though	TBIcare study

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
Prospective Conducted in Finland	Any GCS included but median values consistent with mild TBI (median 14, range 3-15) Age, mean (SD): 50.46 (20.35) years		(GOSE <8)		median values consistent with mild TBI.	
Ryb 2014[29] N=150 Prospective Conducted in USA	Adults (18-64 years) admitted to centre with mild TBI GCS 13-15 Age, mean (SD): 35.3 (12.6) years	S100B - continuous	4+ symptoms at 3, 6 and 12 months Ability to return to work or school at 12 months	AUC	Risk of bias: serious Indirectness: none	
Savola 2003[30] N=172 Prospective Conducted in Finland	People with mild TBI with blood drawn within 6 h of injury GCS 13-15 to be included Age, mean (SD): 31.3 (10.4) years	S100B – threshold of ≥0.50 µg/l	Post-concussion symptoms at 8-30 months Considered positive for symptoms if at least one symptom reported by the person at the time of interview or if they had suffered with them from day of trauma for at least one month, and if they were more severe than before the trauma Based on modified version of Rivermead Post-Concussion Symptoms Questionnaire	AUC, sensitivity and specificity	Risk of bias: very serious Indirectness: possibly a mixture of adults and children, but mean age consistent with adult population	

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
			– modified by dichotomising into yes or no and adding questions about alcohol tolerance and panic attacks			
Townend 2002[34] N=119 Prospective Conducted in UK	Adults with head injury presenting to ED within 6 h of injury 95% had GCS 13-15 Age, mean (SD): 49.0 (21.2) years	S100B – threshold of ≥0.27 µg/l for moderate disability and ≥0.32 µg/l for severe disability	GOSE at 1 month <u>At least moderate disability</u> Scores of 7-8 and <7 on GOSE were considered to indicate good or adverse outcome, respectively <u>Severe disability</u> Scores of 5-8 and <5 on GOSE were considered to indicate good or adverse outcome, respectively	AUC, sensitivity and specificity	Risk of bias: serious Indirectness: none	Mixed severity within the population but not downgraded as 95% reported to have GCS 13-15 (mild).
Ingebrigtsen 1995[12] N=42 Prospective Conducted in Norway	Children and adults (mean age 31 years) with minor head injury GCS 14-15 to be included Age, mean (range): 31 (6-88) years	S100B – threshold of ≥0.5 mg/l , measured as soon as possible after trauma (admission)	Persistent symptoms of concussion after 9 months	Data available to calculate sensitivity and specificity	Risk of bias: very serious Indirectness: mixture of adults and children and proportion is unclear, but mean age consistent with adult population (31.0 years)	
Blood biomarkers – UCHL1						
Diaz-Arrastia 2014[7] N=206 Prospective	Presenting within 24 h of injury with trauma to head sufficient to triage to non-contrast head CT	UCHL1 - continuous	GOSE at 3 and 6 months Assessed as: • incomplete recovery (GOSE <8 and GOSE	AUC	Risk of bias: very serious Indirectness: mixture of adults and children and proportion is unclear, but	TRACK-TBI study Mixed TBI severity but not downgraded for indirectnes

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
Conducted in USA	Any GCS included, but most were mild TBI (GCS 13-15, 83%) Age, mean (SD): 42.0 (18.0) years		=8 groupings) • poor outcome (GOSE ≤4 and GOSE >4 groupings)		mean age consistent with adult population (42.0 years)	s as >75% with mild TBI
Korley 2016[16] N=159 Prospective/retrospective Conducted in USA	Adults (≥16 years) with any severity of TBI Any GCS included but most (84%) were mild TBI (GCS 13-15) Age, median (IQR): 41 (25-56) years	UCHL1 - continuous	Incomplete recovery at 6 months Based on composite outcome of post-concussion syndrome (three or more symptoms on Rivermead Post-Concussion Questionnaire rated as worse than before injury) or GOSE score <8 Also reports results for the two outcomes separately	AUC	Risk of bias: serious Indirectness: none	TRACK-TBI study in addition to data from two other cohorts Mixed TBI severity but not downgraded for indirectness as >75% with mild TBI
Lee 2015[19] N=31 with mild TBI Prospective Conducted in Korea	People with mild TBI (GCS 13-15) GCS: mean, 14.5 Age: mean (range), 58.5 (19 to 84) years for the whole population including severe TBI	UCHL1 – continuous (for AUC) or 0.96 ng/ml cut-off value (for sensitivity and specificity)	Poor outcome based on GOS at 3 months GOS 1-3 was considered poor outcome and GOS4-5 was considered good outcome	AUC, sensitivity and specificity	Risk of bias: very serious Indirectness: none	Includes mild and severe TBI, but in the methods section, results for prognostic accuracy said to be for the mild TBI group.
Blood biomarkers – NSE						
Herrman n 2001[9]	Admitted to Department of	NSE – continuous or	Neuropsychological	AUC, sensitivity	Risk of bias: very serious	2-week time-point also

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
N=29 or 39 Prospective Conducted in Germany	Neurosurgery following TBI GCS at site of accident (median, range): • 13 (3-15) GCS at admission (median, range): • 15 (3-15) Median (range) age: • 29 (17-56) years for those analysed at 2 weeks • 27 (17-54) years for those analysed at 6 months	threshold >5.75 µg/l, measured median 27 hours post-injury Blood also drawn at second and third day of admission (median 49.5 hours and median 80.0 hours post-injury, respectively), but results describe 'initial' serum levels suggesting first time-point included	assessment at 6 months Neuropsychological disorders present if performed <1 SD below (age-adjusted) normal data in at least three cognitive domains. Included the following components: • Global cognitive and behavioural screening • Memory/learning • Language • Visuoperception/construction • Executive functions • Attentional performance Psychomotor speed	and specificity	Indirectness – mixed severity and not limited to mild TBI (proportions unclear). Included as median value at site and on admission was consistent with mild TBI in those analysed at 6 months.	reported but this time-point is less relevant to post-concussion syndrome
Topolovec-Vranic 2011[33] N=95 Prospective Conducted in Canada	Adults (18-65 years) presenting with mild TBI within 4 h GCS 13-15 to be included Age, mean (range): 39.4 (19-65) years	NSE – threshold of ≥14.6 µg/l	Abnormal status at 6 weeks Based on physician assessment, including physical examination with complete history, neurologic examination and tools to assess headache and dizziness Unclear whether this	AUC	Risk of bias: very serious Indirectness: none	

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
			included neurocognitive tests and post-concussion scale mentioned in the paper			
Blood biomarkers – BDNF						
Korley 2016[16] N=159 Prospective/retrospective Conducted in USA	Adults (≥16 years) with any severity of TBI Any GCS included but most (84%) were mild TBI (GCS 13-15) Age, median (IQR): 41 (25-56) years	BDNF - continuous	Incomplete recovery at 6 months Based on composite outcome of post-concussion syndrome (three or more symptoms on Rivermead Post-Concussion Questionnaire rated as worse than before injury) or GOSE score <8 Also reports results for the two outcomes separately	AUC	Risk of bias: serious Indirectness: none	TRACK-TBI study in addition to data from two other cohorts Mixed TBI severity but not downgraded for indirectness as >75% with mild TBI
Blood biomarkers – NF-L						
Hossain 2019[10] N=107 Prospective Conducted in Finland	Adults (≥18 years) with mild TBI with blood samples within 24 h of ED arrival GCS 13-15 to be included Age, mean (SD): 47.6 (20.2) years	NF-L – continuous (for AUC) and <28.15 pg/ml (complete recovery) or <53.6 pg/ml (favourable outcome) for sensitivity and specificity	GOSE at 6-12 months post-injury Complete recovery (GOSE 8) and incomplete recovery groupings (GOSE <8) AND Favourable outcome (GOSE 5-8) and unfavourable outcome (GOSE 1-4) groupings	AUC, sensitivity and specificity	Risk of bias: none Indirectness: none	Where thresholds have been used, these were selected for sensitivity values >90%

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
Lagerstedt 2020[17] N=49 Prospective Conducted in Finland	Adults (≥18 years) with TBI – reports result separately for mild subgroup GCS: 13-15 range in the mild subgroup Age, mean (SD): 44.1 (19.8) years	NF-L – threshold 4.85 pg/ml	Complete recovery based on GOSE at >6 months GOSE 8 considered complete recovery and GOSE ≤7 considered incomplete recovery	Partial AUC, sensitivity and specificity	Risk of bias: none Indirectness: none	Mixed severity within the population but provides results for those with mild TBI separately. Threshold selected based on best threshold with a sensitivity 95-100%
Posti 2020[27] N=137 (n=82 and n=55 in CT-positive and CT-negative groups) Prospective Conducted in Finland	Adults (≥18 years) with TBI with or without confirmed lesion on CT (separately for the two groups) Any GCS included but median values consistent with mild TBI (median 14, range 3-15) Age, mean (SD): 50.46 (20.35) years	NF-L – continuous/threshold	Two outcomes based on GOSE scores at 4-16 months • Unfavourable outcome (GOSE 1-4) Incomplete recovery (GOSE <8)	AUC, sensitivity and specificity	Risk of bias: very serious Indirectness: mixed TBI severity with proportion with mild TBI unclear, though median values consistent with mild TBI.	TBIcare study
αII-Spectrin breakdown products						
Siman 2013[31] N=17 Prospective Conducted in USA	People with mild TBI with plasma collected within 24 h injury from ED GCS 13-15 to be included	SNTF – those that were SNTF+ (defined as at least twice the lower limit of detection of 10 units in an ultrasensit	Cognitive performance – failure to achieve improvement of at least 5 points over 3 months on SDMT Used as measure of	Sensitivity and specificity	Risk of bias: very serious Indirectness – quite a specific age group unlike other studies, unclear proportion of children and adults	Post-hoc analysis only

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
	Age 12-30 years to be included – mean (SD) 20.5 (5.8) for whole population including controls	ive sandwich immunoassay)	processing speed deficits		(mean age consistent with adults)	
Blood biomarkers – GFAP						
Diaz-Arrastia 2014[7] N=206 Prospective Conducted in USA	Presenting within 24 h of injury with trauma to head sufficient to triage to non-contrast head CT Any GCS included, but most were mild TBI (GCS 13-15, 83%) Age, mean (SD): 42.0 (18.0) years	GFAP - continuous	GOSE at 3 and 6 months Assessed as: • incomplete recovery (GOSE <8 and GOSE =8 groupings) • poor outcome (GOSE ≤4 and GOSE >4 groupings)	AUC	Risk of bias: very serious Indirectness: mixture of adults and children and proportion is unclear, but mean age consistent with adult population (42.0 years)	TRACK-TBI study Mixed TBI severity but not downgraded for indirectness as >75% with mild TBI Possibly includes children and adults but mean age consistent with adult population
Hossain 2019[10] N=107 Prospective Conducted in Finland	Adults (≥18 years) with mild TBI with blood samples within 24 h of ED arrival GCS 13-15 to be included Age, mean (SD): 47.6 (20.2) years	GFAP – continuous (for AUC) and <6438.05 pg/ml (complete recovery) or <12189.85 pg/ml (favourable outcome) for sensitivity and specificity	GOSE at 6-12 months post-injury Complete recovery (GOSE 8) and incomplete recovery groupings (GOSE <8) AND Favourable outcome (GOSE 5-8) and unfavourable outcome (GOSE 1-4) groupings	AUC, sensitivity and specificity	Risk of bias: none Indirectness: none	Where thresholds have been used, these were selected for sensitivity values >90%
Korley 2016[16] N=159	Adults (≥16 years) with any severity of TBI	GFAP - continuous	Incomplete recovery at 6 months	AUC	Risk of bias: serious	TRACK-TBI study in addition to data from

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
Prospective/retrospective Conducted in USA	Any GCS included but most (84%) were mild TBI (GCS 13-15) Age, median (IQR): 41 (25-56) years		Based on composite outcome of post-concussion syndrome (three or more symptoms on Rivermead Post-Concussion Questionnaire rated as worse than before injury) or GOSE score <8 Also reports results for the two outcomes separately		Indirectness: none	two other cohorts Mixed TBI severity but not downgraded for indirectness as >75% with mild TBI
Lagerstedt 2020[17] N=49 Prospective Conducted in Finland	Adults (≥18 years) with TBI – reports result separately for mild subgroup GCS: 13-15 range in the mild subgroup Age, mean (SD): 44.1 (19.8) years	GFAP – no threshold	Complete recovery based on GOSE at >6 months GOSE 8 considered complete recovery and GOSE ≤7 considered incomplete recovery	Partial AUC, sensitivity and specificity	Risk of bias: none Indirectness: none	Mixed severity within the population but provides results for those with mild TBI separately. Threshold selected based on best threshold with a sensitivity 95-100%
Lee 2015[19] N=31 with mild TBI Prospective Conducted in Korea	People with mild TBI (GCS 13-15) GCS: mean, 14.5 Age: mean (range), 58.5 (19 to 84) years for the whole population including severe TBI	GFAP – continuous (for AUC) or 18.00 ng/ml cut-off value (for sensitivity and specificity)	Poor outcome based on GOS at 3 months GOS 1-3 was considered poor outcome and GOS4-5 was considered good outcome	AUC, sensitivity and specificity	Risk of bias: very serious Indirectness: none	Includes mild and severe TBI, but in the methods section, results for prognostic accuracy said to be for the mild TBI group.

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
Metting 2012[23] N=94 Prospective Conducted in The Netherlands	Adults (18-65 years) with acute mild TBI and post-traumatic amnesia GCS 13-15 to be included Age, mean (SD): 34.3 (13.9) years	GFAP - continuous	Recovery based on GOSE (score =8) at 6 months Return to work at 6 months	Sensitivity and specificity	Risk of bias: serious Indirectness: none	
Posti 2020[27] N=137 (n=82 and n=55 in CT-positive and CT-negative groups) Prospective Conducted in Finland	Adults (≥18 years) with TBI with or without confirmed lesion on CT (separately for the two groups) Any GCS included but median values consistent with mild TBI (median 14, range 3-15) Age, mean (SD): 50.46 (20.35) years	GFAP – continuous/threshold	Two outcomes based on GOSE scores at 4-16 months • Unfavourable outcome (GOSE 1-4) • Incomplete recovery (GOSE <8)	AUC, sensitivity and specificity	Risk of bias: very serious Indirectness: mixed TBI severity with proportion with mild TBI unclear, though median values consistent with mild TBI.	TBIcare study
Xu 2021[37] N=1206 Prospective Conducted in USA	People with TBI of any severity Any GCS included but most (87%) were mild Age, mean (SD): 40.0 (17.0) years	GFAP – continuous	Favourable outcome based on GOSE at 6 months (score ≥5)	AUC	Risk of bias: very serious Indirectness: possibly includes children and adults but mean age consistent with adult population	TRACK-TBI study
Blood biomarkers – combinations						
Diaz-Arrastia 2014[7] N=206	Presenting within 24 h of injury with trauma to head	UCHL-1 and GFAP - continuous	GOSE at 3 and 6 months Assessed as:	AUC	Risk of bias: very serious Indirectness: mixture of	TRACK-TBI study Mixed TBI severity but

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
Prospective Conducted in USA	sufficient to triage to non-contrast head CT Any GCS included, but most were mild TBI (GCS 13-15, 83%) Age, mean (SD): 42.0 (18.0) years		• incomplete recovery (GOSE <8 and GOSE =8 groupings) • poor outcome (GOSE ≤4 and GOSE >4 groupings)		adults and children and proportion is unclear, but mean age consistent with adult population (42.0 years)	not downgraded for indirectness as >75% with mild TBI Possibly includes children and adults but mean age consistent with adult population
Korley 2016[16] N=159 Prospective/retrospective Conducted in USA	Adults (≥16 years) with any severity of TBI Any GCS included but most (84%) were mild TBI (GCS 13-15) Age, median (IQR): 41 (25-56) years	GFAP and BDNF combined – continuous AND UCLH-1 and BDNF combined – continuous	Incomplete recovery at 6 months Based on composite outcome of post-concussion syndrome (three or more symptoms on Rivermead Post-Concussion Questionnaire rated as worse than before injury) or GOSE score <8	AUC	Risk of bias: serious Indirectness: none	TRACK-TBI study in addition to data from two other cohorts Mixed TBI severity but not downgraded for indirectness as >75% with mild TBI
Hossain 2019[10] N=107 Prospective Conducted in Finland	Adults (≥18 years) with mild TBI with blood samples within 24 h of ED arrival GCS 13-15 to be included Age, mean (SD): 47.6 (20.2) years	GFAP and NF-L combined – threshold of <6438.05 pg/ml and <28.15 pg/ml, respectively or <980.75 pg/ml and <41.85 pg/ml, respectively	GOSE at 6-12 months post-injury Complete recovery (GOSE 8) and incomplete recovery groupings (GOSE <8) AND Favourable outcome (GOSE 5-8) and unfavourable outcome	Sensitivity and specificity	Risk of bias: none Indirectness: none	Where thresholds have been used, these were selected for sensitivity values >90%

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
			(GOSE 1-4) groupings			
Salivary biomarkers – RNA/miRNA						
Fedorchak 2021[8] N=112 Prospective Conducted in USA	People aged 8-24 years with diagnosis of mild TBI enrolled within 14 days of injury GCS not reported but described as mild TBI Age, mean (SD): 16.1 (3.7) years	Salivary non-coding RNA – includes miRNA, snoRNA and wiRNA, measured within 14 days of injury	Persistent post-concussion symptoms at ≥21 days post-injury Measured using Post-Concussion Symptom Scale (0-6 scale) – scores >5 indicated persistent symptoms	AUC, sensitivity and specificity	Risk of bias: very serious Indirectness: • biomarkers measured within 14 days not 48 h • model contains multiple RNAs so unclear utility of each • possibly includes mixture of adults and children but mean age represents adult population	Mixture of adults and children, with mean age just >16 years
MRI						
Bai 2020[2] N=98 Prospective Conducted in China	People with mild TBI based on WHO Collaborating Centre for Neurotrauma Task Force GCS unclear but reported to be mild TBI Age, mean (SD) 35.3	MRI – various white matter fibres combined in model	Information processing speed deficits at 6-12 months post-injury Assessed using Trail Making Test A – deficit based on norms adjusted by age and education level	Accuracy, sensitivity and specificity Separate for original sample and replicate sample	Risk of bias: serious Indirectness: • possibly includes mixture of adults and children but mean age represents	

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
	914.8) years and 37.0 (11.2) years in original and replicate samples				adult population • results for a model containing multiple MRI features so difficult to assess utility of each	
Huovinen 2021[11] N=113 Prospective Conducted in Finland	Mild TBI (according to WHO) from outpatient clinic of hospital aged between 18 and 68 years GCS unclear but described as mild TBI Age, mean (SD): 39.2 (12.2) years	MRI – traumatic microbleeds	Recovery at 1 month (GOSE score of 8)	Sensitivity and specificity from raw data	Risk of bias: very serious Indirectness: none	
Ledig 2017[18] N=67 Prospective Conducted in Finland	Adults (range 45 to 86 years) with TBI of any severity, though median values are consistent with mild TBI Proportion with mild TBI unclear, median GCS in those with low and moderate	MRI – multiple features reported separately	GOSE – severe vs. low disability at follow-up (time-point unclear) GOSE scores of 3-4 and 7-8 for severe and low disability, respectively	Accuracy, sensitivity and specificity	Risk of bias: very serious Indirectness – mixed severity of TBI within the population and proportion with each unclear (median values consistent with mild TBI)	

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
	disability said to be 15, with it being 14 in severe disability group Median age ranges from 58 to 74 years across low-severe disability groups					
Li 2016[20] N=43 Prospective Conducted in China	People with mild TBI, excluding those with abnormal TBI GCS 13-15 to be included Age, mean (SD): 30.6 (8.6) years	MRI 10-20 days post-injury – continuous mean values of multiple measures on MRI	PTSD diagnosis – poor recovery – unclear time-point (measured at 1 and 6 months) Based on Clinician-administered PTSD scale (CAPS)	Sensitivity and specificity	Risk of bias: very serious Indirectness: possibly mixture of children and adults but mean age consistent with adult population	
Messe 2011[22] N=23 Prospective Conducted in France	Adults (aged 18-65 years) with mild TBI GCS 13-15 to be included Age, mean (SD): 29.6 (8.6) years	MRI – various features combined into a model, continuous mean values	Persistent post-concussion symptoms at 3 months Evaluated using questionnaire adapted from another study – defined as at least one complaint in all three domains of questionnaire Those not meeting this criterion considered to have good outcome, those meeting criteria considered to	Sensitivity and specificity	Risk of bias: very serious Indirectness: provides results for a model containing multiple MRI features so difficult to assess utility of each	

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
			have poor outcome			
Niu 2019[25] N=56 Prospective Conducted in China	People with mild TBI based on WHO Collaborating Centre for Neurotrauma Task Force and persistent headache at acute injury GCS unclear but reported to be mild TBI Age, mean (SD): 35.9 (11.9) years	MRI - periaqueductal grey (PAG)-seeded functional connectivity	Persistent post-traumatic headache at 3 months Based on VAS score – score >0 persistent headache and a score of 0 indicating non-persistent headache	AUC, sensitivity and specificity	Risk of bias: very serious Indirectness: possibly includes mixture of adults and children but mean age represents adult population	
Richter 2021[28] N=65 Prospective Conducted in UK	People with mild TBI undergoing head CT and MRI GCS 13-15 to be included Age, median (IQR): 45 (24-59) years	MRI – various imaging strategies (sequencies method and quantitative or qualitative)	Favourable recovery at 3 months – GOS score of 8	AUC	Risk of bias: very serious Indirectness: Unclear if had to be >16 years to be included but median age consistent with adult population	CENTER-TBI MRI study and Cambridge study with similar protocol
Stein 2021[32] N=421 Prospective Conducted in USA	Adults (>16 years) with mild TBI and MRI GCS 13-15 to be included Age, mean (SD): 38.7 (16.1) years	MRI – positive MRI result Definition unclear, but reported that findings were largely microbleeds caused by haemorrhagic axonal injury and small	Probable post-traumatic stress disorder at 3 months and 6 months Measured using PTSD checklist for DSM-5 – score ≥33 indicating PTSD	Sensitivity and specificity from raw data	Risk of bias: very serious Indirectness: none	TRACK-TBI study

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
		contusions				
Waljas 2015[35] N=126 Prospective Conducted in Finland	Adults (≥16 years to 65 years) with mild TBI based on WHO Collaborating Center Task Force on Mild TBI criteria GCS 13-15 to be included Age, mean (SD): 37.8 (13.5) years	MRI – abnormal, conducted between 2 weeks and 2 months post-injury	Post-concussion syndrome at 1 month and 1 year Based on two different questionnaires for post-concussion symptoms Reports mild or greater symptoms and moderate or greater symptoms separately	Sensitivity and specificity from raw data	Risk of bias: very serious Indirectness: none	
Wang 2014[36] N=165 Prospective Conducted in China	People with mild TBI undergoing MRI at admission GCS 13-15 to be included Age >65 years excluded Age, mean (SD): 44.1 (14.8) years	MRI – microbleed lesions Defined as rounded, hypointense homogenous foci up to 5 mm in size not compatible with vascular, bone calcification or artefactual structures	SCID-IV criteria for depressive symptoms – major depression after TBI at 1 year Included those classified into the 'major depressive-like episode' subtype for at least one follow-up visit within 1 year	Sensitivity and specificity from raw data	Risk of bias: serious Indirectness: Possibly a mixture of children and adults, but mean age consistent with adult population	

AUC, area under the curve; BDNF, brain-derived neurotrophic factor; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; ED, emergency department; GCS, Glasgow Coma Scale; GFAP, glial fibrillary acidic protein; GOS, Glasgow Outcome Scale; GOSE, Glasgow Outcome Scale-Extended; miRNA, microRNA; NF-L, neurofilament light; NSE, neuron specific enolase; PTSD, post-traumatic stress disorder; S100B, S100 calcium binding protein B; SCID-IV, Structured Clinical Interview for DSM-IV; SDMT, symbol digit modalities test; snoRNA, small nucleolar RNA; SNTF, calpain-cleaved αII spectrin N-terminal fragment; TBI, traumatic brain injury; UCH-L1, ubiquitin C-terminal hydrolase-L1; VAS, visual analogue scale; WHO, World Health Organisation; wiRNA, piwi-interacting RNA with hierarchical clustering to reduce highly similar sequences.

Table 4: Summary of studies included in the evidence review – children

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
Blood biomarkers – S100B						

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
Babcock 2013[1] N=76 Prospective Conducted in USA	Children (≥5 to 18 years) with mild TBI GCS >13 to be included Age, mean (SD): 13.0 (3.1) years	S100B - continuous	Post-concussion syndrome at 3 months Defined as 3 or more symptoms with score ≥2 (worse relative to pre-injury) on Rivermead Post-Concussion Questionnaire	AUC	Risk of bias: very serious Indirectness: none	
Kelmendi 2021[15] N=60 Prospective Conducted in Kosovo	Children (7-16 years) with mild TBI admitted within 3 h GCS 13-15 to be included Age, mean (SD): 11.1 (2.4) years	S100B – continuous	Post-concussion syndrome symptoms at 3 months Based on Rivermead Post-Concussion Symptoms Questionnaire - ≥3 symptoms graded ≥2 (worse compared to pre-injury) considered post-concussion syndrome	AUC	Risk of bias: very serious Indirectness: none	
Blood biomarkers – combinations						
Berger 2007[6] N=152 Prospective Conducted in USA	Children (<13 years) with TBI of any severity with CT Any GCS included but 61% with mild TBI (GCS 13-15) Age, median (range): 15.2 (0.1	Model including abnormal values for S100B, NSE and MBP, including initial and peak values Abnormal values were >0.017 ng/ml, 11.7 ng/ml and 0.3 ng/ml	GOS at 0-3 months, 4-6 months and 7-12 months post-discharge Scores 1-2 indicated good outcome and scores 3-5 indicated poor outcome	Accuracy	Risk of bias: very serious Indirectness: • not limited to those with mild TBI, with only 61% mild • difficult to assess utility of	

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
	to 150.2) months	for S100B, NSE and MBP, respectively			each of the three biomarkers as results only provided for combined model	
Salivary biomarkers – RNA/miRNA						
Johnson 2018[14] N=52 Prospective Conducted in USA	Children and adolescents aged 7-21 years with clinical diagnosis of mild TBI within 14 days of injury GCS 13-15 to be included Age, mean (SD): 14.0 (3.0) years	Salivary miRNA – continuous Model containing multiple miRNAs	Post-concussion syndrome at 4 weeks Assessed using SCAT3 symptom evaluation section (score of ≥5) based on child and/or parent report	AUC, sensitivity and specificity	Risk of bias: very serious Indirectness: included those presenting within 14 days of injury and having samples taken rather than within 48 h	Mixture of adults and children, though focus of paper is on children and mean age <16 years
MRI						
Barlow 2021[3] N=61 Prospective Conducted in Canada	Children (8-18 years) with mild TBI medically diagnosed and persistent post-concussion symptoms with ≥10-point increase on Post-Concussion Symptom Inventory post-injury compared to pre-injury	MRI – mean absolute cerebral blood flow at 4-6 weeks post-injury	Good recovery based on Post-Concussion Symptom Inventory scores Good recovery if symptoms at or below pre-injury levels and returned to normal activity	AUC	Risk of bias: very serious Indirectness – already diagnosed with persistent post-concussion symptoms	Secondary analysis of intervention trial (Play Game)

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
	GCS unclear, but described as mild TBI Age, mean (SD): 14.2 (2.6) years					
Iyer 2019[13] N=132 Prospective Conducted in Canada	Children with confirmed mild TBI GCS 13-15 to be included Age, mean (SD): 14.5 (2.4) years	MRI – model consisting of MRI variables and age	Recovery based on Post–Concussion Symptom Inventory scores at 8-10 weeks post-injury Grouped into 'symptomatic' and 'recovered' – symptomatic if ≥10-point increase in total score compared to pre-injury score	AUC, sensitivity and specificity	Risk of bias: very serious Indirectness: none	Secondary analysis of intervention trial (Play Game)
Lima Santos 2021[21] N=42 Prospective Conducted in USA	Adolescents (12.1-17.9 years) with recent diagnosis of concussion GCS unclear, but includes those with concussion Age, mean (SD): 15.5 (1.7) years	MRI – model including clinical, demographic and various MRI variables	Time to medical clearance following concussion – short and long groups Short group were those with clearance within first 4 weeks and long group were those that did not receive clearance within 4 weeks Clearance was based on symptoms at rest and	AUC	Risk of bias: very serious Indirectness: none	iCARE study

Study	Population	Prognostic variables	Outcomes	Statistical measures	Limitations	Comments
			following activity, neurocognitive functioning, vestibular and oculomotor functioning and other related medical complaints			
Yeates 2009[38] N=186 Prospective Conducted in USA	Children (8-15 years) with mild TBI GCS 13-15 to be included Age, mean (SD): 11.96 (2.22) years	MRI – abnormal (trauma-related abnormalities) Definition not provided	Persistence of post-concussion symptoms across follow-up (up to 12 months) – moderate increase or high acute symptoms that persisted Assessed based on Post-Concussive Symptom Interview rated by parents	Sensitivity and specificity from raw data	Risk of bias: very serious Indirectness: none	

AUC, area under the curve; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; MBP, myelin basic protein; miRNA, microRNA; NSE, neuron specific enolase; S100B, S100 calcium binding protein B; SCAT3, Sport Concussion Assessment Tool 3; TBI, traumatic brain injury

See Appendix D for full evidence tables.

1.1.6 Prognostic evidence (see separate tables under each biomarker heading for sensitivity/specificity data and AUC data)

Adults – blood biomarkers – S100B

Table 5: Clinical evidence summary: sensitivity and specificity data – S100B in adults

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome											
S100B – continuous variable, samples taken within 4 h of injury	1: Bazarian 2006[4]	96	Mild TBI presenting within 4 h of injury 5.1% with head CT abnormality on initial scan	Post-concussion syndrome at 3 months post-injury Score of ≥5 on Rivermead Post-concussive Questionnaire	0.70 – fixed sensitivity set to assess specificity	<u>Uncorrected:</u> 0.23 (no CIs reported) <u>Corrected for creatinine kinase levels:</u> 0.30 (no CIs reported)	Sensitivity				
							NA – authors used fixed sensitivity of 0.70 to see what corresponding specificity would be at that value				
							Specificity				
							Very serious[a]	Serious[b]	None	Serious[c]	VERY LOW
S100B – continuous variable, samples	1: Bazarian 2006[5]	31	Mild TBI presenting within 6 h of injury	Post-concussion syndrome	0.563 (0.330 to 0.770)	0.357 (0.160 to 0.610)	Sensitivity				
							Very serious[a]	Serious[b]	None	Serious[d]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
taken within 6 h of injury			5.7% had CT traumatic abnormalities	at 3 months post-injury Score of ≥5 on Rivermead Post-concussive Questionnaire			Very serious[a]	Serious[b]	None	None	VERY LOW
S100B – threshold of ≥20 µg/l, samples taken within 6 h of injury	1: Savola 2003[30]	172	Mild head injury with blood drawn within 6 h of injury 38% reported to have skull fracture	Post-concussion symptoms at 8-30 months Positive for symptoms if at least one symptom reported at interview or if reported suffering from a symptom for at least	<u>Before normalisation</u> 0.68 (no CIs reported) <u>After normalisation for time of head injury onset</u> 0.92 (no CIs reported)	<u>Before normalisation</u> 0.67 (no CIs reported) <u>After normalisation for time of head injury onset</u> 0.41 (no CIs reported)	Sensitivity				
							Very serious[a]	Serious[b]	None	Serious[d]	VERY LOW
							Specificity				
							Very serious[a]	Serious[b]	None	Serious[c]	VERY LOW
S100B – threshold of ≥30 µg/l, samples					<u>Before normalisation</u> 0.49 (no CIs reported)	<u>Before normalisation</u> 0.82 (no CIs reported)	Sensitivity				
							Very serious[a]	Serious[b]	None	Serious[d]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
taken within 6 h of injury				one month and more severe than before trauma based on modified version of Rivermead Post-Concussion Symptoms Questionnaire[e]	<u>After normalisation for time of head injury onset</u> 0.78 (no CIs reported)	<u>After normalisation for time of head injury onset</u> 0.59 (no CIs reported)	Very serious[a]	Serious[b]	None	Serious[c]	VERY LOW
S100B – threshold of ≥40 µg/l, samples taken within 6 h of injury					<u>Before normalisation</u> 0.38 (no CIs reported) <u>After normalisation for time of head injury onset</u> 0.73 (no CIs reported)	<u>Before normalisation</u> 0.91 (no CIs reported) <u>After normalisation for time of head injury onset</u> 0.70 (no CIs reported)	Sensitivity				
							Very serious[a]	Serious[b]	None	Serious[d]	VERY LOW
							Specificity				
							Very serious[a]	Serious[b]	None	Serious[c]	VERY LOW
S100B – threshold of ≥50 µg/l, samples					<u>Before normalisation</u> 0.27 (no CIs reported)	<u>Before normalisation</u> 0.93 (no CIs reported)	Sensitivity				
							Very serious[a]	Serious[b]	None	Serious[d]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
taken within 6 h of injury					After normalisation for time of head injury onset 0.65 (no CIs reported)	After normalisation for time of head injury onset 0.79 (no CIs reported)	Very serious[a]	Serious[b]	None	Serious[c]	VERY LOW
S100B – threshold of ≥0.5 µg/l, sample	1: Ingebrigtsen 1995[12]	42	Isolated minor head injury	Persistent symptoms of concussion	0.18 (0.02 to 0.52)	0.77 (0.59 to 0.90)	Sensitivity				
							Very serious[a]	Serious[b]	None	None	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
taken as soon as possible following trauma admission			Limited to GCS 14-15 only No signs of intracranial lesion on CT to be included	after 9 months Unclear how many symptoms required to be included under those with persistent symptoms – asked about 12 most common symptoms of concussion following head injury			Very serious[a]	Serious[b]	None	Serious[c]	VERY LOW
GOS or GOSE used as outcome											
S100B – threshold of ≥23.17 pg/ml, samples	1: Lagerstedt 2020[17]	49	TBI within 24 h and indication for head CT – mild	Complete recovery based on GOSE at >6 months	0.958 (0.875 to 1.00) (threshold selected by	0.12 (0.00 to 28.0)	Sensitivity				
							None	None	None	Serious[d]	MODERATE
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
within 24 h of injury			subgroup results reported separately 57% with no visual pathology on Marshall grade system	GOSE 8 considered complete recovery and GOSE ≤7 considered incomplete recovery	specifying sensitivity of 95-100% and identifying best in terms of balance with specificity)		None	None	None	None	HIGH
S100B – threshold of ≥27.01 ng/ml, samples	1: Lee 2015[19]	31	Any severity TBI – reports results for mild	Poor outcome based on GOS at 3 months	0.92 (no CIs reported)	0.87 (no CIs reported)	Sensitivity				
							Very serious[a]	None	None	Very serious[d]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
within 24 h of trauma			subgroup separately All of those included (any severity) had one of following: haemorrhage (subdural, epidural, contusional or subarachnoid) or diffuse axonal injury or fracture – unclear what injuries were present specifically in the mild subgroup	GOS 1-3 was considered poor outcome and GOS4-5 was considered good outcome			Very serious[a]	None	None	Very serious[c]	VERY LOW
		82					Sensitivity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
S100B – threshold of 2300.8 pg/ml, measured within 24 h	1: Posti 2020[27]		Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-positive subgroup	Unfavourable outcome based on GOSE at 4-16 months GOSE 1-4 represents unfavourable outcome	1.00 (1.00 to 1.00) (threshold selected by specifying sensitivity of 90-100% and identifying best in terms of balance with specificity)	0.02 (0.0 to 0.061)	Very serious[a]	Serious[f]	None	None	VERY LOW
							Specificity				
							Very serious[a]	Serious[f]	None	None	VERY LOW
S100B – 45.3 pg/ml, measured within 24 h		55	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-negative subgroup	Unfavourable outcome based on GOSE at 4-16 months GOSE 1-4 represents unfavourable outcome	1.00 (1.00 to 1.00) (threshold selected by specifying sensitivity of 90-100% and identifying best in terms of balance with specificity)	0.137 (0.059 to 0.235)	Sensitivity				
							Very serious[a]	Serious[f]	None	None	VERY LOW
							Specificity				
							Very serious[a]	Serious[f]	None	None	VERY LOW
		82					Sensitivity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
S100B – continuous, measured within 24 h			Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-positive subgroup	Incomplete recovery based on GOSE at 4-16 months GOSE <8 represents incomplete recovery	1.00 (1.00 to 1.00) (threshold selected by specifying sensitivity of 90-100% and identifying best in terms of balance with specificity)	0.00 (0.00 to 0.00)	Very serious[a]	Serious[f]	None	None	VERY LOW
							Specificity				
							Very serious[a]	Serious[f]	None	None	VERY LOW
S100B – continuous, measured within 24 h		55	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-negative subgroup	Incomplete recovery based on GOSE at 4-16 months GOSE <8 represents incomplete recovery	1.00 (1.00 to 1.00) (threshold selected by specifying sensitivity of 90-100% and identifying best in terms of balance with specificity)	0.00 (0.00 to 0.00)	Sensitivity				
							Very serious[a]	Serious[f]	None	None	VERY LOW
							Specificity				
							Very serious[a]	Serious[f]	None	None	VERY LOW
		118					Sensitivity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
S100B – threshold of ≥0.27 µg/l, samples taken within 48 h	1: Townend 2002[34]		Head injury of any severity (95% GCS 13-15) presenting within 6 h of injury Did not mention excluding those with any abnormalities on imaging	At least moderate disability based on GOSE at 1 month GOSE scores <7 indicated at least moderate disability	0.76 (0.56 to 0.90)	0.69 (0.58 to 0.78)	Serious[a]	None	None	Serious[d]	LOW
							Specificity				
							Serious[a]	None	None	Serious[c]	LOW
S100B – threshold of ≥0.32 µg/l, samples taken within 48 h		118		Severe disability based on GOSE at 1 month GOSE scores <5 indicated severe disability	0.93 (0.68 to 1.00)	0.72 (0.62 to 0.80)	Sensitivity				
							Serious[a]	None	None	Very serious[d]	VERY LOW
							Specificity				
							Serious[a]	None	None	Serious[c]	LOW
		112					Sensitivity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
S100B – threshold of ≥0.48 µg/l, samples taken within 48 h			Mild subgroup (GCS 13-15) of head injury Did not mention excluding those with any abnormalities on imaging	Severe disability based on GOSE at 1 month GOSE scores <5 indicated severe disability	0.90 (0.55 to 0.99)	0.83 (0.75 to 0.90)	Serious[a]	None	None	Very serious[d]	VERY LOW
							Specificity				
							Serious[a]	None	None	None	MODERATE
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)											
S100B – continuous variable, samples taken within 4 h of injury	1: Bazarian 2006[4]	96	Mild TBI presenting within 4 h of injury 5.1% with head CT abnormality on initial scan	Headache at 3 months post-injury No further information provided	0.70 – fixed sensitivity set to assess specificity	Uncorrected: 0.26 (no CIs reported) Corrected for creatinine kinase levels: 0.37 (no CIs reported)	Sensitivity				
							NA – authors used fixed sensitivity of 0.70 to see what corresponding specificity would be at that value				
							Specificity				
							Very serious[a]	Serious[b]	None	Serious[c]	VERY LOW
S100B – threshold of >140 ng/l, samples	1: Hermann 2001[9]	29	Any TBI severity – median GCS at	Neuropsychological assessmen	0.65 (no CIs reported)	0.889 (no CIs reported)	Sensitivity				
							Very serious[a]	Serious[f]	None	Very serious[d]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
taken median 27 h post-trauma			admission: 15 (range 3-15) 55.0% with intracranial pathology on CT	t at 6 months Neuropsychological disorders present if performed <1 SD below (age-adjusted) normal data in at least three cognitive domains[g]			Very serious[a]	Serious[f]	None	Very serious[c]	VERY LOW

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Downgraded by 1 increment as the population was a mixture of children and adults with no proportions given (study was included under the adult population as the average age, for example mean or median age, was consistent with the adult population).

[c] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.95 and 0.75, respectively, which were the thresholds used for specificity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[d] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.9 and 0.7, respectively, which were the thresholds used for sensitivity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[e] This study used a modified version of the Rivermead Post-Concussion Symptoms Questionnaire which involved dichotomising responses into yes and no options and adding questions about alcohol tolerance and panic attacks

[f] Downgraded by 1 increment as the population included any severity of TBI and the proportion of those with mild TBI was unclear

[g] Neuropsychological assessment based on tests covering the following: global cognitive and behavioural screening (neurobehavioral rating scale mini mental state examination and frontal lobe score); memory/learning (digit and visual spans, and selective reminding tests); language (token test); visuoperception/construction (block design); executive functions (semantic and phonological fluency, distractibility, and interference, including Stroop test and concept formation); attentional performance (computerised test battery for attentional performance subtests “alertness” and “go-no go”); and psychomotor speed (finger tapping)

Table 6: Clinical evidence summary: AUC data – S100B in adults

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome										

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
S100B – continuous variable, samples taken within 4 h of injury	1: Bazarian 2006[4]	96	Mild TBI presenting within 4 h of injury 5.1% with head CT abnormality on initial scan	Post-concussion syndrome at 3 months post-injury Score of ≥5 on Rivermead Post-concussive Questionnaire	Uncorrected: 0.45 (no CIs reported) Corrected for creatinine kinase levels: 0.49 (no CIs reported)	Very serious[a]	Serious[b]	None	Serious[c]	VERY LOW
S100B – continuous variable, samples taken within 6 h of injury	1: Bazarian 2006[5]	31	Mild TBI presenting within 6 h of injury 5.7% had CT traumatic abnormalities	Post-concussion syndrome at 3 months post-injury Score of ≥5 on Rivermead Post-concussive Questionnaire	0.589 (0.038 to 0.800)	Very serious[a]	Serious[b]	None	Very serious[c]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
S100B – continuous variable, samples taken on admission (time-point unclear)	1: Ryb 2014[29]	103 - 110	Mild TBI, unclear time-frame since injury Excluded those with brain lesion on CT scan	Post-concussion symptoms at 3, 6 and 12 months Presence of ≥4 symptoms on Mild TBI Symptom Checklist	3 months 0.49 (n=110) (no CIs reported) 6 months 0.50 (n=106) (no CIs reported) 12 months 0.51 (n=103) (no CIs reported)	Serious[a]	None	None	Serious[c]	LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
S100B – continuous variable, samples taken within 6 h of injury	1: Savola 2003[30]	172	Mild head injury with blood drawn within 6 h of injury 38% reported to have skull fracture	Post-concussion symptoms at 8-30 months Positive for symptoms if at least one symptom reported at interview or if reported suffering from a symptom for at least one month and more severe than before trauma based on modified version of Rivermead Post-Concussion Symptoms Questionnaire[d]	<u>Before normalisation</u> 0.702 (0.60 to 0.81) <u>After normalisation for time of head injury onset</u> 0.752 (0.66 to 0.84)	Very serious[a]	Serious[b]	None	Serious[c]	VERY LOW
GOS or GOSE used as outcome										

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
S100B – threshold of ≥23.17 pg/ml, samples within 24 h of injury	1: Lagerstedt 2020[17]	49	TBI within 24 h and indication for head CT – mild subgroup results reported separately 57% with no visual pathology on Marshall grade system	Complete recovery based on GOSE at >6 months GOSE 8 considered complete recovery and GOSE ≤7 considered incomplete recovery	Partial AUC (for 95-100% sensitivity) rather than full AUC: 0.1 (0.0 to 1.00) Unclear max value for partial AUC as not well explained in paper	None	None	None	Very serious[c]	LOW

S100B – continuous variable, samples within 24 h of trauma	1: Lee 2015[19]	31	Any severity TBI – reports results for mild subgroup separately All of those included (any severity) had one of following: haemorrhage (subdural, epidural, contusional or subarachnoid) or diffuse axonal injury or fracture – unclear what injuries	Poor outcome based on GOS at 3 months GOS 1-3 was considered poor outcome and GOS4-5 was considered good outcome	0.95 (no CIs reported)	Very serious[a]	None	None	Very serious[c]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
			were present specifically in the mild subgroup							
S100B – threshold of 2300.8 pg/ml, measured within 24 h	1: Posti 2020[27]	82	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-positive subgroup	Unfavourable outcome based on GOSE at 4-16 months GOSE 1-4 represents unfavourable outcome	Partial AUC (for 90-100% sensitivity) rather than full AUC: 0.2 (0.0 to 1.5) Unclear max value for partial AUC as not well explained in paper	Very serious[a]	Serious[e]	None	Serious[c]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
S100B – threshold of 45.3 pg/ml, measured within 24 h		55	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-negative subgroup	Unfavourable outcome based on GOSE at 4-16 months GOSE 1-4 represents unfavourable outcome	Partial AUC (for 90-100% sensitivity) rather than full AUC: 1.4 (0.6 to 6.7) Unclear max value for partial AUC as not well explained in paper	Very serious[a]	Serious[e]	None	Very serious[c]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
S100B – continuous variable, measured within 24 h		82	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-positive subgroup	Incomplete recovery based on GOSE at 4-16 months GOSE <8 represents incomplete recovery	Partial AUC (for 90-100% sensitivity) rather than full AUC: 0.0 (0.0 to 4.1) Unclear max value for partial AUC as not well explained in paper	Very serious[a]	Serious[e]	None	Serious[c]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
S100B – continuous variable, measured within 24 h		55	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-negative subgroup	Incomplete recovery based on GOSE at 4-16 months GOSE <8 represents incomplete recovery	Partial AUC (for 90-100% sensitivity) rather than full AUC: 0.0 (0.0 to 1.1) Unclear max value for partial AUC as not well explained in paper	Very serious[a]	Serious[e]	None	Very serious[c]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
S100B – continuous variables, samples taken within 48 h	1: Townend 2002[34]	118	Head injury of any severity (95% GCS 13-15) presenting within 6 h of injury Did not mention excluding those with any abnormalities on imaging	At least moderate disability based on GOSE GOSE scores <7 indicated at least moderate disability	0.770 (0.670 to 0.870)	Serious[a]	None	None	Serious[c]	LOW
		118		Severe disability based on GOSE GOSE scores <5 indicated severe disability	0.889 (0.792 to 0.985)	Serious[a]	None	None	None	MODERATE
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)										

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
S100B – continuous variable, samples taken within 4 h of injury	1: Bazarian 2006[4]	96	Mild TBI presenting within 4 h of injury 5.1% with head CT abnormality on initial scan	Headache at 3 months post-injury No further information provided	Uncorrected: 0.46 (no CIs reported) Corrected for creatinine kinase levels: 0.52 (no CIs reported)	Very serious[a]	Serious[b]	None	Serious[c]	VERY LOW
S100B – continuous variable, samples taken on admission (time-point unclear)	1: Ryb 2014[29]	103	Mild TBI, unclear time-frame since injury Excluded those with brain lesion on CT scan	Ability to return to work or school at 12 months No further information provided	0.59 (no CIs reported)	Serious[a]	None	None	Serious[c]	LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
S100B – continuous variable, samples taken median 27 h post-trauma	1: Hermann 2001[9]	29	Any TBI severity – median GCS at admission: 15 (range 3-15) 55.0% with intracranial pathology on CT	Neuropsychological assessment at 6 months Neuropsychological disorders present if performed <1 SD below (age-adjusted) normal data in at least three cognitive domains[f]	0.77 (no CIs reported)	Very serious[a]	Serious[e]	None	Very serious[c]	VERY LOW

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Downgraded by 1 increment as the population was a mixture of children and adults with no proportions given (study was included under the adult population as the average age, for example mean or median age, was consistent with the adult population).

[c] Assessment of imprecision for accuracy/area under the curve was based on whether confidence intervals crossed none (no downgrading), one (downgrading by 1 increment) or both (downgrading by two increments) of the following thresholds: 0.50 and 0.70. The threshold of 0.50 represents the boundary between the predictive value being better than or worse than chance and the threshold of 0.70 separates values indicating a moderate predictive value from those with a poor predictive value. Where confidence intervals were not reported or where partial AUC has been reported and the maximum possible value is unclear, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[d] This study used a modified version of the Rivermead Post-Concussion Symptoms Questionnaire which involved dichotomising responses into yes and no options and adding questions about alcohol tolerance and panic attacks

[e] Downgraded by 1 increment as the population included any severity of TBI and the proportion of those with mild TBI was unclear

[f] Neuropsychological assessment based on tests covering the following: global cognitive and behavioural screening (neurobehavioral rating scale mini mental state examination and frontal lobe score); memory/learning (digit and visual spans, and selective reminding tests); language (token test); visuoperception/construction (block design); executive functions (semantic and phonological fluency, distractibility, and interference, including Stroop test and concept formation); attentional performance (computerised test battery for attentional performance subtests “alertness” and “go-no go”); and psychomotor speed (finger tapping)

Adults – blood biomarkers – UCH-L1

Table 7: Clinical evidence summary: sensitivity and specificity data – UCH-L1 in adults

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome											
No data											
GOS or GOSE used as outcome											

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
UCH-L1 – threshold of ≥0.96 ng/ml, samples within 24 h of trauma	1: Lee 2015[19]	31	Any severity TBI – reports results for mild subgroup separately All of those included (any severity) had one of following: haemorrhage (subdural, epidural, contusional or subarachnoid) or diffuse axonal injury or fracture – unclear what injuries were present specifically in the mild subgroup	Poor outcome based on GOS at 3 months GOS 1-3 was considered poor outcome and GOS4-5 was considered good outcome	0.78 (no CIs reported)	0.96 (no CIs reported)	Sensitivity				
							Very serious[a]	None	None	Very serious[b]	VERY LOW
							Specificity				
							Very serious[a]	None	None	Very serious[c]	VERY LOW
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)											
No data											

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as

some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.9 and 0.7, respectively, which were the thresholds used for sensitivity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[c] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.95 and 0.75, respectively, which were the thresholds used for specificity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

Table 8: Clinical evidence summary: AUC data – UCH-L1 in adults

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome										

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
UCH-L1 – continuous variable, samples taken within 24 h of injury	1: Korley 2016[16]	94	Any severity TBI (84% mild, GCS 13-15) 47.2% with abnormality on head CT	Post-concussion syndrome at 6 months Presence of three or more symptoms on Rivermead Post-Concussion Questionnaire rated as worse than before injury	0.52 (0.40 to 0.64)	Serious[a]	None	None	Serious[b]	LOW
GOS or GOSE used as outcome										
UCH-L1 – continuous variable, samples taken within 24 h of injury	1: Diaz-Arrastia 2014[7] Note: for incomplete recovery at 6 months,	168	Any head injury severity (83% mild, GCS 13-15) and indication for CT Head CT findings in 43% of mild,	Incomplete recovery based on GOSE at 3 months GOSE scores <8 indicated incomplete recovery	0.58 (0.50 to 0.74)	Very serious[a]	Serious[c]	None	Serious[b]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
	some of the same people may be included in this analysis as for results reported for Korley 2016[16] below (both TRACK-TBI study)	145	78% of moderate and 96% of severe cases	Incomplete recovery based on GOSE at 6 months GOSE scores <8 indicated incomplete recovery	0.51 (0.39 to 0.63)	Very serious[a]	Serious[c]	None	Serious[b]	VERY LOW
		NR	Mild subgroup of those with head injury 43% had CT findings	Incomplete recovery based on GOSE at 6 months GOSE scores <8 indicated incomplete recovery	0.511 (no CIs reported)	Very serious[a]	Serious[c]	None	Serious[b]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
		168	Any head injury severity (83% mild, GCS 13-15) and indication for CT Head CT findings in 43% of mild, 78% of moderate and 96% of severe cases	Poor outcome based on GOSE at 3 months GOSE scores ≤4 indicated poor outcome	0.80 (0.70 to 0.90)	Very serious[a]	Serious[c]	None	None	VERY LOW
		145		Poor outcome based on GOSE at 6 months GOSE scores ≤4 indicated poor outcome	0.76 (0.60 to 0.91)	Very serious[a]	Serious[c]	None	Serious[b]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
UCH-L1 – continuous variable, samples taken within 24 h of injury	1: Korley 2016[16] Note: for incomplete recovery at 6 months, some of the same people may be included in this analysis as for results reported for Diaz-Arrastia 2014[7] above (both TRACK-TBI study)	111	Any severity TBI (84% mild, GCS 13-15) 47.2% with abnormality on head CT	Incomplete recovery based on GOSE at 6 months GOSE scores <8 indicated incomplete recovery	0.55 (0.44 to 0.66)	Serious[a]	None	None	Serious[b]	LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
UCH-L1 – continuous variable, samples within 24 h of trauma	1: Lee 2015[19]	31	Any severity TBI – reports results for mild subgroup separately All of those included (any severity) had one of following: haemorrhage (subdural, epidural, contusional or subarachnoid) or diffuse axonal injury or fracture – unclear what injuries were present specifically in the mild subgroup	Severe disability based on GOSE GOSE scores <5 indicated severe disability	0.88 (no CIs reported)	Very serious[a]	None	None	Very serious[b]	VERY LOW
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)										

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
UCH-L1 – continuous variable, samples taken within 24 h of injury	1: Korley 2016[16]	94	Any severity TBI (84% mild, GCS 13-15) 47.2% with abnormality on head CT	Incomplete recovery at 6 months Composite score based on Rivermead Post-Concussion Questionnaire (at least three symptoms rated as worse than before injury) and GOSE (scores <8)	0.55 (0.43 to 0.66)	Serious[a]	None	None	Serious[b]	LOW

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Assessment of imprecision for accuracy/area under the curve was based on whether confidence intervals crossed none (no downgrading), one (downgrading by 1 increment) or both (downgrading by two increments) of the following thresholds: 0.50 and 0.70. The threshold of 0.50 represents the boundary between the predictive value being better than or worse than chance and the threshold of 0.70 separates values indicating a moderate predictive value from those with a poor predictive value. Where confidence intervals were not reported or where partial AUC has been reported and the maximum possible value is unclear, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[c] Downgraded by 1 increment as the population was a mixture of children and adults with no proportions given (study was included under the adult population as the average age, for example mean or median age, was consistent with the adult population).

Adults – blood biomarkers – NSE

Table 9: Clinical evidence summary: sensitivity and specificity data – NSE in adults

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome											
No data											
GOS or GOSE used as outcome											
No data											
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)											
NSE – threshold of >5.75 µg/l, samples taken median 27	1: Hermann 2001[9]	29	Any TBI severity – median GCS at admission: 15 (range 3-15)	Neuropsychological assessment at 6 months Neuropsychological disorders present if performed <1 SD	0.55 (no CIs reported)	0.778 (no CIs reported)	Sensitivity				
							Very serious[b]	Serious[c]	None	Very serious[d]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
h post-trauma			55.0% with intracranial pathology on CT	below (age-adjusted) normal data in at least three cognitive domains[a]			Very serious[b]	Serious[c]	None	Very serious[e]	VERY LOW

[a] Neuropsychological assessment based on tests covering the following: global cognitive and behavioural screening (neurobehavioral rating scale mini mental state examination and frontal lobe score); memory/learning (digit and visual spans, and selective reminding tests); language (token test); visuoperception/construction (block design); executive functions (semantic and phonological fluency, distractibility, and interference, including Stroop test and concept formation); attentional performance (computerised test battery for attentional performance subtests “alertness” and “go-no go”); and psychomotor speed (finger tapping)

[b] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[c] Downgraded by 1 increment as the population included any severity of TBI and the proportion of those with mild TBI was unclear

[d] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.9 and 0.7, respectively, which were the thresholds used for sensitivity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to

lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[e] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.95 and 0.75, respectively, which were the thresholds used for specificity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

Table 10: Clinical evidence summary: AUC data – NSE in adults

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome										
No data										
GOS or GOSE used as outcome										
No data										
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)										

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
NSE – continuous variable, samples taken median 27 h post-trauma	1: Hermann 2001[9]	29	Any TBI severity – median GCS at admission: 15 (range 3-15) 55.0% with intracranial pathology on CT	Neuropsychological assessment at 6 months Neuropsychological disorders present if performed <1 SD below (age-adjusted) normal data in at least three cognitive domains[a]	0.65 (no CIs reported)	Very serious[b]	Serious[c]	None	Very serious[d]	VERY LOW
NSE – threshold of ≥14.6 µg/l, samples taken average 159 min post-injury	1: Topolovec-Vranic 2011[33]	95	Mild TBI within 4 h of injury Does not mention exclusion of those with imaging abnormalities	Abnormal status based on physician assessment at 6 weeks Assessment included physical examination with complete history, neurologic examination and tools to assess headache and dizziness	0.629 (no CIs reported)	Very serious[b]	None	None	Serious[d]	VERY LOW

[a] Neuropsychological assessment based on tests covering the following: global cognitive and behavioural screening (neurobehavioral rating scale mini mental state examination and frontal lobe score); memory/learning (digit and visual spans, and selective reminding tests); language (token test); visuoperception/construction (block design); executive functions (semantic and phonological fluency, distractibility, and interference, including Stroop test and concept formation); attentional performance (computerised test battery for attentional performance subtests “alertness” and “go-no go”); and psychomotor speed (finger tapping)

[b] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[c] Downgraded by 1 increment as the population included any severity of TBI and the proportion of those with mild TBI was unclear

[d] Assessment of imprecision for accuracy/area under the curve was based on whether confidence intervals crossed none (no downgrading), one (downgrading by 1 increment) or both (downgrading by two increments) of the following thresholds: 0.50 and 0.70. The threshold of 0.50 represents the boundary between the predictive value being better than or worse than chance and the threshold of 0.70 separates values indicating a moderate predictive value from those with a poor predictive value. Where confidence intervals were not reported or where partial AUC has been reported and the maximum possible value is unclear, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

Adults – blood biomarkers – BDNF

Table 11: Clinical evidence summary: sensitivity and specificity data –BDNF in adults

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome											
No data											
GOS or GOSE used as outcome											
No data											
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)											
No data											

Table 12: Clinical evidence summary: AUC data – BDNF in adults

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome										

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
BDNF – continuous variable, samples taken within 24 h of injury	1: Korley 2016[16]	94	Any severity TBI (84% mild, GCS 13-15) 47.2% with abnormality on head CT	Post-concussion syndrome at 6 months Presence of three or more symptoms on Rivermead Post-Concussion Questionnaire rated as worse than before injury	0.55 (0.43 to 0.68)	Serious[a]	None	None	Serious[b]	LOW
GOS or GOSE used as outcome										
BDNF – continuous variable, samples taken within 24 h of injury	1: Korley 2016[16]	111	Any severity TBI (84% mild, GCS 13-15) 47.2% with abnormality on head CT	Incomplete recovery based on GOSE at 6 months GOSE scores <8 indicated incomplete recovery	0.56 (0.44 to 0.68)	Serious[a]	None	None	Serious[b]	LOW
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)										

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
BDNF – continuous variable, samples taken within 24 h of injury	1: Korley 2016[16]	94	Any severity TBI (84% mild, GCS 13-15) 47.2% with abnormality on head CT	Incomplete recovery at 6 months Composite score based on Rivermead Post-Concussion Questionnaire (at least three symptoms rated as worse than before injury) and GOSE (scores <8)	0.65 (0.52 to 0.78)	Serious[a]	None	None	Serious[b]	LOW

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Assessment of imprecision for accuracy/area under the curve was based on whether confidence intervals crossed none (no downgrading), one (downgrading by 1 increment) or both (downgrading by two increments) of the following thresholds: 0.50 and 0.70. The threshold of 0.50 represents the boundary between the predictive value being better than or worse than chance and the threshold of 0.70 separates values indicating a moderate predictive value from those with a poor predictive value. Where confidence intervals were not reported or where partial AUC

has been reported and the maximum possible value is unclear, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

Adults – blood biomarkers – NF-L

Table 13: Clinical evidence summary: sensitivity and specificity data – NF-L in adults

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome											
No data											
GOS or GOSE used as outcome											
NF-L – threshold of <28.15 pg/ml, samples taken within 24 h of admission	1: Hossain 2019[10]	107	Mild TBI and indication for head CT 48.6% with no visual pathology according to Marshall Grade	Complete recovery based on GOSE at 6-12 months post-injury Complete recovery indicated by GOSE score =8	0.94 (0.82 to 0.99)	0.44 (0.32 to 0.57)	Sensitivity				
							None	None	None	Serious[a]	MODERATE
							Specificity				
							None	None	None	None	HIGH
NF-L – threshold of <53.60 pg/ml, samples taken within				Favourable outcome based on GOSE at 6-12 months post-injury	0.90 (0.82 to 0.95)	0.57 (0.38 to 0.88)	Sensitivity				
							None	None	None	Serious[a]	MODERATE
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
24 h of admission				Favourable outcome indicated by GOSE scores 5-8			None	None	None	Serious[b]	MODERATE
NF-L – threshold of ≥4.85 pg/ml, samples within 24 h of injury	1: Lagerstedt 2020[17]	49	TBI within 24 h and indication for head CT – mild subgroup results reported separately 57% with no visual pathology on Marshall grade system	Complete recovery based on GOSE at >6 months GOSE 8 considered complete recovery and GOSE ≤7 considered incomplete recovery	0.958 (0.875 to 1.00) (threshold selected by specifying sensitivity of 95-100% and identifying best in terms of balance with specificity)	0.12 (0.00 to 0.241)	Sensitivity				
							None	None	None	Serious[a]	MODERATE
							Specificity				
							None	None	None	None	HIGH
NF-L – threshold of 179.6 pg/ml, measured within 24 h	1: Posti 2020[27]	82	Diagnosis of TBI (any severity, median GCS consistent with mild	Unfavourable outcome based on GOSE at 4-16 months	0.909 (0.788 to 1.00) (threshold selected by specifying sensitivity of 90-	0.224 (0.122 to 0.347)	Sensitivity				
							Very serious[c]	Serious[d]	None	Serious[a]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
			TBI) and indication for head CT CT-positive subgroup	GOSE 1-4 represents unfavourable outcome	100% and identifying best in terms of balance with specificity)		Very serious[c]	Serious[d]	None	None	VERY LOW
NF-L – threshold of 8.3 pg/ml, measured within 24 h		55	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-negative subgroup	Unfavourable outcome based on GOSE at 4-16 months GOSE 1-4 represents unfavourable outcome	1.00 (1.00 to 1.00) (threshold selected by specifying sensitivity of 90-100% and identifying best in terms of balance with specificity)	0.412 (0.275 to 0.549)	Sensitivity				
							Very serious[c]	Serious[d]	None	None	VERY LOW
							Specificity				
							Very serious[c]	Serious[d]	None	None	VERY LOW
NF-L – threshold of 245.1 pg/ml, measured within 24 h		82	Diagnosis of TBI (any severity, median GCS consistent with mild	Incomplete recovery based on GOSE at 4-16 months	0.931 (0.861 to 0.986) (threshold selected by specifying sensitivity of 90-	0.200 (0.000 to 0.500)	Sensitivity				
							Very serious[c]	Serious[d]	None	Serious[a]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
			TBI) and indication for head CT CT-positive subgroup	GOSE <8 represents incomplete recovery	100% and identifying best in terms of balance with specificity)		Very serious[c]	Serious[d]	None	None	VERY LOW
NF-L – threshold of 4.9 pg/ml, measured within 24 h		55	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-negative subgroup	Incomplete recovery based on GOSE at 4-16 months GOSE <8 represents incomplete recovery	0.938 (0.844 to 1.00) (threshold selected by specifying sensitivity of 90-100% and identifying best in terms of balance with specificity)	0.174 (0.043 to 0.348)	Sensitivity				
							Very serious[c]	Serious[d]	None	Serious[a]	VERY LOW
							Specificity				
							Very serious[c]	Serious[d]	None	None	VERY LOW
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)											
No data											

[a] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.9 and 0.7, respectively, which were the thresholds used for sensitivity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[b] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.95 and 0.75, respectively, which were the thresholds used for specificity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[c] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[d] Downgraded by 1 increment as the population included any severity of TBI and the proportion of those with mild TBI was unclear

Table 14: Clinical evidence summary: AUC data – NF-L in adults

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome										
No data										
GOS or GOSE used as outcome										

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
NF-L – continuous variable, samples taken within 24 h of admission	1: Hossain 2019[10]	107	Mild TBI and indication for head CT 48.6% with no visual pathology according to Marshall Grade	Complete recovery based on GOSE at 6-12 months post-injury Complete recovery indicated by GOSE score =8	0.66 (0.561 to 0.768)	None	None	None	Serious[a]	MODERATE
				Favourable outcome based on GOSE at 6-12 months post-injury Favourable outcome indicated by GOSE scores 5-8	0.826 (0.694 to 0.958)	None	None	None	Serious[a]	MODERATE

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
NF-L – threshold of ≥4.85 pg/ml, samples within 24 h of injury	1: Lagerstedt 2020[17]	49	TBI within 24 h and indication for head CT – mild subgroup results reported separately 57% with no visual pathology on Marshall grade system	Complete recovery based on GOSE at >6 months GOSE 8 considered complete recovery and GOSE ≤7 considered incomplete recovery	Partial AUC (for 95-100% sensitivity) rather than full AUC: 0.1 (0.0 to 1.2) Unclear max value for partial AUC as not well explained in paper	None	None	None	Very serious[a]	LOW
NF-L – threshold of 179.6 pg/ml, measured within 24 h	1: Posti 2020[27]	82	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-positive subgroup	Unfavourable outcome based on GOSE at 4-16 months GOSE 1-4 represents unfavourable outcome	Partial AUC (for 90-100% sensitivity) rather than full AUC: 0.6 (0.0 to 3.2) Unclear max value for partial AUC as not well explained in paper	Very serious[b]	Serious[c]	None	Serious[a]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
NF-L – threshold of 8.3 pg/ml, measured within 24 h		55	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-negative subgroup	Unfavourable outcome based on GOSE at 4-16 months GOSE 1-4 represents unfavourable outcome	Partial AUC (for 90-100% sensitivity) rather than full AUC: 4.1 (2.7 to 10.0) Unclear max value for partial AUC as not well explained in paper	Very serious[b]	Serious[c]	None	Very serious[a]	VERY LOW
NF-L – threshold of 245.1 pg/ml, measured within 24 h		82	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-positive subgroup	Incomplete recovery based on GOSE at 4-16 months GOSE <8 represents incomplete recovery	Partial AUC (for 90-100% sensitivity) rather than full AUC: 1.2 (0.0 to 4.1) Unclear max value for partial AUC as not well explained in paper	Very serious[b]	Serious[c]	None	Serious[a]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
NF-L – threshold of 4.9 pg/ml, measured within 24 h		55	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-negative subgroup	Incomplete recovery based on GOSE at 4-16 months GOSE <8 represents incomplete recovery	Partial AUC (for 90-100% sensitivity) rather than full AUC: 0.9 (0.0 to 2.9) Unclear max value for partial AUC as not well explained in paper	Very serious[b]	Serious[c]	None	Very serious[a]	VERY LOW
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)										
No data										

[a] Assessment of imprecision for accuracy/area under the curve was based on whether confidence intervals crossed none (no downgrading), one (downgrading by 1 increment) or both (downgrading by two increments) of the following thresholds: 0.50 and 0.70. The threshold of 0.50 represents the boundary between the predictive value being better than or worse than chance and the threshold of 0.70 separates values indicating a moderate predictive value from those with a poor predictive value. Where confidence intervals were not reported or where partial AUC has been reported and the maximum possible value is unclear, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[b] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of

uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[c] Downgraded by 1 increment as the population included any severity of TBI and the proportion of those with mild TBI was unclear

Adults – blood biomarkers - αII-Spectrin breakdown products

Table 15: Clinical evidence summary: sensitivity and specificity data – αII-Spectrin breakdown products in adults

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome											
No data											
GOS or GOSE used as outcome											
No data											
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)											
Calpain-cleaved αII spectrin N-terminal fragment (SNTF) –	1: Siman 2013[31]	13	Mild TBI No abnormal findings on CT was an	Cognitive performance – failure to achieve improvement of at least 5	0.71 (0.29 to 0.96)	1.00 (0.54 to 1.00)	Sensitivity				
							Very serious[a]	Serious[b]	None	Very serious[c]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
SNFT+ in plasma SNTF+ defined as levels at least twice lower limit of detection of 10 units in ultrasensitive sandwich immunoassay, samples collected within 24 h of injury			inclusion criterion	points over 3 months on SDMT SDMT used as measure of processing speed deficits			Very serious[a]	Serious[b]	None	Very serious[c]	VERY LOW

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Downgraded by 1 increment as the population was a mixture of children and adults with no proportions given (study was included under the adult population as the average age, for example mean or median age, was consistent with the adult population); this study is also quite a specific age group including those between 12 and 30 years

[c] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.95 and 0.75, respectively, which were the thresholds used for specificity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

Table 16: Clinical evidence summary: AUC data – αII-Spectrin breakdown products in adults

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome											
No data											
GOS or GOSE used as outcome											
No data											
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)											
No data											

1 Adults – blood biomarkers – GFAP

2 Table 17: Clinical evidence summary: sensitivity and specificity data – GFAP in adults

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome											
No data											
GOS or GOSE used as outcome											
GFAP – threshold of <6438.05 pg/ml, samples taken within 24 h of admission	1: Hossain 2019[10]	107	Mild TBI and indication for head CT 48.6% with no visual pathology according to Marshall Grade	Complete recovery based on GOSE at 6-12 months post-injury Complete recovery indicated by GOSE score =8	0.97 (0.86 to 1.00)	0.26 (0.68 to 0.99) – an error in CIs reported, possibly 0.18 to 0.99?	Sensitivity				
							None	None	None	Serious[a]	MODERATE
							Specificity				
							None	None	None	Very serious[b]	LOW
GFAP – threshold of <12189.85 pg/ml, samples taken within 24 h of admission				Favourable outcome based on GOSE at 6-12 months post-injury Favourable outcome indicated by GOSE scores 5-8	0.92 (0.85 to 0.99)	0.47 (0.16 to 0.68)	Sensitivity				
							None	None	None	Serious[a]	MODERATE
							Specificity				
							None	None	None	None	HIGH

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
GFAP – continuous, samples within 24 h of injury	1: Lagerstedt 2020[17]	49	TBI within 24 h and indication for head CT – mild subgroup results reported separately 57% with no visual pathology on Marshall grade system	Complete recovery based on GOSE at >6 months GOSE 8 considered complete recovery and GOSE ≤7 considered incomplete recovery	1.00 (1.00 to 1.00) (threshold selected by specifying sensitivity of 95-100% and identifying best in terms of balance with specificity)	0.00 (0.00 to 0.00)	Sensitivity				
							None	None	None	None	HIGH
							Specificity				
							None	None	None	None	HIGH
GFAP – threshold of ≥18.00 ng/ml, samples	1: Lee 2015[19]	31	Any severity TBI – reports results for mild subgroup separately	Poor outcome based on GOS at 3 months GOS 1-3 was considered poor	0.92 (no CIs reported)	0.93 (no CIs reported)	Sensitivity				
							Very serious[c]	None	None	Very serious[a]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
within 24 h of trauma			All of those included (any severity) had one of following: haemorrhage (subdural, epidural, contusional or subarachnoid) or diffuse axonal injury or fracture – unclear what injuries were present specifically in the mild subgroup	outcome and GOS4-5 was considered good outcome			Very serious[c]	None	None	Very serious[b]	VERY LOW
GFAP – continuous variable, samples taken on admission	1: Metting 2012[23]	94	Mild TBI (GCS 13-15) and post-traumatic amnesia	Full recovery based on GOSE at 6 months	0.47 (no CIs reported)	0.72 (no CIs reported)	Sensitivity				
							Serious[c]	None	None	Serious[a]	LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
(average 2.4 h post-injury)			20% with CT abnormalities	Score of 8 indicated full recovery			Serious[c]	None	None	Serious[b]	LOW
GFAP – threshold of 94.7 pg/ml, measured within 24 h	1: Posti 2020[27]	82	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-positive subgroup	Unfavourable outcome based on GOSE at 4-16 months GOSE 1-4 represents unfavourable outcome	0.909 (0.818 to 1.00) (threshold selected by specifying sensitivity of 90-100% and identifying best in terms of balance with specificity)	0.122 (0.041 to 0.224)	Sensitivity				
							Very serious[c]	Serious[d]	None	Serious[a]	VERY LOW
							Specificity				
							Very serious[c]	Serious[d]	None	None	VERY LOW
GFAP – threshold of 0.4 pg/ml, measured within 24 h		55	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-negative subgroup	Unfavourable outcome based on GOSE at 4-16 months GOSE 1-4 represents unfavourable outcome	1.00 (1.00 to 1.00) (threshold selected by specifying sensitivity of 90-100% and identifying best in terms of balance with specificity)	0.0 (0.0 to 0.0)	Sensitivity				
							Very serious[c]	Serious[d]	None	None	VERY LOW
							Specificity				
							Very serious[c]	Serious[d]	None	None	VERY LOW
		82					Sensitivity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
GFAP – threshold of 113.9 pg/ml, measured within 24 h			Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-positive subgroup	Incomplete recovery based on GOSE at 4-16 months GOSE <8 represents incomplete recovery	0.944 (0.889 to 0.986) (threshold selected by specifying sensitivity of 90-100% and identifying best in terms of balance with specificity)	0.224 (0.122 to 0.347)	Very serious[c]	Serious[d]	None	Serious[a]	VERY LOW
							Specificity				
							Very serious[c]	Serious[d]	None	None	VERY LOW
GFAP – continuous variable, measured within 24 h		55	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-negative subgroup	Incomplete recovery based on GOSE at 4-16 months GOSE <8 represents incomplete recovery	1.00 (1.00 to 1.00) (threshold selected by specifying sensitivity of 90-100% and identifying best in terms of balance with specificity)	0.00 (0.00 to 0.00)	Sensitivity				
							Very serious[c]	Serious[d]	None	None	VERY LOW
							Specificity				
							Very serious[c]	Serious[d]	None	None	VERY LOW
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)											
GFAP – continuous variable,	1: Metting 2012[23]	94	Mild TBI (GCS 13-15) and post-	Complete return to work at 6 months	0.45 (no CIs reported)	0.65 (no CIs reported)	Sensitivity				
							Serious[c]	None	None	Serious[a]	LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
samples taken on admission (average 2.4 h post-injury)			traumatic amnesia 20% with CT abnormalities	Scores of 0 on a 0-3 scale (from completely resumed to not working at all) represented complete return to work			Serious[c]	None	None	Serious[b]	LOW

[a] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.9 and 0.7, respectively, which were the thresholds used for sensitivity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[b] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.95 and 0.75, respectively, which were the thresholds used for specificity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[c] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[d] Downgraded by 1 increment as the population included any severity of TBI and the proportion of those with mild TBI was unclear

Table 18: Clinical evidence summary: AUC data – GFAP in adults

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome										
GFAP – continuous variable, samples taken within 24 h of injury	1: Korley 2016[16]	94	Any severity TBI (84% mild, GCS 13-15) 47.2% with abnormality on head CT	Post-concussion syndrome at 6 months Presence of three or more symptoms on Rivermead Post-Concussion Questionnaire rated as worse than before injury	0.56 (0.44 to 0.68)	Serious[a]	None	None	Serious[b]	LOW
GOS or GOSE used as outcome										
GFAP – continuous variable, samples taken within 24 h of injury	1: Diaz-Arrastia 2014[7] Note: for outcomes at 6 months,	168	Any head injury severity (83% mild, GCS 13-15) and indication for CT Head CT findings in 43% of mild,	Incomplete recovery based on GOSE at 3 months GOSE scores <8 indicated incomplete recovery	0.65 (0.55 to 0.74)	Very serious[a]	Serious[c]	None	Serious[b]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
	some of the same people may be included in these analyses as for results reported for Korley 2016[16] (incomplete recovery) and Xu 2021[37] (poor outcome/favourable outcome) below (all TRACK-TBI study)	145	78% of moderate and 96% of severe cases	Incomplete recovery based on GOSE at 6 months GOSE scores <8 indicated incomplete recovery	0.60 (0.43 to 0.77)	Very serious[a]	Serious[c]	None	Very serious[b]	VERY LOW
		168		Poor outcome based on GOSE at 3 months GOSE scores ≤4 indicated poor outcome	0.74 (0.61 to 0.87)	Very serious[a]	Serious[c]	None	Serious[b]	VERY LOW
		145		Poor outcome based on GOSE at 6 months GOSE scores ≤4 indicated poor outcome	0.74 (0.61 to 0.87)	Very serious[a]	Serious[c]	None	Serious[b]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
GFAP – continuous variable, samples taken within 24 h of admission	1: Hossain 2019[10]	107	Mild TBI and indication for head CT 48.6% with no visual pathology according to Marshall Grade	Complete recovery based on GOSE at 6-12 months post-injury Complete recovery indicated by GOSE score =8	0.598 (0.489 to 0.706)	None	None	None	Very serious[b]	LOW
				Favourable outcome based on GOSE at 6-12 months post-injury Favourable outcome indicated by GOSE scores 5-8	0.755 (0.628 to 0.882)	None	None	None	Serious[b]	MODERATE

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
GFAP – continuous variable, samples taken within 24 h of injury	1: Korley 2016[16] Note: for incomplete recovery at 6 months, some of the same people may be included in this analysis as for results reported for Diaz-Arrastia 2014[7] above (both TRACK-TBI study)	111	Any severity TBI (84% mild, GCS 13-15) 47.2% with abnormality on head CT	Incomplete recovery based on GOSE at 6 months GOSE scores <8 indicated incomplete recovery	0.61 (0.50 to 0.71)	Serious[a]	None	None	Serious[b]	LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
GFAP – continuous, samples within 24 h of injury	1: Lagerstedt 2020[17]	49	TBI within 24 h and indication for head CT – mild subgroup results reported separately 57% with no visual pathology on Marshall grade system	Complete recovery based on GOSE at >6 months GOSE 8 considered complete recovery and GOSE ≤7 considered incomplete recovery	Partial AUC (for 95-100% sensitivity) rather than full AUC: 0.0 (0.0 to 0.6) Unclear max value for partial AUC as not well explained in paper	None	None	None	Very serious[b]	LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
GFAP – continuous variable, samples within 24 h of trauma	1: Lee 2015[19]	31	Any severity TBI – reports results for mild subgroup separately All of those included (any severity) had one of following: haemorrhage (subdural, epidural, contusional or subarachnoid) or diffuse axonal injury or fracture – unclear what injuries were present specifically in the mild subgroup	Poor outcome based on GOS at 3 months GOS 1-3 was considered poor outcome and GOS4-5 was considered good outcome	0.99 (no CIs reported)	Very serious[a]	None	None	Very serious[b]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
GFAP – threshold of 94.7 pg/ml, measured within 24 h	1: Posti 2020[27]	82	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-positive subgroup	Unfavourable outcome based on GOSE at 4-16 months GOSE 1-4 represents unfavourable outcome	Partial AUC (for 90-100% sensitivity) rather than full AUC: 0.2 (0.0 to 2.6) Unclear max value for partial AUC as not well explained in paper	Very serious[a]	Serious[d]	None	Serious[b]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
GFAP – threshold of 0.4 pg/ml, measured within 24 h		55	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-negative subgroup	Unfavourable outcome based on GOSE at 4-16 months GOSE 1-4 represents unfavourable outcome	Partial AUC (for 90-100% sensitivity) rather than full AUC: 0.2 (0.0 to 1.3) Unclear max value for partial AUC as not well explained in paper	Very serious[a]	Serious[d]	None	Very serious[b]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
GFAP – threshold of 113.9 pg/ml, measured within 24 h		82	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-positive subgroup	Incomplete recovery based on GOSE at 4-16 months GOSE <8 represents incomplete recovery	Partial AUC (for 90-100% sensitivity) rather than full AUC: 1.0 (0.0 to 3.2) Unclear max value for partial AUC as not well explained in paper	Very serious[a]	Serious[d]	None	Serious[b]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
GFAP – continuous variable, measured within 24 h		55	Diagnosis of TBI (any severity, median GCS consistent with mild TBI) and indication for head CT CT-negative subgroup	Incomplete recovery based on GOSE at 4-16 months GOSE <8 represents incomplete recovery	Partial AUC (for 90-100% sensitivity) rather than full AUC: 0.2 (0.0 to 1.3) Unclear max value for partial AUC as not well explained in paper	Very serious[a]	Serious[d]	None	Very serious[b]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
GFAP – continuous variable (on log scale), samples taken within 24 h of injury	1: Xu 2021[37] Note: for favourable outcome at 6 months, some of the same people may be included in this analysis as for results for poor outcome reported in Diaz-Arrastia 2014[7] above (both TRACK-TBI study)	185 (though unclear)	TBI of any severity (87% mild, GCS 13-15) 39% CT positive	Favourable outcome based on GOSE at 6 months Scores ≥5 indicated favourable outcome	0.768 (0.662 to 0.875)	Very serious[a]	Serious[c]	None	Serious[b]	VERY LOW
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)										

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
GFAP – continuous variable, samples taken within 24 h of injury	1: Korley 2016[16]	94	Any severity TBI (84% mild, GCS 13-15) 47.2% with abnormality on head CT	Incomplete recovery at 6 months Composite score based on Rivermead Post-Concussion Questionnaire (at least three symptoms rated as worse than before injury) and GOSE (scores <8)	0.61 (0.49 to 0.73)	Serious[a]	None	None	Very serious[b]	VERY LOW

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Assessment of imprecision for accuracy/area under the curve was based on whether confidence intervals crossed none (no downgrading), one (downgrading by 1 increment) or both (downgrading by two increments) of the following thresholds: 0.50 and 0.70. The threshold of 0.50 represents the boundary between the predictive value being better than or worse than chance and the threshold of 0.70 separates values indicating a moderate predictive value from those with a poor predictive value. Where confidence intervals were not reported or where partial AUC

has been reported and the maximum possible value is unclear, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[c] Downgraded by 1 increment as the population was a mixture of children and adults with no proportions given (study was included under the adult population as the average age, for example mean or median age, was consistent with the adult population).

[d] Downgraded by 1 increment as the population included any severity of TBI and the proportion of those with mild TBI was unclear

Adults – blood biomarkers – combinations of different biomarkers

Table 19: Clinical evidence summary: sensitivity and specificity data – combinations of blood biomarkers in adults

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome											
No data											
GOS or GOSE used as outcome											
GFAP + NF-L – thresholds of <6438.95 pg/ml and <28.15 pg/ml, samples taken within 24 h of admission	1: Hossain 2019[10]	107	Mild TBI and indication for head CT 48.6% with no visual pathology according to Marshall Grade	Complete recovery based on GOSE at 6-12 months post-injury Complete recovery indicated by GOSE score =8	0.946 (0.865 to 1.000)	0.471 (0.353 to 0.588)	Sensitivity				
							None	None	None	Serious[a]	MODERATE
							Specificity				
							None	None	None	None	HIGH
							Sensitivity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
GFAP + NF-L – thresholds of <980.75 pg/ml and <41.85 pg/ml, samples taken within 24 h of admission				Favourable outcome based on GOSE at 6-12 months post-injury Favourable outcome indicated by GOSE scores 5-8	0.900 (0.833 to 0.956)	0.867 (0.667 to 1.000)	None	None	None	Serious[a]	MODERATE
							Specificity				
							None	None	None	Very serious[b]	LOW
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)											
No data											

[a] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.9 and 0.7, respectively, which were the thresholds used for sensitivity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[b] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.95 and 0.75, respectively, which were the thresholds used for specificity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

Table 20: Clinical evidence summary: AUC data – combinations of blood biomarkers in adults

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome										
No data										
GOS or GOSE used as outcome										
GFAP + UCH-L1 combination – continuous variable, samples taken within 24 h of injury	1: Diaz-Arrastia 2014[7]	168	Any head injury severity (83% mild, GCS 13-15) and indication for CT Head CT findings in 43% of mild, 78% of moderate and 96% of severe cases	Incomplete recovery based on GOSE at 3 months GOSE scores <8 indicated incomplete recovery	0.64 (0.55 to 0.72)	Very serious[a]	Serious[b]	None	Serious[c]	VERY LOW
		145		Incomplete recovery based on GOSE at 6 months GOSE scores <8 indicated incomplete recovery	0.61 (0.48 to 0.75)	Very serious[a]	Serious[b]	None	Very serious[c]	VERY LOW
		168		Poor outcome based on GOSE at 3 months GOSE scores ≤4 indicated poor outcome	0.83 (0.75 to 0.91)	Very serious[a]	Serious[b]	None	None	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
		145		Poor outcome based on GOSE at 6 months GOSE scores ≤4 indicated poor outcome	0.81 (0.70 to 0.91)	Very serious[a]	Serious[b]	None	None	VERY LOW
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)										
BDNF + UCH-L1 – continuous variable, samples taken within 24 h of injury	1: Korley 2016[16]	94	Any severity TBI (84% mild, GCS 13-15) 47.2% with abnormality on head CT	Incomplete recovery at 6 months Composite score based on Rivermead Post-Concussion Questionnaire (at least three symptoms rated as worse than before injury) and GOSE (scores <8)	0.66 (no CIs reported)	Serious[a]	None	None	Serious[c]	LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
BDNF + GFAP – continuous variable, samples taken within 24 h of injury	1: Korley 2016[16]	94	Any severity TBI (84% mild, GCS 13-15) 47.2% with abnormality on head CT	Incomplete recovery at 6 months Composite score based on Rivermead Post-Concussion Questionnaire (at least three symptoms rated as worse than before injury) and GOSE (scores <8)	0.66 (no CIs reported)	Serious[a]	None	None	Serious[c]	LOW

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Downgraded by 1 increment as the population was a mixture of children and adults with no proportions given (study was included under the adult population as the average age, for example mean or median age, was consistent with the adult population).

[c] Assessment of imprecision for accuracy/area under the curve was based on whether confidence intervals crossed none (no downgrading), one (downgrading by 1 increment) or both (downgrading by two increments) of the following thresholds: 0.50 and 0.70. The threshold of 0.50 represents the boundary between the predictive value being better than or worse than chance and the threshold of 0.70 separates values indicating a moderate predictive value from those with a poor predictive value. Where confidence intervals were not reported or where partial AUC has been reported and the maximum possible value is unclear, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

Adults – salivary biomarkers – salivary miRNAs

Table 21: Clinical evidence summary: sensitivity and specificity data – salivary miRNAs in adults

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome											
Salivary non-coding RNA (includes miRNA, snoRNA and wiRNA), samples	1: Fedorchak 2021[8]	112	Mild TBI (definition based on 2016 Concussion in Sport Group)	Persistent post-concussion symptoms at ≥21 days post-injury	Training set (n=184 samples) 0.77 (no CIs reported) Evaluation set (n=72 samples)	Training set (n=184 samples) 0.78 (no CIs reported) Evaluation set (n=72 samples)	Sensitivity				
							Very serious[a]	Very serious[b]	None	Serious[c]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
taken within 14 days of injury – **model 1 (16 ncRNAs and age)**			Neurological injury (intracranial bleeding, spina cord injury and skull fracture) was excluded	Scores ≥5 on Post-Concussion Symptom Scale Training, evaluation and testing sets	0.81 (no CIs reported) Testing set (n=72 samples) 0.83 (no CIs reported)	0.73 (no CIs reported) Testing set (n=72 samples) 0.80 (no CIs reported)	Very serious[a]	Very serious[b]	None	Serious[d]	VERY LOW
GOS or GOSE used as outcome											
No data											
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)											
No data											

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Downgraded by 2 increments as the population was a mixture of children and adults with no proportions given (study was included under the adult population as the average age, for example mean or median age, was consistent with the adult population); the paper provides results for a

model consisting of various ncRNAs combined making it difficult to assess the utility of individual biomarkers; and biomarkers measured within 14 days of injury (mean value not given), which is >48 h specified in the protocol

[c] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.9 and 0.7, respectively, which were the thresholds used for sensitivity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[d] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.95 and 0.75, respectively, which were the thresholds used for specificity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

Table 22: Clinical evidence summary: AUC data – salivary miRNAs in adults

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome										

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Salivary non-coding RNA (includes miRNA, snoRNA and wiRNA), samples taken within 14 days of injury – **model 1 (16 ncRNAs and age)**	1: Fedorchak 2021[8]	112	Mild TBI (definition based on 2016 Concussion in Sport Group) Neurological injury (intracranial bleeding, spinal cord injury and skull fracture) was excluded	Persistent post-concussion symptoms at ≥21 days post-injury Scores ≥5 on Post-Concussion Symptom Scale <u>Training, evaluation and testing sets</u>	<u>Training set (n=184 samples)</u> 0.85 (no CIs reported) <u>Evaluation set (n=72 samples)</u> 0.83 (no CIs reported) <u>Testing set (n=72 samples)</u> 0.87 (no CIs reported)	Very serious[a]	Very serious[b]	None	Serious [c]	VERY LOW
				Persistent post-concussion symptoms at ≥21 days post-injury Scores ≥5 on Post-Concussion Symptom Scale <u>Ten-fold cross-validation of model</u>	<u>Ten-fold cross-validation of model</u> 0.83 (0.81 to 0.85)	Very serious[a]	Very serious[b]	None	None	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Salivary non-coding RNA (includes miRNA, snoRNA and wiRNA), samples taken within 14 days of injury – **model 2 (11 ncRNAs and age)**				Persistent post-concussion symptoms at ≥21 days post-injury Scores ≥5 on Post-Concussion Symptom Scale Ten-fold cross-validation of model	Ten-fold cross-validation of model 0.83 (0.79 to 0.86)	Very serious[a]	Very serious[b]	None	None	VERY LOW
GOS or GOSE used as outcome										
No data										
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)										
No data										

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of

measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Downgraded by 2 increments as the population was a mixture of children and adults with no proportions given (study was included under the adult population as the average age, for example mean or median age, was consistent with the adult population); the paper provides results for a model consisting of various ncRNAs combined making it difficult to assess the utility of individual biomarkers; and biomarkers measured within 14 days of injury (mean value not given), which is >48 h specified in the protocol

[c] Assessment of imprecision for accuracy/area under the curve was based on whether confidence intervals crossed none (no downgrading), one (downgrading by 1 increment) or both (downgrading by two increments) of the following thresholds: 0.50 and 0.70. The threshold of 0.50 represents the boundary between the predictive value being better than or worse than chance and the threshold of 0.70 separates values indicating a moderate predictive value from those with a poor predictive value. Where confidence intervals were not reported or where partial AUC has been reported and the maximum possible value is unclear, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

Adults – MRI biomarkers

Table 23: Clinical evidence summary: sensitivity and specificity data – MRI biomarkers in adults

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome											
MRI – various features combined into a model –	1: Messe 2011[22]	23	Mild TBI Those with	Persistent post-concussion symptoms at 3 months	Posterior probability threshold of P=0.5	Posterior probability threshold of P=0.5 (all	Sensitivity				
							Very serious[a]	Serious[b]	None	Very serious[c]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
continuous mean values Mean diffusivity (MD) values of six regions (forceps major and forceps minor of the corpus callosum, left and right inferior fronto-occipital fasciculus, and left and right inferior longitudinal fasciculus) MRI performed between 7 and 28 days post-injury			skull fractures excluded	Presence of at least one complaint in each of three domains of questionnaire – adapted from Gillum and Bosworth 2002	(all patients classified) 0.69 (no CIs reported) Posterior probability threshold of P=0.95 (only those with high level of confidence classified) 0.34 (no CIs reported)	patients classified) 0.77 (no CIs reported) Posterior probability threshold of P=0.95 (only those with high level of confidence classified) 0.89 (no CIs reported)	Very serious[a]	Serious[b]	None	Very serious[d]	VERY LOW
MRI – abnormality on MRI, conducted between 2 weeks and 2 months post-injury Defined as trauma-related findings with	1: Waljas 2015[35]	124	Mild TBI (GCS 13-15) 13.5% had intracranial trauma-related abnormality on CT	Post-concussion syndrome at 1 month – mild or greater symptoms Mild or greater symptoms in each domain on	0.11 (0.05 to 0.20)	0.86 (0.74 to 0.94)	Sensitivity Very serious[a]	None	None	None	LOW

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
minor incidental findings not included				Rivermead Post-Concussion Questionnaire			Specificity				
							Very serious[a]	None	None	Serious[d]	VERY LOW
		122		Post-concussion syndrome at 1 month – moderate or greater symptoms Moderate or greater symptoms in each domain on Rivermead Post-Concussion Questionnaire	0.04 (0.00 to 0.21)	0.86 (0.77 to 0.92)	Sensitivity				
							Very serious[a]	None	None	None	LOW
							Specificity				
							Very serious[a]	None	None	None	LOW
		103					Sensitivity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
				Post-concussion syndrome at 1 year – mild or greater symptoms Mild or greater symptoms in each domain on Rivermead Post-Concussion Questionnaire	0.05 (0.01 to 0.17)	0.83 (0.71 to 0.91)	Very serious[a]	None	None	None	LOW
							Specificity				
							Very serious[a]	None	None	Serious[d]	VERY LOW
		103		Post-concussion syndrome at 1 year – moderate or greater symptoms Moderate or greater symptoms in each domain on Rivermead Post-Concussion Questionnaire	0.00 (0.00 to 0.26)	0.86 (0.77 to 0.92)	Sensitivity				
							Very serious[a]	None	None	None	LOW
							Specificity				
							Very serious[a]	None	None	None	LOW

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
GOS or GOSE used as outcome											
MRI – presence of traumatic microbleeds Single/several small haemorrhagic lesions in white matter or grey/white interface on susceptibility-weighted imaging MRI performed between 3 and 17 days post-injury	1: Huovinen 2021[11]	100	Mild TBI (WHO definition) Unclear if/proportion with abnormalities on imaging other than MRI microbleeds	Incomplete recovery at 1 month based on GOSE GOSE scores <8 indicated incomplete recovery	0.18 (0.08 to 0.33)	0.80 (0.68 to 0.90)	Sensitivity				
							Very serious[a]	None	None	None	LOW
							Specificity				
							Very serious[a]	None	None	Serious[d]	VERY LOW
MRI – provides results for large list of individual MRI areas/features See separate Table 25 below for long	1: Ledig 2017[18]	67	Mild-severe TBI with MRI performed (% with mild unclear but median GCS consistent with mild TBI)	Severe vs. low disability (GOSE scores 3-4 vs. GOSE scores 7-8) at chronic stage (median 229 days post-injury)	Ranges from 0.26 (asymmetry of ventral diencephalon) to 0.91	Ranges from 0.45 (asymmetry of inferior lateral ventricle) to 0.94 (asymmetry	Sensitivity				
							Very serious[a]	Serious[e]	None	Very serious[c]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
list of MRI features and results for each MRI performed at acute state of TBI (time-point unclear)			Marshall score ranges from 1-5 across low, moderate and severe disability groups at baseline based on GOSE scores		(volumetric measurement of accumbens area) No CIs provided for each of the features – see Table 25 below for results for each individual feature	of thalamus proper) No CIs provided for each of the features – see Table 25 below for results for each individual feature	Very serious[a]	Serious[e]	None	Very serious[d]	VERY LOW
				Moderate vs. low disability (GOSE scores 5-6 vs. GOSE scores 7-8) at chronic stage (median 229 days post-injury)	Ranges from 0.31 (asymmetry of cortical grey matter) to 0.71 (volumetri	Ranges from 0.33 (asymmetry of cerebellum exterior) to 0.80 (asymmetry in all	Sensitivity				
							Very serious[a]	Serious[e]	None	Very serious[c]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
					c measure of cortical grey matter) No CIs provided for each of the features – see Table 25 below for results for each individual feature	measured areas) No CIs provided for each of the features – see Table 25 below for results for each individual feature	Very serious[a]	Serious[e]	None	Very serious[d]	VERY LOW
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)											
MRI – various white matter fibres combined in a single model[f] MRI performed within 7 days of injury	1: Bai 2020[2] – original sample	60	Mild TBI within 1-week post-injury Structural abnormality on conventional imaging excluded	Information-processing speed deficit assessed using Trail Making Test Part A at 6-12 months	0.990 (0.991 to 0.995)	0.949 (0.839 to 0.859)	Sensitivity				
							Serious[a]	Very serious[g]	None	None	VERY LOW
							Specificity				
							Serious[a]	Very serious[g]	None	None	VERY LOW
		38					Sensitivity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
	1: Bai 2020[2] – replicate sample				0.907 (0.899 to 0.915)	0.741 (0.729 to 0.754)	Serious[a]	Very serious[g]	None	Serious[c]	VERY LOW
							Specificity				
							Serious[a]	Very serious[g]	None	Serious[d]	VERY LOW
MRI – continuous mean values of 12 mean diffusivity values, performed	1: Li 2016[20]	43	Mild TBI Abnormal findings on	PTSD diagnosis – poor recovery – unclear time-point (measured at 1 and 6 months)	0.73 (no CIs reported)	0.78 (no CIs reported)	Sensitivity				
							Very serious[a]	Serious[h]	None	Very serious[c]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
10-20 days post-injury Included genu of corpus callosum, splenium corpus callosom, bilateral (left and right) superior longitudinal fasciculus, bilateral (left and right) inferior fronto-occipital fasciculus, bilateral (left and right) anterior thalamic radiation, bilateral (left and right) corticospinal tract, left inferior longitudinal fasciculus and left Uncinate fasciculus			MRI exclusion criterion	Evaluation of PTSD included psychometric measures for PTSD diagnosis and symptom severity using the clinician-administered PTSD scale (CAPS).	(Posterior probability threshold of P=0.50)	(Posterior probability threshold of P=0.50)	Very serious[a]	Serious[h]	None	Very serious[d]	VERY LOW
MRI – periaqueductal grey (PAG)-seeded functional connectivity in default mode network (right	1: Niu 2019[25]	56	Mild TBI within 1 week post-injury Structural abnormality on conventional	Persistent post-traumatic headache at 3 months Based on VAS score – score >0	1.00 (0.66 to 1.00)	0.78 (0.63 to 0.89)	Sensitivity				
							Very serious[a]	Serious[h]	None	Very serious[c]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
praecuneus and right inferior parietal lobule), In combination with other non-imaging characteristics (age, sex, education and loss of conciousness) MRI performed within 7 days of injury			neuroimaging was an exclusion criterion	persistent headache and a score of 0 indicating non-persistent headache.			Very serious[a]	Serious[h]	None	Serious[d]	VERY LOW
MRI – positive MRI result, performed within 2 weeks of injury Definition unclear but reported that findings on MRI were largely microbleeds caused by haemorrhagic axonal injury and small contusions	1: Stein 2021[32]	421	Mild TBI (GCS 13-15) 28.0% were CT positive and 44.4% MRI-positive	Probable post-traumatic stress disorder at 3 months Measured using PTSD checklist for DSM-5 – score ≥33 indicating PTSD.	0.43 (0.32 to 0.55)	0.55 (0.50 to 0.61)	Sensitivity				
							Very serious[a]	None	None	None	LOW
							Specificity				
							Very serious[a]	None	None	None	LOW
							Sensitivity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
				Probable post-traumatic stress disorder at 6 months Measured using PTSD checklist for DSM-5 – score ≥33 indicating PTSD.	0.37 (0.26 to 0.50)	0.54 (0.49 to 0.59)	Very serious[a]	None	None	None	LOW
							Specificity				
							Very serious[a]	None	None	None	LOW
MRI – microbleed lesions	1: Wang 2014[36]	165	Mild TBI Normal appearance on	SCID-IV criteria for depressive symptoms –	0.71 (0.51 to 0.87)	0.91 (0.85 to 0.95)	Sensitivity				
							Serious[a]	Serious[h]	None	Serious[c]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Solitary microbleed lesions defined as rounded, hypointense homogenous foci up to 5 mm in size not compatible with vascular, bone calcification or artefactual structures on the susceptibility-weighted imaging sequence. Multiple microbleeds were defined as multiple hypointense homogeneous foci that integrated with each other and yielded a mass <5 mm in diameter. MRI performed on admission, with admission times ranging between 2 h and 3 days post-injury			conventional CT and MRI on admission was inclusion criterion	major depression after TBI at 1 year Those meeting criteria for 'Mood Disorder Due to General Medical Condition' (MDD-GMC), major depressive-like episode subtype for at least one follow-up visit within 1 year were considered as major depression after TBI.			Serious[a]	Serious[h]	None	None	LOW

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Downgraded by 1 increment as results are provided or a model containing multiple MRI measurements making it difficult to assess utility of individual findings on MRI

[c] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.9 and 0.7, respectively, which were the thresholds used for sensitivity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[d] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.95 and 0.75, respectively, which were the thresholds used for specificity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[e] Downgraded by 1 increment as the population included any severity of TBI and the proportion of those with mild TBI was unclear

[f] Model included Thalamus-anterior cingulate L; Thalamus-anterior cingulate R; Thalamus-inferior frontal gyrus R; Thalamus-superior frontal gyrus L; Thalamus-superior frontal gyrus R; Anterior thalamic radiation L; Anterior thalamic radiation R; Corticospinal tract L; Cingulum (cingulate gyrus) L; Cingulum (hippocampus) L; Cingulum (hippocampus) R; Forceps minor; Inferior fronto-occipital fasciculus R; Inferior longitudinal fasciculus L; Superior longitudinal fasciculus R; Uncinate fasciculus L; Uncinate fasciculus R; Superior longitudinal fasciculus (temporal) R; Genu of corpus callosum; Body of corpus callosum; and Splenium of corpus callosum.

[g] Downgraded by 2 increments as the population was a mixture of children and adults with no proportions given (study was included under the adult population as the average age, for example mean or median age, was consistent with the adult population); and the paper provides results for a model consisting of multiple measurements on MRI making it difficult to assess the utility of individual biomarkers

[h] Downgraded by 1 increment as the population was a mixture of children and adults with no proportions given (study was included under the adult population as the average age, for example mean or median age, was consistent with the adult population).

Table 24: Clinical evidence summary: AUC data – MRI biomarkers in adults

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome										
No data										
GOS or GOSE used as outcome										

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
MRI – provides results for large list of individual MRI areas/features See separate Table 25 below for long list of MRI features and results for each MRI performed at acute state of TBI (time-point unclear)	1: Ledig 2017[18]	67	Mild-severe TBI with MRI performed (% with mild unclear but median GCS consistent with mild TBI) Marshall score ranges from 1-5 across low, moderate and severe disability groups at baseline based on GOSE scores	Severe vs. low disability (GOSE scores 3-4 vs. GOSE scores 7-8) at chronic stage (median 229 days post-injury)	Ranges from 0.40 (asymmetry of inferior lateral ventricle) to 0.82 (volumetric measurement of accumbens area and asymmetry of amygdala) No CIs provided for each of the features – see Table 25 below for results for each individual feature	Very serious[a]	Serious[b]	None	Very serious[c]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
				Moderate vs. low disability (GOSE scores 5-6 vs. GOSE scores 7-8) at chronic stage (median 229 days post-injury)	Ranges from 0.40 (total brain volume) to 0.71 (volumetric measurement of inferior lateral ventricle) No CIs provided for each of the features – see Table 25 below for results for each individual feature	Very serious[a]	Serious[b]	None	Very serious[c]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
MRI within 72 h – DTI and T1-weighted sequences combined, qualitative and quantitative imaging	1: Richter 2021[28]	65	Mild TBI (GCS 13-15) with indication for head CT 68% Marshall score 1 – no visible pathology on CT	Favourable outcome at 3 months based on GOSE Favourable recovery defined as a GOSE score of 8	0.87 (0.78 to 0.96)	Very serious[a]	Serious[d]	None	None	VERY LOW
MRI within 72 h – DTI and T1-weighted sequences combined, qualitative imaging only					0.69 (0.56 to 0.82)	Very serious[a]	Serious[d]	None	Serious[c]	VERY LOW
MRI within 72 h – DTI and T1-weighted sequences combined, quantitative imaging only					0.87 (0.78 to 0.96)	Very serious[a]	Serious[d]	None	None	VERY LOW
MRI within 72 h – T1-weighted sequence only, qualitative and quantitative imaging					0.76 (0.64 to 0.88)	Very serious[a]	Serious[d]	None	Serious[c]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
MRI within 72 h – DTI sequence only, qualitative and quantitative imaging					0.76 (0.64 to 0.88)	Very serious[a]	Serious[d]	None	Serious[c]	VERY LOW
MRI at 2-3 weeks – DTI and T1-weighted sequences combined, qualitative and quantitative imaging					0.75 (0.62 to 0.87)	Very serious[a]	Serious[d]	None	Serious[c]	VERY LOW
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)										
MRI – various white matter fibres combined in a single model[h]	1: Bai 2020[2] – original sample	60	Mild TBI within 1-week post-injury	Information-processing speed deficit assessed using Trail Making Test Part A at 6-12 months	0.921 (0.916 to 0.926)	Serious[a]	Very serious[e]	None	None	VERY LOW
MRI performed within 7 days of injury	1: Bai 2020[2] – replicate sample	38	Structural abnormality on conventional imaging excluded		0.824 (0.817 to 0.831)	Serious[a]	Very serious[e]	None	None	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
MRI – continuous mean values of 12 mean diffusivity values, performed 10-20 days post-injury Included genu of corpus callosum, splenium corpus callosom, bilateral (left and right) superior longitudinal fasciculus, bilateral (left and right) inferior fronto-occipital fasciculus, bilateral (left and right) anterior thalamic radiation, bilateral (left and right) corticospinal tract, left inferior longitudinal fasciculus and left Uncinate fasciculus	1: Li 2016[20]	43	Mild TBI Abnormal findings on MRI exclusion criterion	PTSD diagnosis – poor recovery – unclear time-point (measured at 1 and 6 months) Evaluation of PTSD included psychometric measures for PTSD diagnosis and symptom severity using the clinician-administered PTSD scale (CAPS).	0.7556 (no CIs reported) (Posterior probability threshold of P=0.50)	Very serious[a]	Serious[d]	None	Very serious[c]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
MRI – periaqueductal grey (PAG)-seeded functional connectivity in default mode network (right praecuneus and right inferior parietal lobule), In combination with other non-imaging characteristics (age, sex, education and loss of consciousness) MRI performed within 7 days of injury	1: Niu 2019[25]	56	Mild TBI within 1 week post-injury Structural abnormality on conventional neuroimaging was an exclusion criterion	Persistent post-traumatic headache at 3 months Based on VAS score – score >0 persistent headache and a score of 0 indicating non-persistent headache.	0.8935 (no CIs reported)	Very serious[a]	Serious[d]	None	Very serious[c]	VERY LOW

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study

participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Downgraded by 2 increments as the population was a mixture of children and adults with no proportions given (study was included under the adult population as the average age, for example mean or median age, was consistent with the adult population); the paper provides results for a model consisting of various ncRNAs combined making it difficult to assess the utility of individual biomarkers; and biomarkers measured within 14 days of injury (mean value not given), which is >48 h specified in the protocol

[c] Assessment of imprecision for accuracy/area under the curve was based on whether confidence intervals crossed none (no downgrading), one (downgrading by 1 increment) or both (downgrading by two increments) of the following thresholds: 0.50 and 0.70. The threshold of 0.50 represents the boundary between the predictive value being better than or worse than chance and the threshold of 0.70 separates values indicating a moderate predictive value from those with a poor predictive value. Where confidence intervals were not reported or where partial AUC has been reported and the maximum possible value is unclear, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[d] Downgraded by 1 increment as the population was a mixture of children and adults with no proportions given (study was included under the adult population as the average age, for example mean or median age, was consistent with the adult population).

[e] Downgraded by 2 increments as the population was a mixture of children and adults with no proportions given (study was included under the adult population as the average age, for example mean or median age, was consistent with the adult population); and provides results for model containing multiple MRI measurements combined so difficult to assess utility of individual findings on MRI

Table 25: Clinical evidence summary: data from Ledig 2017[18] for MRI as a biomarker for predicting severe vs. low and moderate vs. low disability based on GOSE (see MRI GRADE tables above for summary of data)

Structure on MRI	ACC (bACC) – accuracy (balanced accuracy accounting for differences in group size	Sensitivity	Specificity
Prediction of severe vs. low disability (GOSE scores 3-4 vs. 7-8) at chronic stage (median 229 days post-injury)			
Ventricles	72 (71)	68	74
CorticalGreyMatter	70 (70)	70	71
DeepGreyMatter	74 (74)	74	75
BrainTissue	60 (60)	60	60

Structure on MRI	ACC (bACC) – accuracy (balanced accuracy accounting for differences in group size	Sensitivity	Specificity
Brain	58 (59)	62	57
WhiteMatter	50 (46)	37	55
AccumbensArea	**82 (85)**	**91**	**79**
Hippocampus	80 (81)	83	79
Amygdala	73 (76)	83	68
LateralVentricle	75 (74)	73	76
InfLatVent	81 (75)	62	89
ThalamusProper	73 (74)	76	72
BasalForebrain	74 (75)	77	72
CerebellarVermalLobulesI-V	75 (74)	72	76
3rdVentricle	71 (71)	69	72
Putamen	76 (76)	77	75
BrainStem	69 (69)	71	68
CerebellumWhiteMatter	73 (72)	69	74
VentralDC	56 (55)	54	56
CerebellarVermalLobulesVIII-X	57 (62)	74	51
CerebellumExterior	64 (64)	63	64
4th Ventricle	60 (55)	45	66
Caudate	53 (47)	35	60
Pallidum	52 (51)	48	54
CerebellarVermanlLobulesVI-VIII	54 (54)	54	54
CSF	47 (45)	42	48
CerebralWhiteMatter	43 (38)	28	49
AsymmetryAllCortical	76 (74)	69	79
AsymmetryAll	81 (73)	54	91
AsymmetryWhiteMatter	75 (69)	55	82
AsymmetryCerebralWhiteMatter	76 (68)	48	88

Structure on MRI	ACC (bACC) – accuracy (balanced accuracy accounting for differences in group size	Sensitivity	Specificity
AsymmetryAmygdala	82 (78)	68	87
AsymmetryBrain	75 (72)	64	79
AsymmetryBrainTissue	81 (73)	54	92
AsymmetryCorticalGreyMatter	79 (72)	55	89
AsymmetryAllNonCortical	79 (71)	50	91
AsymmetryCerebellumWhiteMatter	69 (69)	69	69
AsymmetryPutamen	75 (63)	34	92
AsymmetryAccumbensArea	66 (62)	53	71
AsymmetryCaudate	71 (63)	46	81
AsymmetryDeepGreyMatter	72 (66)	52	81
AsymmetryThalamusProper	75 (60)	27	94
AsymmetryVentricles	68 (59)	39	79
AsymmetryHippocampus	63 (57)	43	71
AsymmetryPallidum	68 (56)	28	84
AsymmetryLateralVentricle	66 (57)	38	77
AsymmetryVentralDC	65 (56)	26	76
AsymmetryBasalForebrain	63 (55)	37	74
AsymmetryCerebellumExterior	68 (64)	54	74
AsymmetryInfLatVent	40 (37)	29	45
Prediction of moderate vs. low disability (GOSE scores 5-6 vs. 7-8) at chronic stage (median 229 days post-injury)			
Ventricles	61 (61)	58	64
CorticalGreyMatter	66 (67)	71	63
DeepGreyMatter	42 (41)	38	44
BrainTissue	49 (49)	49	48
Brain	40 (40)	39	40
WhiteMatter	46 (44)	35	54
AccumbensArea	58 (59)	64	53

Structure on MRI	ACC (bACC) – accuracy (balanced accuracy accounting for differences in group size	Sensitivity	Specificity
Hippocampus	54 (53)	49	58
Amygdala	60 (60)	58	62
LateralVentricle	62 (61)	57	65
InfLatVent	**71 (69)**	**60**	**78**
ThalamusProper	60 (61)	68	54
BasalForebrain	52 (51)	46	55
CerebellarVermalLobulesI-V	60 (61)	64	58
3rdVentricle	61 (61)	56	65
Putamen	57 (56)	51	61
BrainStem	44 (44)	47	42
CerebellumWhiteMatter	56 (54)	45	64
VentralDC	44 (44)	47	41
CerebellarVermalLobulesVIII-X	65 (65)	66	65
CerebellumExterior	45 (44)	40	49
4th Ventricle	62 (62)	59	65
Caudate	51 (51)	50	51
Pallidum	49 (48)	41	54
CerebellarVermanlLobulesVI-VIII	48 (47)	43	52
CSF	45 (45)	42	47
CerebralWhiteMatter	43 (41)	33	50
AsymmetryAllCortical	59 (56)	42	71
AsymmetryAll	63 (59)	37	80
AsymmetryWhiteMatter	55 (53)	42	64
AsymmetryCerebralWhiteMatter	59 (57)	46	68
AsymmetryAmygdala	45 (44)	34	53
AsymmetryBrain	57 (55)	46	65
AsymmetryBrainTissue	50 (48)	39	57

Structure on MRI	ACC (bACC) – accuracy (balanced accuracy accounting for differences in group size	Sensitivity	Specificity
AsymmetryCorticalGreyMatter	59 (55)	31	79
AsymmetryAllNonCortical	58 (56)	47	65
AsymmetryCerebellumWhiteMatter	46 (47)	53	41
AsymmetryPutamen	59 (55)	34	76
AsymmetryAccumbensArea	60 (59)	53	64
AsymmetryCaudate	53 (50)	33	66
AsymmetryDeepGreyMatter	41 (41)	41	41
AsymmetryThalamusProper	61 (58)	43	74
AsymmetryVentricles	42 (42)	42	41
AsymmetryHippocampus	48 (46)	36	57
AsymmetryPallidum	58 (56)	47	65
AsymmetryLateralVentricle	45 (46)	54	38
AsymmetryVentralDC	62 (62)	64	61
AsymmetryBasalForebrain	55 (54)	50	58
AsymmetryCerebellumExterior	43 (45)	58	33
AsymmetryInfLatVent	45 (44)	34	53

Note: green shading indicates features where the AUC value indicates at least good overall accuracy (values >0.80) and where the sensitivity is >90%; orange shading indicates features where the AUC value indicates at least good overall accuracy (values >0.80) but where the sensitivity does not reach 90%; bold text indicates the best performing feature according to AUC values and sensitivity values.

Features that do not have ‘asymmetry’ in the name refer to volumetric measurements. A total of 21 non-cortical features were considered. Individual structural volumes were added up into surrogate structures (ventricles, cortical grey matter, deep grey matter, white matter, brain tissue - BrainTissue and total brain volume - Brain – 6 features). The difference between BrainTissue and Brain is exclusion/inclusion of ventricular/CSF volume, respectively. Cerebral exterior, vessel and optic chiasm were excluded from analysis due to their very small size. Cortical structures only measured as surrogate structure (cortical grey matter) and not considered as individual features.

Structural asymmetry was quantified as absolute asymmetry index (AAI) based on a structure’s volume in the left and right hemisphere. AAI was calculated for the 14 non-cortical structures appearing in both brain hemispheres and the six surrogate structures. AAIs of all individual non-cortical, cortical and all brain structures were also added up

1 Children – blood biomarkers – S100B

2 Table 26: Clinical evidence summary: sensitivity and specificity data – S100B in children

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome											
No data											
GOS or GOSE used as outcome											
No data											
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)											
No data											

3 Table 27: Clinical evidence summary: AUC data – S100B in children

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome										

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
S100B – continuous variable, samples taken within 6 h of injury	1: Babcock 2013[1]	76	Mild TBI presenting within 6 h of injury 4.0% with abnormal CT	Post-concussion syndrome at 3 months Defined as 3 or more symptoms rated with score of 2 or more (rated as worse at follow-up compared to pre-injury) at 3 months. Using Rivermead Post-Concussion Questionnaire	0.47 (no CIs reported)	Very serious[a]	None	None	Serious[b]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
S100B – continuous variable, samples taken within 3 h of injury	1: Kelmendi 2021[15]	60	Mild TBI presenting within 3 h of injury 75.0% were CT-positive (lesions on head CT)	Post-concussion syndrome present at 3 months Development of PCS at 3 months defined as 3 or more symptoms on questionnaire rated as worse (scale of 2 or more) than at pre-injury. Based on Rivermead Post-Concussion Questionnaire	0.893 (0.786 to 0.987)	Very serious[a]	None	None	None	LOW
GOS or GOSE used as outcome										
No data										
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)										
No data										

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Assessment of imprecision for accuracy/area under the curve was based on whether confidence intervals crossed none (no downgrading), one (downgrading by 1 increment) or both (downgrading by two increments) of the following thresholds: 0.50 and 0.70. The threshold of 0.50 represents the boundary between the predictive value being better than or worse than chance and the threshold of 0.70 separates values indicating a moderate predictive value from those with a poor predictive value. Where confidence intervals were not reported or where partial AUC has been reported and the maximum possible value is unclear, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

Children – blood biomarkers – combinations of different biomarkers

Table 28: Clinical evidence summary: sensitivity and specificity data – combinations of different biomarkers in children

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome											
No data											
GOS or GOSE used as outcome											
No data											
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)											
No data											

Table 29: Clinical evidence summary: AUC data – combinations of different biomarkers in children

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome										
No data										
GOS or GOSE used as outcome										
Abnormal values of S100B (>0.017 ng/ml), NSE (>11.7 ng/ml) and MBP (0.3 ng/ml) in a combined model, samples taken as soon as possible after hospital arrival and second time after 12-24 h when vascular access available Included peak and initial levels in serum	1: Berger 2007[6]	152	TBI of any severity (61% mild) with CT performed within 24 h Does not mention excluding those with imaging abnormalities	Good vs. poor outcome according to GOSE at 0-3 months GOSE scores 1-2 indicate good outcome and scores 3-5 indicate poor outcome	0.77 (no CIs reported)	Very serious[a]	Very serious[b]	None	Serious[c]	VERY LOW
				Good vs. poor outcome according to GOSE at 4-6 months GOSE scores 1-2 indicate good outcome and scores 3-5 indicate poor outcome	0.78 (no CIs reported)	Very serious[a]	Very serious[b]	None	Serious[c]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
				Good vs. poor outcome according to GOSE at 7-12 months GOSE scores 1-2 indicate good outcome and scores 3-5 indicate poor outcome	0.78 (no CIs reported)	Very serious[a]	Very serious[b]	None	Serious [c]	VERY LOW
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)										
No data										

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Downgraded by 2 increments as the study included any severity of TBI with only 61% having mild TBI; and difficult to assess the utility of each of the three biomarkers as only results for a combined model are reported

[c] Assessment of imprecision for accuracy/area under the curve was based on whether confidence intervals crossed none (no downgrading), one (downgrading by 1 increment) or both (downgrading by two increments) of the following thresholds: 0.50 and 0.70. The threshold of 0.50 represents the boundary between the predictive value being better than or worse than chance and the threshold of 0.70 separates values indicating a moderate predictive value from those with a poor predictive value. Where confidence intervals were not reported or where partial AUC has been reported and the maximum possible value is unclear, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

Children – salivary biomarkers – salivary miRNAs

Table 30: Clinical evidence summary: sensitivity and specificity data – salivary miRNAs in children

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome											
Salivary miRNA – continuous, collected	1: Johnson 2018[14]	61	Mild TBI evaluated within 14	Post-concussion symptoms at 4 weeks based on Sport	0.80 (no CIs reported)	0.75 (no CIs reported)	Sensitivity				
							Very serious[a]	Serious[b]	None	Very serious[c]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
within 14 days of injury Model containing following 5 miRNAs: miR-320c-1, miR-133a-5p, miR-769-5p, let-7a-3p, and miR-1307-3p			days of injury Those with skull fracture and intracranial bleeding were excluded	Concussion Assessment Tool (SCAT3) Those with scores ≥5 considered to have post-concussion symptoms			Very serious[a]	Serious[b]	None	Very serious[d]	VERY LOW
GOS or GOSE used as outcome											
No data											
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)											
No data											

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of

measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Downgraded by 1 increment as the study included people presenting within 14 days of injury and having samples taken, which is >48 time-point specified in the protocol

[c] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.9 and 0.7, respectively, which were the thresholds used for sensitivity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[d] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.95 and 0.75, respectively, which were the thresholds used for specificity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

Table 31: Clinical evidence summary: AUC data – salivary miRNAs in children

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome										

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Salivary miRNA – continuous, collected within 14 days of injury Model containing following 5 miRNAs: miR-320c-1, miR-133a-5p, miR-769-5p, let-7a-3p, and miR-1307-3p	1: Johnson 2018[14]	61	Mild TBI evaluated within 14 days of injury Those with skull fracture and intracranial bleeding were excluded	Post-concussion symptoms at 4 weeks based on Sport Concussion Assessment Tool (SCAT3) Those with scores ≥5 considered to have post-concussion symptoms	0.856 (0.822 to 0.890)	Very serious[a]	Serious[b]	None	None	VERY LOW
GOS or GOSE used as outcome										
No data										
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)										
No data										

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of

uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Downgraded by 1 increment as the study included people presenting within 14 days of injury and having samples taken, which is >48 time-point specified in the protocol

Children – MRI biomarkers

Table 32: Clinical evidence summary: sensitivity and specificity data – MRI biomarkers in children

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome											
MRI – model consisting of MRI variables and age, MRI within 4-6 weeks post-injury	1: Iyer 2019 [13]	99	Mild TBI Unclear if abnormalities on imaging was an	Recovery based on Post-Concussion Symptom Inventory scores at 8-10 weeks post-injury	Training sample (n=85), 10-fold average 0.94 (no CIs reported)	Training sample (n=85), 10-fold average 0.69 (no CIs reported)	Sensitivity				
							Very serious[a]	None	None	Serious (training)/very serious (testing) [b]	VERY LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
MRI variables: grey matter volume (eigenvariates) extracted from posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC), regional homogeneity (ReHo) estimates from PCC and PCC-mPFC functional connectivity values			exclusion criterion	Grouped into 'symptomatic' and 'recovered' – symptomatic if ≥10-point increase in total score compared to pre-injury score and recovered if score returned to pre-injury level.	Testing sample (n=14), 10-fold average 0.75 (no CIs reported)	Testing sample (n=14), 10-fold average 0.82 (no CIs reported)	Very serious[a]	None	None	Serious (training)/very serious (testing)[c]	VERY LOW
MRI – abnormal (trauma-related intracranial abnormalities), MRI performed	1: Yeates 2009[38]	180	Mild TBI Did not exclude those with	Persistence of post-concussion symptoms across follow-up (up to 12 months) – moderate or high	0.18 (0.08 to 0.34)	0.82 (0.75 to 0.88)	Sensitivity				
							Very serious[a]	None	None	None	LOW
							Specificity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
within 3 weeks of injury No further definition provided			mild injuries on CT, 18% with abnormality on MRI	increase vs. baseline persisting at 12 months Assessed using Post-Concussive Symptom Interview (15 symptoms rated by parents). Moderate increase described as those with moderate acute increases at 2 weeks that persisted up to 12 months			Very serious[a]	None	None	None	LOW
							Sensitivity				

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
				Persistence of post-concussion symptoms across follow-up (up to 12 months) – high increase vs. baseline persisting at 12 months Assessed using Post-Concussive Symptom Interview (15 symptoms rated by parents). High increase described as those with large acute increases at 2 weeks and where at least moderate symptoms continued at 12 months	0.18 (0.04 to 0.43)	0.82 (0.75 to 0.88)	Very serious[a]	None	None	None	LOW
							Specificity				
							Very serious[a]	None	None	None	LOW
GOS or GOSE used as outcome											
No data											

Biomarker	Studies	n	Population	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)											
No data											

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.9 and 0.7, respectively, which were the thresholds used for sensitivity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

[c] Downgraded by 1 or 2 increments if the confidence intervals crossed one or both of 0.95 and 0.75, respectively, which were the thresholds used for specificity to determine a biomarker should be recommended or was of no clinical use. Where confidence intervals could not be calculated due to lack of raw data reporting, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

1 **Table 33: Clinical evidence summary: AUC data – MRI biomarkers in children**

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Post-concussion symptoms/questionnaire used as outcome										
MRI – mean absolute cerebral blood flow at 4-6 weeks post-injury Includes averaged cerebral blood flow of grey matter as a continuous measure	1: Barlow 2021[3]	61	Mild TBI with persistent post-concussion symptoms and ≥10-point increase in total symptom score on Post-Concussion Symptom Inventory post-injury compared to pre-injury scorse	Good recovery at 8-10 weeks post-injury Good recovery defined as symptoms at or below pre-injury levels and return to normal activities Recovery status based on clinical interview and examination and Post-Concussion Symptom Inventory Youth Report at 8-10 weeks post-injury	0.77 (0.69 to 0.89)	Very seriou s[a]	Serious[b]	None	Serious [c]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
MRI – model consisting of MRI variables and age, MRI within 4-6 weeks post-injury MRI variables: grey matter volume (eigenvariates) extracted from posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC), regional homogeneity (ReHo) estimates from PCC and PCC-mPFC functional connectivity values	1: Iyer 2019 [13]	99	Mild TBI Unclear if abnormalities on imaging was an exclusion criterion	Recovery based on Post-Concussion Symptom Inventory scores at 8-10 weeks post-injury Grouped into 'symptomatic' and 'recovered' – symptomatic if ≥10-point increase in total score compared to pre-injury score and recovered if score returned to pre-injury level.	Training sample (n=85), 10-fold average 0.86 (no CIs reported) Testing sample (n=14), 10-fold average 0.79 (no CIs reported)	Very serious[a]	None	None	Serious (training)/very serious (testing)[c]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
MRI – posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC) functional connectivity values MRI within 4-6 weeks post-injury					Training sample (n=85), 10-fold average 0.55 (no CIs reported)	Very serious[a]	None	None	Serious[c]	VERY LOW
MRI – regional homogeneity (ReHo) estimates from posterior cingulate cortex (PCC) MRI within 4-6 weeks post-injury					Training sample (n=85), 10-fold average 0.53 (no CIs reported)	Very serious[a]	None	None	Serious[c]	VERY LOW
							None	None		

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
MRI – grey matter volume (eigenvariates) extracted from posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC) MRI within 4-6 weeks post-injury					Training sample (n=85), 10-fold average 0.73 (no CIs reported)	Very serious[a]			Serious[c]	VERY LOW
GOS or GOSE used as outcome										
No data										
Other outcome measure (for example, neurocognitive assessment, individual symptoms or return to work/activity)										

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
MRI – mean fractional anisotropy of left inferior longitudinal fasciculus temporal cluster MRI acquired within 10 days of concussion Possibly adjusted for other clinical, demographic and neuroimaging variables	1: Lima Santos 2021[21]	42	Recent diagnosis of concussion (1-10 days) No mention of imaging abnormalities being excluded	Short vs. long recovery time (medical clearance within 4 weeks vs. those not receiving clearance) Medical clearance if no symptoms at rest for at least 24 h, no provocation of symptoms with typical and cognitive activities, typical neurocognitive functioning at typical baseline, normal vestibular and oculomotor functioning and no other related medical complaints. Included use of various	0.728 (no CIs reported)	Very serious[a]	None	None	Very serious[c]	VERY LOW

Biomarker	Studies (no. of studies)	n	Population	Outcome	Accuracy (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
MRI – mean fractional anisotropy of right inferior longitudinal fasciculus temporal cluster MRI acquired within 10 days of concussion Possibly adjusted for other clinical, demographic and neuroimaging variables				symptom questionnaires.	0.803 (no CIs reported)	Very serious[a]	None	None	Very serious[c]	VERY LOW

[a] Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (mostly commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of

measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients). See individual evidence tables for specific details about risk of bias issues for each study.

[b] Downgraded by 1 increment as the population already had persistent post-concussion symptoms when enrolled, which is different to the review protocol and other studies included

[c] Assessment of imprecision for accuracy/area under the curve was based on whether confidence intervals crossed none (no downgrading), one (downgrading by 1 increment) or both (downgrading by two increments) of the following thresholds: 0.50 and 0.70. The threshold of 0.50 represents the boundary between the predictive value being better than or worse than chance and the threshold of 0.70 separates values indicating a moderate predictive value from those with a poor predictive value. Where confidence intervals were not reported or where partial AUC has been reported and the maximum possible value is unclear, studies were downgraded by 1 increment if the sample size was ≥70 and <350 and by 2 increments if the sample size was <70.

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix F.

1.1.8 Summary of included economic evidence

None

1.1.9 Economic model

Modelling was not conducted for this review.

1.1.10 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Code	Description	Unit cost
RD01A	Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over	£146.75
RD01B	Magnetic Resonance Imaging Scan of One Area, without Contrast, between 6 and 18 years	£215.63
RD01C	Magnetic Resonance Imaging Scan of One Area, without Contrast, 5 years and under	£140.83
RD20A	Computerised Tomography Scan of One Area, without Contrast, 19 years and over	£88.06
RD20B	Computerised Tomography Scan of One Area, without Contrast, between 6 and 18 years	£159.25
RD20C	Computerised Tomography Scan of One Area, without Contrast, 5 years and under	£104.27
PF	Plain Film (including x-ray)	£28.62

Direct access costs from NHS Reference costs: 2019-2020 version 2

1.1.11 Evidence statements

Economic

- No relevant economic evaluations were identified.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

Prognostic accuracy

Prognostic accuracy for post-concussion syndrome (confirmed by a constellation of symptoms, including cognitive, physical, emotional and sleep-related, as reported in studies) was the outcome relevant for the prognostic accuracy component of this review. Sensitivity and specificity were the measures agreed for use in assessing prognostic accuracy and studies reporting area under the curve (AUC) data were also included as this is a common measure of overall accuracy (taking both sensitivity and specificity into account) reported by studies where multiple thresholds of a prognostic test are possible, such as with biomarkers measured in the blood.

It was agreed in the protocol that sensitivity and specificity were of equal value. In addition, the committee agreed that for the use of these biomarkers to be practical specificity would have to be very high, ideally at least 95%, as the mild head injury population is large and false positives would have a negative impact on resources if biomarkers were to be used to direct people towards interventions or monitoring, given that only a small proportion will go on to develop post-concussion syndrome. Other limitations of a low specificity included the possibility people may delay their return to work, school or sport and become hypervigilant for symptoms.

Prognostic test and treat

For the prognostic test and treat component of the review, all outcomes were considered equally important for decision-making and were primary outcomes, including quality of life at ≥3 months, objectively reported scores of disability (such as the Glasgow Outcome Score) at ≥3 months, time to return to education/work/usual activities and duration of post-concussion

syndrome (at three time-points separately of: 2 weeks to <3 months, 3 months and >3 months).

No studies suitable for this part of the review were identified, as there were no studies comparing clinical outcomes between two different strategies (for example, biomarkers followed by appropriate treatment compared to usual care or to a strategy using a different biomarker followed by appropriate treatment).

1.1.12.2 The quality of the evidence

Population

It was noted that the majority of the evidence was in those with mild traumatic brain injury (defined as GCS 13-15), which is the population relevant to post-concussion syndrome. Studies including any severity of traumatic brain injury were included only if at least 60% of the population had mild injury or, if the proportion with each severity was unclear, the mean/median GCS values were consistent with the mild traumatic brain injury population. Studies were downgraded for population indirectness if <75% of the study population had mild traumatic brain injury or the proportion with each severity was unclear, which was only the case for three studies for adults and one study for children. One important difference in population between studies was the presence of abnormalities on imaging; some specifically excluded those with abnormalities on imaging such as CT or MRI, while others did not exclude them. Of those that did not exclude these abnormalities, some had a very small proportion of people with abnormalities (for example, 5.0%) and others had a much larger proportion (for example, >40%). This was an important difference as the committee noted that those with imaging abnormalities are likely to be followed up anyway so symptoms of post-concussion are more likely to be picked up compared to those that do not have an indication for imaging or who are CT-negative; however, others also noted that post-concussion symptoms can still be missed in those that are CT-positive, meaning it was important to consider both groups.

Some studies were also downgraded for population indirectness as the protocol aimed to look at results for adults and children separately and these studies included both with the proportion of each included not being reported.

Prognostic factor

Overall, prognostic factors in the included studies matched the protocol well and there was no indirectness. However, four studies (three in adults and one in children) were downgraded by one increment as they used models containing multiple variables (such as multiple MRI features, multiple RNAs or MRI features in combination with other clinical or demographic factors not listed in the protocol), making it difficult to interpret which features/biomarkers were most useful. In addition, two studies (one for adults and one for children) were downgraded by one increment as samples were taken within 14 days of injury and not within 48 as specified in the protocol; these were both studies looking at RNAs or specifically microRNAs (miRNAs) in the saliva.

Reference standard/outcome definition

The protocol description of post-concussion syndrome and symptoms used for diagnosis allowed for various outcome measures to be used as a reference standard for post-concussion syndrome, including specific post-concussion symptom questionnaires and scales, Glasgow Outcome Scale (GOS) and GOS-extended (GOSE), tests or questionnaires assessing cognitive, emotional or sleep-related symptoms and measures of return to work or usual activities. On discussion of the evidence, the committee noted that there is controversy about the definition of post-concussion syndrome and how it is diagnosed. It was also noted that although GOS/GOSE does contribute to the consideration of whether post-concussion syndrome is present, studies looking at predicting more severe GOS/GOSE scores (for

example, scores 1-4 on GOSE) may be less relevant as scores of 1-4 on GOSE would be considered too severe to represent post-concussion syndrome.

Grouping and meta-analysis

There was little overlap between studies such that meta-analysis of results from more than one study was not possible and results from each study were considered alongside each other for each specific biomarker. Differences between studies that meant pooling was not possible included: prognostic factor definition (for example, some studies reported the measure as a continuous variable while others report results for a specific threshold of biomarker measured in the blood); outcome (for example post-concussion symptom scales vs. Glasgow Outcome Scale); and statistical measures reported (for example, some only reported AUC while others only reported sensitivity and specificity measures). The lack of ability to pool results meant that data for each combination of prognostic factor, outcome and statistical measure was based on a small number of people, with all but one study including <200 people and many including even smaller numbers (<100 and in some cases <50 people).

Risk of bias

Most of the included evidence was graded low to very low based on the assessment of risk of bias using the QUIPS checklist, which was used without the confounding section of the checklist as although this is relevant for prognostic reviews reporting odds ratios, this is less relevant to studies reporting accuracy measures such as sensitivity and specificity. Across all included studies, the most common reasons that studies were downgraded for risk of bias were attrition, as a large proportion of people enrolled were not subsequently analysed, and reporting of results, as some studies were selective in the results they reported (for example, only reporting for certain thresholds or reporting results incompletely for some results and not for others) and/or did not report data completely (most commonly not reporting confidence intervals to provide a measure of uncertainty in the results or the raw data available to calculate confidence intervals). A smaller proportion of studies had issues with study participation (such as concerns that not all of those eligible were included in the study), prognostic factor measurement (such as unclear definition of prognostic factor provided or time-point of measurement possibly differing between patients) and outcome measurement (such as the method of measuring outcome being unclear, for example which scale or questionnaire was used, or method or timing of outcome assessment possibly different between patients).

Imprecision

Imprecision was assessed separately for sensitivity, specificity and area under the curve. Default thresholds of ≥90% and ≥60% for sensitivity and specificity respectively were initially used as the upper thresholds for assessing imprecision and values of 0.7 and 0.4 used as lower thresholds for assessing imprecision. However, as the committee agreed during the discussion of the evidence that a much higher specificity (~95%) would be required for the use of these biomarkers to be practical, imprecision thresholds were revised in line with this to 0.95 for the upper threshold and 0.75 as the lower threshold. The reason the committee agreed a very high threshold would be required is because the mild head injury population is large and false positives would have a negative impact on resources if biomarkers were to be used to direct people towards interventions or monitoring, given that only a small proportion will go on to develop post-concussion syndrome.

For AUC, the following threshold groupings were used to assess overall accuracy:

- ≤0.50: worse than chance
- 0.51-0.60: very poor
- 0.61-0.70: poor

- 0.71-0.80: moderate
- 0.81-0.90: good
- 0.91-1.00: excellent or perfect test

For assessing imprecision of AUC data, thresholds of 0.70 and 0.50 were used, as these represent the difference between poor and moderate tests and worse than chance and better than chance tests respectively.

Imprecision was an issue for most of the data reported, including for sensitivity/specificity data and AUC data. This is likely because of the small studies of most included studies. This meant that there was uncertainty in the results obtained making it difficult to make firm conclusions about the accuracy of biomarkers and MRI for predicting post-concussion syndrome.

1.1.12.3 Benefits and harms

Overall, the committee agreed that the evidence included in the review was too limited to be able to make recommendations for the use of biomarkers and/or MRI in the prediction of post-concussion syndrome in those with mild traumatic brain injury. The committee also highlighted that even if there was strong evidence identified suggesting that certain biomarkers or MRI features could predict future development of post-concussion syndrome in this population with good accuracy, this is of limited use clinically. Currently, knowing that someone is at a higher risk of developing it would not change management as there is not an intervention for preventing its development and using the biomarkers or MRI features may not therefore lead to a benefit for patients. Further limitations noted were the lack of any studies comparing clinical outcomes in the form of prognostic test and treat studies and the lack of any health economic evidence, which would be important considering these biomarkers and MRI are not used currently in practice for the purpose of predicting post-concussion syndrome.

In terms of the accuracy of biomarkers and MRI in the prediction of post-concussion outcomes, it was agreed that the evidence did show some signs that certain biomarkers and MRI features or sequences could be useful in predicting outcomes; however, thresholds used for biomarkers or features measured on MRI, populations (for example whether or not CT abnormalities were present) and outcomes differed across studies. Individual results were from small studies with imprecision, making it difficult to be sure about the accuracy of the prognostic factors. In addition, in terms of GOS/GOSE outcomes, often biomarkers or MRI demonstrated good results for predicting severely reduced scores (scores 1-4) but showed poorer results for predicting anyone with reduced disability (scores <8), suggesting they are not as good at picking up anyone with even mildly impaired GOSE scores, and the committee noted that GOSE scores 1-4 are not consistent with post-concussion syndrome given their severity. Although good sensitivity values (>90%) could be achieved for some prognostic factors depending on the threshold or feature included, the committee noted that specificity values were not high enough across the evidence and considered this extremely important given the large population of mild traumatic brain injury they would be used in and the small proportion that would go on to develop post-concussion syndrome.

Despite not making any recommendations about using these biomarkers or MRI in practice for predicting post-concussion syndrome, the committee agreed that it was important that people that might be experiencing post-concussion symptoms were not lost to follow-up but noted that they are included in the recommendation on follow up for people with persisting problems. A research recommendation for a prognostic study including biomarkers/MRI was made. The committee decided that more evidence from prognostic studies was required before research on effectiveness from randomised trials is planned.

1.1.12.4 Cost effectiveness and resource use

No economic evaluations were identified for this review, so unit costs were presented to aid the committee's consideration of cost effectiveness.

Currently magnetic resonance imaging and biomarker testing are not currently used for predicting post-concussion syndrome. Given the number of people having concussion each year is over a million, the cost impact of routine testing would be considerable.

Due to the lack of test and treat evidence, it is not clear how testing would change management. Testing is unlikely to be cost-effective until a clear management pathway is developed based on test results. However, the committee decided that more prognostic research was needed before treatment pathways could be trialled.

1.1.12.5 Other factors the committee took into account

The committee highlighted that it is important for health professionals to know which services and health professionals to refer people to if they experience post-concussion syndrome. They emphasised that early intervention is more likely to lead to better outcomes.

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Appendices

Appendix A – Review protocols

Review protocol for prognostic accuracy of brain injury biomarkers and/or MRI for predicting post-concussion syndrome

ID	Field	Content
0.	PROSPERO registration number	CRD42021296136 once allocated]
1.	Review title	2.2a What is the prognostic accuracy of brain injury biomarkers and/or MRI for predicting post-concussion syndrome? Post- concussion syndrome definition: Post-concussion syndrome occurs when concussion symptoms last beyond the expected recovery period after the initial injury. The usual recovery period is weeks to months. These symptoms could be physical, cognitive, emotional or sleep related. This may include multiple physical symptoms such as headaches, dizziness, nausea, balance and co-ordination problems, changes in appetite, sleep, vision, and hearing; and cognitive and behavioural symptoms such as fatigue, anxiety, depression, irritability; problems with memory, concentration, and decision-making. In some people these symptoms may persist from 2 weeks to longer than 3 months post injury. GCS in such patients will be 14-15. The symptoms will be essentially the same for both adults and children. In adults, diagnosis is based on:

		A) Glasgow Coma outcome scale (GOS) and GOSE (Glasgow Outcome Score Extended. B) Rivermead Post-Concussion Score C) Other symptoms commonly used to define include: - Duration of post-traumatic amnesia - Abnormalities in cognition – most common include: Rey Auditory Verbal Learning Test (RAVLT), Trails Making Test Part A/B, WAIS IV Processing Speed Index, NIH Toolbox Cognitive Battery, CANTAB, - Patient reported outcomes - Quality of Life After Brain Injury – Overall Scale (QOLIBRI-OS) and SF-12/SF-36 - Markers of mental health problems - PTSD Checklist (PCL-5), Participant Health Questionnarie-9 (PHQ-9), Generalised Anxiety Disorder-7 (GAD-7), Brief Symptom Inventory (BSI), Hospital Anxiety and Depression Scale (HADS) - Scales of sleep disturbance and fatigue In children diagnosis is based on symptoms, The Rivermead Post-concussion Symptoms Questionnaire (RPQ) and acute stress response.
2.	Review question	What is the prognostic accuracy of brain injury biomarkers and/or MRI for predicting post-concussion syndrome?
3.	Objective	To determine the prognostic accuracy of brain injury biomarkers and/or MRI for predicting post-concussion syndrome

4.	Searches	The following databases (from inception) will be searched: • Embase • MEDLINE • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Epistemonikos Searches will be restricted by: • English language studies • Human studies • Comments and letters excluded Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Post-concussion syndrome in patients who have experienced a head injury.

6.	Population	Inclusion: Infants, children and adult with suspected head injury • Strata : • Adults (aged ≥16 years) • Children and babies (aged 0 to <16 years) If data is available from studies report separately for children: 0-4 years, 5-15 years, > 15 years This strata is better for PCS as it is more difficult to assess concussion in preverbal children Mixed population studies will be included but downgraded for indirectness. Cut-off of 60% will be used for all age groups Exclusion: Adults, and children (including infants under 1 year) with superficial injuries to the eye or face without suspected or confirmed head or brain injury.
7.	Prognostic factors	• Biomarkers <u>Blood biomarkers</u> - S100 calcium binding protein B (S100B) -Ubiquitin C-terminal Hydrolase-L1 (UCHL1) -Neuron Specific Enolase (NSE) -Brain-derived neurotrophic factor (BDNF) -Neurofilament light (NFL) - Neurofilament Heavy (NF-H) - αII-Spectrin breakdown products (SBDP) - Myelin basic protein (MBP) - glial fibrillary acidic protein (GFAP)

		<u>Salivary biomarkers</u> -salivary microRNAs (miRNAs) -Extracellular vesicles (EVs) -S100B <u>Urine biomarkers</u> -Extracellular vesicles (EVs) • MRI • Combination of MRI and blood/salivary biomarkers Each test must be followed by an appropriate treatment for complication after brain injury Subsequent treatment to include but not limited to: • Neuropsychologist interventions e.g. CBT, coping strategies • multimodal therapy delivered by uni or multidisciplinary team. • physical therapy • sleep hygiene interventions including pharmacological treatment • fatigue management • vestibular rehabilitation • management of headache (including medications) • psychoeducation

		Timings: Biomarkers are used within 48 hrs of head injury. Biomarkers of TBI are often measured in body fluids. Measurements are obtained from CSF is not in common use hence it is not included. There will be access to CSF only in people with significant (severe) head injury. Most of the patients with post-concussion syndrome have mild head injury (GCS 13-15) and lumbar puncture to analyse CSF biomarkers is not indicated for such patients. MR imaging is booked during acute presentation (it could be done 3 weeks to a month after injury) MRI to be left open for signs (and sequences) used to predict PCS.
8.	Reference standard	Post-concussion syndrome confirmed by constellation of symptoms • Range of symptoms including cognitive, physical, emotional and sleep related. Reference standard to include symptoms as reported in the studies.
9.	Types of study to be included	Prospective cohort studies Retrospective cohort studies will be included only if no sufficient prospective cohort studies are identified Systematic reviews and meta-analyses of the above

10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	If brain injury biomarkers and/or MRI can predict post-concussion syndrome
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: Prognostic accuracy outcomes • Prognostic accuracy of MRI for predicting post-concussion syndrome • Prognostic accuracy of biomarkers for predicting post-concussion syndrome • Prognostic accuracy of biomarkers and MRI for predicting post-concussion syndrome Prognostic test accuracy to be reported by test sensitivity/specificity For measurement of imprecision, clinical decision thresholds for sensitivity and specificity are set at 90% and 60%. Both sensitivity and specificity are considered to be of equal value. Sensitivity is important as at the moment treatment of post-concussion syndrome is symptom based so patients are not likely to be given treatments unless in need. If the specificity is too low there is the potential to harm many people who will delay their return to work/school/sport and become hypervigilant for symptoms etc.
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated.

		10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. This review will make use of the priority screening functionality within the EPPI-reviewer software. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
14.	Risk of bias (quality) assessment	For prognostic reviews • QUIPs
15.	Strategy for data synthesis	For prognostic accuracy evidence: • Aggregate data on prognostic accuracy of investigations will be collected and synthesized in a quantitative data analysis depending on the appropriateness of data.

		• If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software. • Endnote will be used for bibliography, citations, sifting and reference management. WinBUGS will be used for meta-analysis of prognostic accuracy studies if included studies are sufficiently homogeneous. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software. • Where available, outcome data from new studies will be meta-analysed with corresponding data included in CG 176.	
16.	Analysis of sub-groups	NA	
17.	Type and method of review	☐	Intervention
		☐	Diagnostic
		☒	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
18.	Language	English	
19.	Country	England	

<table>
<tr><td>20.</td><td>Anticipated or actual start date</td><td colspan="3">[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins.

A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]</td></tr>
<tr><td>21.</td><td>Anticipated completion date</td><td colspan="3">[Give the date by which the guideline is expected to be published. This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.]</td></tr>
<tr><td rowspan="7">22.</td><td rowspan="7">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☐</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☐</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☐</td></tr>
<tr><td>Data extraction</td><td>☐</td><td>☐</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☐</td><td>☐</td></tr>
<tr><td>Data analysis</td><td>☐</td><td>☐</td></tr>
<tr><td>23.</td><td>Named contact</td><td colspan="3">5a. Named contact
National Guideline Centre

5b Named contact e-mail
[Guideline email]@nice.org.uk
[Developer to check with Guideline Coordinator for email address]</td></tr>
</table>

		5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and [National Guideline Alliance / National Guideline Centre / NICE Guideline Updates Team / NICE Public Health Guideline Development Team] [Note it is essential to use the template text here and one of the centre options to enable PROSPERO to recognise this as a NICE protocol]
24.	Review team members	[Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.] From the National Guideline Centre: [Guideline lead] [Senior systematic reviewer] Systematic reviewer [Health economist] [Information specialist] [Others]
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a

		meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
28.	Other registration details	[Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.]
29.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. [Add in any additional agree dissemination plans.]
31.	Keywords	[Give words or phrases that best describe the review.]
32.	Details of existing review of same topic by same authors	[Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible. NOTE: most NICE reviews will not constitute an update in PROSPERO language. To be an update it needs to be the same review question/search/methodology. If anything has changed it is a new review]

33.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
35.	Details of final publication	www.nice.org.uk	

1

Review protocol for clinical and cost-effectiveness of biomarkers and/or MRI followed by appropriate treatment for post-concussion syndrome

ID	Field	Content
0.	PROSPERO registration number	CRD42021296140
1.	Review title	2.2b What is the clinical and cost effectiveness of biomarkers and/or MRI when each is followed by the appropriate treatment for post-concussion syndrome to improve patient outcomes? Post- concussion syndrome definition: Post-concussion syndrome occurs when concussion symptoms last beyond the expected recovery period after the initial injury. The usual recovery period is weeks to months. These symptoms could be physical, cognitive, emotional or sleep related. This may include multiple physical symptoms such as headaches, dizziness, nausea, balance and co-ordination problems, changes in appetite, sleep, vision, and hearing; and cognitive and behavioural symptoms such as fatigue, anxiety, depression, irritability; problems with memory, concentration, and decision-making. GCS in such patients will be 14-15. The symptoms will be essentially the same for both adults and children. In adults, diagnosis is based on symptoms and Glasgow Coma outcome scale (GCOS). In children diagnosis is based on symptoms, The Rivermead Post-concussion Symptoms Questionnaire (RPQ) and acute stress response.

2.	Review question	What is the clinical and cost effectiveness of biomarkers and/or MRI when each is followed by the appropriate treatment for post-concussion syndrome and other complications after brain injury to improve patient outcomes?
3.	Objective	To understand the clinical and cost efficacy of brain injury biomarkers and/or MRI for post-concussion syndrome.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies • Comments and letters excluded Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).

5.	Condition or domain being studied	Post-concussion syndrome in patients who have experienced a head injury.
6.	Population	Inclusion: Infants, children and adult with suspected head injury Strata: • Adults (aged ≥16 years) • Children (aged ≥1 to <16 years) • Infants (aged <1 year) Mixed population studies will be included but downgraded for indirectness. Cut-off of 60% will be used for all age groups Exclusion: Adults, and children (including infants under 1 year) with superficial injuries to the eye or face without suspected or confirmed head or brain injury.
7.	Intervention	• Biomarkers <u>Blood biomarkers</u> - S100 calcium binding protein B (S100B) -Ubiquitin C-terminal Hydrolase-L1 (UCHL1) -Neuron Specific Enolase (NSE) -Brain-derived neurotrophic factor (BDNF) -Neurofilament light (NFL) - Neurofilament Heavy (NF-H) - αII-Spectrin breakdown products (SBDP) - Myelin basic protein (MBP) - glial fibrillary acidic protein (GFAP) <u>Salivary biomarkers</u>

		-salivary microRNAs (miRNAs) -Extracellular vesicles (EVs) -S100B -Urine biomarkers -Extracellular vesicles (EVs) • MRI • Combination of MRI and blood/salivary biomarkers Each test must be followed by an appropriate treatment for post-concussion syndrome after brain injury. Subsequent treatment to include but not limited to: • Neuropsychologist interventions e.g. CBT, coping strategies • multimodal therapy delivered by uni or multidisciplinary team. • physical therapy • sleep hygiene interventions including pharmacological treatment • fatigue management • vestibular rehabilitation • management of headache (including medications) • psychoeducation Timings: Biomarkers are used within 48 hrs of head injury. Biomarkers of TBI are often measured in body fluids. Measurements are obtained from CSF, saliva, blood (serum or plasma) and urine. CSF not in common use hence it is not included. There will be access to CSF only in people with significant (severe) head injury. Most of the patients with post-concussion

		syndrome have mild head injury (GCS 13-15) and lumbar puncture to analyse CSF biomarkers is not indicated for such patients. MR imaging is booked during acute presentation (it could be done 3 weeks to a month after injury)
9.	Comparator	Comparators: • To usual care (no testing with MRI/biomarkers) • To each other
9.	Types of study to be included	• Randomised controlled trials (RCTs), systematic reviews of RCTs. • If no RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders, starting with prospective cohort studies. Key confounders (only include studies adjusting for all 3 confounders below): • Age • Gender • GCS or pupillary response at presentation Other confounding factors (to include studies even if they do not adjust for these factors) • Anxiety, depression • Sleep disorder • Gender • Extra cranial injury • Migraine

		• Previous concussion and or head injury • Learning disability (paediatric population) • atypical neuro development (paediatric population) • ADHD (paediatric population) • Autism Spectrum Disorder (ASD) (paediatric population) • Mechanism of injury
10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria. Include relevant details if these form part of the review's eligibility criteria but are not reported elsewhere in the PROSPERO record. Also include details of any previous guidelines that will be updated by this question]
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Quality of life - 3 months or more • Objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or extended GOS - at 3 months or more • Time to return to education/work/usual activities • Duration of post-concussion syndrome (to analyse 2 weeks to <3 months and 3 months and longer than 3 months separately)

13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. This review will make use of the priority screening functionality within the EPPI-reviewer software. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I

15.	Strategy for data synthesis	For clinical effectiveness evidence: • Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. • Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. • The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.	
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: Older adults • older/frail adults who have suffered a fall	
17.	Type and method of review	☒	Intervention
		☐	Diagnostic

		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
18.	Language	English	
19.	Country	England	
20.	Anticipated or actual start date	[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins. A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]	
21.	Anticipated completion date	[Give the date by which the guideline is expected to be published. This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.]	
22.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☐ / ☐
		Piloting of the study selection process	☐ / ☐
		Formal screening of search results against eligibility criteria	☐ / ☐
		Data extraction	☐ / ☐
		Risk of bias (quality) assessment	☐ / ☐

		Data analysis	☐	☐
23.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail [Guideline email]@nice.org.uk [Developer to check with Guideline Coordinator for email address] 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and [National Guideline Alliance / National Guideline Centre / NICE Guideline Updates Team / NICE Public Health Guideline Development Team] [Note it is essential to use the template text here and one of the centre options to enable PROSPERO to recognise this as a NICE protocol]		
24.	Review team members	[Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.] From the National Guideline Centre: [Guideline lead] [Senior systematic reviewer] Systematic reviewer [Health economist] [Information specialist] [Others]		

25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
28.	Other registration details	[Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.]
29.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.

		[Add in any additional agree dissemination plans.]	
31.	Keywords	[Give words or phrases that best describe the review.]	
32.	Details of existing review of same topic by same authors	[Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible. NOTE: most NICE reviews will not constitute an update in PROSPERO language. To be an update it needs to be the same review question/search/methodology. If anything has changed it is a new review]	
33.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
35.	Details of final publication	www.nice.org.uk	

Table 34: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.

Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. The search covered all years
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published in 2006 or later that were included in the previous guidelines will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[24] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

	• OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2006 or later (including any such studies included in the previous guidelines) but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'. • Studies published before 2006 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

This literature search strategy was used for the following questions:

- What is the prognostic accuracy of brain injury biomarkers and/or MRI for predicting post-concussion syndrome?
- What is the clinical and cost effectiveness of biomarkers and/or MRI when each is followed by the appropriate treatment for post-concussion syndrome to improve patient outcomes?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[24]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve.

Table 35: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 22 June 2022	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 22 June 2022	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Reviews to 2022 Issue 6 of 12 CENTRAL to 2022 Issue 6 of 12	
Epistemonikos (The Epistemonikos Foundation)	Inception to 22 June 2022	Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries, closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/
2.	((skull or cranial) adj3 fracture*).ti,ab.
3.	((head or brain or craniocerebral or cranial or cerebral or skull) adj4 (injur* or trauma*)).ti,ab.
4.	(trauma* and ((subdural or intracranial) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
5.	or/1-4
6.	(concuss* or postconcuss* or PCSS).ti,ab.
7.	5 or 6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice or rodent*).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	exp Biomarkers/
29.	exp S100 Proteins/
30.	Glial Fibrillary Acidic Protein/
31.	Phosphopyruvate Hydratase/
32.	Ubiquitin Thiolesterase/
33.	exp MicroRNAs/
34.	Brain-Derived Neurotrophic Factor/
35.	Neurofilament Proteins/
36.	Spectrin/
37.	Myelin Basic Protein/
38.	exp Extracellular Vesicles/
39.	tau Proteins/
40.	(Ubiquitin Thiolesterase* or "Ubiquitin C-terminal hydrolase*" or "Ubiquitin C-Terminal Esterase*" or "Ubiquitin Carboxy-Terminal Hydrolase*" or "Ubiquitin Carboxy-Terminal Esterase*" or uch-l1 or UCHL1).ti,ab.

41.	(S100* or GFAP or "glial fibrillary acid* protein*" or "brain-derived neurotrophic factor*" or "brain-derived nerve growth factor*" or BDNF or spectrin* or tau or proteomic* or microRNA* or miRNA* or micro-rna*).ti,ab.
42.	((muscle or nervous or neuron* or alpha or beta or gamma) adj3 enolase*).ti,ab.
43.	(Phosphopyruvate Hydratase* or 2-phosphoglycerate* or 2-phospho-D-glycerate* or NSE).ti,ab.
44.	((neurofilament* adj3 (protein* or chain* or polypeptide*)) or NF-L or NF-H).ti,ab.
45.	((myelin basic or nerve tissue* or golli* or hog* or mbp*) adj2 protein*).ti,ab.
46.	(((extracellular or secretory) adj vesicle*) or exovesicle* or apoptotic bod* or exosome* or endosome* or ectosome* or microvesicle* or ((membrane or cell-derived) adj microparticle*)).ti,ab.
47.	biomarker*.ti,ab,kf.
48.	marker*.ti,ab.
49.	or/28-48
50.	exp magnetic resonance imaging/
51.	((MR or magnetic resonance or NMR) adj2 (imag* or tomograph* or angiograph* or functional or advanced or structural)).ti,ab.
52.	((echo-planar or echoplanar or EPI) adj2 (imag* or sequenc*)).ti,ab.
53.	(diffusion adj3 imag*).ti,ab.
54.	neuroimag*.ti,ab.
55.	MRI.ti,ab.
56.	or/50-55
57.	49 or 56
58.	27 and 57
59.	randomized controlled trial.pt.
60.	controlled clinical trial.pt.
61.	randomi#ed.ti,ab.
62.	placebo.ab.
63.	randomly.ti,ab.
64.	Clinical Trials as topic.sh.
65.	trial.ti.
66.	or/59-65
67.	Meta-Analysis/
68.	exp Meta-Analysis as Topic/
69.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
70.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
71.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
72.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
73.	(search* adj4 literature).ab.
74.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
75.	cochrane.jw.
76.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
77.	or/67-76
78.	Epidemiologic studies/
79.	Observational study/

80.	exp Cohort studies/
81.	(cohort adj (study or studies or analys* or data)).ti,ab.
82.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
83.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
84.	Controlled Before-After Studies/
85.	Historically Controlled Study/
86.	Interrupted Time Series Analysis/
87.	(before adj2 after adj2 (study or studies or data)).ti,ab.
88.	exp case control study/
89.	case control*.ti,ab.
90.	Cross-sectional studies/
91.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
92.	or/78-91
93.	predict.ti.
94.	(validat* or rule*).ti,ab.
95.	(predict* and (outcome* or risk* or model*)).ti,ab.
96.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
97.	decision*.ti,ab. and Logistic models/
98.	(decision* and (model* or clinical*)).ti,ab.
99.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
100.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
101.	ROC curve/
102.	Or/93-101
103.	58 and (66 or 77 or 92 or 102)

20 **Embase (Ovid) search terms**

1.	head injury/
2.	exp brain injury/
3.	skull injury/ or exp skull fracture/
4.	((head or brain or craniocerebral or cranial or cerebral or skull) adj4 (injur* or trauma*)).ti,ab.
5.	((skull or cranial) adj3 fracture*).ti,ab.
6.	(trauma* and ((subdural or intracranial) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
7.	or/1-6
8.	(concuss* or postconcuss* or PCSS).ti,ab.
9.	or/7-8
10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	(conference abstract or conference paper).pt.
14.	case report/ or case study/
15.	(letter or comment*).ti.

16.	or/10-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animal/ not human/
20.	nonhuman/
21.	exp Animal Experiment/
22.	exp Experimental Animal/
23.	animal model/
24.	exp Rodent/
25.	(rat or rats or mouse or mice or rodent*).ti.
26.	or/18-25
27.	9 not 26
28.	limit 27 to English language
29.	*biological marker/
30.	*protein S 100/
31.	*glial fibrillary acidic protein/
32.	*enolase/
33.	*ubiquitin thiolesterase/
34.	exp *microRNA/
35.	*brain derived neurotrophic factor/
36.	*neurofilament protein/
37.	*spectrin/
38.	*myelin basic protein/
39.	*exosome/
40.	*tau protein/
41.	(Ubiquitin Thiolesterase* or "Ubiquitin C-terminal hydrolase*" or "Ubiquitin C-Terminal Esterase*" or "Ubiquitin Carboxy-Terminal Hydrolase*" or "Ubiquitin Carboxy-Terminal Esterase*" or uch-l1 or UCHL1).ti,ab.
42.	(S100* or GFAP or "glial fibrillary acid* protein*" or "brain-derived neurotrophic factor*" or "brain-derived nerve growth factor*" or BDNF or spectrin* or tau or proteomic* or microRNA* or miRNA* or micro-rna*).ti,ab.
43.	((muscle or nervous or neuron* or alpha or beta or gamma) adj3 enolase*).ti,ab.
44.	(Phosphopyruvate Hydratase* or 2-phosphoglycerate* or 2-phospho-D-glycerate* or NSE).ti,ab.
45.	((neurofilament* adj3 (protein* or chain* or polypeptide*)) or NF-L or NF-H).ti,ab.
46.	((myelin basic or nerve tissue* or golli* or hog* or mbp*) adj2 protein*).ti,ab.
47.	(((extracellular or secretory) adj vesicle*) or exovesicle* or apoptotic bod* or exosome* or endosome* or ectosome* or microvesicle* or ((membrane or cell-derived) adj microparticle*)).ti,ab.
48.	biomarker*.ti,ab,kw.
49.	marker*.ti,ab.
50.	or/29-49
51.	exp *nuclear magnetic resonance imaging/
52.	((MR or magnetic resonance or NMR) adj2 (imag* or tomograph* or angiograph* or functional or advanced or structural)).ti,ab.
53.	((echo-planar or echoplanar or EPI) adj2 (imag* or sequenc*)).ti,ab.
54.	(diffusion adj3 imag*).ti,ab.

55.	neuroimag*.ti,ab.
56.	MRI.ti,ab.
57.	or/51-56
58.	50 or 57
59.	28 and 58
60.	random*.ti,ab.
61.	factorial*.ti,ab.
62.	(crossover* or cross over*).ti,ab.
63.	((doubl* or singl*) adj blind*).ti,ab.
64.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
65.	crossover procedure/
66.	single blind procedure/
67.	randomized controlled trial/
68.	double blind procedure/
69.	or/60-68
70.	systematic review/
71.	Meta-Analysis/
72.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
73.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
74.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
75.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
76.	(search* adj4 literature).ab.
77.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
78.	cochrane.jw.
79.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
80.	or/70-79
81.	Clinical study/
82.	Observational study/
83.	Family study/
84.	Longitudinal study/
85.	Retrospective study/
86.	Prospective study/
87.	Cohort analysis/
88.	Follow-up/
89.	cohort*.ti,ab.
90.	88 and 89
91.	(cohort adj (study or studies or analys* or data)).ti,ab.
92.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
93.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
94.	(before adj2 after adj2 (study or studies or data)).ti,ab.
95.	exp case control study/
96.	case control*.ti,ab.

97.	cross-sectional study/
98.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
99.	or/81-87,90-98
100.	predict.ti.
101.	(validat* or rule*).ti,ab.
102.	(predict* and (outcome* or risk* or model*)).ti,ab.
103.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
104.	decision*.ti,ab. and Statistical model/
105.	(decision* and (model* or clinical*)).ti,ab.
106.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
107.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
108.	Receiver operating characteristic/
109.	Or/100-108
110.	59 and (69 or 80 or 99 or 109)

21 Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Craniocerebral Trauma] this term only
#2.	MeSH descriptor: [Brain Injuries] explode all trees
#3.	MeSH descriptor: [Coma, Post-Head Injury] this term only
#4.	MeSH descriptor: [Head Injuries, Closed] explode all trees
#5.	MeSH descriptor: [Head Injuries, Penetrating] this term only
#6.	MeSH descriptor: [Intracranial Hemorrhage, Traumatic] explode all trees
#7.	MeSH descriptor: [Skull Fractures] explode all trees
#8.	((skull or cranial) near/3 fracture*):ti,ab
#9.	((head or brain or craniocerebral or cranial or skull) near/3 (injur* or trauma*)):ti,ab
#10.	(trauma* and ((subdural or intracranial) near/2 (h?ematoma* or h?emorrhage* or bleed*))):ti,ab
#11.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12.	(concuss* or postconcuss* or PCSS):ti,ab
#13.	#11 or #12
#14.	MeSH descriptor: [Biomarkers] explode all trees
#15.	MeSH descriptor: [S100 Proteins] explode all trees
#16.	MeSH descriptor: [Glial Fibrillary Acidic Protein] this term only
#17.	MeSH descriptor: [Phosphopyruvate Hydratase] this term only
#18.	MeSH descriptor: [Ubiquitin Thiolesterase] this term only
#19.	MeSH descriptor: [MicroRNAs] explode all trees
#20.	MeSH descriptor: [Brain-Derived Neurotrophic Factor] this term only
#21.	MeSH descriptor: [Neurofilament Proteins] this term only
#22.	MeSH descriptor: [Spectrin] this term only
#23.	MeSH descriptor: [Myelin Basic Protein] this term only
#24.	MeSH descriptor: [Extracellular Vesicles] explode all trees
#25.	MeSH descriptor: [tau Proteins] this term only

#26.	(Ubiquitin Thiolesterase* or "Ubiquitin C-terminal hydrolase*" or "Ubiquitin C-Terminal Esterase*" or "Ubiquitin Carboxy-Terminal Hydrolase*" or "Ubiquitin Carboxy-Terminal Esterase*" or uch-l1 or UCHL1):ti,ab
#27.	(S100* or GFAP or "glial fibrillary acid* protein*" or "brain-derived neurotrophic factor*" or "brain-derived nerve growth factor*" or BDNF or spectrin* or tau or proteomic* or microRNA* or miRNA* or micro-rna*):ti,ab
#28.	((muscle or nervous or neuron* or alpha or beta or gamma) near/3 enolase*):ti,ab
#29.	(Phosphopyruvate Hydratase* or 2phosphoglycerate* or 2phospho-D-glycerate* or NSE):ti,ab
#30.	((neurofilament* near/3 (protein* or chain* or polypeptide*)) or NF-L or NF-H):ti,ab
#31.	((myelin basic or nerve tissue* or golli* or hog* or mbp*) near/2 protein*):ti,ab
#32.	(((extracellular or secretory) near vesicle*) or exovesicle* or apoptotic bod* or exosome* or endosome* or ectosome* or microvesicle* or ((membrane or cell-derived) near microparticle*)):ti,ab
#33.	biomarker*:ti,ab,kw
#34.	marker*:ti,ab
#35.	#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34
#36.	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#37.	((MR or magnetic resonance or NMR) near/2 (imag* or tomograph* or angiograph* or functional or advanced or structural)):ti,ab
#38.	((echo-planar or echoplanar or EPI) near/2 (imag* or sequenc*)):ti,ab
#39.	(diffusion near/3 imag*):ti,ab
#40.	neuroimag*:ti,ab
#41.	MRI:ti,ab
#42.	#36 or #37 or #38 or #39 or #40 or #41
#43.	#35 or #42
#44.	#13 and #43

22 Epistemonikos search terms

1.	(advanced_title_en:(((trauma OR traumatic) AND (injury OR injuries))) OR advanced_abstract_en:(((trauma OR traumatic) AND (injury OR injuries)))) OR (advanced_title_en:(((skull OR cranial) AND fracture*)) OR advanced_abstract_en:(((skull OR cranial) AND fracture*))) OR (advanced_title_en:(((head OR brain OR craniocerebral OR cranial OR cerebral OR skull) AND (injur* OR trauma*))) OR advanced_abstract_en:(((head OR brain OR craniocerebral OR cranial OR cerebral OR skull) AND (injur* OR trauma*)))) OR (advanced_title_en:((concuss* OR PCSS OR post-concuss*)) OR advanced_abstract_en:((concuss* OR PCSS OR post-concuss*))) AND (advanced_title_en:((biomarker* OR marker*)) OR advanced_abstract_en:((biomarker* OR marker*))) OR (advanced_title_en:((S100* OR GFAP OR "glial fibrillary acid* protein*" OR "brain-derived neurotrophic factor*" OR "brain-derived nerve growth factor*" OR BDNF OR spectrin* OR tau OR proteomic* OR microRNA* OR miRNA* OR micro-rna*)) OR advanced_abstract_en:((S100* OR GFAP OR "glial fibrillary acid* protein*" OR "brain-derived neurotrophic factor*" OR "brain-derived nerve growth factor*" OR BDNF OR spectrin* OR tau OR proteomic* OR microRNA* OR miRNA* OR micro-rna*))) OR (advanced_title_en:((Ubiquitin Thiolesterase* OR "Ubiquitin C-terminal hydrolase*" OR "Ubiquitin C-Terminal Esterase*" OR "Ubiquitin Carboxy-Terminal Hydrolase*" OR "Ubiquitin Carboxy-Terminal Esterase*" OR uch-l1 OR UCHL1)) OR advanced_abstract_en:((Ubiquitin Thiolesterase* OR "Ubiquitin C-terminal hydrolase*" OR "Ubiquitin C-Terminal Esterase*" OR "Ubiquitin Carboxy-Terminal Hydrolase*" OR "Ubiquitin Carboxy-Terminal Esterase*" OR uch-l1 OR UCHL1))) OR (advanced_title_en:((enolase* OR Phosphopyruvate Hydratase* OR 2-phosphoglycerate* OR 2-phospho-D-glycerate* OR NSE)) OR advanced_abstract_en:((enolase* OR Phosphopyruvate Hydratase* OR 2-

	phosphoglycerate* OR 2-phospho-D-glycerate* OR NSE))) OR (advanced_title_en:((neurofilament protein* OR myelin basic protein* OR extracellular vesicle* OR exovesicle* OR apoptotic bod* OR exosome* OR endosome* OR ectosome* OR microvesicle* OR cell-derived microparticle*)) OR advanced_abstract_en:((neurofilament protein* OR myelin basic protein* OR extracellular vesicle* OR exovesicle* OR apoptotic bod* OR exosome* OR endosome* OR ectosome* OR microvesicle* OR cell-derived microparticle*))) OR (advanced_title_en:((tomograph* OR magnetic resonance OR neuroimag* OR MRI Or echoplanar* OR diffusion tensor imag* OR diffusion weight* imag*)) OR advanced_abstract_en:((tomograph* OR magnetic resonance OR neuroimag* OR MRI Or echoplanar* OR diffusion tensor imag* OR diffusion weight* imag*)))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Head Injury population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 36: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 22 June 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 22 June 2022	
Embase (OVID)	Health Economics 1 January 2014 – 22 June 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 22 June 2022	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception – 22 June 2022	English language

32 **Medline (Ovid) search terms**

1.	craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries, closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/
2.	((skull or cranial) adj3 fracture*).ti,ab.
3.	((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)).ti,ab.
4.	(trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
5.	or/1-4
6.	letter/
7.	editorial/
8.	news/
9.	exp historical article/
10.	Anecdotes as Topic/
11.	comment/
12.	case report/
13.	(letter or comment*).ti.
14.	or/6-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animals/ not humans/
18.	exp Animals, Laboratory/
19.	exp Animal Experimentation/
20.	exp Models, Animal/
21.	exp Rodentia/
22.	(rat or rats or mouse or mice or rodent*).ti.
23.	or/16-22
24.	5 not 23
25.	limit 24 to English language
26.	economics/
27.	value of life/
28.	exp "costs and cost analysis"/
29.	exp Economics, Hospital/
30.	exp Economics, medical/
31.	Economics, nursing/
32.	economics, pharmaceutical/
33.	exp "Fees and Charges"/
34.	exp budgets/
35.	budget*.ti,ab.
36.	cost*.ti.
37.	(economic* or pharmaco?economic*).ti.

38.	(price* or pricing*).ti,ab.
39.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
40.	(financ* or fee or fees).ti,ab.
41.	(value adj2 (money or monetary)).ti,ab.
42.	or/26-41
43.	quality-adjusted life years/
44.	sickness impact profile/
45.	(quality adj2 (wellbeing or well being)).ti,ab.
46.	sickness impact profile.ti,ab.
47.	disability adjusted life.ti,ab.
48.	(qal* or qtime* or qwb* or daly*).ti,ab.
49.	(euroqol* or eq5d* or eq 5*).ti,ab.
50.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/43-61
63.	25 and (42 or 62)

33 **Embase (Ovid) search terms**

1.	head injury/
2.	exp brain injury/
3.	skull injury/ or exp skull fracture/
4.	((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)).ti,ab.
5.	((skull or cranial) adj3 fracture*).ti,ab.
6.	(trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	(conference abstract or conference paper).pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.

14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to English language
27.	health economics/
28.	exp economic evaluation/
29.	exp health care cost/
30.	exp fee/
31.	budget/
32.	funding/
33.	budget*.ti,ab.
34.	cost*.ti.
35.	(economic* or pharmaco?economic*).ti.
36.	(price* or pricing*).ti,ab.
37.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38.	(financ* or fee or fees).ti,ab.
39.	(value adj2 (money or monetary)).ti,ab.
40.	or/27-39
41.	quality-adjusted life years/
42.	"quality of life index"/
43.	short form 12/ or short form 20/ or short form 36/ or short form 8/
44.	sickness impact profile/
45.	(quality adj2 (wellbeing or well being)).ti,ab.
46.	sickness impact profile.ti,ab.
47.	disability adjusted life.ti,ab.
48.	(qal* or qtime* or qwb* or daly*).ti,ab.
49.	(euroqol* or eq5d* or eq 5*).ti,ab.
50.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.

56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/41-61
63.	26 and (40 or 62)

34 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Brain Injuries EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Craniocerebral Trauma
#3.	MeSH DESCRIPTOR Coma, Post-Head Injury
#4.	MeSH DESCRIPTOR Head Injuries, Closed EXPLODE ALL TREES
#5.	MeSH DESCRIPTOR Head Injuries, Penetrating
#6.	MeSH DESCRIPTOR Intracranial Hemorrhage, Traumatic EXPLODE ALL TREES
#7.	MeSH DESCRIPTOR Skull Fractures EXPLODE ALL TREES
#8.	(((skull or cranial) adj3 fracture*))
#9.	(((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)))
#10.	((trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))))
#11.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

35 **INAHTA search terms**

1.	((((trauma* and ((subdural or intracranial or brain) and (haematoma* or hematoma* or haemorrhage* or hemorrhage* or bleed*))))[Title]) AND (((trauma* and ((subdural or intracranial or brain) and (haematoma* or hematoma* or haemorrhage* or hemorrhage* or bleed*))))[Title])) OR ((((skull or cranial) and fracture*))[Title] OR (((skull or cranial) and fracture*))[abs]) OR ((((head or brain or craniocerebral or intracranial or cranial or skull) and (injur* or trauma*)))[Title] OR (((head or brain or craniocerebral or intracranial or cranial or skull) and (injur* or trauma*)))[abs]) OR ("Skull Fractures"[mhe]) OR ("Intracranial Hemorrhage, Traumatic"[mhe]) OR ("Head Injuries, Penetrating"[mh]) OR ("Head Injuries, Closed"[mhe]) OR ("Coma, Post-Head Injury"[mh]) OR ("Brain Injuries"[mhe]) OR ("Craniocerebral Trauma"[mh])

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Appendix C –Prognostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of brain injury biomarkers and/or MRI for predicting post-concussion syndrome – prognostic accuracy

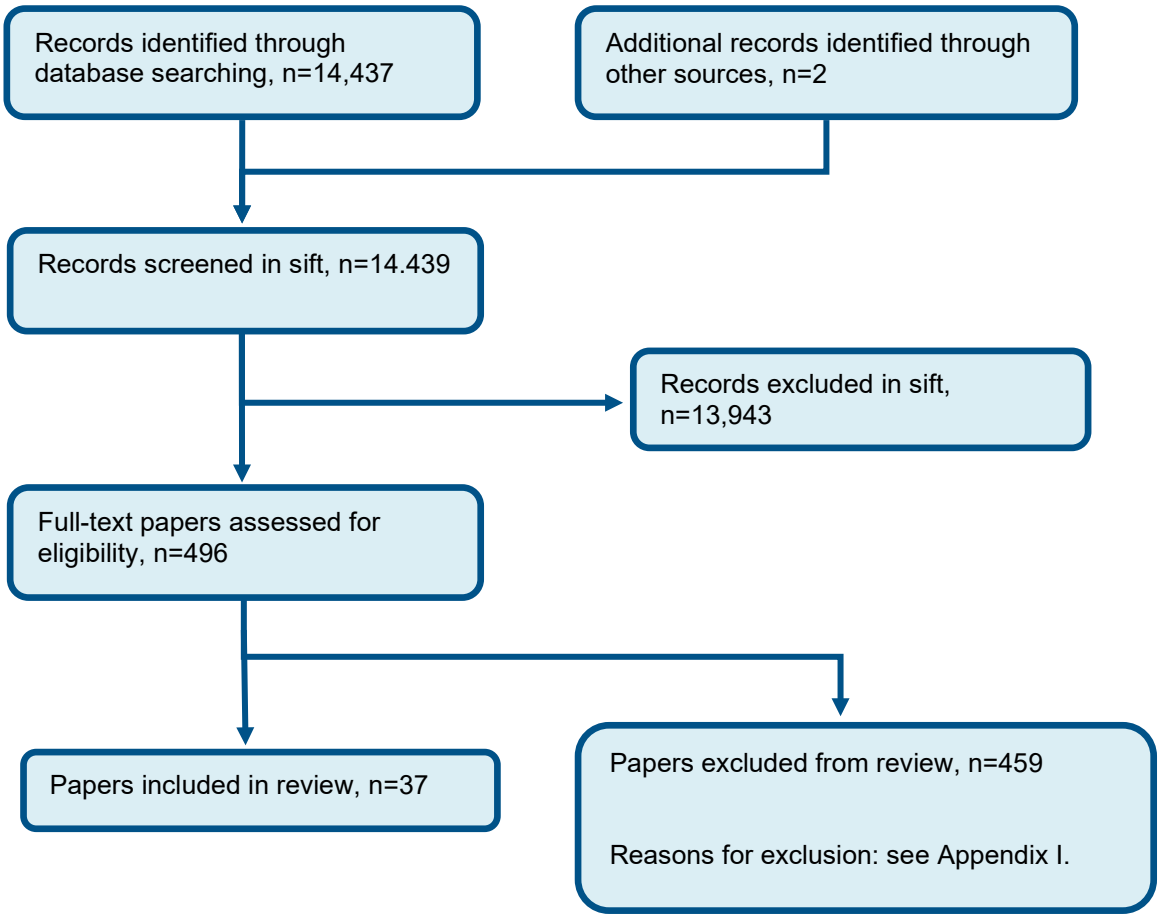
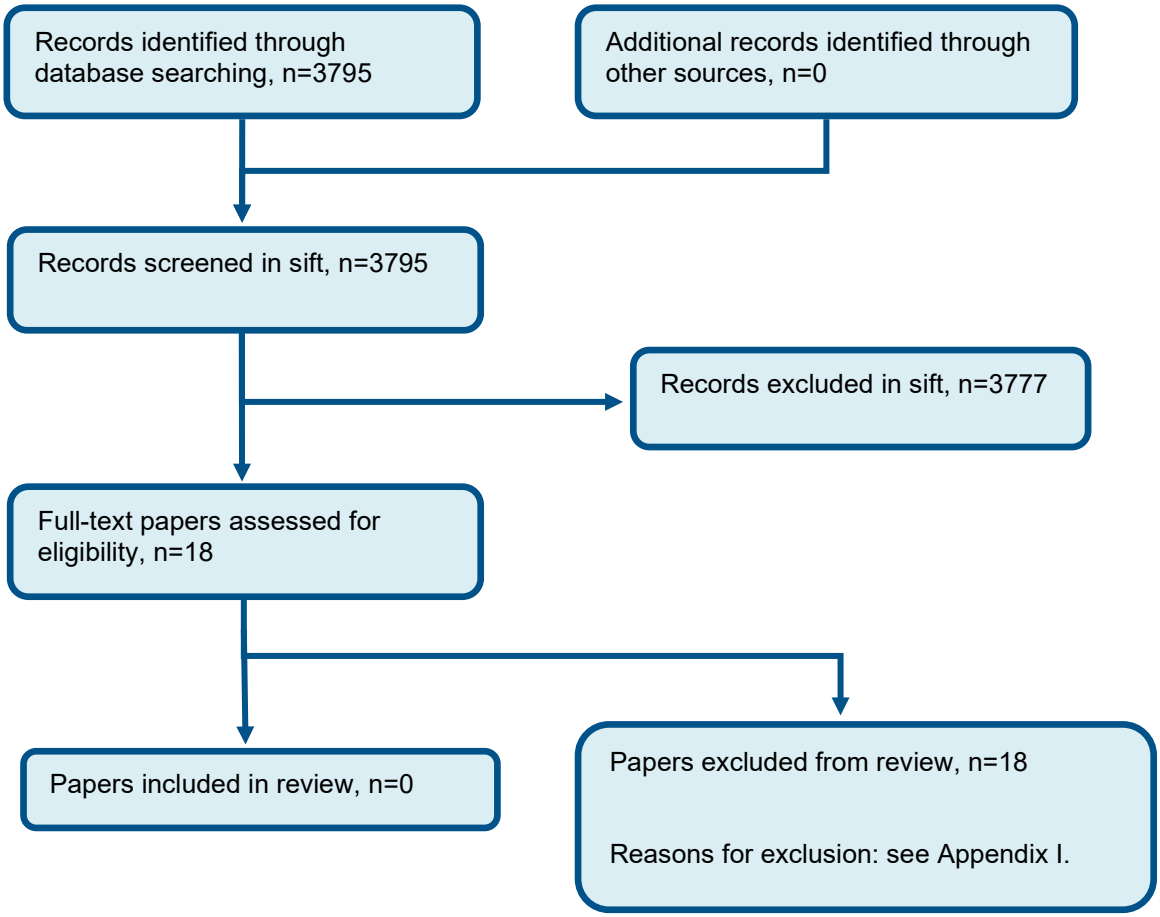


Figure 2: Flow chart of clinical study selection for the review of brain injury biomarkers and/or MRI for predicting post-concussion syndrome – prognostic test and treat



Appendix D –Prognostic evidence (prognostic accuracy only; no evidence for prognostic test and treat)

D.1 Adults

Reference	Bai 2020[2]
Study type and analysis	Prospective study consisting of mild TBI patients from two independent cohorts (original and replicate samples). Healthy controls also included but not relevant to review protocol. Prognostic model developed containing various MRI features. Performance of model assessed using accuracy, sensitivity and specificity.
Number of participants and characteristics	N=98 (n=60 in original sample and n=38 in replicate sample) Inclusion criteria: mild TBI (based on WHO Collaborating Centre for Neurotrauma Task Force) within 1 week post-injury. Exclusion criteria: people with structural abnormality on conventional neuroimaging and a premorbid condition, such as a previous brain injury, pre-existing headache, neurological disease or concurrent substance or alcohol abuse. Characteristics of population: <u>Original sample (n=60)</u> • Age, mean (SD): 35.3 (14.8) years • Gender – 58%/42% split but unclear which is for male and female • Neuropsychological testing, mean (SD): ○ Trail-making test part A (initial), 58.7 (44.5) ○ Trail-making test Part A (follow-up), 51.2 (39.3) ○ Backward Digit Span (initial), 3.9 (1.6) ○ Backward Digit Span (follow-up), 3.7 (1.4) • Mechanism of injury ○ Motor vehicle accident, 70%

Reference	Bai 2020[2]
	○ Assault, 13% ○ Fall, 17% • None had visible contusion lesions using conventional neuroimaging techniques and exhibited cerebral microbleeds on susceptibility weighted imaging <u>Replicate sample (n=38)</u> • Age, mean (SD): 37.0 (11.2) years • Gender – 53%/47% split but unclear which is for male and female • Neuropsychological testing, mean (SD): ○ Trail-making test part A (initial), 58.7 (26.8) ○ Trail-making test Part A (follow-up), 59.3 (38.9) ○ Backward Digit Span (initial), 3.2 (1.8) ○ Backward Digit Span (follow-up), 3.9 (1.7) • Mechanism of injury ○ Motor vehicle accident, 57% ○ Assault, 25% ○ Fall, 18% • None had visible contusion lesions using conventional neuroimaging techniques and exhibited cerebral microbleeds on susceptibility weighted imaging Population source: original cohort enrolled between March 2014 and October 2015 and replicated sample between April 2016 and December 2018. All datasets for the two cohorts collected from same centre using the same scanner.
Prognostic variable	MRI – various white matter fibres combined in a single model: Thalamus-anterior cingulate L; Thalamus-anterior cingulate R; Thalamus-inferior frontal gyrus R; Thalamus-superior frontal gyrus L; Thalamus-superior frontal gyrus R; Anterior thalamic radiation L; Anterior thalamic radiation R; Corticospinal tract L; Cingulum (cingulate gyrus) L; Cingulum (hippocampus) L; Cingulum (hippocampus) R; Forceps minor; Inferior fronto-occipital fasciculus R; Inferior longitudinal fasciculus L; Superior longitudinal fasciculus R; Uncinate fasciculus L; Uncinate fasciculus R; Superior longitudinal fasciculus (temporal) R; Genu of corpus callosum; Body of corpus callosum; and Splenium of corpus callosum.

Reference	Bai 2020[2]
	High-resolution T1-weighted 3D MPRAGE sequence and DTI. Presence of micro-haemorrhagic and non-haemorrhagic lesions determined by experienced clinical neuroradiologists by assessing multiple modalities of neuroimaging data acquired at baseline (T1-flair, T2-flair, susceptibility-weighted imaging). For DTI analysis, fractional anisotropy (FA) generated using software. By comparing with control reference groups, thresholds for discrimination between patients and normal controls based on ROC curves were identified and fibre tracts with abnormally high or low diffusion respectively were identified. This included 26 fibre tract and 43 clusters. Mean value of FA for each cluster was used as the predictor feature from each mild TBI patient. Tractography also used to define additional thalamo-cortical tracts. Performed using thalamus as seed and anterior cingulate gyrus, inferior frontal gyrus and superior frontal gyrus as target regions. Tracts then averaged across independent cohort of 10 control subjects. Of these, 6 fibres and 10 clusters (for either high or low diffusion) met criteria. For each participant in this study, there were 53 imaging cluster features. The 53 features then used in feature selection procedures to reduce the number of features for model development. Recursive feature elimination used. Number of features used for classifier was determined by optimal accuracy of classification performance. Support vector machines then used selected imaging features to determine whether the features can divide patients into two groups (improved or not). Leave-one-subject-out cross-validation used to estimate classification and prediction accuracies. Repeated subsampling validation used to randomly select subjects as test sample. Model trained on diffusion metric to identified patients with information processing speed deficit was then adopted to predict information processing speed deficit. Model externally validated by testing in the replicate sample dataset, including samples not involved in the development of the model.
Confounders or Stratification strategy	Model includes various MRI fibre clusters and tracts but no mention of other factors adjusted for.
Outcomes and effect sizes	**Information processing speed deficits at 6-12 months post-injury – incomplete recovery** Original sample: 33% of n=60 with incomplete recovery – classifiers trained on FA Accuracy: 92.1% (95% CI, 91.6% to 92.6%) Sensitivity: 99.0%, (95% CI, 99.1% to 99.5%) Specificity: 94.9% (95% CI, 83.9% to 85.9%) PPV: not reported in paper but calculated to be 0.91 NPV: not reported in paper but calculated to be 0.99 Replicate sample: unclear how many with incomplete recovery, n=38 analysed – classifiers trained on FA Accuracy: 82.4% (95% CI, 81.7% to 83.1%) Sensitivity: 90.7% (95% CI, 89.9% to 91.5%)

Reference	Bai 2020[2]
	Specificity: 74.1% (95% CI, 72.9% to 75.4%) PPV: not reported and could not be calculated NPV: not reported and could not be calculated Information processing speed assessed using Trail Making Test part A. Assessing recovery was based on norms adjusted by age and education level – specific threshold not given. PPV and NPV calculated using prevalence of 33% and n=60 analysed for first sample group.
Comments	Risk of bias: moderate – concerns about attrition (moderate) Indirectness: very serious – population was a mixture of children and adults with no proportions given. Study was included under adult population as the mean age was consistent with the adult population; and provides results for model containing multiple MRI measurements so difficult to assess utility of individual findings on MRI.

4

Reference	Bazarian 2006[4]
Study type and analysis	Nested cohort study identified from larger prospective cohort study that had agreed to participate in a NIH registry study between 3rd February 2003 and 20th September 2003. Larger study designed to describe epidemiology and three month outcome of mild TBI. Area under receiver operating characteristics (ROC) curves used to assess ability of S100B to predict outcomes.
Number of participants and characteristics	N=96 Inclusion criteria: mild TBI (definition by Mild Traumatic Brain Injury Committee of American Congress of Rehabilitation Medicine – blow to head or acceleration/deceleration movement of head resulting in one of more of following: loss of consciousness <30 min, amnesia <24 h or any alteration in mental state at time of injury) with GCS 13-15 measured 30 min or more following injury; presenting within 4 h of injury (as S100B levels peak at 6 h); agreed to have blood drawn for analysis in ED; had head CT scan performed in ED as part of clinical care; and completed three-month follow-up; Exclusion criteria: people presenting >4 h after injury; pre-existing medical or psychiatric conditions known to be associated with S100B level in absence of TBI (for example, Alzheimer's disease, Down's Syndrome, schizophrenia and those running >10 miles in last 12 h). Suspected or established drug/alcohol use was not an exclusion criterion.

Reference	Bazarian 2006[4]
	Characteristics of population: • Age, mean (SD): 39.9 (19.5) years, range 8-79 years, median 39.5 years • Gender – 37.5% female • White, 100% (excluded n=4 African-Americans and reason not given) • Presenting GCS: ○ 15, 91.7% ○ 14, 5.2% ○ 13, 3.1% • Isolated TBI, 53.1% • Admission/discharge: ○ Discharge directly from ED, 53.1% ○ Kept in ED for 23 h observation, 2.1% ○ Admitted to hospital, 21.3% • Head CT abnormality on initial scan, 5.2% • Mechanism of injury ○ Motor vehicle accident, 35.4% ○ Fall, 34.4% ○ Sports-related, 7.3% ○ Cycling, 4.2% ○ Pedestrian struck, 3.1% ○ Motorcycle crash, 3.1% ○ Assault, 1.0% ○ Other, 11.5% Population source: patients enrolled between 3rd February 2003 and 20th September 2003 from a single centre ED.
Prognostic variable	S100B – continuous as no results provided for thresholds Blood drawn within 4 h of injury. S100B measured in serum using sandwich immunoassay.

Reference	Bazarian 2006[4]
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Post-concussion syndrome (PCS) at 3 months post-injury – score of ≥5** AUC *Continuous* AUC – S100B uncorrected: 0.45 AUC – S100B corrected for creatinine kinase levels: 0.49 No statistically significant difference between corrected and uncorrected versions. Improvements due to improvements in specificity and not sensitivity. Sensitivity and specificity *Continuous* At a fixed sensitivity of 0.70, specificity was 0.23 and 0.30 for S100B uncorrected and corrected for creatinine kinase, respectively (P=0.047 for difference). There were no significant changes in sensitivity between corrected and uncorrected versions when given a fixed specificity of 0.70. PPV: not reported and could not be calculated NPV: not reported and could not be calculated *Thresholds* Some data relating to thresholds mentioned but insufficient information provided to be able to calculate accuracy data. **Headache at 3 months post-injury - poorly defined** AUC *Continuous* AUC – S100B uncorrected: 0.46 AUC – S100B corrected for creatinine kinase levels: 0.52 P=0.02 for difference between corrected and uncorrected versions. Improvements due to improvements in specificity and not sensitivity. Sensitivity and specificity *Continuous*

Reference	Bazarian 2006[4]
	At a fixed sensitivity of 0.70, specificity was 0.26 and 0.37 for S100B uncorrected and corrected for creatinine kinase, respectively (P=0.03 for difference). There were no significant changes in sensitivity between corrected and uncorrected versions when given a fixed specificity of 0.70. PPV: not reported and could not be calculated NPV: not reported and could not be calculated *Thresholds* Some data relating to thresholds mentioned but insufficient information provided to be able to calculate accuracy data. PCS assessed using Rivermead Post-Concussion Questionnaire by telephone interview. Interviewers blinded to details of initial ED presentation and serum results. Scores range from 0-64. Total scores used to determine presence of absence of PCS – scores <5 defined as 'no PCS' and those with scores ≥5 defined as 'PCS'. Cut-off based on one SD below mean scores previously reported for mild TBI patients with Diagnostic and Statistical Manual IV-defined PCS and on sick leave at three months from another study. No further details given for the 'headache at 3 months' outcome. Also reports values corrected for creatinine kinase using a correction factor. Obtained S100B and creatinine kinase levels from 18 German marathon runners from another publication and used these to derive correction factor. Correlation co-efficient was 0.679, which along with regression equation was then used to obtain correction factor for S100B in mild TBI cohort.
Comments	Risk of bias: • PCS at 3 months – high – concerns about study participation (moderate), attrition (moderate) and reporting of results (high) • Headache at 3 months – high – concerns about study participation (moderate), attrition (moderate), outcome measurement (moderate) and reporting of results (high) Indirectness: PCS and headache outcomes – serious – population was a mixture of children and adults with no proportions given. Study was included under adult population as the mean age was consistent with the adult population.

5

Reference	Bazarian 2006[5]
Study type and analysis	Prospective cohort study Area under receiver operating curve (ROC) used to determine ability to predict development of post-concussion syndrome (PCS). Sensitivity and specificity also reported

Reference	Bazarian 2006[5]
Number of participants and characteristics	N=35 (N=4 not followed-up) Developed PCS N=16 Did not develop PCS N=15 Inclusion criteria: People presenting to the ED within 6 hrs of injury meeting the definition of mild TBI were included. People of all ages were eligible for inclusion if they met the case definition of mild TBI developed by the Mild Traumatic Brain Injury Committee of the American Congress of Rehabilitation Medicine. This definition consists of a blow to the head or accelerated/deceleration movement of the head resulting in one or more of the following: loss of consciousness < 10 mins, amnesia < 24 hr or any alteration in mental state at the time of injury. All subjects must have a GCS score of greater than or equal to 13 measured 30 mins or more after injury. A head CT performed in the CT was not required for inclusion. Exclusion criteria: People presenting more than 6 hrs after injury. Patients with pre-existing medical or psychiatric conditions known to be associated with an elevated S-100B level in the absence of TBI. Population characteristics Mean 37.0 (range 10-83, SD 18.8 yrs) Female 51.4% 82.9% Caucasian 94.29% presenting GCS 15 85.7% head CT in the ED Traumatic abnormalities N=2
Prognostic variable(s)	S100B levels in serum Mean S-100B level 0.35 (SD 0.79) $\mu g L^{-1}$
Confounders OR Stratification strategy	NA
Outcomes and effect sizes	At three months: Rivermead Post Concussion Questionnaire – presence of post-concussion syndrome (defined as those with scores ≥5) Total scores ranged from 0-47. Mean score 13.0 (SD 13.6), median 9.5 AUC 0.589, 95%CI 0.038-0.80

Reference	Bazarian 2006[5]
	Sensitivity (95%CI) 0.563 (0.33-0.77) Specificity (95%CI) 0.357 (0.16-0.61) PPV: 0.438 (95% CI 0.23 to 0.67) NPV: 0.333 (95% CI 0.15 to 0.58)
Comments	Risk of bias – high – concerns about study participation (moderate) and attrition (moderate) Indirectness – serious – population was a mixture of children and adults with no proportions given. Study was included under adult population as the mean age was consistent with the adult population.

6

Reference	Diaz-Arrastia 2014[7]
Study type and analysis	Enrolled as part of the TRACK-TBI study, a multi-centre prospective study. Area under ROC curve analysis used to assess ability of biomarkers to predict outcomes
Number of participants and characteristics	N=206 Inclusion criteria: present within 24 h of injury; history of trauma to head sufficient to triage to non-contrast head CT (any severity of TBI included) using American College of Emergency Physicians/Centers for Disease Control evidence-based joint practice guideline; and with serum UCH-L1 data available. Exclusion criteria: not reported Characteristics of population: • Age, mean (SD): 42.0 (18.0) years • Gender: 73% male • Severity of injury: **not limited to mild TBI but >75% had mild TBI. Some results provided separately for mild subgroup.** ○ Mild (GCS 13-15), 83% ○ Moderate (GCS 9-12), 4% ○ Severe (GCS 3-8), 13% • CT scan findings: ○ Intracranial pathology, 43% of mild, 78% of moderate and 96% of severe TBI cases

Reference	Diaz-Arrastia 2014[7]
	Population source: recruited upon arrival at one of three level 1 trauma centres as part of TRACK-TBI study.
Prognostic variable	UCH-L1 in serum – continuous GFAP in serum – continuous UCH-L1 and GFAP in serum combined – continuous Blood samples collected within 24 h of injury. Sample analysis done at single laboratory using sandwich ELISA for UCH-L1 and GFAP.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Glasgow Outcome Scale-Extended (GOSE) at 3 months post-injury – incomplete recovery (GOSE score <8), n=168** *Whole cohort of patients (83% with mild TBI)* UCH-L1 – continuous: 0.58 (95% CI, 0.50 to 0.74) GFAP – continuous: 0.65 (95% CI, 0.55 to 0.74) UCH-L1 + GFAP – continuous: 0.64 (95% CI, 0.55 to 0.72) **Glasgow Outcome Scale-Extended (GOSE) at 6 months post-injury – incomplete recovery (GOSE score <8), n=145** *Mild subgroup of patients, n=unclear (as no CIs reported and sample size analysed for this subgroup unclear, number of people with mild head injury enrolled used to assess imprecision based on sample size, n=171 – fewer people followed up to 6 months)* AUC – UCH-L1 – continuous: AUC: 0.511 *Whole cohort of patients (83% with mild TBI)* AUC – UCH-L1 – continuous: 0.51 (95% CI, 0.39 to 0.63) AUC – GFAP – continuous: 0.60 (95% CI, 0.43 to 0.77) AUC – UCH-L1 + GFAP – continuous: 0.61 (95% CI, 0.48 to 0.75) **Glasgow Outcome Scale-Extended (GOSE) at 3 months post-injury – poor outcome (GOSE score ≤4), n=168** *Whole cohort of patients (83% with mild TBI)* AUC – UCH-L1 – continuous: 0.80 (95% CI, 0.70 to 0.90) AUC – GFAP – continuous: 0.74 (95% CI, 0.61 to 0.87)

Reference	Diaz-Arrastia 2014[7]
	AUC – UCH-L1 + GFAP – continuous: 0.83 (95% CI, 0.75 to 0.91) **Glasgow Outcome Scale-Extended (GOSE) at 6 months post-injury – poor outcome (GOSE score ≤4), n=145** *Whole cohort of patients (83% with mild TBI)* AUC – UCH-L1 – continuous: 0.76 (95% CI, 0.60 to 0.91) AUC – GFAP – continuous: 0.74 (95% CI, 0.61 to 0.87) AUC – UCH-L1 + GFAP – continuous: 0.81 (95% CI, 0.70 to 0.91) GOSE score of 8 indicates good recovery and is return to pre-injury baseline with no residual effects of the TBI. Unfavourable outcome described as GOSE scores ≤4 and incomplete recovery described as GOSE scores <8.
Comments	Risk of bias: high – concerns about attrition (moderate) and reporting of results (moderate) Indirectness: serious – population was possible a mixture of children and adults with no proportions given. Study was included under adult population as the mean age was consistent with the adult population.

7

Reference	Fedorchak 2021[8]
Study type and analysis	Multicentre prospective study Area under curve analysis performed to assess ability to predict outcome
Number of participants and characteristics	N=112 • N=80 with no persistent post-concussion symptoms • N=32 with persistent post-concussion symptoms Inclusion criteria: aged 8-24 years; and clinical diagnosis of mild TBI (defined by 2016 Concussion in Sport Group) Exclusion criteria: non-English speaking; neurologic injury (e.g., intracranial bleeding, spinal cord injury, skull fracture); periodontal disease; upper respiratory infection; secondary oropharynx injury; baseline hearing/vision loss; drug or alcohol dependency; presentation for clinical care >14 days after injury; incomplete symptom reports necessary for persistent post-concussion symptoms classification; and falling outside the desired age range.

Reference	Fedorchak 2021[8]
	Characteristics of population: • Age, mean (SD): 16.0 (4.0) • Gender: 44% female • White, 87% • Medical: ○ ADHD, 4% ○ Anxiety, 1% ○ Depression, 2% ○ Chronic headaches, 9% • Concussion characteristics ○ Days since injury, initial assessment, mean (SD): 5 (3.6) ○ Sports cause, 73% ○ Football cause, 30% ○ Loss of consciousness, 20% ○ Post-traumatic amnesia, 65% ○ Previous concussion, 33% ○ Number of previous concussions: 1, 59.3%; 2, 29.6%; and 3, 11.1% Population source: enrolled from 6 institutions, including from emergency departments, sports medicine clinics, urgent care centres, concussion speciality clinics, and outpatient primary care clinics at initial clinical presentation (within 14 days of injury). Repeatedly assessed for symptoms, balance, cognitive test performance and saliva non-coding RNA levels up to 60 days post-injury.
Prognostic variable	Salivary non-coding RNA (ncRNA) – includes microRNA (miRNA), small nucleolar RNA (snoRNA) and piwi-interacting RNA with hierarchical clustering to reduce highly similar sequences (wiRNA) – continuous measure in single model. Final model included 16 ncRNA, including 7 miRNA, 1 snoRNA and eight piRNA clusters as well as age OR 11 ncRNA (4 miRNA, 4 wiRNA and 3 snoRNA) as well as age Non-fasting saliva samples collected from all participants. RNA sequencing performed at 10 million reads per sample using 50 base-pair single end reads on Illumina NextSeq 500 instrument. Fastq files aligned to miRBase 22 (miRNA), RefSeq v90 (snoRNA) and piRBase v2 with hierarchical clustering to reduce highly similar sequences (wiRNA). Aligned reads filtered to remove low counts

Reference	Fedorchak 2021[8]
	(<0.01% total reads per RNA category), normalised using total sum scaling and inverse hyperbolic sine transformed to correct for skew. Multiple samples taken from some participants, with samples subsequently divided into training set, evaluation set and semi-naïve testing test. Training set used to select ncRNA features and create the algorithm. Testing set used to validate accuracy of resulting predictive algorithms and evaluation set used to minimise bias that could arise from class imbalance by shifting probability threshold of classified away from standard of 0.5, while avoiding artificial performance inflation. 37/112 participants were represented in both training and testing sets. Maximum of five samples per person allowed in training and testing sets, with remaining samples incorporated into evaluation set. For feature selection, top features appearing in >50% of folds combined with ncRNAs from differential expression and penalised generalised linear model analyses. RNAs with significant Pearson correlation coefficients (P<0.05 unadjusted) chosen from linear regression models with highest ranked RNAs in terms of variable importance from logistic regression models with 'fair' predictive accuracy. Reduced feature set used to train algorithm and recursive feature elimination used to refine panel further.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Persistent post-concussion symptoms at ≥21 days post-injury – score ≥5 on Post-Concussion Symptom Scale** ***Model 1 – 16 ncRNAs and age*** *Training set, n=184 samples* AUC: 0.85 Sensitivity: 0.77 Specificity: 0.78 PPV: 0.59 NPV: 0.89 *Evaluation set, n=72 samples* *AUC: 0.83* Sensitivity: 0.81 Specificity: 0.73 PPV: 0.65 NPV: 0.87

Reference	Fedorchak 2021[8]
	Testing set, n=62 samples AUC: 0.87 Sensitivity: 0.83 Specificity: 0.80 PPV: 0.63 NPV: 0.92 *Ten-fold cross-validation of ncRNA model (used to compare against a clinical model previously reported but not relevant to this review)* AUC: 0.83 (95% CI, 0.81 to 0.85) ***Model 2 – 11 ncRNAs and age*** *Ten-fold cross-validation of ncRNA model (used to compare against balance/cognition model but not relevant to this review)* AUC: 0.83 (95% CI, 0.79 to 0.86) Measured using Post-Concussion Symptom Scale (0-6 scale) – scores >5 indicated persistent symptoms. This threshold determined using upper 95% confidence interval of mean symptom severity score on Post-Concussion Symptom Scale from 170 age-matched participants without mild TBI (score ≥5). Cut-off of 21 days chosen based on literature showing most children report concussion recovery within 2 weeks, but symptom change flattens between 2 and 4 weeks.
Comments	Risk of bias: high – concerns about attrition (moderate), prognostic factor measurement (moderate) and reporting of results (high) Indirectness: very serious – population was possible a mixture of children and adults with no proportions given (study was included under adult population as the mean age was consistent with the adult population); and provides data for a model of various ncRNAs combined so difficult to assess utility of individual biomarkers; and biomarkers measured within 14 days of injury (mean value not given), which is >48 h specified in the protocol.

8

Reference	Hermann 2001[9]
Study type and analysis	Prospective study Receiver operating characteristics (ROC) curve analyses used to assess predictive ability of NSE and S100B serum concentrations for neuropsychological outcome

Reference	Hermann 2001[9]
Number of participants and characteristics	N=69 (n=29 analysed at 6 months) Inclusion criteria: admitted to Department of Neurosurgery following TBI (any severity); no history of neurological or psychiatric disorder or alcohol or drug dependency; aged between 16 and 65 years; blood sampling according to the scheduled time scale; and informed and written consent to participate in the study Exclusion criteria: not reported Characteristics of population (for n=29 analysed): • Age, median (range): 27 (17-54) years • Gender: 79% female • GCS score at site of accident, median (range): 13 (3-15) • GCS score at admission, median (range): 15 (3-15) – **not limited to mild TBI but median value consistent with mild TBI, proportions unclear so downgrade for indirectness** • GCS score at third day, median (range): 15 (3-15) • Focal neurological deficit, 14% • Intracranial pathology on CT, 55% ○ Cortical contusion, 24% ○ Diffuse axonal injury, 21% ○ Subdural or epidural haematoma, 38% ○ Diffuse haemorrhage, 31% ○ Signs of intracerebral pressure, 21% • Neuropsychological disorder, 69% • Functional status (FIM), median (range): 126 (114-126) Population source: consecutive series of patients admitted to Department of Neurosurgery following TBI over 18 months
Prognostic variable	Biomarkers measured in serum, analysed as continuous variables and with thresholds: • S100B (continuous or threshold of >140 ng/l) • NSE (continuous or threshold of >5.75 µg/l)

Reference	Hermann 2001[9]
	Venous blood samples taken at first (median 27 hours post-trauma), second (median 49.5 hours post-trauma) and third (median 80.0 hours post-trauma) day after admission to Department of Neurosurgery – results section describes 'initial' serum levels, suggesting results from first admission are included in the analyses. Serum obtained and frozen for analysis using immunoluminometric assays. Analyses performed by member of study group who was blind to clinical and neuroradiological data of patients.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Presence of neuropsychological disorder at 6 months based on neuropsychological assessment** S100B *As a continuous variable* AUC: 0.77 *Threshold of >140 ng/l* Sensitivity: 65.0% Specificity: 88.9% Positive likelihood ratio: 5.9 PPV: not reported but calculated to be 0.93 NPV: not reported but calculated to be 0.53 NSE *As a continuous variable* AUC: 0.65 *Threshold of >5.75 µg/l* Sensitivity: 55.0% Specificity: 77.8% Positive likelihood ratio: 2.5 PPV: not reported but calculated to be 0.85 NPV: not reported but calculated to be 0.44 Neuropsychological assessment based on tests covering the following: global cognitive and behavioural screening (neurobehavioral rating scale mini mental state examination and frontal lobe score); memory/learning (digit and visual spans, and selective reminding

Reference	Hermann 2001[9]
	tests); language (token test); visuoperception/construction (block design); executive functions (semantic and phonological fluency, distractibility, and interference, including Stroop test and concept formation); attentional performance (computerised test battery for attentional performance subtests “alertness” and “go-no go”); and psychomotor speed (finger tapping). Patients were classified as presenting neuropsychological disorders if they performed less than 1 SD below (age adjusted) normal data in at least three cognitive domains. PPV and NPV calculated using prevalence of 69.0% and n=29 analysed.
Comments	Risk of bias: high – concerns about attrition (moderate) and reporting of results (moderate) Indirectness: serious – includes a population with mixed TBI severity (ranging from GCS 3-15) and proportion with each severity unclear, although median value consistent with mild TBI.

9

Reference	Hossain 2019[10]
Study type and analysis	Prospective study part of EU-funded TBIcare project (Evidence-based Diagnostic and Treatment Planning Solution for Traumatic Brain Injuries) Receiver operating characteristics (ROC) curve analyses used to evaluate prognostic ability of biomarkers.
Number of participants and characteristics	N=107 Inclusion criteria: mild TBI (GCS 13-15); blood samples available within 24 h from arrival to ED; aged ≥18 years; and indications for acute head CT according to NICE criteria Exclusion criteria: age <18 years; blast-induced or penetrating injury; chronic subdural haematoma; inability to live independently due to pre-existing brain disease; TBI or suspected TBI not needing head CT; ≥2 weeks since injury; not living in the district and preventing follow-up visits; not speaking the native language; or no consent received. Characteristics of population: • Age, mean (SD): 47.64 (20.19) years • Gender: 68.2% male • Marshall Grade ○ No visual pathology, 48.6% ○ Diffuse injury, 22.4%

Reference	Hossain 2019[10]
	○ Diffuse injury with swelling, 0.9% ○ Diffuse injury with shift, 0.9% ○ Mass lesions, 27.1% • Pupil reactivity ○ Unreactive, 0.9% ○ Sluggish, 1.9% ○ Reactive, 92.5% ○ Missing data, 4.7% • GOSE score ○ 1, 3.7% ○ 2, 0.0% ○ 3, 5.6% ○ 4, 4.7% ○ 5, 6.5% ○ 6, 13.1% ○ 7, 29.9% ○ 8, 34.6% ○ Missing data, 1.9% • Focal neurological deficit, 14% • Intracranial pathology on CT, 55% ○ Cortical contusion, 24% ○ Diffuse axonal injury, 21% ○ Subdural or epidural haematoma, 38% ○ Diffuse haemorrhage, 31% ○ Signs of intracerebral pressure, 21% • Neuropsychological disorder, 69% • Functional status (FIM), median (range): 126 (114-126)

Reference	Hossain 2019[10]
	Population source: recruited from ED of single university hospital in Finland, time-period unclear and unclear if consecutive
Prognostic variable	Biomarkers measured in plasma, analysed as continuous variables: • NF-L (continuous or thresholds of <28.15 and <53.6 pg/ml depending on outcome) • GFAP (continuous or thresholds of <6438.05 and <12189.8 pg/ml depending on outcome) • Combination of NF-L and GFAP (thresholds of <28.15 and <6438.05 and pg/ml, respectively, or <41.85 and <980.75 pg/ml, respectively, depending on outcome) Plasma levels of GFAP and NF-L measured using assays. Performed in one round of experiments using one batch of reagents by board-certified laboratory technicians who were blinded to clinical data. Measured within 24 h of admission to ED. Cut-off values used were derived from ROC curves of full cohort for predicting complete recovery and favourable outcome, with minimum sensitivity level set to 90%.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Complete recovery – GOSE score of 8 at 6-12 months** GFAP *As a continuous variable* AUC: 0.598 (95% CI, 0.489 to 0.706), P=0.099 *Threshold of <6438.05 pg/ml* Sensitivity: 97% (95% CI, 86 to 100%) Specificity: 26% (95% CI, 68 to 99%) – confidence interval error as does not fall below 26% specificity reported, possibly 0.18 to 0.99? PPV: not reported but calculated to be 0.41 NPV: not reported but calculated to be 0.94 NF-L *As a continuous variable* AUC: 0.665 (95% CI, 0.561 to 0.768), P=0.005 *Threshold of <28.15 pg/ml*

Reference	Hossain 2019[10]
	Sensitivity: 94% (95% CI, 82 to 99%) Specificity: 44% (95% CI, 32 to 57%) PPV: not reported but calculated to be 0.47 NPV: not reported but calculated to be 0.93 Combination of GFAP and NF-L *Threshold of <6438.95 pg/ml for GFAP and <28.15 pg/ml for NF-L* Sensitivity: 94.6% (95% CI, 86.5 to 100.0%) Specificity: 47.1% (95% CI, 35.3 to 58.8%) PPV: not reported but calculated to be 0.49 NPV: not reported but calculated to be 0.94 **Favourable outcome – GOSE score of 5-8 at 6-12 months** GFAP *As a continuous variable* AUC: 0.755 (95% CI, 0.628 to 0.882), P=0.002 *Threshold of <12189.85 pg/ml* Sensitivity: 92% (95% CI, 85 to 99%) Specificity: 47% (95% CI, 16 to 68%) PPV: not reported but calculated to be 0.90 NPV: not reported but calculated to be 0.53 NF-L *As a continuous variable* AUC: 0.826 (95% CI, 0.694 to 0.958), P<0.001 *Threshold of <53.6 pg/ml*

Reference	Hossain 2019[10]
	Sensitivity: 90% (95% CI, 82 to 95%) Specificity: 67% (95% CI, 38 to 88%) PPV: not reported but calculated to be 0.94 NPV: not reported but calculated to be 0.56 <u>Combination of GFAP and NF-L</u> *Threshold of <980.75 pg/ml for GFAP and <41.85 pg/ml for NF-L* Sensitivity: 90.0% (95% CI, 83.3 to 95.6%) Specificity: 86.7% (95% CI, 66.7 to 100.0%) PPV: not reported but calculated to be 0.97 NPV: not reported but calculated to be 0.62 GOSE was measured at 6-12 months and two separate groupings used for outcome analysis: complete recovery vs. incomplete recovery (with GOSE score of 8 indicating complete recovery) and favourable vs. unfavourable outcome (with GOSE scores 5-8 indicating favourable recovery). Prevalence of complete recovery was 34.6% and of favourable outcome was 84.1% with n=105 analysed (used to calculate PPV and NPV).
Comments	Risk of bias: low Indirectness: none

10

Reference	Huovinen 2021[11]
Study type and analysis	Prospective cohort study Possible to calculate sensitivity and specificity from the raw data provided
Number of participants and characteristics	N=113 • N=91 without traumatic microbleeds on MRI • N=22 with traumatic microbleeds on MRI Inclusion criteria: mild TBI (based on WHO definition of mild TBI); and aged between 18 and 68 years.

Reference	Huovinen 2021[11]
	Exclusion criteria: previously diagnosed schizophrenia or schizoaffective disorder; visual or auditory disability; presence of alcohol or drug addiction; contraindications for MRI; first language other than Finnish; patients not currently employed at time of injury; or underwent MRI more than 17 days after injury. Characteristics of population: • Age, mean (SD): 39.2 (12.2) years • Gender: 43.4% female • Previous or current illnesses, 42.5% (including cardiovascular diseases, diabetes and various neurological and psychiatric conditions) • Type of labour o Entrepreneur, 14.2% o Management, 10.6% o Expert, 32.7% o Manual labour, 20.4% o Other, 22.1% • Students o Full-time, 11.5% o Part-time, 5.3% • Mechanism of injury o Motor vehicle accident, 6.2% o Traffic accident as a pedestrian, 0.9% o Sports, 12.3% o Bicycle accident, 25.7% o Ground level fall, 28.3% o Fall from height, 20.4% o Violence, 3.5% o Other, 1.8% o Unknown, 0.9%

Reference	Huovinen 2021[11]
	Population source: recruited those with mild TBI from single TBI Outpatient Clinic of Helsinki University Hospital. Prospectively recruited between 2015 and 2018 and were evaluated in outpatient clinic by board-certified neurologist experienced in patients with TBI 1 month following injury.
Prognostic variable	Traumatic microbleeds identified on MRI – yes/no MRI performed between 3 and 17 days post-injury (mean, SD: 9.6, 3.2 days). All scans interpreted by board-certified neuroradiologist. Lesions assessed systematically using Common Dataset Elements for TBI neuroimaging. Traumatic microbleeds defined as single or several small haemorrhagic lesions in white matter or grey-white interface detected by susceptibility weighted imaging sequence. Presence of traumatic microbleeds was used as a dichotomous variable in analyses. Imaging performed with 3T Siemens Magnetom Verio with 32-channel head coil. Imaging protocol consisted of FLAIR, SPACE, MPRAGE, 3D SWI sequence, resting-state blood-oxygen-level-dependent functional MRI repeated twice with single image volume with reversed phase encoding direction acquired after rs-fMRI time series for susceptibility-induced distortion correction. Analysis in this study based on conventional 3T MRI and SWI sequence results.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Incomplete recovery – GOSE score <8 at 1 month** *Raw data* 45/81 people without traumatic microbleeds had GOSE 8, with 36/81 people having GOSE ≤8 11/19 people with traumatic microbleeds had GOSE 8, with 8/19 people having GOSE ≤8 (For incomplete recovery: TPs, 8; FPs, 11; TNs, 45; and FNs, 36) *Sensitivity/specificity calculated from raw data* Sensitivity: 18.18 Specificity: 80.36 PPV: 42.0 NPV: 56.0 At 1 month post-injury, GOSE was used to assess overall recovery by a board-certified neurologist. Score ranging from 1 (dead) to 8 (good recovery), with a score ≥6 reported to indicate favourable outcome. 56% reported to have good functional recovery (GOSE score =8) – 58% of those with traumatic microbleeds had GOSE 8 and 56% of those without traumatic microbleeds had GOSE 8.
Comments	Risk of bias: high – concerns about study participation (moderate), attrition (moderate) and reporting of results (moderate)

Reference	Huovinen 2021[11]
	Indirectness: none

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Reference	Ingebrigtsen 1995[12]
Study type and analysis	Prospective study Possible to calculate prognostic accuracy measures from data reported in paper
Number of participants and characteristics	N=50 (n=42 analysed at 9 months) Inclusion criteria: aged 6-88 years with isolated minor head injury (head injury with loss of consciousness; GCS 14-15; absence of focal neurological deficits; and no signs of intracranial lesion on CT); brain CT within 12 h Exclusion criteria: not reported Characteristics of population – limited information provided: • Age, mean: 31 years • 70% male Population source: consecutive patients enrolled
Prognostic variable	S100B levels in serum – threshold of ≥0.5 µg/l Two blood samples collected as early as possible after trauma (at admission) and at 12 h post-injury. S100B serum concentrations analysed with immunoradiometric assay kit. Analysed in duplicate. Value of ≥0.5 µg/l was considered pathological. First sample drawn between 0.5 and 9.0 (mean 3.2) h following trauma. In 37 patients a second sample was drawn 12 h post-injury – however, values at admission were used in analysis.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Persistent symptoms of concussion after 9 months** *Raw data reported in paper*

Reference	Ingebrigtsen 1995[12]
	TPs, 2; FPs, 7; FNs, 9; TNs, 24 *Sensitivity/specificity calculated from raw data* Sensitivity: 18.18% Specificity: 77.42% PPV: 22.22% NPV: 72.73% At 9 months, n=42/50 followed up including personal interview. Asked about 12 of most frequent complaints described after head injury with concussion (headache, impaired memory, fatigue, dizziness, irritability, impaired concentration, insomnia, tinnitus, hearing defect, depression, anxiety and double vision). Unclear if any or more than one required to be classed as persistent symptoms of concussion at 9 months.
Comments	Risk of bias: high – concerns about study participation (moderate), attrition (moderate) and outcome measurement (moderate) Indirectness: serious – mixture of adults and children with proportion unclear. Included under adults as mean age is consistent with the adult population.

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Reference	Korley 2016[16]
Study type and analysis	Prospective cohort study AUCs for PCS and other outcomes at 6 months
Number of participants and characteristics	N=159 (validation cohort with relevant outcomes measured TRACK-TBI) N=94=Rivermead Post-Concussion Questionnaire measured N=58 PCS present N=150 non-TBI controls Inclusion criteria: Patients were included in the study if they presented to the ED within 24 h of acute blunt force head trauma and met the ACEP criteria for obtaining a head CT in TBI. Only subjects from TRACK-TBI Pilot who had serum samples available for testing were included in the present study. Subjects in the validation cohort were enrolled from April 2010 to June 2011.

Reference	Korley 2016[16]
	All patients enrolled in TRACK-TBI Pilot received head CT scans at the time of presentation to the ED. Each head CT was de-identified and read by a blinded board-certified neuroradiologist following the recommendations of the TBI-CDE Neuroimaging Working Group Patients included as control subjects were JHH ED patients who were evaluated for suspected acute coronary syndrome,23 had no blunt head trauma in the preceding 7 days, and were deemed to have a non-cardiac condition and discharged home from the ED. Eligible control subjects were excluded if they met any of the exclusion criteria for cases (see below). Control subjects did not receive head CT scans since there was no clinical indication for doing so Exclusion criteria: Eligible cases were excluded if they had one of the following prior medical conditions: demyelinating disease, neurodegenerative disease, dementia, stroke, brain tumour, intracranial surgery, or active cancer. Characteristics: TBI site 3 Non-TBI site 1 Median age yrs (IQR) 41 (25-56) 54 (47-62) Female % 28.3 79 White % 83.5 20 Mechanisms of injury % Assault 14.6 Fall 31.6 Motor vehicle 32.3 Traumatic intracranial Abnormality on head CT % 47.2 At 6 mths 70% had a Glasgow Outcome Scale Extended < 8
Prognostic variable(s)	Samples were randomized and BDNF assayed in batches with an electrochemiluminescent sandwich immunoassay and read with a Sector Imager 2400 (Meso Scale Discovery, Rockville, MD). BDNF assay capture (MAB848) and detection antibodies (MAB648) and assay standard (248BD005) were obtained from R&D Systems (Duoset reagents, Cat. # DY248; Minneapolis, MN). Assays were performed within a single laboratory by staff blinded to clinical outcomes or study cohort R&D Systems (Duoset reagents, Cat. # DY248; Minneapolis, MN). Assays were performed within a single laboratory by staff blinded to clinical outcomes or study cohort. Samples from the different cohorts were shipped to this single academic laboratory. The assay lower limit of detection (LOD) was 0.0125 ng/mL and the lower limit of quantification was 0.5 ng/mL

Reference	Korley 2016[16]
	GFAP and UCH-L1 were previously measured in TRACK-TBI Pilot in a single laboratory (Banyan Biomarkers, Alachua, FL).15,18 The LOD of GFAP and UCH-L1 were 0.1 ng/mL and 0.03 ng/mL, respectively
Confounders OR Stratification strategy	NA
Outcomes and effect sizes	Incomplete recovery - based on composite outcome of post-concussion syndrome (three or more symptoms on Rivermead Post-Concussion Questionnaire rated as worse than before injury) or GOSE score <8 at 6 months, n=94 GFAP AUC 0.61 (95%CI 0.49-0.73) UCH-LI AUC 0.55 (95%CI 0.43-0.66) BDNF AUC 0.65 (0.52-0.78) GFAP + BDNF AUC 0.66 (no CIs reported) UCH-L1 +BDNF AUC 0.66 (no CIs reported) PCS (three or more symptoms on Rivermead Post-Concussion Questionnaire rated as worse than before injury) at 6 months, n=94 GFAP AUC 0.56 (95%CI 0.44-0.68) UCH-LI AUC 0.52 (95%CI 0.40-0.64) BDNF AUC 0.55 (0.43-0.68) GOSE score <8 at 6 months, n=111 GFAP AUC 0.61 (95%CI 0.50-0.71) UCH-LI AUC 0.55 (95%CI 0.44-0.66) BDNF AUC 0.56 (0.44-0.68)
Comments	Risk of bias – moderate – attrition (moderate) Indirectness – none (although includes mixed severity TBI, >75% had mild TBI (84% with GCS 13-15) so study was not downgraded).

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Reference	Lagerstedt 2020[17]
Study type and analysis	Prospective cohort study Consecutive patients NFL, S100B and GFAP to predict score on GOSE
Number of participants and characteristics	N=49 mTBI GCS 13-15 Inclusion criteria: In this single-centre study, patients were recruited at Turku University Hospital (a tertiary care university hospital with a combined primary and tertiary care emergency department) in Finland between the years 2011–2013. All the consecutive patients with TBI were evaluated for eligibility to be recruited in the study by the research team between 8 a.m. to 10 p.m. To be included in the study, the following inclusion criteria needed to be fulfilled; age ≥18 years, hospital admission within 24 h after trauma, clinical diagnosis of a TBI with an indication for a head computed tomography (CT) scan according to the NICE criteria (27) as judged by an emergency physician on call, and outcome data at 6–12 months after injury had to be available. Exclusion criteria were penetrating or blast-induced injury, chronic subdural hematoma, inability to live independently due to a previous brain disease, no performed CT scan, or no written consent. Population characteristics: Complete recovery GOSE 8 GOSE 1-7 Age mean (SD) 40.0 (20.3) 47.5 (18.7) Male % 68 37.5 Marshall grade No visual pathology grade 1 68 45.8 Injury Severity Score % Minor 1-8 64 41.7 Moderate 9-15 16 33.3 Serious 16-24 16 16.7 Severity (GCS and duration post traumatic amnesia combined) % Very mild 1 4 0 Mild 2 92 75 Moderate 3 0 16.6

Reference	Lagerstedt 2020[17]		
	GCS % Mild 13-15 Time from injury to blood sampling mean hrs (SD)	100 6.2 (4.8)	100 12.9 (5.7)
Prognostic variable(s)	Serum samples were drawn within 24 h after trauma. However, as these different time points did not appear to correlate with biomarker levels, all of them were considered as a common time point. Only admission samples were assessed. After obtaining the blood samples, the samples were centrifuged and stored at −70 °C. The proteins GFAP and NF-L were measured using the Human Neurology 4-plex A assay (N4PA) on HD-1 single molecule array (Simoa) device from Quanterix (Lexington, MA, USA). The lower limit of quantification (LLoQ) for each kit was 0.104 pg/mL for NF-L and 0.221 pg/mL for GFAP. The protein S100β was measured using the EZHS100B-33K kit from Millipore (Millipore, Billerica, MA, USA) with an LloQ of 2.74 pg/mL. H-FABP and IL-10 were analyzed using the K151HTD and K151QUD kits, respectively, Meso Scale (Meso Scale Diagnostics, Rockville, MD, USA). The LloQ for H-FABP was 0.137 ng/mL and for IL-10 0.298 pg/mL. All proteins were measured according to manufacturers' recommendations by board-certified laboratory technicians who were blinded to clinical data.		
Confounders OR Stratification strategy	NA		
Outcomes and effect sizes	Differentiation between complete (GOSE 8) and incomplete (GOSE ≤ 7) at > 6 mths in mTBI NF-L % partial AUC (95%CI) 0.1 (0.0-1.2), threshold 4.85 specificity % (95%CI) 12 (0.0-24.1) 95-100 %Sensitivity (95%CI) 95.8 (87.5-100) PPV not reported in paper but calculated to be 51.0% NPV not reported in paper but calculated to be 75.0% S100B % partial AUC (95%CI) 0.1 (0.0-1.0), threshold 23.17 specificity % (95%CI) 12 (0.0-28.0) 95-100 %Sensitivity (95%CI) 95.8 (87.5-100) PPV not reported in paper but calculated to be 51.0% NPV not reported in paper but calculated to be 75.0% GFAP % partial AUC (95%CI) 0.0 (0.0-0.6), no threshold specificity (95%CI) 0.0 (0-0) 95-100 %sensitivity (95%CI) 100 (100-100) PPV not reported in paper but calculated to be 49.0% NPV not reported in paper and cannot be calculated given specificity is 0.0% Note that PPV and NPV were calculated based on prevalence of 49.0% and n=49 analysed.		
Comments	Risk of bias – low Indirectness – none (reports results separately for the mild TBI subgroup)		

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Reference	Ledig 2017[18]
Study type and analysis	Prospective study Prognostic model developed containing various MRI features. Performance of model assessed using accuracy, sensitivity and specificity.
Number of participants and characteristics	N=67 (originally n=114 but n=67 as obtained age-matched patient groups) Inclusion criteria: mild to severe TBI with MR images taken at acute stage of injury (baseline) and chronic phase (follow-up) of the disease Exclusion criteria: not reported Characteristics of population, given separately for low (GOSE 7 and 8), moderate (GOSE 5 and 6) and severe (GOSE 3 and 4) disability groups: *Low disability, n=32* • Age, median (min; max): 64 (45; 82) years • Gender – 66% male • Days since injury, acute scan, median (min; max): 15 (1; 50) • Days since injury, chronic scan, median (min; max): 225 (151; 276) • GCS, median (min; max): 15 (3; 15) • Marshall score, median (min; max): 1 (1; 5) • TBI severity (1 very mild to 5 very severe), median (min; max): 2 (1; 4) *Moderate disability, n=22* • Age, median (min; max): 58 (46; 83) years • Gender – 64% male • Days since injury, acute scan, median (min; max): 23 (2; 51) • Days since injury, chronic scan, median (min; max): 227 (177; 429) • GCS, median (min; max): 15 (3; 15) • Marshall score, median (min; max): 2 (1; 5) • TBI severity (1 very mild to 5 very severe), median (min; max): 3 (2; 4)

Reference	Ledig 2017[18]
	Severe disability, n=13 • Age, median (min; max): 74 (33; 86) years • Gender – 44% male • Days since injury, acute scan, median (min; max): 22 (4; 51) • Days since injury, chronic scan, median (min; max): 251 (180; 422) • GCS, median (min; max): 14 (3; 15) • Marshall score, median (min; max): 5 (2; 5) • TBI severity (1 very mild to 5 very severe), median (min; max): 3 (2; 5) Population source: included as part of the TBI-care project, no further details about recruitment, for example time-period, provided
Prognostic variable	MRI, with results provided separately for individual features on MRI as well as groupings of multiple features (see results section below for further details) MR images and MPRAGE sequence acquired on Siemens Verio 3T system. Group differences between GOS groups assessed, with classification experiments performed to assess accuracy of predicting GOS outcome when using automatically calculated features based on imaging data available at acute disease stage. Features refer to single measured biomarker (e.g. structural volume, asymmetry, atrophy). All 67 subjects assessed cross-sectionally at acute state of TBI and longitudinally as part of follow-up MRI image obtained in chronic phase of disease. All available non-cortical structural volumes were used as features. A total of 21 non-cortical features were considered. Individual structural volumes were added up into surrogate structures (ventricles, cortical grey matter, deep grey matter, white matter, brain tissue - BrainTissue and total brain volume - Brain – 6 features). The difference between BrainTissue and Brain is exclusion/inclusion of ventricular/CSF volume, respectively. Cerebral exterior, vessel and optic chiasm were excluded from analysis due to their very small size. Cortical structures only measured as surrogate structure (cortical grey matter) and not considered as individual features. At acute stage, structural asymmetry was quantified as absolute asymmetry index (AAI) based on a structure's volume in the left and right hemisphere. AAI was calculated for the 14 non-cortical structures appearing in both brain hemispheres and the six surrogate structures. AAIs of all individual non-cortical, cortical and all brain structures were also added up. Segmentations at acute stage calculated with MALPEM and MALPEM4D, but when assessing ability of acute stage features to predict outcome only information available from acute images were included.

<table>
<tr><td>Reference</td><td>Ledig 2017[18]</td></tr>
<tr><td></td><td>For classifications, 100 runs of a 6-fold cross-validation were performed using linear discriminant analysis or individual features and support vector machine or random forest classifiers when multiple features were combined. All classifiers trained to discriminate between two disease severity categories (e.g. severe vs. low or moderate vs. low disability).

In summary, measured ability of volumetric and asymmetry measures of particular areas in brain to predict outcome, including individually and as surrogate groupings of larger areas.</td></tr>
<tr><td>Confounders or Stratification strategy</td><td>NA</td></tr>
<tr><td>Outcomes and effect sizes</td><td>Prediction of severe vs. low disability (GOSE scores 3-4 vs. 7-8) at chronic stage (median 229 days post-injury)
<table>
<tr><th>Structure</th><th>ACC (bACC) – accuracy (balanced accuracy accounting for differences in group size)</th><th>Sensitivity</th><th>Specificity</th></tr>
<tr><td>Ventricles</td><td>72 (71)</td><td>68</td><td>74</td></tr>
<tr><td>CorticalGreyMatter</td><td>70 (70)</td><td>70</td><td>71</td></tr>
<tr><td>DeepGreyMatter</td><td>74 (74)</td><td>74</td><td>75</td></tr>
<tr><td>BrainTissue</td><td>60 (60)</td><td>60</td><td>60</td></tr>
<tr><td>Brain</td><td>58 (59)</td><td>62</td><td>57</td></tr>
<tr><td>WhiteMatter</td><td>50 (46)</td><td>37</td><td>55</td></tr>
<tr><td>AccumbensArea</td><td>82 (85)</td><td>91</td><td>79</td></tr>
<tr><td>Hippocampus</td><td>80 (81)</td><td>83</td><td>79</td></tr>
<tr><td>Amygdala</td><td>73 (76)</td><td>83</td><td>68</td></tr>
<tr><td>LateralVentricle</td><td>75 (74)</td><td>73</td><td>76</td></tr>
<tr><td>InfLatVent</td><td>81 (75)</td><td>62</td><td>89</td></tr>
<tr><td>ThalamusProper</td><td>73 (74)</td><td>76</td><td>72</td></tr>
<tr><td>BasalForebrain</td><td>74 (75)</td><td>77</td><td>72</td></tr>
<tr><td>CerebellarVermalLobulesI-V</td><td>75 (74)</td><td>72</td><td>76</td></tr>
<tr><td>3rdVentricle</td><td>71 (71)</td><td>69</td><td>72</td></tr>
<tr><td>Putamen</td><td>76 (76)</td><td>77</td><td>75</td></tr>
<tr><td>BrainStem</td><td>69 (69)</td><td>71</td><td>68</td></tr>
</table></td></tr>
</table>

Reference	Ledig 2017[18]			
	CerebellumWhiteMatter	73 (72)	69	74
	VentralDC	56 (55)	54	56
	CerebellarVermalLobulesVIII-X	57 (62)	74	51
	CerebellumExterior	64 (64)	63	64
	4th Ventricle	60 (55)	45	66
	Caudate	53 (47)	35	60
	Pallidum	52 (51)	48	54
	CerebellarVermanlLobulesVI-VIII	54 (54)	54	54
	CSF	47 (45)	42	48
	CerebralWhiteMatter	43 (38)	28	49
	AsymmetryAllCortical	76 (74)	69	79
	AsymmetryAll	81 (73)	54	91
	AsymmetryWhiteMatter	75 (69)	55	82
	AsymmetryCerebralWhiteMatter	76 (68)	48	88
	AsymmetryAmygdala	82 (78)	68	87
	AsymmetryBrain	75 (72)	64	79
	AsymmetryBrainTissue	81 (73)	54	92
	AsymmetryCorticalGreyMatter	79 (72)	55	89
	AsymmetryAllNonCortical	79 (71)	50	91
	AsymmetryCerebellumWhiteMatter	69 (69)	69	69
	AsymmetryPutamen	75 (63)	34	92
	AsymmetryAccumbensArea	66 (62)	53	71
	AsymmetryCaudate	71 (63)	46	81
	AsymmetryDeepGreyMatter	72 (66)	52	81
	AsymmetryThalamusProper	75 (60)	27	94
	AsymmetryVentricles	68 (59)	39	79

Reference **Ledig 2017[18]**

AsymmetryHippocampus	63 (57)	43	71
AsymmetryPallidum	68 (56)	28	84
AsymmetryLateralVentricle	66 (57)	38	77
AsymmetryVentralDC	65 (56)	26	76
AsymmetryBasalForebrain	63 (55)	37	74
AsymmetryCerebellumExterior	68 (64)	54	74
AsymmetryInfLatVent	40 (37)	29	45

Prediction of moderate vs. low disability (GOSE scores 5-6 vs. 7-8) at chronic stage (median 229 days post-injury)

Structure	ACC (bACC) – accuracy (balanced accuracy accounting for differences in group size)	Sensitivity	Specificity
Ventricles	61 (61)	58	64
CorticalGreyMatter	66 (67)	71	63
DeepGreyMatter	42 (41)	38	44
BrainTissue	49 (49)	49	48
Brain	40 (40)	39	40
WhiteMatter	46 (44)	35	54
AccumbensArea	58 (59)	64	53
Hippocampus	54 (53)	49	58
Amygdala	60 (60)	58	62
LateralVentricle	62 (61)	57	65
InfLatVent	71 (69)	60	78
ThalamusProper	60 (61)	68	54
BasalForebrain	52 (51)	46	55
CerebellarVermalLobulesI-V	60 (61)	64	58
3rdVentricle	61 (61)	56	65
Putamen	57 (56)	51	61
BrainStem	44 (44)	47	42

Reference	Ledig 2017[18]			
	CerebellumWhiteMatter	56 (54)	45	64
	VentralDC	44 (44)	47	41
	CerebellarVermalLobulesVIII-X	65 (65)	66	65
	CerebellumExterior	45 (44)	40	49
	4th Ventricle	62 (62)	59	65
	Caudate	51 (51)	50	51
	Pallidum	49 (48)	41	54
	CerebellarVermanlLobulesVI-VIII	48 (47)	43	52
	CSF	45 (45)	42	47
	CerebralWhiteMatter	43 (41)	33	50
	AsymmetryAllCortical	59 (56)	42	71
	AsymmetryAll	63 (59)	37	80
	AsymmetryWhiteMatter	55 (53)	42	64
	AsymmetryCerebralWhiteMatter	59 (57)	46	68
	AsymmetryAmygdala	45 (44)	34	53
	AsymmetryBrain	57 (55)	46	65
	AsymmetryBrainTissue	50 (48)	39	57
	AsymmetryCorticalGreyMatter	59 (55)	31	79
	AsymmetryAllNonCortical	58 (56)	47	65
	AsymmetryCerebellumWhiteMatter	46 (47)	53	41
	AsymmetryPutamen	59 (55)	34	76
	AsymmetryAccumbensArea	60 (59)	53	64
	AsymmetryCaudate	53 (50)	33	66
	AsymmetryDeepGreyMatter	41 (41)	41	41
	AsymmetryThalamusProper	61 (58)	43	74
	AsymmetryVentricles	42 (42)	42	41

Reference	Ledig 2017[18]			
	AsymmetryHippocampus	48 (46)	36	57
	AsymmetryPallidum	58 (56)	47	65
	AsymmetryLateralVentricle	45 (46)	54	38
	AsymmetryVentralDC	62 (62)	64	61
	AsymmetryBasalForebrain	55 (54)	50	58
	AsymmetryCerebellumExterior	43 (45)	58	33
	AsymmetryInfLatVent	45 (44)	34	53
	The GOSE groups 3 & 4, 5 & 6 and 7 & 8 are summarised into three patient groups with severe, moderate and low disability outcome respectively. Note that where asymmetry is not mentioned, the feature refers to a volumetric measurement.			
Comments	Risk of bias – high – concerns about attrition (moderate), prognostic factor measurement (moderate) and reporting of results (moderate) Indirectness – serious – includes population with mixed severity of TBI, with proportion with each severity not reported, though the study was included as median values across the three disability groups are consistent with mild TBI (GCS 13-15).			

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Reference	Lee 2015[19]
Study type and analysis	Prospective study Accuracy assessed using area under the curve to assess probability that those with disability following head injury have a higher S100B, GFAP or UCH-L1 level, with sensitivity and specificity for cut-off values reported
Number of participants and characteristics	N=31 with mild TBI relevant to review protocol Inclusion criteria: patients with TBI; GCS 13-15 to be included as part of group B (mild TBI) Exclusion criteria: not reported Characteristics of population – only reported for n=45 mixed group of severe and mild TBI, not separately for mild subgroup analysed • Age, median (range); 58.5 (19.0-84.0) years • Gender: 73% male

Reference	Lee 2015[19]
	• Time to sample withdrawal, median (range): 3.2 (1.5-4.0) hours • GCS score, mean (severe/mild groups): 5.3/14.5 • Main injury: ○ Subdural haemorrhage, 17.8% ○ Epidural haemorrhage, 24.4% ○ Contusional haemorrhage, 37.8% ○ Subarachnoid haemorrhage, 8.9% ○ Diffuse axonal injury/fracture, 6.7%/4.4% Population source: participants recruited between July 2013 and August 2014.
Prognostic variable	Serum levels of the following biomarkers: • S100B – continuous and threshold of 27.01 ng/ml • GFAP – continuous and threshold of 18.00 ng/ml • UCH-L1 – continuous and threshold of 0.96 ng/ml Initial blood sampling performed within 24 h of trauma. Blood examinations performed through peripheral veins. First blood sample taken within 4 h of arrival at hospital. Serum samples analysed using ELISA. Cut-off points selected were those found to be the best operating points.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Poor outcome based on GOS at 3 months post-injury (poor outcome indicated by scores 1-3) in mild TBI group (methods of paper suggests prognostic accuracy results are for those mildly injured only)** <u>S100B</u> *Continuous variable* AUC: 0.95 *Threshold of 27.01 ng/ml* Sensitivity: 92% Specificity: 87%

Reference	Lee 2015[19]
	PPV: not reported and could not be calculated NPV: not reported and could not be calculated GFAP *Continuous variable* AUC: 0.99 *Threshold of 18.00 ng/ml* Sensitivity: 92% Specificity: 93% PPV: not reported and could not be calculated NPV: not reported and could not be calculated UCH-L1 *Continuous variable* AUC: 0.88 *Threshold of 0.96 ng/ml* Sensitivity: 78% Specificity: 96% PPV: not reported and could not be calculated NPV: not reported and could not be calculated At 3 months post-injury, clinical outcome was assessed by GOS. Poor outcome was indicated by scores of 1-3 on GOS and good outcome by scores of 4-5 on GOS.
Comments	Risk of bias: high – concerns about study participation (moderate), attrition (moderate) and reporting of results (moderate) Indirectness: none

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Reference	Li 2016[20]
Study type and analysis	Prospective multi-centre longitudinal study Sensitivity and specificity values reported based on multiple simulations
Number of participants and characteristics	N=48 (n=43 analysed as others insufficient MRI quality) Inclusion criteria: mild TBI (according to mild TBI committee of Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine – loss of consciousness <20 min, post-traumatic amnesia <24 h and an initial GCS 13–15) Exclusion criteria: abnormal findings on MRI (such as parenchymal haematoma, subarachnoid haemorrhage, or subdural haematoma); history of head injury or neurological or psychiatric disease; or had contraindications to MRI Characteristics of population: • Age, mean (SD): 30.6 (8.6) years • 51.2% female • Cause of injury: ○ Traffic crash, 72.1% ○ Assault, 18.6% ○ Fall, 9.3% • PTSD ○ At 1 month, 34.9% ○ At 6 months, 14.0% • GCS, median: 13 in PTSD group and 14 in no PTSD group • Duration of loss of consciousness, mean (SD): 5.67 (5.80) and 3.72 (4.05) in PTSD and no PTSD groups, respectively • Duration of post-traumatic amnesia, mean (SD): 3.82 (6.75) and 2.96 (7.34) in PTSD and no PTSD groups, respectively Population source: consecutive patients recruited in EDs of three hospitals in China
Prognostic variable	MRI – continuous mean values of multiple measures on MRI

Reference	Li 2016[20]
	• Mean of 12 mean diffusivity values: genu of corpus callosum, splenium corpus callosom, bilateral (left and right) superior longitudinal fasciculus, bilateral (left and right) inferior fronto-occipital fasciculus, bilateral (left and right) anterior thalamic radiation, bilateral (left and right) corticospinal tract, left inferior longitudinal fasciculus and left Uncinate fasciculus MRI performed 10-20 days post-injury. Performed with same 3T MRI scanner with standard head coil. Procedure included: the conventional MRI (including localiser sequence, T1-weighted imaging, T2-weightd imaging and fluid-attenuated inversion recovery imaging). Conventional MRI data acquired to exclude those with brain abnormalities. Processing of MRI data done using software. Whole brain analysis technique. Differences in fractional anisotropy and mean diffusivity (diffusion tensor imaging-based metrics) could then be compared between good and poor outcome groups based on PTSD. To assess predictive accuracy, Bayesian discrimination analysis used to investigate for DTI metrics ability to classify patients into good and poor recovery groups. Optimal posterior probabilities acquired using cross-validation bootstrap method randomly choosing three subjects from each group to be in a test set and then calculating posterior probability that those six subjects were classified into each category. The remaining patients were used as the training set. Simulation repeated 1000 times to increase accuracy of overall classification. Sensitivity and specificity calculated, with posterior probability thresholds set at P=0.5.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**PTSD diagnosis – poor recovery – unclear time-point (measured at 1 and 6 months)** MRI – mean of 12 mean diffusivity values, with posterior probability threshold of P=0.50 Sensitivity: 73.0% Specificity: 78.0% Accuracy: 75.56% PPV: not reported but calculated to be 76.0% NPV: not reported but calculated to be 75.0% Reported that fractional anisotropy values did not show the same discriminative significance. Evaluation of PTSD included psychometric measures for PTSD diagnosis, which is based on Diagnostic and Statistical Manual of Mental Disorders-V criteria, and symptom severity using the clinician-administered PTSD scale (CAPS). Longitudinal studies that repeatedly assessed cognitive performance in controlled intervals divided the patients into two groups with successful or poor recovery

Reference	Li 2016[20]
	(PR) patterns over time. Patients without PTSD were considered as having a successful recovery (SR), while patients with PTSD were considered as having a PR. PPV and NPV calculated using prevalence of 48.8% and n=43 analysed.
Comments	Risk of bias: high – concerns about attrition (moderate), outcome measurement (moderate) and reporting of results (high) Indirectness: serious – possibly a mixture of adults and children with proportion unclear. Included under adults as mean age is consistent with the adult population.

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Reference	Messe 2011[22]
Study type and analysis	Prospective multi-site open and longitudinal study Predictive accuracy of biomarkers in discriminating two groups based on outcome assessed with sensitivity and specificity reported
Number of participants and characteristics	N=55 (n=23 analysed) Inclusion criteria: aged 18-65 years; and mild TBI (as defined by mild TBI Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine) – trauma-induced physiological disruption of brain function manifested by at least one of the following signs: loss of consciousness (of less than 30 min; Glasgow Coma Scale (GCS) score between 13 and 15) and/or post-traumatic amnesia less than 24 h and/or any alteration in mental state at the time of the injury (for example, confusion or disorientation), and/or focal neurological deficit possibly transient. Exclusion criteria: history of chronic alcohol or drug abuse, previous TBI, contraindications to MRI, intubation and/or presence of a skull fracture and administration of sedatives on arrival in the emergency department, spinal cord injury, neurological signs or multiple disabilities (including at least one life-threatening injury associated), head injury following autolysis, patients with psychiatric or psychological disabilities that may interfere with the monitoring and/or evaluation, psychotropic medication at the time of TBI, history of hospitalization especially in psychiatry and/or arrest for psychological reasons, pre-existing neurological condition; presence of a major depressive syndrome according to the [DSM-IV, 1994]; or patients not participating fully in the procedure. Characteristics of population, for n=23 analysed: • Age, mean (SD): 30.6 (8.6) years • Gender – 73.9% male • Mechanism of injury

Reference	Messe 2011[22]
	○ Motor vehicle accident – car or motorbike, 26.1% ○ Motor vehicle accident – bicycle, 4.3% ○ Motor vehicle accident – pedestrian, 17.4% ○ Falls, 39.1% ○ Aggressions, 13.4% Population source: recruited from EDs of three hospitals in Kremlin-Bicetre, Nantes and Lille.
Prognostic variable	MRI – model consisting of mean diffusivity (MD) values of six regions (forceps major and forceps minor of the corpus callosum, left and right inferior fronto-occipital fasciculus, and left and right inferior longitudinal fasciculus) MRI performed between 7 and 28 days following injury (mean, SD: 17.2, 7.2 days). Consisted of axial 3D t1 weighted acquisition, a FLAIR acquisition, axial T2 weighted gradient-echo acquisition and axial echo-planar diffusion tensor imaging acquisition. Images acquired using 1.5T scanners in all three hospitals. MRI pre-processing was performed using software and measurements such as fractional anisotropy (FA), mean diffusivity (MD) and axial and radial diffusivity maps were computed. Structural data were analysed using voxel-based morphometry including structural images and microstructural images using mapping and creation of clusters, assessing differences in these between groups of good and poor outcome. Initial analyses determined whether FA, MD, axial or radial diffusivity was the most discriminant biomarker between good and poor outcome patients and to identify which white matter tracts had the highest differences between groups. Predictive accuracy of the most discriminant biomarker measured in the tracts was assessed by classifying patients into good and poor outcome groups using linear discriminant analysis. This involved first randomly choosing two patients from each outcome group, computing the linear discriminant analysis function using 19 remaining mild TBI patients and then calculating the posterior probability that the four test patients belong to each group. Procedure was repeated 1000 times. Classification accuracy assessed by calculating sensitivity and specificity. This was done using two thresholds for posterior probability – one here P=0.5 (all cases were classified) and one where P=0.95 (only cases with a high level of confidence were classified).
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Persistent post-concussion symptoms at 3 months** *Using posterior probability threshold (probability that a patient belongs to a particular group) of P=0.5 – all patients were classified* Sensitivity: 0.69 Specificity: 0.77 PPV: not reported but calculated to be 0.73

Reference	Messe 2011[22]
	NPV: not reported but calculated to be 0.73 PPV and NPV above calculated using prevalence of 47.8% and n=23 analysed. *Using posterior probability threshold (probability that a patient belongs to a particular group) of P=0.95 – only those patients with a high level of confidence were classified* Sensitivity: 0.34 Specificity: 0.89 Could not calculate PPV and NPV for this subgroup **For this second analysis, only half of the patients were classified due to the others not having a high level of certainty about which group they belong to based on the posterior probability and no conclusion could be drawn for the other half of the sample.** Persistent post-concussion symptoms evaluated using complaint questionnaire adapted from Gillum and Bosworth 2002. Performed at 3 months post-injury and included assessment of three categories of symptoms: behavioural and emotional disorders (irritability, anxiety, depression, and emotional labiality), subjective cognitive impairment (concentration, memory, processing speed, and divided attention) and somatic complaint (headache, fatigue, dizziness, noise intolerance). Post-concussion syndrome defined by presence of at least one complaint in each of three domains of questionnaire. Patients divided into good outcome and poor functional outcome groups based on presence or absence of persistent post-concussion symptoms. Various psychological and neuropsychological tets used to evaluate emotional, cognitive and somatic disorders, including forward and backward digit spans of the Wechsler Memory Scale, 3rd edition (WMS III), the trail making test B (TMT B), the number/letter sequence of WMS III, the board Stroop test [Stroop, 1935], the verbal fluency (categorical with animals and phonemic with the letter ‘‘m’’) released at 1 min, the dual task of Baddeley [Baddeley, 1986], a test of overall quality of life (EVA), the hospital anxiety depression scale (HADS) and visual analogue scale (VAS) of pain intensity for headaches and other pains [Scott and Huskisson, 1979].
Comments	Risk of bias: high – concerns about attrition (moderate for P=0.5 analysis and high for P=0.95 analysis) and reporting of results (moderate for both) Indirectness: serious – provides results for model containing multiple MRI measurements so difficult to assess utility of individual findings on MRI.

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Reference	Metting 2012[23]
Study type and analysis	Prospective study

Reference	Metting 2012[23]
	Sensitivity and specificity of dichotomised GFAP levels was assessed.
Number of participants and characteristics	N=94 Inclusion criteria: aged 18-65 years; mild TBI (initial GCS 13-15); and presence of post-traumatic amnesia. Exclusion criteria: history of neurological or psychiatric disease; mental retardation; addiction to alcohol or drugs; or inability for long-term follow-up. Characteristics of population – missing outcome in n=3 patients: • Age, mean (SD): 34.3 (13.9) years • Gender – not reported • Post-traumatic amnesia duration, mean (SD): 12.8 (25.9) h • CT abnormalities, 20% • MRI axonal injury (% of n=50 that had MRI), 28% • GOSE score ○ 5, 3% ○ 6, 19% ○ 7, 32% ○ 8, 46% • Complete return to work, 76% Population source: between May 2005 and June 2007 consecutive patients admitted and meeting inclusion criteria were prospectively identified for enrolment.
Prognostic variable	GFAP measured in serum – continuous variable Blood samples taken following admission to ED. Obtained an average of 2.4 h (SD, 2.1) following injury. Serum samples stored and analysed twice per sample using ELISA. S100B levels also measured but no prognostic accuracy data provided for this biomarker.
Confounders or Stratification strategy	NA

Reference	Metting 2012[23]
Outcomes and effect sizes	**Full recovery based on GOSE (score of 8 vs. <8) at 6 months** Sensitivity: 0.47 Specificity: 0.72 PPV: 0.50 NPV: 0.56 **Complete return to work at 6 months** Sensitivity: 0.45 Specificity: 0.65 PPV: 0.29 NPV: 0.67 Outcome at 6 months measured using GOSE, scored from 1 (death) to 8 (good recovery). Outcome dichotomised into complete vs. incomplete recovery (score of 8 vs. <8). Return to work at 6 months was scored from 0 to 3 (work/study completely resumed to not working at all) and for the purposes of analysis was dichotomised into completely returned to work (score of 0) and incompletely returned to work (score ≥1).
Comments	Risk of bias: moderate – concerns about reporting of results (moderate) Indirectness: none

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Reference	Niu 2019[25]
Study type and analysis	Prospective study Sensitivity, specificity and area under the receiver operating characteristics curve (AUC) were calculated for a model for predicting chronic post-traumatic headache
Number of participants and characteristics	N=70 (n=56 analysed at 3 months) Inclusion criteria: mild TBI (WHO Collaborating Centre for Neurotrauma Task Force) within 1 week post-injury. Exclusion criteria: structural abnormality on conventional neuroimaging and a premorbid condition, such as a previous brain injury, pre-existing headache, neurological disease, concurrent substance or alcohol abuse.

Reference	Niu 2019[25]
	Characteristics of population, for n=70 originally included (separated into those with acute and those without acute post-traumatic headache, n=54 and n=16, respectively): • Age, mean (SD): 35.87 (11.92) and 30.94 (12.94) years • Gender – 68.5% male and 50% male • Present headache pain intensity: 89.5 and 31.5 • Present general pain intensity: 76.75 and 45.78 • Average pain intensity over past week: 88.65 and 40.13 • Post-concussive symptoms (RPQ-6), mean (SD): 14.78 (16.11) and 9.75 (14.21) • Duration after onset of mild TBI, mean (SD): 2.63 (2.59) and 2.25 (1.34) days • Duration of loss of consciousness, mean (SD): 9.41 (8.75) and 9.38 (10.3) min • Duration of post-traumatic amnesia, mean (SD): 0.28 (1.05) and 0.19 (0.54) h • Fear of brain damage with a hypochondrial concern: 0.39 (0.60) and 0.13 (0.34) Population source: all consecutive patients from local ED with non-contrast head CT due to acute head trauma enrolled as initial population.
Prognostic variable	MRI – periaqueductal grey (PAG)-seeded functional connectivity in default mode network **(right praecuneus and right inferior parietal lobule)**, in combination with other non-imaging characteristics (age, sex, education and loss of consciousness) combined into single signature for predicting chronic post-traumatic headache using logistic regression MRI scanning originally evaluated within 7 days post-injury (acute phase, mean (SD): 2.0 (2.3) days). MRI scanning conducted on 3T MRI scanner including T1 weighted 3D BRAVO sequence, a single shot, gradient-recalled echo planar imaging sequence, conventional T1 weighted and T2 weighted image and susceptibility weighted imaging. Resting state included 180 volumes. Pre-processing of MRI data was performed using software. PAG-seeded functional connectivity analysis performed for right ventrolateral PAG as the seed. This was chosen as seed as it was: based on previous resting-state functional connectivity of the PAG and pain-related studies; located within ventrolateral PAG playing role in opioid antinociception; and PAG is vulnerable to mild TBI and closely related to pain symptoms following mild TBI. Resting state functional connectivity performed using MATLAB. Mean time courses across all voxels within region of interest for each participant was extracted and used as model response function in generalised linear model. Functional connectivity maps generated and compared across groups. This provided mask of mild TBI-induced pain associated regions for later analysis. Individual functional connectivity values (mean z scores) within region of interest were extracted.

Reference	Niu 2019[25]
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Persistent post-traumatic headache at 3 months** Sensitivity: 1.00 (95% CI, 0.66 to 1.00) Specificity: 0.78 (95% CI, 0.63 to 0.89) AUC: 0.8935, P<0.005 PPV and NPV could not be calculated as prevalence at 3 months not reported Based on VAS score – score >0 persistent headache and a score of 0 indicating non-persistent headache. Scores could range from 0 to 10, with 0 meaning no pain at all and 10 meaning worst possible pain.
Comments	Risk of bias: high – concerns about attrition (moderate) and reporting of results (moderate) Indirectness: serious – population was a mixture of children and adults with no proportions given. Study was included under adult population as the mean age was consistent with the adult population

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Reference	Okonkwo 2013[26] – reports same results as those in Diaz-Arrastia 2014[7], but suggests they are 3-month rather than 6-month results
Study type and analysis	Part of the prospective Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study Predictive accuracy of biomarker assessed by area under the receiver operating curve (AUC)
Number of participants and characteristics	N=215 (n=145 analysed at 6 months) Inclusion criteria: adults ≥16 years presenting within 24 h of injury and have a history of trauma to the head sufficient to be triaged to non-contrast head CT using the American College of Emergency Physicians/Centers for Disease Control (ACEP/CDC) evidence-based joint practice guideline. Exclusion criteria: not reported Characteristics of population, for n=215 initially included: • Age, mean (SD): 42.0 (18.0) years

Reference	**Okonkwo 2013[26] – reports same results as those in Diaz-Arrastia 2014[7], but suggests they are 3-month rather than 6-month results**
	• 73% male • TBI severity ○ Mild (GCS 13-15), 83% ○ Moderate (GCS 9-12), 4% ○ Severe (GCS 3-8), 13% • Mechanism of injury ○ Fall, 36% ○ Motor vehicle accident, 27% • Positive CT findings, 42.5% for mild, 77.8% for moderate and 96.3% for severe Of those lacking data at 6 months, there was a significant difference in terms of GCS score compared to those remaining. 94% of those without data sustained mild TBI, whereas 78% of patients with 6 month follow-up data sustained mild TBI. Population source: identified and recruited upon arrival at one of three level I trauma centres as part of the multicentre prospective TRACK-TBI study
Prognostic variable	Plasma levels of GFAP-breakdown products Blood samples collected within 24 h of injury. Mean (SD) 10.9 (6.4) h for time-point of sample collection. Plasma samples frozen for analysis. Analysed using ELISA which detected whole GFAP as well as GFAP-breakdown products.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Full recovery based on GOSE at 6 months (score of 8 vs. <8)** AUC: 0.65 (95% CI, 0.55 to 0.74) **Unfavourable recovery based on GOSE at 6 months (score of 1-4 vs. ≥5)** AUC: 0.74 (95% CI, 0.61 to 0.87)

Reference	**Okonkwo 2013[26] – reports same results as those in Diaz-Arrastia 2014[7], but suggests they are 3-month rather than 6-month results**
	GOSE used to assess patient outcome at 6 months. Scored from 1-8 with 1 representing death and 8 representing upper good recovery. Ratings based on patient consciousness, independence, ability to work, social and leisure activities, social relationships and other sequalae of TBI. Upper good recovery (score of 8) indicates return to pre-injury baseline with no residual effects of the TBI. **NOTE: this outcome data was not included in the analysis as the values are identical to some of those reported in the slightly later Diaz-Arrastia 2014[7] paper but the Okonkwo 2013 paper suggests they are for the 6-month time-point rather than the 3-month time-point in the later paper. Data from the 2014 paper has been used, with the values reported used for 3 months, as the later paper provides other data for the 6 month time-point.**
Comments	Risk of bias: high – concerns about attrition (high) Indirectness: none

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Reference	**Posti 2020[27]**
Study type and analysis	Prospective study part of European Union-funded TBIcare (Evidence-Based Diagnostic and Treatment Planning Solution For Traumatic Brain Injuries) project Partial area under the curve (pAUC) of the receiver operating characteristic (ROC) was used to compare only a portion of the biomarkers AUC curves, which was set to the clinically relevant range of 90–100% sensitivity.
Number of participants and characteristics	N=160 (n=137 with outcome assessed at 4-16 months post-injury) Inclusion criteria: age ≥ 18 years and clinical diagnosis of TBI and indications for acute head CT according to the National Institute for Health and Care Excellence criteria; and admission levels of various plasma biomarkers measured within 24 h of hospital admission **– provides results separately for subsets with confirmed CT positive finding (n=82) and those negative on CT (n=55)** Exclusion criteria: blast-induced or penetrating injury, (ii) chronic subdural hematoma, (iii) inability to live independently due to a pre-existing brain disease, (iv) TBI or suspected TBI not needing head CT, (v) more than 2 weeks from the injury, (vi) not living in the hospital district thereby preventing follow-up visits, (vii) not speaking the native language (Finnish), or (viii) no consent received. Characteristics of population

Reference	Posti 2020[27]
	For n=82 in CT-positive group • Age, mean (SD): 50.46 (20.35) years • 78% male • GCS, median (range): 14 (3-15) • Pupil reactivity ○ Unreactive, 11% ○ Sluggish, 4% ○ Reactive, 74% • Injury severity score, median (range): 18 (1-50) • Isolated TBI, 60% • Evacuated mass lesion, 29% • Hypoxia, 7% • Hypotension, 4% • Anaemia, 4% • Admitted to hospital, 93% • Mass lesion types: ○ Subdural haematoma, 65% ○ Intracerebral haematoma, 13% ○ Epidural haematoma, 32% ○ Mass lesion size >25 cm^3, 32% • TBI-related deaths, 12% • Outcome based on GOSE: ○ Favourable (GOSE 5-8), 60% ○ Unfavourable (GOSE 1-4), 40% ○ Complete recovery (GOSE 8), 12% ○ Incomplete recovery (GOSE 1-7), 88% *For n=55 in CT-negative group* • Age, mean (SD): 43.67 (18.21) years

Reference	Posti 2020[27]
	• 62% male • GCS, median (range): 15 (3-15) • Pupil reactivity ○ Unreactive, 2% ○ Sluggish, 2% ○ Reactive, 95% • Injury severity score, median (range): 6 (1-57) • Isolated TBI, 59% • Evacuated mass lesion, 0% • Hypoxia, 2% • Hypotension, 0% • Anaemia, 0% • Admitted to hospital, 60% • Mass lesion types: NA • TBI-related deaths, 2% • Outcome based on GOSE: ○ Favourable (GOSE 5-8), 93% ○ Unfavourable (GOSE 1-4), 7% ○ Complete recovery (GOSE 8), 42% ○ Incomplete recovery (GOSE 1-7), 58% Population source: recruited patients with acute TBIs at the Turku University Hospital, Finland, from November 2011 to October 2013
Prognostic variable	Plasma levels of the following biomarkers: • GFAP – thresholds of 94.7 pg/ml (favourable outcome, CT-positive group), 113.9 pg/ml (complete recovery, CT-positive group) and 0.4 pg/ml (favourable outcome, CT-negative group); and continuous measure for complete recovery in CT-negative group • NF-L – thresholds of 179.6 pg/ml (favourable outcome, CT-positive group), 245.1 pg/ml (complete recovery, CT-positive group), 8.3 pg/ml (favourable outcome, CT-negative group) and 4.9 pg/ml (complete recovery, CT-negative group) • S100B – threshold of 2300.8 pg/ml (favourable outcome, CT-positive group), continuous measure for complete recovery in CT-positive group, threshold of 45.3 pg/ml (favourable outcome, CT-negative group) and continuous measure for complete recovery in CT-negative group

Reference	Posti 2020[27]
	Note: thresholds not given in some cases but results still provided, suggesting the results are for the biomarker as a continuous variable as there was no threshold identified. Blood samples of all patients obtained within 24 h from admission. In those where exact time of injury was available, mean (SD) time from injury to blood sampling was 13.1 (10.4) h (n=62). Levels of biomarkers analysed using assay kits specific to each biomarker. All biomarker measurements were performed by board-certified laboratory technicians who were blinded to clinical data.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Full recovery based on GOSE at 4-16 months (score of 8 vs. <8)** *CT positive group, n=82* • GFAP, threshold 113.9 pg/ml: o Partial AUC (95% CI): 1.0 (0.0 to 3.2) o Sensitivity (95% CI): 94.4 (88.9 to 98.6) o Specificity (95% CI): 22.4 (12.2 to 34.7) o PPV calculated: 14.0% o NPV calculated: 97.0% • NF-L, threshold 245.1 pg/ml: o Partial AUC (95% CI): 1.2 (0.0 to 4.1) o Sensitivity (95% CI): 93.1 (86.1 to 98.6) o Specificity (95% CI): 20.0 (0.0 to 50.0) o PPV calculated: 14.0% o NPV calculated: 96.0% • S100B, no threshold given, assume continuous measure o Partial AUC (95% CI): 0.0 (0.0 to 1.4) o Sensitivity (95% CI): 100.0 (100.0 to 100.0) o Specificity (95% CI): 0 (0.0 to 0.0) o PPV calculated: 12.0% o NPV could not be calculated as specificity was 0.0%

Reference	Posti 2020[27]
	PPV and NPV values above calculated using prevalence of 12.0% and n=82 analysed. *CT negative group, n=55* • GFAP, no threshold given, assume continuous measure: ○ Partial AUC (95% CI): 0.2 (0.0 to 1.3) ○ Sensitivity (95% CI): 100.0 (100.0 to 100.0) ○ Specificity (95% CI): 0.0 (0.0 to 0.0) ○ PPV calculated: 42.0% ○ NPV could not calculate as specificity was 0.0% • NF-L, threshold 4.9 pg/ml: ○ Partial AUC (95% CI): 0.9 (0.0 to 2.9) ○ Sensitivity (95% CI): 93.8 (84.4 to 100.0) ○ Specificity (95% CI): 17.4 (4.3 to 34.8) ○ PPV calculated: 45.0% ○ NPV calculated: 79.0% • S100B, no threshold given, assume continuous measure ○ Partial AUC (95% CI): 0.0 (0.0 to 1.1) ○ Sensitivity (95% CI): 100.0 (100.0 to 100.0) ○ Specificity (95% CI): 0 (0.0 to 0.0) ○ PPV calculated: 42.0% ○ NPV could not calculate as specificity was 0.0% PPV and NPV values above calculated using prevalence of 42.0% and n=55 analysed. **Unfavourable recovery based on GOSE at 4-16 months (score of 1-4 vs. ≥5)** *CT positive group, n=82* • GFAP, threshold 94.7 pg/ml: ○ Partial AUC (95% CI): 0.2 (0.0 to 2.6)

Reference	Posti 2020[27]
	○ Sensitivity (95% CI): 90.9 (81.8 to 100.0 ○ Specificity (95% CI): 12.2 (4.1 to 22.4) ○ PPV calculated: 41.0% ○ NPV calculated: 67.0% • NF-L, threshold 179.6 pg/ml: ○ Partial AUC (95% CI): 0.6 (0.0 to 3.2) ○ Sensitivity (95% CI): 90.9 (78.8 to 100.0) ○ Specificity (95% CI): 22.4 (12.2 to 34.7) ○ PPV calculated: 44.0% ○ NPV calculated: 79.0% • S100B, threshold 2300.8 pg/ml: ○ Partial AUC (95% CI): 0.2 (0.0 to 1.5) ○ Sensitivity (95% CI): 100.0 (100.0 to 100.0) ○ Specificity (95% CI): 2.0 (0.0 to 6.1) ○ PPV calculated: 40.0% ○ NPV calculated: 100.0% PPV and NPV values above calculated using prevalence of 40.0% and n=82 analysed. *CT negative group, n=55* • GFAP, threshold 0.4 pg/ml: ○ Partial AUC (95% CI): 0.2 (0.0 to 1.3) ○ Sensitivity (95% CI): 100.0 (100.0 to 100.0) ○ Specificity (95% CI): 0.0 (0.0 to 0.0) ○ PPV calculated: 7.0% ○ NPV could not calculate as specificity was 0.0% • NF-L, threshold 8.3 pg/ml:

Reference	Posti 2020[27]
	○ Partial AUC (95% CI): 4.1 (2.7 to 10.0) ○ Sensitivity (95% CI): 100.0 (100.0 to 100.0) ○ Specificity (95% CI): 41.2 (27.5 to 54.9) ○ PPV calculated: 11.0% ○ NPV calculated: 100.0% • S100B, threshold 45.3 pg/ml ○ Partial AUC (95% CI): 1.4 (0.6 to 6.7) ○ Sensitivity (95% CI): 100.0 (100.0 to 100.0) ○ Specificity (95% CI): 13.7 (5.9 to 23.5) ○ PPV calculated: 8.0% ○ NPV calculated: 100.0% PPV and NPV values above calculated using prevalence of 7.0% and n=55 analysed. GOSE used to assess patient outcome at 4-16 months post injury, with mean (SD) for time since injury to GOSE measurement of 7.82 (3.33) months. Outcomes were defined as favourable (GOSE 5–8) and unfavourable (GOSE 1–4), and complete recovery (GOSE 8) and incomplete recovery (GOSE < 8). Partial area under the curve (pAUC) of the receiver operating characteristic (ROC) was used to compare only a portion of the biomarkers AUC curves, which here was set to the clinically relevant range of 90–100% sensitivity. Higher values for pAUC are better, but will not be 100% - not sure what % is possible/good for pAUC as not well explained in paper.
Comments	Risk of bias: high – concerns about attrition (moderate) and reporting of results (moderate) Indirectness: serious – mixed TBI severity with proportion with mild TBI unclear, though median values consistent with mild TBI.

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Reference	Richter 2021[28]
Study type and analysis	Prospective multi-centre cohort study – including participants from 2 prospective observation cohorts (CENTER-TBI) and a Cambridge study with a similar protocol Models consisting of multiple variables were compared using area under receiver operating characteristic curve (AUC)

Reference	Richter 2021[28]
Number of participants and characteristics	N=81 (n=73 from CENTER-TBI and n=8 from Cambridge local study) – **n=65 analysed as sufficient data for outcome analysis** Inclusion criteria: mild TBI (GCS 13-15 on presentation); satisfied local criteria for CT head imaging, and underwent an initial MRI within 72 hours and a second MRI within 31 days (2-3 weeks). Exclusion criteria: not reported Characteristics of population, n=65 analysed for outcomes: • Age, median (IQR): 47 (25-59) years • 72% male • Mechanism of injury ○ Acceleration/deceleration, 12% ○ Blow to head, 11% ○ Fall from height, 25% ○ Ground level fall, 25% ○ Head against object, 12% ○ Multi-mechanistic, 15% • GCS, median (IQR): 15 (15-15) • Injury Severity Score, median (IQR): 8.0 (4.0-10.0) • Stratum ○ ED, 55% ○ Admission, 32% ○ ICU, 12% • Marshall score ○ 1, 68% ○ 2, 25% ○ 3-4, 0% ○ 5, 2% ○ 6, 6%

Reference	Richter 2021[28]
	• GOSE, median (IQR): 8.0 (7.0-8.0) Supplementary material provides data for those not included in analysis, with some possible differences between groups, with only one <0.05 (Injury Severity Score). Population source: all eligible patients included from 2 prospective observation cohorts (CENTER-TBI; between 19th December 2014 and 17th December 2017) and a Cambridge study with a similar protocol (between 20th November 2012 and 19th December 2013).
Prognostic variable	MRI – various imaging strategies (sequencies method and quantitative or qualitative): o DTI imaging alone at first MRI scan, qualitative and quantitative (within 72 h) o T1 weighted imaging alone at first MRI scan, qualitative and quantitative (within 72 h) o T1 and DTI imaging combined at first MRI scan, qualitative and quantitative (within 72 h) o T1 and DTI imaging combined at second MRI scan, qualitative and quantitative (31 days) o T1 and DTI imaging combined at first MRI scan, qualitative only (within 72 h) o T1 and DTI imaging combined at first MRI scan, quantitative only (within 72 h) MRI obtained on 3T and included volumetric T1-weighted, volumetric fluid-attenuated inversion recovery, T2-weighted and susceptibility-weighted imaging and diffusion tensor imaging. Reported centrally by Cambridge or icometrix investigators blinded to patient outcome. 138 anatomical regions collapsed into 15 regions of interest. White matter parcellation into 72 tracts performed. Mixed models fitted for brain regions that changed significantly between scans in patients. Corpus callosum included as it is commonly implicated in mild TBI. Region of interest volume (normalised to intracranial volume), fractional anisotropy or mean diffusivity were y variables, group (patient vs. control, age and sex were the covariates. Scanner was a random intercept. Association between scan evolution of diffusion tensor imaging and symptoms was assessed. Change in fractional anisotropy measured as a log (value at second MR scan/value at first MR scan) as was mean diffusivity. Logistic regression examined association between imaging findings and favourable recovery at 3 months. Patients with missing DTI or outcome data excluded from analyses.
Confounders or Stratification strategy	Covariates included number of tracts for which fractional anisotropy, mean diffusivity or both were abnormal (>2 SD above or below mean of controls), as well as age and sex.
Outcomes and effect sizes	**Favourable recovery at 3 months – GOSE score of 8** *Imaging findings at first MRI scan (within 72 h)*

Reference	Richter 2021[28]
	DTI and T1-weighted sequences combined, qualitative and quantitative imaging AUC (95% CI): 0.87 (0.78 to 0.96), P=0.009 vs. second MRI scan results (31 days) below PPV: 0.79 NPV: 0.81 DTI and T1-weighted sequences combined, qualitative imaging only AUC (95% CI): 0.69 (0.56 to 0.82), P<0.001 vs. qualitative and quantitative results above PPV: 0.68 NPV: 0.65 DTI and T1-weighted sequences combined, quantitative imaging only AUC (95% CI): 0.87 (0.78 to 0.96) PPV: 0.72 NPV: 0.76 T1-weighted sequence alone, qualitative and quantitative imaging AUC (95% CI): 0.76 (0.64 to 0.88), P=0.02 vs. combined both sequences above PPV: 0.81 NPV: 0.71 DTI sequence alone, qualitative and quantitative imaging AUC (95% CI): 0.76 (0.64 to 0.88), P=0.01 vs. combined both sequences above PPV: 0.62 NPV: 0.65 *Imaging findings at second MRI scan (within 2-3 weeks, 31 days)* DTI and T1-weighted sequences combined, qualitative and quantitative imaging AUC (95% CI): 0.75 (0.62 to 0.87) PPV: 0.59 NPV: 0.67

Reference	Richter 2021[28]
	Favourable recovery at 3 months, defined as an extended Glasgow Outcome Scale score of 8. Recovery was favourable for 33/65 patients (51%) at 3 months.
Comments	Risk of bias: high – concerns about attrition (high) Indirectness: serious – unclear if had to be >16 years to be included and if limited to adults, though median age is consistent with an adult population

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Reference	Ryb 2014[29]
Study type and analysis	Prospective cohort study AUC to predict post-injury PCS
Number of participants and characteristics	N=180 (N=150 with S100B levels available within 6 hrs of admission) N=103 12 mths Inclusion criteria: People aged 18-64 yrs who were admitted to a trauma centre with a diagnosis of mild TBI following blunt trauma. Mild TBI was defined as an admitting GCS of 13-15 with the presence of at least one of the following: loss of consciousness lasting less than 30 mins, loss of memory for events immediately before or after injury or alteration of mental status following the injury such as confusion, disorientation or feeling dazed. Exclusion criteria: Brain lesion on CT scan or skull fracture or CSF leak requiring intervention, moderate/severe multiple trauma, focal neurological findings, post-traumatic amnesia lasting more than 24 hrs, seizures, spinal fracture, previous moderate/severe brain injury, active duty military or being on probation or parole Age > 330 49.2% Female 35.8% Extra-cranial injury 49.2% ISS ≥ 9 61.9% History of previous mild TBI 22.5%

Reference	Ryb 2014[29]
	≥4 symptoms pre-injury 19.2% Return to school or work (12 mths) 89.1%
Prognostic variable(s)	S100B
Confounders OR Stratification strategy	NA
Outcomes and effect sizes	**Mild TBI symptom checklist – presence of four or more symptoms** *3 months, n=110* AUC: 0.49 *6 months, n=106* AUC: 0.50 *12 months, n=103* AUC 0.51 **Ability to return to work or school at 12 months, n=103** AUC: 0.59
Comments	Risk of bias - moderate – attrition (moderate) Indirectness - none

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Reference	Savola 2003[30]
Study type and analysis	Prospective study Predictive value of S100B threshold assessed by reporting area under curve and sensitivity and specificity

Reference	Savola 2003[30]
Number of participants and characteristics	N=199 with mild TBI (n=172 analysed with outcome data) Inclusion criteria: aged 16-49 years; mild head injury (GCS 13-15 on admission, loss of consciousness <30 min if present, and no focal deficits in a neurological examination on admission) admitted to ED of Oulu University Hospital; and blood sample drawn within 6 h of injury Exclusion criteria: not reported Characteristics of population, reported separately for those with (n=37) and without (n=135) post-concussion symptoms at follow-up *With post-concussion symptoms (n=37)* Age, mean (SD): 33.7 (10.6) years 27% female Unemployed, 35% Psychiatric illness in childhood, 22% Previous brain injury, 38% Current heavy drinking, 38% Loss of consciousness, 59% Post-traumatic amnesia, 84% Dizziness on admission, 49% Headache on admission, 65% Vomiting on admission, 14% Presence of extra-cranial injury, 24% Skull fracture, 38% Serum protein S100 = 0.5 µg/l, 27% *Without post-concussion symptoms (n=135)* Age, mean (SD): 33.0 (24.0) years 24% female Unemployed, 22% Psychiatric illness in childhood, 8% Previous brain injury, 30%

Reference	Savola 2003[30]
	Current heavy drinking, 33% Loss of consciousness, 35% Post-traumatic amnesia, 65% Dizziness on admission, 21% Headache on admission, 36% Vomiting on admission, 10% Presence of extra-cranial injury, 16% Skull fracture, 6% Serum protein S100 = 0.5 µg/l, 7% Population source: consecutive patients meeting inclusion criteria from single hospital
Prognostic variable	Serum levels of S100B – thresholds of ≥0.50 µg/l, ≥0.40 µg/l, ≥0.30 µg/l and ≥0.20 µg/l and continuous • Provides results separately for S100B before and after normalisation of S100B values (to correspond to the time of onset of head injury) Venous blood samples obtained within 6 h of trauma and serum samples stored until analysed. Concentrations measured using immunoluminometric assay. Values of 0.50 µg/l or higher were considered pathological.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Post-concussion symptoms at 8-30 months** S100B – threshold of ≥*0.50 µg/l* *Before normalisation* Sensitivity: 27% Specificity: 93% PPV: 53% NPV: 82% *After normalisation for the time of onset of head injury* Sensitivity: 65% Specificity: 79% PPV calculated: 46.0%

Reference	Savola 2003[30]
	NPV calculated: 89.0% S100B – threshold of ≥*0.40 µg/l* *Before normalisation* Sensitivity: 38% Specificity: 91% PPV calculated: 54.0% NPV calculated: 84.0% *After normalisation for the time of onset of head injury* Sensitivity: 73% Specificity: 70% PPV calculated: 40.0% NPV calculated: 90.0% S100B – threshold of ≥*0.30 µg/l* *Before normalisation* Sensitivity: 49% Specificity: 82% PPV calculated: 43.0% NPV calculated: 85.0% *After normalisation for the time of onset of head injury* Sensitivity: 78% Specificity: 59% PPV calculated: 34.0% NPV calculated: 91.0% S100B – threshold of ≥*0.20 µg/l*

Reference	Savola 2003[30]
	Before normalisation Sensitivity: 68% Specificity: 67% PPV calculated: 36.0% NPV calculated: 88.0% *After normalisation for the time of onset of head injury* Sensitivity: 92% Specificity: 41% PPV calculated: 30.0% NPV calculated: 95.0% PPV and NPV values calculated using prevalence of 21.5% and n=172 analysed for all groups above. <u>S100B – continuous</u> *Before normalisation* AUC: 0.702 (95% CI, 0.60 to 0.81) *After normalisation for the time of onset of head injury* AUC: 0.752 (95% CI, 0.66 to 0.84) Considered positive for symptoms if at least one symptom reported by the person at the time of interview or if they had suffered with them from day of trauma for at least one month, and if they were more severe than before the trauma Based on modified version of Rivermead Post-Concussion Symptoms Questionnaire – modified by dichotomising into yes or no and adding questions about alcohol tolerance and panic attacks. Interviews conducted by telephone at 8-30 months post-injury, with the aim of assessing whether post-concussion symptoms had lasted for over a month since the trauma. Interviewers were blind to laboratory data for patients. 37/172 patients had post-concussion symptoms, with n=30 suffering from at least 2 symptoms lasting for 1 month or longer. Mean number of symptoms was 5.0 (3.6) per person, ranging from 1 to 14. Authors noted that results for normalising S100B values to correspond to time of onset of head injury improved results (increased area under curve), suggesting that normalisation of S100B values may be justified. However, it was noted that in practice it may be difficult to know the exact time of injury in patients in order to normalise values and to exclude the presence of secondary brain injury.

Reference	Savola 2003[30]
	For normalised S100B values, normalisation of S100B was done according to a half-life of 120 min as follows: normalised S100B = 2 exp (time from trauma to blood sampling in minutes/120 min) x measured S100B.
Comments	Risk of bias: high – concerns about attrition (moderate) and reporting of results (moderate) Indirectness: serious – population was possibly a mixture of children and adults with no proportions given (study was included under adult population as the mean age was consistent with the adult population)

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Reference	Siman 2013[31]
Study type and analysis	Prospective study Sensitivity and specificity of SNTF for predicting failure to improve cognitive performance over 3 months reported
Number of participants and characteristics	N=17 (n=13 analysed for cognitive SDMT test at both time-points) Inclusion criteria: mild TBI (defined by criteria from the Centers for Disease Control: had an injury to the head from blunt trauma, acceleration, or deceleration forces with one or more of the following conditions: (1) observed or self-reported confusion, disorientation, or impaired consciousness, dysfunction of memory at the time of the injury, loss of consciousness lasting <30 min; and, (2) symptoms such as headache, dizziness, fatigue, irritability, and poor concentration soon after the injury. Additional inclusion criteria were a Glasgow Coma Scale score of 13–15 upon examination at an emergency centre, no abnormal findings on head CT, duration of loss of consciousness for no more than 30 min, post-traumatic amnesia for <24 h, and an Abbreviated Injury Score (AIS) ≤3 and an ISS of <12 modified to exclude the head region); and aged 12-30 years. Exclusion criteria: non-fluency in either English or Spanish, failure to provide adequate contact information for scheduling follow-up assessments, blood alcohol level (200 mg/dL, previous hospitalisation for head injury, pregnancy when screened prior to brain imaging, pre-existing neurologic disorder associated with cerebral dysfunction and/or cognitive deficit (e.g., cerebral palsy, mental retardation, epilepsy) or diagnosed dyslexia, pre-existing severe psychiatric disorder (e.g., bipolar disorder, schizophrenia), and contraindications to undergoing MRI Characteristics of population – only provides for n=38 which includes mild TBI, controls and those with orthopaedic disc injury controls: Age, mean (SD): 20.5 (5.8) years 26% female % non-black, 60% GCS <15 (for mild TBI subgroup, n=17): 25%

Reference	Siman 2013[31]
	Non-cranial injury severity, mean (SD): 1.37 (1.42) Population source: participants were part of a larger study comprising right-handed participants of ages 12–30 years, who were recruited and tested on neuropsychological and brain imaging measures at baseline (within 96 h of injury), and at follow-up sessions at 1 month (neuropsychological measures only) and 3 months. Participant recruitment was from a random, unselected series of patients admitted to emergency centers in the Texas Medical Center, Houston, including Ben Taub General Hospital, Texas Children's Hospital, and Memorial Herman Hospital. The smaller biomarker study subgroup was selected randomly from the overall mild TBI study.
Prognostic variable	Plasma levels of calpain-cleaved αII spectrin N-terminal fragment (SNTF) – SNTF+ defined as at least twice the lower limit of detection of 10 units in an ultrasensitive sandwich immunoassay ELISA used to assess concentrations in plasma samples. Plasma samples were collected within 24 h of injury.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Cognitive performance – failure to achieve improvement of at least 5 points over 3 months on SDMT** Sensitivity: 100% Specificity: 75% Note: values above don't match those generated using raw data, therefore not used in analysis. 6/8 SNTF-ve patients showed improvement in cognitive performance over 3 months compared to 0/5 SNTF+ve patients. Sensitivity calculated based on this raw data differed to that reported above: 71 (29 to 96%). Specificity calculated was 100 (54 to 100)% **- results based on raw data used in analysis.** PPV calculated to be 100.0% and NPV calculated to be 75.0%. PPV and NPV calculated using raw data above. SDMT used as measure of processing speed deficits. Timed substitution task with written and oral response modalities and is highly sensitive to processing speed deficits in the 8–78 year age range. Using a reference key, each examinee was asked to pair specific numbers with given geometric symbols within 90 seconds. The number of correct responses in the written modality was the variable used in this study. The analyses were conducted by investigators blinded to the plasma biomarker data.
Comments	Risk of bias: high – concerns about study participation (moderate), attrition (moderate) and reporting of results (moderate)

Reference	Siman 2013[31]
	Indirectness: serious – population was a mixture of children and adults with no proportions given (study was included under adult population as the mean age was consistent with the adult population) and is also quite a specific age group of 12-30 years.

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Reference	Stein 2021[32]
Study type and analysis	Prospective study, part of TRACK-TBI study – subset of TRACK-TBI with mild TBI Provides sufficient data to be able to calculate sensitivity and specificity
Number of participants and characteristics	N=421 (n=57 excluded as did not have outcome data at 3 and 6 months) Inclusion criteria: adults (≥17 years); GCS ED arrival scores of 13-15; PCL-5 outcome measure (PTSD Checklist for DSM-5) collected at 3 and 6 months; and MR volumetric measures analysed from research-acquired 3D T1-weighted MRI at 2 weeks post-injury. Exclusion criteria: significant polytrauma that would affect follow-up; penetrating TBI; prisoners or patients in custody; pregnancy; patients on psychiatric hold; non-English or non-Spanish speakers; contraindication to MRI; and major debilitating mental (e.g. schizophrenia or bipolar disorder) or neurological (e.g. stroke, dementia) disorders or any other disorder that would interfere with the assessment and follow-up or provision of informed consent. Characteristics of population: • Age, mean (SD): 38.7 (16.1) years • ~66.5% male • Patient type: ○ ED discharge, 41.6% ○ Hospital admission no ICU, 40.4% ○ Hospital admission with ICU, 18.1% • Race: ○ White, 73.4% ○ Black, 18.1% ○ Other, 7.8% • Cause of injury

Reference	Stein 2021[32]
	○ Road traffic accident, 63.4% ○ Incidental fall, 21.6% ○ Violence/assault, 5.5% ○ Other, 9.5% • Psychiatric history ○ Yes, 17.6% • Prior TBI, 34.2% • CT +ve, 28.0% • MRI +ve, 44.4% Population source: enrolled at 11 academic level 1 trauma centres in US within 24 h of injury following evaluation in ED for TBI as part of TRACK-TBI study.
Prognostic variable	MRI – positive MRI result Patients had 3D T1-weighted imaging at ~2 weeks following injury using 3T MRI scanners. Imaging protocol also included 3D T2-weighted FLAIR, 3D T2-weighted gradient echo and 3D T2 weighted sequences for radiological interpretation of an abnormal MRI. Scans interpreted by board-certified neuroradiologist blinded to patient clinical information. Those with any acute abnormal MRI findings classified as MRI positive. Definition unclear, but reported that findings on MRI were largely microbleeds caused by haemorrhagic axonal injury and small contusions.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Probable post-traumatic stress disorder at 3 months** *Raw data reported* For those with PTSD at 3 months, 33/77 were MRI +ve and 44/77 were MRI -ve. For those without PTSD at 3 months, 154/344 were MRI +ve and 190/344 were MRI -ve. *Sensitivity/specificity calculated from raw data*

Reference	Stein 2021[32]
	Sensitivity: 42.86% Specificity: 55.23% PPV: 17.65% NPV: 81.20% **Probable post-traumatic stress disorder at 6 months** *Raw data reported* For those with PTSD at 6 months, 26/70 were MRI +ve and 44/70 were MRI -ve. For those without PTSD at 6 months, 161/351 were MRI +ve and 190/351 were MRI -ve. *Sensitivity/specificity calculated from raw data* Sensitivity: 37.14% Specificity: 54.13% PPV: 13.90% NPV: 81.20% Measured using PTSD checklist for DSM-5 – score ≥33 indicating PTSD. Range on this scale is 0-80. Previous analyses demonstrated that scores on this scale of 31-33 are optimally efficient for diagnosing PTSD. For 3 months, assessment performed at mean (range) of 3 (2.7-3.5) months from time of injury and for 6 months, assessment performed at mean (range) of 6 (5.9-6.2) months from time of injury.
Comments	Risk of bias: high – concerns about attrition (moderate) and prognostic factor measurement (moderate) Indirectness: none

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Reference	Topolovec-Vranic 2011[33]
Study type and analysis	Prospective observational study Receiver operating characteristic curves plotted to examine sensitivity and specificity, with c-statistic/area under the curve reported.
Number of participants	N=141 (n=95 analysed at 6 weeks)

Reference	Topolovec-Vranic 2011[33]
and characteristics	Inclusion criteria: sustained non-penetrating physical or mechanical trauma to head within last 4 h; aged 18-65 years; GCS between 13 and 15 at time of triage by ED nurse; fluent in English language or a translator was available; and were available for follow-up appointments. Exclusion criteria: positive alcohol or toxicology screens; significant extracranial trauma; premorbid history of active neurological or psychiatric disorders or pre-existing medical conditions requiring anticoagulant medication (not including acetylsalicylic acid or clopidogrel). Characteristics of population for n=141 initially enrolled: • Age, mean (range): 39.4 (19-65) years • 63% male • Cause of injury: o Motor vehicle collision, 37% o Assault, 6% o Sport-related, 1% o Fall, 45% o Pedestrian struck, 4% o Other, 7% • ED GCS: o 15, 93% o 14, 6% o 13, 1% • History of head trauma o Yes, 23% o No, 62% o Unknown, 15% • Galveston Orientation and Amnesia Test (GOAT) symptoms: o Headache, 39% o Dizziness, 68%

Reference	Topolovec-Vranic 2011[33]
	○ Vomiting, 13% • Mean (range) biomarker values: ○ NSE, 14.67 (6.9-39.6) µg/l ○ S100B, 0.18 (0.02-4.5) µg/l Population source: recruited from ED of St. Michael's Hospital, a level 1 trauma centre in Toronto, Ontario, Canada. Patients presenting between October 2007 and August 2009.
Prognostic variable	Serum levels of following biomarkers: • S100B – threshold of ≥0.10 µg/l (reported but no data for relevant time-points – only reports at 1 week not 6 weeks) • NSE – threshold of ≥14.6 µg/l Blood samples collected average of 159 min post-injury (range 30-360 min; 7 samples collected >4 h from injury). Stored samples were analysed using automated immunochemistry kits. Cut-offs used were optimal scores identified following simulations of logistic regression models.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Abnormal status at 6 weeks** NSE – threshold of ≥14.6 µg/l AUC: 0.629 At 6 weeks, 58/95 patients had been discharged as normal (including n=36 discharged at week 1 and not reassessed at week 6). Based on physician assessment, including physical examination with complete history, neurologic examination and tools to assess headache and dizziness. These assessments were also done at 1-week post-injury – anyone that was discharged from study at 1 week as they were deemed eligible for discharge without further medical care were coded as 'normal' on all measures scheduled for the 6-week follow-up and were not reviewed at 6 weeks. Used to minimise burden of study participation but may lead to bias. Patients requiring further evaluation of treatment after 6 weeks continued as patients in clinic or were referred to appropriate healthcare services. Physicians blinded to results of biomarker assays. Unclear whether this outcome included neurocognitive tests and post-concussion scale mentioned in the paper. Rivermead Post-Concussion Questionnaire, impairment in postural stability (Balance Error Scoring System) and neurocognitive test battery (COWAT

Reference	Topolovec-Vranic 2011[33]
	test, Rey Auditory-Verbal Learning Test without delay, divided attention, visual scanning, tracking, motor speed using SDMT and motor speed and visual attention using Trail Making Test part B) were all performed at 6 weeks – unclear if all contributed to rating of normal/abnormal or whether it was just physician assessment, which seems to be described as a separate assessment to other tests mentioned.
Comments	Risk of bias: high – concerns about attrition (moderate), outcome measurement (moderate) and reporting of results (high) Indirectness: none

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Reference	Townend 2002[34]
Study type and analysis	Prospective study Receiver operating characteristic plots and diagnostic accuracy calculated, including sensitivity and specificity
Number of participants and characteristics	N=148 (n=119 analysed at 1 month) Inclusion criteria: adults with head injury (any blow to head causing a clinical diagnosis of head injury even if insufficient to cause definite loss of consciousness); and presenting to ED within 6 h of injury (6 h cut-off as S100B thought to be rapidly cleared from serum with half-life ~2 h). Exclusion criteria: reported to be no specific exclusion criteria Characteristics of population for n=119 with follow-up: • Age, mean (SD): 49.0 (21.2) years • 60% male • Initial GCS 15, 87% • GCS 13-15, 95% • Loss of consciousness, 36% • Discharged from ED, 61% Note that for the few characteristics reported, there were no significant differences (P<0.05) between those initially enrolled and those actually analysed at follow-up.

Reference	Townend 2002[34]
	Population source: recruited from February 2000 for 7 months. Recruited from EDs of four hospitals in Greater Manchester (two teaching hospital departments and two within district general hospitals).
Prognostic variable	Serum levels of S100B: • threshold of ≥0.27 µg/l for moderate disability outcome all GCS (95% GCS 13-15) • threshold of ≥0.32 µg/l for severe disability outcome in all GCS (95% GCS 13-15) • threshold of ≥0.48 µg/l for severe disability outcome in GCS 13-15 subgroup • Continuous value Venous blood sample taken from each patient and transferred to laboratory within 48 h. Levels in serum measured in duplicate using commercially available kit. Cut-off points were selected from ROC plots to ensure high sensitivity at cost of a relatively high false positive rate (low specificity) – thresholds selected to ensure largest proportion of those disabled were detected with the least compromise of specificity. Median time of sampling was 130 min post-injury (range 18-360 min). One blood sample misplaced so data analysed for 118/119 patients.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**At least moderate disability at 1 month – GOSE scores <7** *All GCS groups combined (95% GCS 13-15), n=118 – threshold of ≥0.27 µg/l* Sensitivity: 76% (95% CI, 56 to 90%) Specificity: 69% (95% CI, 58 to 78%) PPV calculated from raw data: 44.0% NPV: 90% (95% CI, 79 to 96%) Raw data: TPs, 22; FPs, 28; FNs, 7; TNs, 61 *All GCS groups combined (95% GCS 13-15), n=118 – continuous* AUC: 0.770 (95% CI, 0.67 to 0.87), P<0.001 **Severe disability at 1 month – GOSE scores <5** *All GCS groups combined (95% GCS 13-15), n=118 – threshold of ≥0.32 µg/l* Sensitivity: 93% (95% CI, 68 to 100%) Specificity: 72% (95% CI, 62 to 80%) PPV calculated from raw data: 33.0%

Reference	Townend 2002[34]
	NPV: 99% (95% CI, 93 to 100%) Raw data: TPs, 14; FPs, 29; FNs, 1; TNs, 74 *All GCS groups combined (95% GCS 13-15), n=118 – continuous* AUC: 0.889 (95% CI, 0.792 to 0.985), P<0.001 *Mild subgroup, GCS 13-15, n=112 – threshold of ≥0.48 µg/l* Sensitivity: 90% (95% CI, 55 to 99%) Specificity: 83% (95% CI, 75 to 90%) PPV could not be calculated as no prevalence reported for this subgroup NPV: 99% (95% CI, 94 to 100%) Neurological disability assessed at 1 month using GOSE. 8-point scoring system administered using interview. Delivered by telephone. Outcome assessed blinded to S100B levels. GOSE scores between 5 and 7 indicates moderate disability and includes people with significant restrictions in lifestyle or work capacity, or both. GOSE scores ≤4 indicate severe disability, including those unable to support themselves for 24 h in the community. Patients with previous morbidity were assessed for any change associated with their head injury and assigned a good outcome if able to function at the same levels as before the injury. Those with scores 7-8 were considered to have good outcome. For analysis, results were given for at least moderate disability (GOSE scores <7, including moderate and severe disability) and separately for those with more severe disability (GOSE scores <5).
Comments	Risk of bias: moderate – concerns about attrition (moderate) Indirectness: none

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Reference	Waljas 2015[35]
Study type and analysis	Prospective study Possible to calculate sensitivity and specificity from the raw data provided
Number of participants and characteristics	N=126 (n=126 analysed at 1 month and n=103 analysed at 1 year post-injury with outcome data) Inclusion criteria: biomechanical force applied to the head; loss of consciousness, if present, for less than 30 min; GCS score between 13 and 15 after 30 min following injury; and post-traumatic amnesia, if present, of less than 24 h.

Reference	Waljas 2015[35]
	Exclusion criteria: age younger than 16 or older than 65; history of previous major substance abuse; history of psychiatric disorder; or past neurological condition or disease Characteristics of population, for n=126 enrolled: • Age, average (SD): 37.8 (13.5) years, range 16-64 years • 56.3% female • Caucasian, 100% • Previous TBI ○ None, 65.1% ○ One, 32.5% ○ Two, 2.4% • Psychiatric history ○ None, 90.5% ○ Yes, 7.1% ○ Unknown, 2.4% • Mechanism of injury: ○ Motor vehicle accident, 32.5% ○ Pedestrian-motor vehicle accident, 4.0% ○ Sports, 8.7% ○ Low fall, 36.5% ○ High fall, 7.1% ○ Assault, 7.1% ○ Other, 4.0% • GCS, average (SD): 14.96 (0.20), range 14-15, with 96% GCS 15 • Loss of consciousness: ○ None, 71.6% ○ ≤1 min, 12.0% ○ >1 and ≤5 min, 13.8%

Reference	Waljas 2015[35]
	○ >5 min and ≤10 min, 1.8% ○ >10 min, 0.9% ○ Average (SD) duration: 0.8 (2.2) min, range 0-15 min • Post-traumatic amnesia: ○ None, 48.0% ○ ≤2 h, 22.0% ○ >2 h, 30% ○ Average (SD) duration: 196.2 (353.2) min, range 0-1440 min • Sick leave duration, average (SD): 42.1 (112.1) days, range 0-729 days Included some (13.5%, 17 patients) with an intracranial trauma-related abnormality on day-of-injury CT or follow-up MRI (termed complicated mild TBI). Population source: consecutively enrolled patients from ED of single University hospital in Finland.
Prognostic variable	MRI – abnormality on MRI (trauma-related findings, with minor incidental findings not included) MRI conducted between 2 weeks and 2 months post-injury for most participants (n=119, with n=7 missing MRI) – mean (SD): 29.1 (19.9) days post-injury, range 1-159 days. MRI performed on 1.5 Tesla or 3T Siemens Trio machine. Sequences evaluated by certified neuroradiologist. Protocol included sagittal T1-weighted three-dimensional sagittal T1-weighted inversion recovery prepared gradient echo, axial T2 turbo spin echo, conventional axial and high resolution sagittal FLAIR, axial T2* and axial susceptibility weighted imaging series. A 12-channel head matrix coil was used. Only trauma-related findings were considered to be abnormal – minor incidental findings such as isolated white matter hyperintensities were not counted as abnormal. N=89 had 3T MRI, with diffusion tensor imaging acquired from n=84 of these. N=13 of these were excluded due to presence of major incidental findings (e.g. ischaemic lesions, numerous white matter hyperintensities or enlarged lateral ventricles). N=3 also excluded due to CT abnormalities and n=10 due to incidental findings on MRI. Of those having 3T MRI, this left 71 mild TBI patients included.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Post-concussion syndrome at 1 month** Abnormal MRI – Mild or greater symptoms for post-concussion syndrome, n=124 *Raw data in paper*

Reference	Waljas 2015[35]
	TPs, 8; FPs, 7; FNs, 65; TNs, 44 *Sensitivity/specificity data calculated from raw data* Sensitivity: 10.96% Specificity: 86.27% PPV: 53.33% NPV: 40.37% Abnormal MRI – Moderate or greater symptoms for post-concussion syndrome, n=122 *Raw data in paper* TPs, 1; FPs, 14; FNs, 23; TNs, 84 *Sensitivity/specificity data calculated from raw data* Sensitivity: 4.17% Specificity: 85.71% PPV: 6.67% NPV: 78.50% **Post-concussion syndrome at 1 year** Abnormal MRI – Mild or greater symptoms for post-concussion syndrome n=103 *Raw data in paper* TPs, 2; FPs, 11; FNs, 37; TNs, 53 *Sensitivity/specificity data calculated from raw data* Sensitivity: 5.13% Specificity: 82.81% PPV: 15.38% NPV: 58.89% Abnormal MRI – Moderate or greater symptoms for post-concussion syndrome, n=103

Reference	Waljas 2015[35]
	Raw data in paper TPs, 0; FPs, 13; FNs, 12; TNs, 78 *Sensitivity/specificity data calculated from raw data* Sensitivity: 0.0% Specificity: 85.71% PPV: 0.0% NPV: 86.67% Based on Rivermead Post-Concussion Symptoms Questionnaire. For 1 month interview, conducted at mean (SD) of 24.1 (5.4, range 8-38) days post-injury. For 1 year interview, conducted at mean (SD) of 383 (30.6, range 316-488) days post-injury. *Definition based on Rivermead Post-Concussion Questionnaire* Patients rated the presence of the symptoms over the past 24 h on a scale from 0 to 4 (0 = not experienced at all after the injury; 1 = experienced but no more of a problem compared with before the injury; 2 = a mild problem; 3 = a moderate problem; and 4 = a severe problem). A total score was calculated by adding all items with a score greater than 1. Post-concussion syndrome was classified as being present based on this questionnaire; syndrome defined in two ways: based on mild or greater symptom reporting in each domain, and based on moderate or greater symptom reporting in each domain.
Comments	Risk of bias: high • For 1 month time-point, concerns about prognostic factor measurement (moderate) and outcome measurement (moderate) • For 1 -year time-point, concerns about attrition (moderate), prognostic factor measurement (moderate) and outcome measurement (moderate) Indirectness: none

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Reference	Wang 2014[36]
Study type and analysis	Prospective study Possible to calculate sensitivity and specificity from the raw data provided
Number of participants	N=200 (n=165 analysed at 1 year)

Reference	Wang 2014[36]
and characteristics	Inclusion criteria: mild TBI (GCS 13–15) admitted 2 h to 3 days post-TBI; post-traumatic amnesia duration <1 day; and normal appearance on conventional CT and MRI (performed on admission). Exclusion criteria: history of depression (prior to TBI, if they reported one of the following: diagnosis of depression, treatment for depression, depression-related counselling, or a suicide attempt); history of disorders related to substance abuse or psychotropic drugs; age over 65 years; prior TBI; or any other type of brain illness (e.g. stroke, encephalitis, haemorrhagic diseases, amyloid degeneration , hypertension, metabolic disease); and the new onset of these diseases during follow-up. Characteristics of population, for n=165 analysed at 1 year, split into depressive (n=28) and non-depressive (n=137) patients: *Depressive patients, n=28* • Age, mean (SD): 39.9 (16.5) years • 71.4% male • Microbleed lesions present, 71.4% • GCS, mean (SD): 13.7 (0.7) • Cause of injury ○ Motor vehicle accident, 46.4% ○ Fall injury, 25.0% ○ Assault, 17.9% ○ Sporting accident, 10.7% *Non-depressive patients, n=137* • Age, mean (SD): 44.9 (14.3) years • 60.6% male • Microbleed lesions present, 8.8% • GCS, mean (SD): 13.9 (0.8) • Cause of injury ○ Motor vehicle accident, 49.6% ○ Fall injury, 40.1% ○ Assault, 5.1% ○ Sporting accident, 5.1%

Reference	Wang 2014[36]
	Population source: consecutive patients between June 2009 and December 2012 enrolled
Prognostic variable	MRI – microbleed lesions Solitary microbleed lesions defined as rounded, hypointense homogenous foci up to 5 mm in size not compatible with vascular, bone calcification or artefactual structures on the susceptibility-weighted imaging sequence. Multiple microbleeds were defined as multiple hypointense homogeneous foci that integrated with each other and yielded a mass <5 mm in diameter. The microbleeds were semiautomatically outlined and then lesions were counted. The area of each lesion was multiplied by the effective slice thickness to calculate the lesion volume All patients had MRI on 3T MRI scanner with 12-channel head coil. Sequences included conventional MR sequences (T1-weighted imaging, T2-weighted imaging, diffusion-weighted imaging) and susceptibility-weighted imaging. MRI data post-processed using software. Two neuroradiologists (with 8 and 5 years' experience) independently reviewed the MR images and any disagreement between two observers was resolved by consensus. The two neuroradiologists visually determined the presence, location and number of any abnormalities.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**SCID-IV criteria for depressive symptoms – major depression after TBI at 1 year** *Raw data in paper* TPs, 20; FPs, 12; FNs, 8; TNs, 125 *Sensitivity/specificity data calculated from raw data* Sensitivity: 71.43% Specificity: 91.24% PPV: 62.50% NPV: 93.98% SCID-IV depression questionnaire administered by neuropsychiatrist who was blinded to the imaging results. Depressive disorders after TBI were grouped as 'Mood Disorder Due to General Medical Condition' (MDD-GMC), with subtypes of (1) major depressive-like episode (if the full criteria for a major depressive episode were met); or (2) depressive features (prominent depressed mood but full criteria for a major depressive episode were not met). Only those who met criteria for 'Mood Disorder Due to General Medical Condition' (MDD-GMC), major depressive-like episode subtype for at least one follow-up visit within 1 year were considered as major depression after TBI.
Comments	Risk of bias: moderate – concerns about attrition (moderate)

Reference	Wang 2014[36]
	Indirectness: serious – population was likely a mixture of children and adults with no proportions given. Study was included under adult population as the mean age was consistent with the adult population.

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Reference	Xu 2021[37]
Study type and analysis	Enrolled as part of the TRACK-TBI study, a multi-centre prospective study. Receiver operating characteristic (ROC) analysis performed to assess ability of biomarkers to predict GOSE 6 months post-injury
Number of participants and characteristics	N=1375 (prespecified biomarker cohort from TRACK-TBI study) (n=1206 with serum samples, possibly only n=185 analysed but unclear) Inclusion criteria: presenting with TBI (GCS 3-15); presenting within 24 h of injury; and warranting non-contrast head CT based on practice guidelines. Exclusion criteria: positive pregnancy test or known pregnancy; imminent death or current life-threatening disease; incarceration; or evidence of serious psychiatric and neurological disorders that would interfere with consent or follow-up outcome assessment. Characteristics of population, for n=1206 with serum samples: • Age, mean (SD): 40.0 (17.0) years • 67.7% male • Race ○ White, 77.3% ○ Black, 16.4% ○ Other, 6.3% • Care pathway ○ ED discharge, 28.4% ○ Hospital admission, 36.2% ○ ICU admission, 35.3% • Cause of injury ○ Road traffic accident, 58.5%

Reference	Xu 2021[37]
	○ Incidental fall, 26.1% ○ Violence/assault, 6.8% ○ Other, 8.6% • GCS on ED arrival ○ 3-8, 9.8% ○ 9-12, 3.6% ○ 13-15, 86.6% • CT ○ CT-positive, 38.7% ○ CT-negative, 61.3% Population source: recruited from 18 US level 1 trauma centres between February 26th 2014 and July 27th 2018, enrolled prospectively as part of TRACK-TBI study.
Prognostic variable	GFAP levels in serum – continuous (on log scale) Blood samples collected within 24 h of injury – day 1 measurement results. Serum samples obtained and stored frozen. Blinded sample analysis of high-sensitivity C-reactive protein (hsCRP) performed by single laboratory using assays. Serum samples were thawed before testing. Repeated in duplicate. GFAP concentrations measured using prototype immunoassays using ELISA method.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Favourable outcome based on GOSE at 6 months (score ≥5)** AUC (95% CI): 0.768 (0.662 to 0.875) Primary outcome assessment was 6 month GOSE scores, which was used to assess patient-reported global disability attributable only to TBI. Complete recovery defined as GOSE=8, with incomplete recovery a score of <8. Unfavourable outcome defined as GOSE <5 and favourable outcome as GOSE ≥5. Unfavourable outcome was the analysis where data reported for prognostic accuracy.
Comments	Risk of bias: high – concerns about attrition (high) and reporting of results (moderate)

Reference	Xu 2021[37]
	Indirectness: serious – population was likely a mixture of children and adults with no proportions given. Study was included under adult population as the mean age was consistent with the adult population.

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D.2 Children

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Reference	Babcock 2013[1]
Study type and analysis	Secondary analysis of a larger group included in a prospective cohort study. Area under receiver operating curve (ROC) used to determine ability to predict development of post-concussion syndrome (PCS)
Number of participants and characteristics	N=76 Developed PCS, n=28 Did not develop PCS, n=48 Inclusion criteria: mild TBI (blow to head or acceleration/deceleration movement of head leading to one or more of following: loss of consciousness <30 min, amnesia <24 h or any alteration in mental state and a GCS >13 measured 30 min or more after injury); had blood drawn for biomarker analysis; completed follow-up; and could verbally communicate (≥5 to 18 years). Exclusion criteria: participants presenting >6 h post injury (as S100B levels peak and normalise within 6 h of TBI); and pre-existing medical or psychiatric conditions known to be associated with an elevated S-100B level in the absence of TBI. Characteristics of population: • Age, mean (SD): 14.0 (3.1) years • Male, 60.5% • Prior TBI, 31.6% • Severe mechanism of injury, 52.6% • GCS <15 at ED, 10.5% • Loss of consciousness at ED, 59.2% • Amnesia at ED, 45.3% • Nausea/vomiting at ED, 32.7%

Reference	Babcock 2013[1]
	• Abnormal CT, 4.0% • Admitted to ED, 23.7% Population source: convenience sample of those enrolled in larger cohort study approached to have blood drawn for biomarker analysis. Recruited at single University Centre ED. Identified by research assistants and attending emergency physician confirmed presence of mild TBI.
Prognostic variable	S100B levels in serum (continuous measure as no thresholds mentioned)
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**PCS – 3 or more symptoms rated with score of 2 or more (rated as worse at follow-up compared to pre-injury) at 3 months** Area under ROC curve for S100B level: 0.47 Assessed using Rivermead Post-concussive Questionnaire by telephone (participants or parent/guardians interviewed). Interviewers blinded to details of initial ED presentation.
Comments	Risk of bias: high – concerns about attrition, outcome measurement and reporting of results. Indirectness: none

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Reference	Barlow 2021[3]
Study type and analysis	Prospective enrolment as part of the Play Game trial (NCT01874847), which was an RCT comparing melatonin with placebo for those with persistent post-concussion symptoms. No description of the methods used to calculate AUC, unclear if any adjustment performed for this result.
Number of participants and characteristics	N=61 Good recovery from persistent post-concussion symptoms at 8-10 weeks, n=23 Poor recovery from persistent post-concussion symptoms at 8-10 weeks, n=38

Reference	Barlow 2021[3]
	Inclusion criteria: aged 8-18 years; medically diagnosed mild TBI (American Academy of Neurology criteria confirmed by physician at medical assessment); persistent post-concussion symptoms and ≥10-point increase in total symptom score on Post-Concussion Symptom Inventory post-injury compared to pre-injury scores (assessed at enrolment); and MRI imaging performed. Exclusion criteria: significant medical or psychiatric history; previous concussion with last 3 months; persistent symptoms following previous concussion; a more severe TBI previously; use of neuroactive drugs; claustrophobia; and inability to complete questionnaires. Characteristics of population, given for those in good and poor recovery groups, respectively: • Age, mean (SD): 14.4 (2.9) years and 14.0 (2.4) years • Male, 52.0% and 48% • Migraine, 33% and 41% • ADHD, 10% and 7% • Learning support, 20% and 21% • Injury details: ○ Loss of consciousness, 9% and 14% ○ Cause of injury ▪ Sport-related, 83% and 68% ▪ Fall, 4% and 11% ▪ Motor vehicle accident, 0% and 8% ▪ Other, 13% and 13% • Days post-injury for assessment sessions: ○ Session 1, mean (SD) 37.0 (6.5) days and 37 (5.3) days ○ Session 2, mean (SD) 69.0 (6.7) days and 70 (6.5) days • Post-Concussion Symptom Inventory score, median (IQR) ○ Pre-injury, 8 (3, 24) and 2.5 (1, 7) ○ Session 1 (pre-treatment with melatonin/placebo), 30 (17, 43) and 43 (27, 70) ○ Session 2 (post-treatment with melatonin/placebo), 1 (0, 10) and 20 (11, 43) Population source: enrolled by telephone at 2-4 weeks and in person 2 weeks later. Eligible children from Play Game RCT invited to participate. Recruited from single children's hospital ED.
Prognostic variable	Mean absolute cerebral blood flow (aCBF) measured on MRI at 4-6 weeks post-injury– averaged CBF of gray matter – continuous measure

Reference	Barlow 2021[3]
	MRI performed at 4-6 weeks post-injury and repeated again 4-6 weeks later. High resolution 3D T1-weighted Bravo scan and 3D pseudo-continuous arterial spine-labelled (pCASL) MRI scan performed. Automatically processed into quantitative CBF maps.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Recovery status (good recovery if symptoms at or below pre-injury levels and returned to normal activity) at 8-10 weeks post-injury** Area under ROC curve for aCBF of gray matter measured at 4-6 weeks post-injury: 0.77 (95% CI, 0.69 to 0.89) Ability to distinguish between good and poor recovery at 8-10 weeks post-injury assessed. Recovery status was based on clinical interview and examination, and Post-Concussion Symptom Inventory Youth Report at 8-10 weeks post-injury, with good recovery indicated if symptoms were at or below pre-injury levels and they had returned to normal activity.
Comments	Risk of bias: high – concerns about study participation, attrition, outcome measurement and reporting of results. Indirectness: serious – population already had persistent post-concussion symptoms when enrolled, which is different to the review protocol where the aim was to identify biomarkers predicting the development of post-concussion symptoms in those with mild TBI. This paper was still included as it still provides accuracy data for post-concussion symptoms but further down the line for a group that already have these symptoms.

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Reference	Berger 2007[6]
Study type and analysis	Prospective cohort Binary logistic regression used to predict outcome status using combination of three biomarkers measured in serum.
Number of participants and characteristics	N=152 Inclusion criteria: children <13 years; clinical diagnosis of TBI; admitted to Children's Hospital of Pittsburgh; and had cranial CT within 24 h Exclusion criteria: not reported

Reference	Berger 2007[6]
	Characteristics of population: • Age, median (range): 15.2 (0.1-150.2) months • Race: ○ Caucasian, 76% ○ African-American, 18% ○ Asian, 2% ○ Multi-racial, 4% • Mechanism of injury ○ Fall, 34% ○ Motor vehicle crash/pedestrian vs. motor vehicle, 11% ○ Child abuse, 37% ○ Other, 18% • GCS score – **population indirectness as <75% mild and results not reported separately for the mild subgroup** ○ Mild (13-15), 61% ○ Moderate (9-12), 9% ○ Severe (≤8), 30% • Earliest Glasgow Outcome Scale (GOS) score ○ Good (score of 1), 68% ○ Moderate disability (score of 2), 10% ○ Severe disability of vegetative (score of 3-4), 12% ○ Dead (score of 5), 10% Population source: recruited from a single level 1 trauma centre between April 2000 and March 2005. Enrolment was not consecutive and was based on availability of investigators.
Prognostic variable	Model including abnormal values for following three biomarkers, including peak levels and initial levels in serum: • Abnormal S100B – threshold of >0.017 ng/ml used to define abnormal • Abnormal NSE – threshold of 11.7 ng/ml used to define abnormal • Abnormal MBP – threshold of 0.3 ng/ml used to define abnormal

Reference	Berger 2007[6]
	Blood samples taken as soon as possible after arrival at hospital and again after 12-24 h when vascular access available. For those with severe TBI, additional samples collected every 12 h for up to 5 days when vascular access available and intravenous catheters were being accessed for routine care. Concentrations of S100B quantified using ELISA. Not all patients had same number of blood samples taken and analysed.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**GOS at 0-3 months post-discharge – good vs. poor outcome (score 1-2 indicate good outcome and scores 3-5 indicate poor outcome), n=82** Correct classification into good/poor outcome: 77% Negative predictive value of normal biomarker concentration: 97% Positive predictive value of abnormal biomarker concentration: 75% **GOS at 4-6 months post-discharge – good vs. poor outcome (score 1-2 indicate good outcome and scores 3-5 indicate poor outcome), n=48** Correct classification into good/poor outcome: 78% Negative predictive value of normal biomarker concentration: 96% Positive predictive value of abnormal biomarker concentration: 42% **GOS at 7-12 months post-discharge – good vs. poor outcome (score 1-2 indicate good outcome and scores 3-5 indicate poor outcome), n=62** Correct classification into good/poor outcome: 78% Negative predictive value of normal biomarker concentration: 97% Positive predictive value of abnormal biomarker concentration: 33% GOS assessed by a psychometrician with extensive experience in the assignment of GOS score who was blinded to the serum biomarker concentrations and the initial GCS score. Assigned prospectively at time of clinic visit or retrospectively based on notes from clinic visit. N=118 with scores 1-2 (good outcome) and n=34 with scores 3-5 (poor outcome) – not given for individual time-points.
Comments	Risk of bias: high – concerns about study participation (moderate), attrition (moderate), outcome measurement (moderate) and reporting of results (high)

Reference	Berger 2007[6]
	Indirectness: very serious – mixed severity TBI population with only 61% having mild TBI (GCS 13-15) and difficult to assess individual utility of each of the three biomarkers as only results for a combined model reported

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Reference	Iyer 2019[13]
Study type and analysis	Prospective study Development of a model using support vector machine methods to predict recovery from persistent post-concussion symptoms
Number of participants and characteristics	N=132 (n=99 analysed) Symptomatic at 1 month, n=68 Recovery at 1 month, n=31 Inclusion criteria: children with mild TBI (defined using American Academy of Neurology Criteria) Exclusion criteria: a previous concussion within 3 months; a more moderate to severe head injury (e.g. GCS less than 13); significant medical or psychiatric history; medications that likely affect participation in neuroimaging and/or sleep; and inability to complete questionnaires and/or neuropsychological evaluation. Characteristics of population, given for n=99 analysed: • Age, median (SD): 14.5 (2.4) years • Male, 48.5% • Symptoms ○ Total score on Post-Concussion Symptom Inventory, median: 18.2 Population source: convenience sample of those enrolled in larger cohort study (PlayGame Trial: NCT01874847) investigating effect of melatonin in persistent post-concussion symptoms conducted at Alberta Children's Hospital. Purpose of this study was to identify neuroimaging biomarkers for recovery in children following mild TBI. Those with medically diagnosed mild TBI recruited through ED and gave consent to follow-up 4-weeks post-injury.
Prognostic variable	MRI – model consisting of MRI variables and age

Reference	Iyer 2019[13]
	• Model 1 based on support vector machine classifier – including four brain indices and age: grey matter volume (eigenvariates) extracted from posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC), regional homogeneity (ReHo) estimates from PCC and PCC-mPFC functional connectivity values, as well as age. A machine learning classifier was trained to predict dichotomous outcomes (symptomatic and recovered) while a complementary support vector machine regression was used to assess possibility of predicting outcome along a continuum (i.e. change in Post-Concussion Symptom Inventory score from 4 to 8-10 weeks post-injury). Processing and analyses of neuroimaging was conducted on imaging data collected at time-point 1 (4-6 weeks post-injury). Images obtained in oblique axial plane using 3.0 T GE scanner. Visual inspection of each T1 scan by radiologist and/or neurologist excluded obvious signs of contusion or bleeding in grey and white matter. Ten subjects with <95% data remaining after removal of contaminated volumes and one excluded due to incomplete clinical measures, meaning 11 of 110 were excluded, leaving 99 included. Association between structural and functional brain indices and total sleep scores initially performed. Subsequently, using machine learning approaches (support vector machine), these indices implemented in independent group to test ability to predict recovery outcomes unbiased by total sleep scores collected at time-point 1 (4-6 weeks post-injury). For these analyses, total sleep scores were excluded from Post-Concussion Symptom Inventory score. Train-test approach used to train brain indices within a support vector machine classifier on 85% of subjects and tested classifier accuracy on remaining individuals. Classification repeated 10 times with different subgroups comprising a similar ratio of symptomatic and recovered individuals.
Confounders or Stratification strategy	Model consisting of various MRI variables and also incorporating age.
Outcomes and effect sizes	**Recovery based on Post-Concussion Symptom Inventory scores at 8-10 weeks post-injury** Model 1 – four brain indices and age based on support vector machine classifier, results are 10-fold average *Training sample (85 participants)* AUC (accuracy): 86%, range 78% and 92% across 10-fold repetitions Sensitivity: 94% Specificity: 69% PPV and NPV could not be calculated as prevalence for this sample unclear. *Testing sample (14 participants)* AUC (accuracy): 79%, range 65% and 95% across 10-fold repetitions

Reference	Iyer 2019[13]
	Sensitivity: 75% Specificity: 82% PPV and NPV could not be calculated as prevalence for this sample unclear. Individual brain indices in training sample (85 participants), 10-fold average *PCC-mPFC functional connectivity* AUC (accuracy): 0.55 *ReHo estimates from PCC* AUC (accuracy): 0.53 *Grey matter volumes from PCC and mPFC* AUC: 0.73 Grouped into 'symptomatic' and 'recovered' – symptomatic if ≥10-point increase in total score compared to pre-injury score and recovered if score returned to pre-injury level.
Comments	Risk of bias: high – concerns about attrition (moderate) and reporting of results (high) Indirectness: none

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Reference	Johnson 2018[14]
Study type and analysis	Prospective cohort study To evaluate the efficacy of salivary miRNAs for identifying children with concussion who are at risk for prolonged symptoms.
Number of participants and characteristics	Total n= 61 Excluded n=6 (failed to complete follow up at 4 wks) Excluded n=3 (inadequate saliva samples) N=22 acute concussion symptoms N=30 prolonged concussion symptoms

Reference	Johnson 2018[14]
	Inclusion criteria: Participants aged 7 to 21 years with a clinical diagnosis of mTBI. Presented to a medical centre for evaluation of mTBI within 14 days of injury. Exclusion criteria: Patients with a Glasgow Coma Scale score of 12 or less at injury, skull fracture, or intracranial bleeding were excluded from the study. Additional exclusion criteria included periodontal disease, respiratory infection, focal neurologic deficits, and history of migraine. Population: Female 42% Age, mean (SD) 14 (3) White 92% Days since injury, mean (SD) 6.8 (3.8) Sport participation 42% Motor vehicle collision 15% Loss of consciousness 27% Amnesia 48% Previous concussion 46% Method of patient selection (random or consecutive) not stated)
Prognostic variable(s)	Nonfasting saliva was collected from each participant at enrollment following orally rinsing with tap water. Participants expectorated into Oragene-RNA RE-100 Expression Analysis Self-Collection Kit (DNA Genotek). RNA was extracted with Plasma/Serum Circulating and Exosomal RNA Purification Kits (Norgen Biotek), as previously reported.24RNA yield and quality were assessed with the Agilent 2100 Bioanalyzer (Agilent Technologies). Sequencing of salivary RNA occurred at the Penn State Genomics Core Facility using a NEXTflex Small RNA Sequencing Kit version 3 (Bioo Scientific), a HiSeq 2500 Instrument (Illumina), and a targeted depth of 3 million reads. Reads were aligned to the hg38 build of the human genome using Partek Flow (Partek) and the SHRiMP2 aligner. Total miRNA counts within each sample were quantified with miRBase microRNA version 21. Three saliva samples with less than 2.5 × 104 total miRNA counts were excluded from the final analysis, resulting in 52 participants with mTBI. Individual miRNAs with raw read counts greater than 10 in at least 22 of 52 samples (42%) were evaluated for differential expression. This criterion was based on the ratio of participants with ACS vs PCS and the possibility that an miRNA might be present in only 1 group. Raw read counts were quantile normalized, mean-centred, and divided by the standard deviation of each variable. The data set for this study will be made available in the NCBI GenBank

Reference	Johnson 2018[14]
Confounders OR Stratification strategy	The 15 miRNAs with the largest variable importance in projection scores were reported. A multivariate logistic regression analysis was used to evaluate the PCS classification accuracy of those 15miRNAs. Concentrations of miRNAs were used in the regression as ratios, providing a second level of control for variation in total miRNA across samples.
Outcomes and effect sizes	Sport Concussion Assessment Tool (SCAT3) 4 wks Participant with a score of 5 or greater on child report/or parent report at 4 wks were classified as having post-concussion symptoms. When possible, the presence of PCS at a follow-up clinical visit was confirmed through medical record review. A multivariate logistic regression analysis was used to evaluate PCS classification accuracy of the 15miRNAs. A model using 5 miRNAs (miR-320c-1, miR-133a-5p, miR-769-5p, let-7a-3p, and miR-1307-3p) demonstrated the highest classification accuracy (AUC, 0.856; 95% CI, 0.822-0.890) with a sensitivity of 80% and a specificity of 75% for PCS status – PPV was calculated to be 81.0% and NPV was calculated to be 73.0% (PPV and NPV calculated using prevalence of 57.7% and n=52 analysed). Logistic regression model using the total child Sport Concussion Assessment Tool (SCAT3) severity score demonstrated an AUC of 0.649 (95% CI, 0.388-0.887) for determining PCS status. E, Logistic regression model using total parent SCAT3 severity score demonstrated an AUC of 0.562 (95% CI, 0.219-0.734) for identifying PCS status. F, Modified clinical risk score including sex, age, previous concussion history, headache, fatigue, processing difficulty, and migraine history demonstrated an AUC of 0.625 (95% CI, 0.093-0.848) for determining PCS status. These additional results were not included in the analyses as they either were not a biomarker or the outcome was not specifically post-concussion symptoms.
Comments	Risk of bias – high – concerns about study participation (moderate), attrition (moderate) and outcome measurement (moderate) Indirectness – serious – included those presenting within 14 days of injury and having samples taken, which is >48 h specified in the protocol

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Reference	Kelmendi 2021[15]
Study type and analysis	Prospective study Reports results for area under curve of S100B in predicting post-concussion syndrome (PCS)
Number of participants and characteristics	N=86 (n=60 analysed as completed follow-up) PCS at 3 months, n=22 No PCS at 3 months, n=38 Inclusion criteria: children between 7 and 16 years; mild TBI (GCS 13-15, loss of consciousness <30 min and post-traumatic amnesia <1 h); and head trauma with no other complaints

Reference	Kelmendi 2021[15]
	Exclusion criteria: admitted >3 h post-trauma (as serum half-life of S100B is short); history of syncope or seizure before head trauma; and children with Down syndrome Characteristics of population, given for n=60 analysed: • Age, mean (SD): 11.1 (2.4) years • Male, 56.7% • CT results: ○ +ve, 75.0% ○ -ve, 25.0% • Mechanism of trauma ○ Traffic accident, 33.3% ○ Sport injury, 25.0% ○ Falling from height, 23.3% ○ Other, 18.3% • GCS ○ 15, 20.0% ○ 14, 36.7% ○ 13, 43.3% • Symptoms ○ Amnesia, 36.7% ○ Loss of consciousness, 60.0% ○ Nausea, 48.3% ○ Vomiting, 61.7% ○ Headache, 93.3% ○ Dizziness, 41.7% Population source: unclear if from single centre, recruitment period unclear

Reference	Kelmendi 2021[15]
Prognostic variable	S100B measured in serum – continuous, measured within 3 h of injury Blood samples obtained from each patient via cubital vein at 3 h after head injury. No further details.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**PCS present at 3 months post-injury** AUC: 0.893 (95% CI, 0.786 to 0.987) Participants or parents/guardians interviewed about symptoms using Rivermead Post-Concussion Symptoms Questionnaire. Interviewers blinded to details of initial ED presentation. Assesses 16 post-concussion symptoms. Total score is sum of these 16 symptom scores. Development of PCS at 3 months defined as 3 or more symptoms on questionnaire rated as worse (scale of 2 or more) than at pre-injury. This is consistent with DSM-IV definition of PCS.
Comments	Risk of bias: high – concerns about study participation (moderate), attrition (high) and prognostic factor measurement (moderate) Indirectness: none

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Reference	Lima Santos 2021[21]
Study type and analysis	Prospective study Models consisting of demographic variables, clinical and various MRI variables developed and Receiver Operating Characteristic (ROC) curve and Area Under the Curve (AUC) were used to assess the diagnostic ability of the models
Number of participants and characteristics	N=42 Short recovery, n=21 Long recovery, n=21 Inclusion criteria: recent diagnosis of concussion (range between concussion and study entry 1-10 days, mean (SD): 7.2 (2.4) days) Exclusion criteria: loss of consciousness over 5 minutes; neurological, neurodevelopmental or systemic medical (e.g., metabolic, chronic inflammatory) disease; personal history of major psychiatric disorders; current alcohol and illicit substance abuse/dependence (past three months); left/mixed handedness; IQ below 70; contraindication to participating in MRI, and intoxication or use of illicit

Reference	Lima Santos 2021[21]
	substances (except cannabis) in urine tests on the day of the scan. History of major psychiatric disorders was excluded using the Mini International Neuropsychiatric Interview for children and adolescents. Characteristics of population: • Age, mean (SD): 15.5 (1.7) years • Male, 57.1% • Race ○ Caucasian, 88.1% ○ Non-Caucasian, 11.9% • Time between injury and MRI, mean (SD): 7.0 (2.5) days • History of previous concussion, 33.3% • History of headaches, 47.5% • History of nausea, 17.5% Population source: initial sample of 50 adolescents with recent concussion were recruited through longitudinal Investigating Concussion in Adolescents at Risk for Emotion Dysregulation (iCARE) study, with some exclusions due to loss to follow-up or incomplete neuroimaging data.
Prognostic variable	Model combining clinical, demographic and neuroimaging variables – reports data for two clusters on MRI separately possibly after adjustment for other factors • Clinical and demographic variables (six variables) – verbal memory composite score; visual memory composite score; three post-concussion symptom factors (affective, sleep and cognitive-migraine fatigue measured on Post-Concussion Symptom Scale (PCSS)); and VOMS total symptom score (measure of vestibular and ocular motor impairment) • Neuroimaging variables (seven variables) – mean fractional anisotropy (FA) of seven node clusters identified from level 1 analysis (neural correlates of recovery groups) – left and right inferior longitudinal fasciculus temporal clusters, left inferior fronto-occipital fasciculus frontal cluster and middle cluster, right inferior fronto-occipital fasciculus middle cluster, and left and right uncinate fasciculus temporal clusters Reports AUC of two neuroimaging features separately **(mean FA of left and right inferior longitudinal fasciculus temporal clusters)** MRI acquired up to 10 days post-concussion (mean, SD: 7.0, 2.6 days). Reviewed by clinical board-certified radiologist to rule out major structural abnormalities. For each tract, overall mean and nodal values were extracted to depict the collinearity of the fibers

Reference	Lima Santos 2021[21]
	across (mean) and along (tractometry/tract-profile) the entire tract. Tract-profile analyses allow for the characterization of dMRI properties along each tract (5 consecutive nodes, each node covering 20% of the entire tract) and thus for the identification of focal abnormalities in tracts of interest.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Short vs. long recovery time (medical clearance within 4 weeks vs. those not receiving clearance in 4 weeks)** Mean FA of left inferior longitudinal fasciculus temporal cluster AUC: 0.728 Mean FA of right inferior longitudinal fasciculus temporal cluster AUC: 0.803 Follow-up was up to 13 months, mean (SD): 5.4 (4.9) months. Medical clearance received if meeting following criteria: no symptoms at rest for a minimum of 24 h; no provocation of symptoms with typical physical and cognitive activities; neurocognitive functioning at typical baseline; normal vestibular and oculomotor functioning; and no other related medical complaints. Based on recovery time and the fact that concussion symptoms usually resolve within 4 weeks in this population, participants divided into short and long recovery groups based on whether or not medical clearance obtained within 4 weeks. Concussion symptoms measured using various symptom questionnaires, including Immediate Post-concussion Assessment and Cognitive Testing, PCSS and Vestibular/Ocular-Motor Screening (VOMS). Interviews conducted by staff trained to administer the assessments.
Comments	Risk of bias: high – concerns about study participation (moderate), attrition (moderate) and reporting of results (high). Indirectness: none

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Reference	Yeates 2009[38]
Study type and analysis	Prospective longitudinal cohort study Possible to calculate diagnostic accuracy data from raw data provided
Number of participants and characteristics	N=186 (n=183 at 1 month, n=178 at 3 months and n=169 at 12 months).

Reference	Yeates 2009[38]
	Inclusion criteria: children aged 8-15 years; mild TBI (sustained a blunt head trauma resulting in an observed loss of consciousness no longer than 30 minutes, a GCS score of 13 or 14, or at least 2 acute symptoms of concussion as documented by emergency department medical personnel) Acute symptoms included posttraumatic amnesia, vomiting, nausea, headache, diplopia, dizziness, disorientation to time, place or person, or any other indications of mental status changes (ie, dazed, foggy, slow to respond, lethargic, confused, asking repetitive questions, sleepy). Exclusion criteria: any GCS score below 13; delayed neurologic deterioration; any medical contraindication to MRI; neurosurgical or surgical intervention; any associated injury with an AIS score of >3; any associated injury that interfered with neuropsychological testing; hypoxia, hypotension, or shock; ethanol or drug ingestion involved with the injury; previous head injury requiring medical treatment; premorbid neurologic disorder or mental retardation; any injury resulting from child abuse or assault; or premorbid severe psychiatric disorder requiring hospitalisation Those that were hospitalised or demonstrated intracranial lesions or skull fractures on acute computed tomography were not excluded – therefore included some described as complicated mild TBI (intracranial abnormalities), but excluded injuries that would typically be defined as moderate in severity. Of those meeting criteria for mild TBI, participation rate in study was 48%. Participants and non-participants did not differ significantly in age, gender, ethnic/racial status or census tract measures of socioeconomic status. Characteristics of population, n=186 enrolled: • Age, mean (SD): 11.96 (2.22) years • Male, 71.0% • Number of premorbid post-concussion symptoms, mean (SD): 1.05 (1.41) • Modified Injury Severity Scale, mean (SD): 4.62 (4.54) • White, 71.0% • Loss of consciousness, 40% • Duration of loss of consciousness, median (range): 1 (<1 to 15) min • GCS score <15, 13% • Symptoms o Persistent post-traumatic amnesia, 32% o Vomiting, 44% o Nausea, 41%

Reference	Yeates 2009[38]
	○ Headache, 76% ○ Diplopia, 12% ○ Dizziness, 26% ○ Disorientation, 10% ○ Other mental status changes, 33% • Presence of other injuries, 25% • Intracranial abnormality on MRI< 18% Population source: recruited from consecutive admissions to emergency departments in 2 large children's hospitals.
Prognostic variable	MRI – abnormal (trauma-related intracranial abnormalities) Definition of these abnormalities not provided. MRI pulse sequence included sagittal T1-weighted spin echo images, axial T2-weighted and proton density fast spin echo images, coronal 2-dimensional gradient echo images, coronal fluid attenuated inversion recovery images, and axial diffusion-weighted echo planar images. Board-certified radiologists blinded to results of other assessments reviewed each MRI by using a standard protocol. MRI scans interpreted dichotomously in terms of presence of absence of trauma-related intracranial abnormalities.
Confounders or Stratification strategy	NA
Outcomes and effect sizes	**Persistence of post-concussion symptoms across follow-up (up to 12 months) – moderate or high increase vs. baseline persisting at 12 months** *Raw data reported in paper, n=180 appear to be analysed based on numbers* TPs, 7; FPs, 25; FNs, 31; TNs, 117 *Sensitivity/specificity calculated from raw data* Sensitivity: 18.42% Specificity: 82.39% PPV: 21.88% NPV: 79.05%

Reference	Yeates 2009[38]
	Persistence of post-concussion symptoms across follow-up (up to 12 months) – high increase vs. baseline persisting at 12 months *Raw data reported in paper, n=180 appear to be analysed based on numbers* TPs, 3; FPs, 29; FNs, 14; TNs, 134 *Sensitivity/specificity calculated from raw data* Sensitivity: 17.67% Specificity: 82.21% PPV: 9.38% NPV: 90.54% Post-concussion symptoms assessed using Post-concussive Symptom Interview, which involves parents rating presence or absence of 15 symptoms during the preceding week (tiredness, headaches, memory, bright light hurting eyes, dizziness, irritability, nervousness/fear, ability to pay attention, sad/depression, difficulty thinking, trouble with vision, sensitivity to loud noise, trouble sleeping, lack of interest in doing things and difference in personality). Symptoms similar to those listed for post-concussion syndrome in ICD-10 post-concussional disorder in DSM-IV. Total number of symptoms used as the measure of symptoms. Moderate increase group described as those with moderate increase in symptoms compared to pre-injury that persisted across all assessments up to 12 months. High acute symptoms that persisted group described as those that demonstrated large acute increases in symptoms compared to pre-injury at 2 weeks after injury and where moderate persistent symptoms continued even 12 months after injury. The group with no post-concussion symptoms were those where there was a small increase in symptoms at 2 weeks post-injury followed by few if any symptoms after that. The group with high acute symptoms with resolution were those that demonstrated large increases in symptoms at 2 weeks compared to pre-injury, but where gradual resolution of symptoms occurred.
Comments	Risk of bias: high – concerns about study participation (moderate), attrition (moderate), prognostic factor measurement (moderate) and reporting of results (moderate). Indirectness: none

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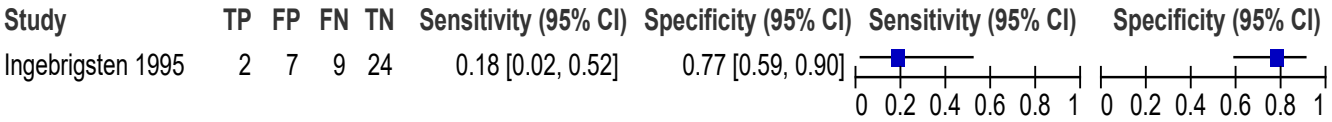
47

Appendix E – Forest plots

Note that Forest plots are only provided for those where raw data was reported as where this is not reported sensitivity and specificity cannot be entered into Review Manager. As this review included biomarkers, which is measured as a continuous variable in many studies rather than using a specific threshold, it was often the case that only accuracy data was reported with no breakdown of raw data informing those accuracy results. Even for those reporting thresholds of a particular biomarker raw data was not well reported. For a complete view of all available evidence for each biomarker GRADE tables should therefore be reviewed.

E.1 S100B – threshold of ≥0.5 µg/l

Figure 3: Persistent post-concussion symptoms at 9 months



E.2 Traumatic microbleeds on MRI

Figure 4: Incomplete recovery based on GOSE score <8 at 1 month

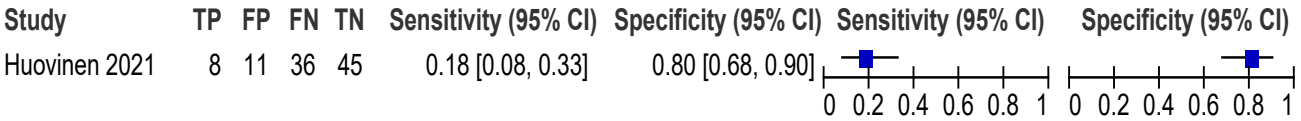
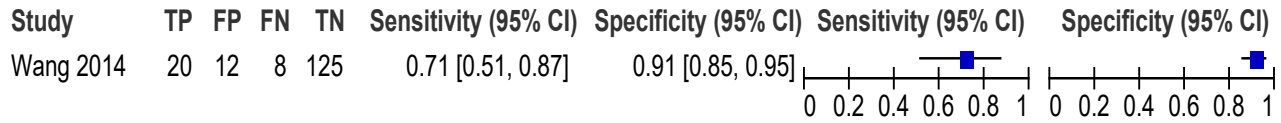


Figure 5: SCIV-IV criteria for major depression at 1 year



E.3 Abnormal MRI/MRI-positive

Figure 6: Post-concussion syndrome at 1 month (at least mild symptoms)

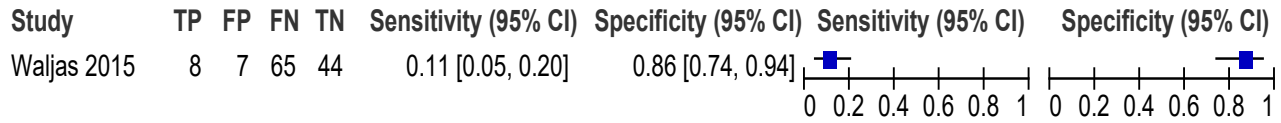


Figure 7: Post-concussion syndrome at 1 month (at least moderate symptoms)

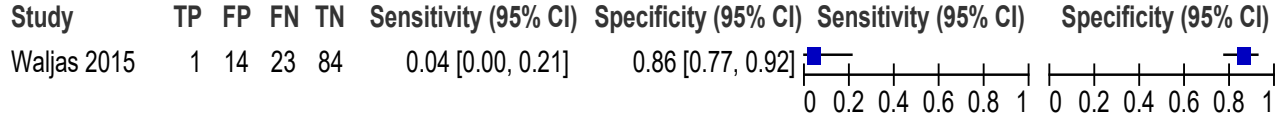


Figure 8: Post-concussion syndrome at 1 year (at least mild symptoms)

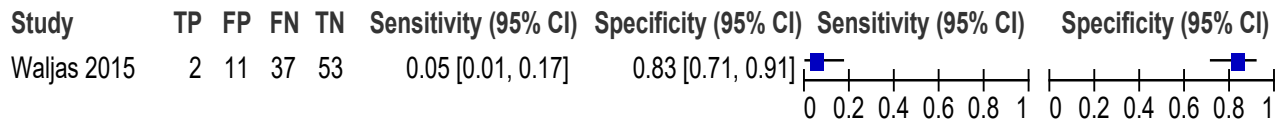


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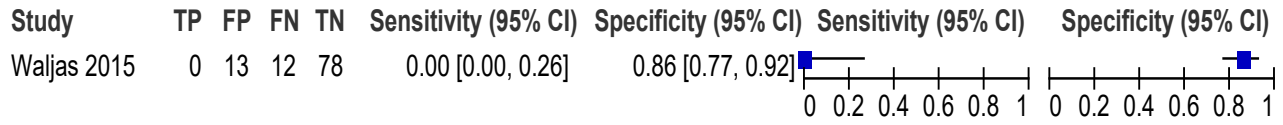
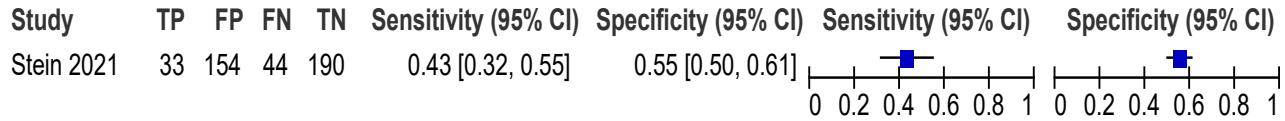
Figure 9: Post-concussion syndrome at 1 year (at least moderate symptoms)



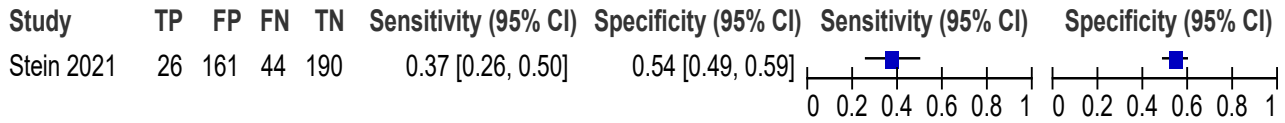
63

Figure 10: Probable Post-Traumatic Stress Disorder at 3 months (PTSD checklist for DSM-5 – score ≥33)



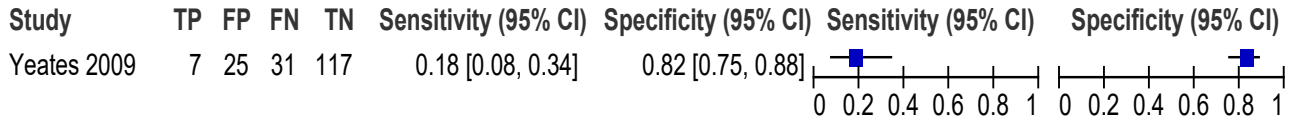
64

Figure 11: Probable Post-Traumatic Stress Disorder at 6 months (PTSD checklist for DSM-5 – score ≥33)



65

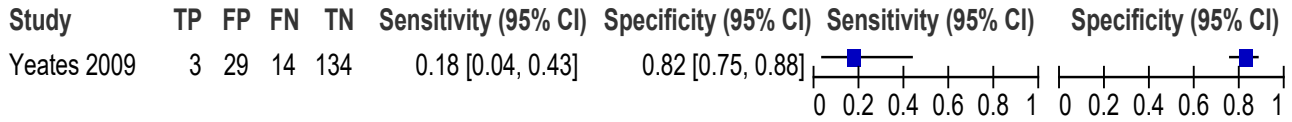
Figure 12: Persistence of post-concussion symptoms across follow-up (up to 12 months) – moderate or high increase vs. baseline persisting at 12 months



66 *Moderate increase described as those with moderate acute increases at 2 weeks that persisted up to 12 months*

67

Figure 13: Persistence of post-concussion symptoms across follow-up (up to 12 months) – high increase vs. baseline persisting at 12 months



High increase described as those with large acute increases at 2 weeks and where at least moderate symptoms continued at 12 months

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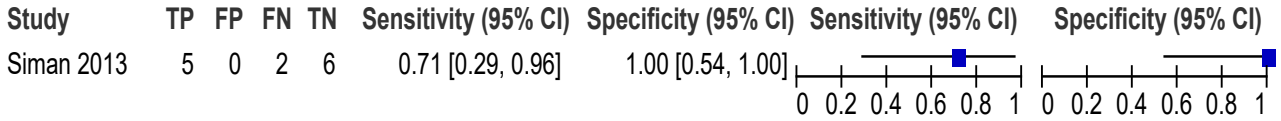
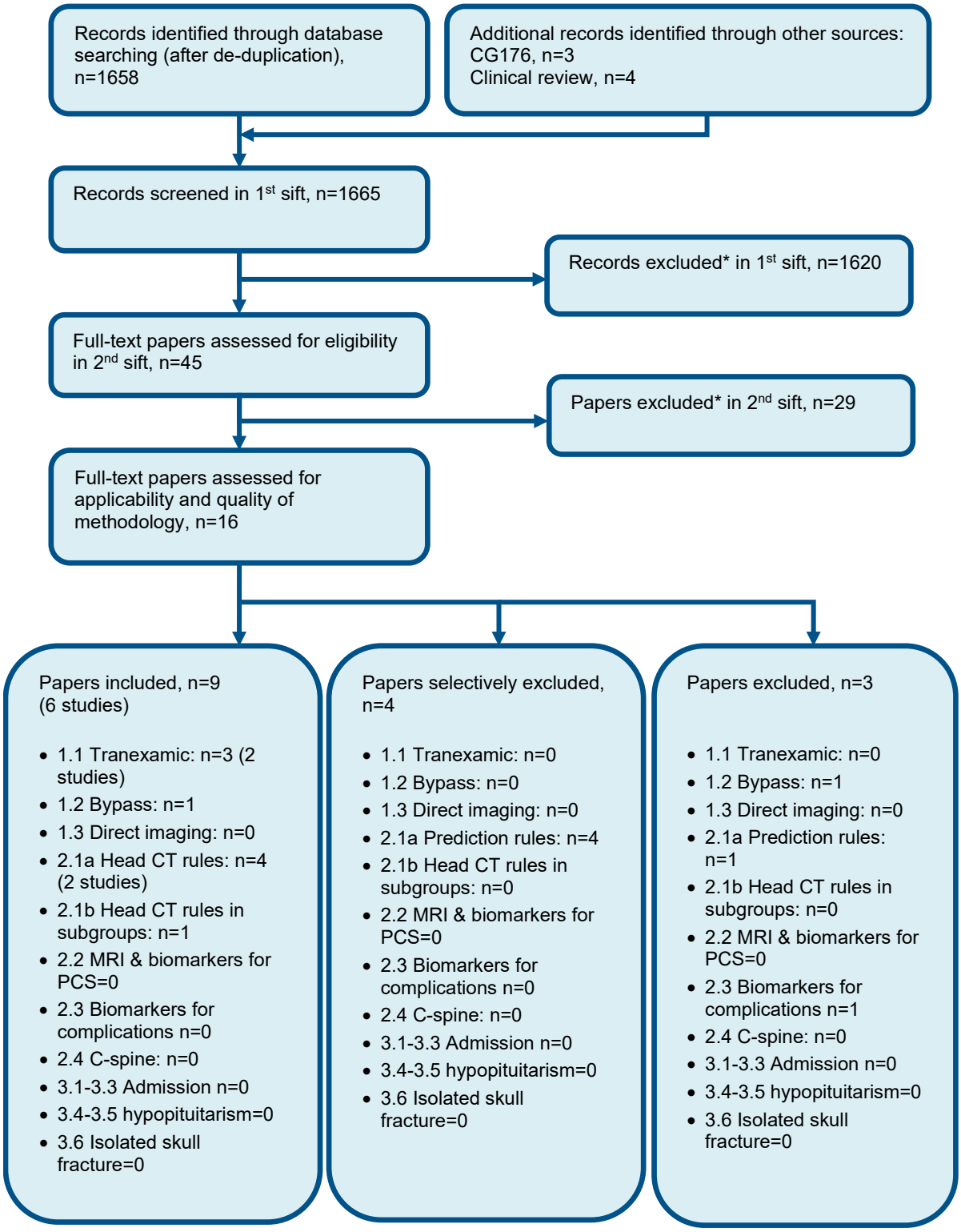
E.4 SNTF +ve (levels at least twice lower limit of detection of 10 units in ultrasensitive sandwich immunoassay)

Figure 14: Failure to improve SDMT at least 5 points at 3 months



Appendix F – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix G – Economic evidence tables

None

Appendix H – Health economic model

Modelling was not conducted for this question.

6 Appendix I – Excluded studies

7 Clinical studies

8 **Table 36: Studies excluded from the clinical review – prognostic accuracy**

Study	Code [Reason]
Aaen, G. S., Holshouser, B. A., Sheridan, C. et al. (2010) Magnetic resonance spectroscopy predicts outcomes for children with nonaccidental trauma. Pediatrics 125(2): 295-303	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Abbasi, M., Sajjadi, M., Fathi, M. et al. (2014) Serum S100B Protein as an Outcome Prediction Tool in Emergency Department Patients with Traumatic Brain Injury. Turkish Journal of Emergency Medicine 14(4): 147-52	- Study design not relevant to this review protocol - Not relevant to post-concussion syndrome
Abu Hamdeh, S., Marklund, N., Lannsjo, M. et al. (2017) Extended Anatomical Grading in Diffuse Axonal Injury Using MRI: Hemorrhagic Lesions in the Substantia Nigra and Mesencephalic Tegmentum Indicate Poor Long-Term Outcome. Journal of Neurotrauma 34(2): 341-352	- No prognostic accuracy measures reported
Adam, O., Mac Donald, C. L., Rivet, D. et al. (2015) Clinical and imaging assessment of acute combat mild traumatic brain injury in Afghanistan. Neurology 85(3): 219-27	- No prognostic accuracy measures reported
Affonseca, C. A., Carvalho, L. F., Guerra, S. D. et al. (2007) Coagulation disorder in children and adolescents with moderate to severe traumatic brain injury. Jornal de Pediatria 83(3): 274-82	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Akiyama, Y., Miyata, K., Harada, K. et al. (2009) Susceptibility-weighted magnetic resonance imaging for the detection of cerebral microhemorrhage in patients with traumatic brain injury. Neurologia Medico-Chirurgica 49(3): 97-9; discussion 99	- No prognostic accuracy measures reported - Not relevant to post-concussion syndrome
Al Nimer, F., Thelin, E., Nystrom, H. et al. (2015) Comparative Assessment of the Prognostic Value of Biomarkers in Traumatic Brain Injury Reveals an Independent Role for Serum Levels of Neurofilament Light. PLoS ONE [Electronic Resource] 10(7): e0132177	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome

Study	Code [Reason]
Aldossary, N. M.; Kotb, M. A.; Kamal, A. M. (2019) Predictive value of early MRI findings on neurocognitive and psychiatric outcomes in patients with severe traumatic brain injury. Journal of Affective Disorders 243: 1-7	- Study design not relevant to this review protocol *cross-sectional study*
Anderson, T. N., Hwang, J., Munar, M. et al. (2020) Blood-based biomarkers for prediction of intracranial hemorrhage and outcome in patients with moderate or severe traumatic brain injury. The Journal of Trauma and Acute Care Surgery 89(1): 80-86	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Anderson, V., Beauchamp, M. H., Yeates, K. O. et al. (2013) Social competence at 6 months following childhood traumatic brain injury. Journal of the International Neuropsychological Society 19(5): 539-50	- Not relevant to post-concussion syndrome
Ashwal, S., Holshouser, B. A., Shu, S. K. et al. (2000) Predictive value of proton magnetic resonance spectroscopy in pediatric closed head injury. Pediatric Neurology 23(2): 114-25	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Ashwal, S., Holshouser, B., Tong, K. et al. (2004) Proton spectroscopy detected myoinositol in children with traumatic brain injury. Pediatric Research 56(4): 630-8	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Asken, B. M., Bauer, R. M., DeKosky, S. T. et al. (2018) Concussion BASICS III: Serum biomarker changes following sport-related concussion. Neurology 91(23): e2133-e2143	- Prognostic accuracy measures reported but not for outcomes relevant to the review protocol
Asken, B. M., DeKosky, S. T., Clugston, J. R. et al. (2018) Diffusion tensor imaging (DTI) findings in adult civilian, military, and sport-related mild traumatic brain injury (mTBI): a systematic critical review. Brain Imaging & Behavior 12(2): 585-612	- Systematic review used as source of primary studies
Asken, B. M., Yang, Z., Xu, H. et al. (2020) Acute Effects of Sport-Related Concussion on Serum Glial Fibrillary Acidic Protein, Ubiquitin C-Terminal Hydrolase L1, Total Tau, and Neurofilament Light Measured by a Multiplex Assay. Journal of Neurotrauma 37(13): 1537-1545	- Study design not relevant to this review protocol - Not relevant to post-concussion syndrome
Avci, A., Yilmaz, H. L., Satar, S. et al. (2013) The correlation between S-100B protein levels	- Study not reported in English

Study	Code [Reason]
and prognosis in children with head trauma. Turkiye Klinikleri Journal of Medical Sciences 33(1): 149-158	
Babikian, T., Freier, M. C., Tong, K. A. et al. (2005) Susceptibility weighted imaging: neuropsychologic outcome and pediatric head injury. Pediatric Neurology 33(3): 184-94	- No prognostic accuracy measures reported
Bagley, L. J., McGowan, J. C., Grossman, R. I. et al. (2000) Magnetization transfer imaging of traumatic brain injury. Journal of Magnetic Resonance Imaging 11(1): 1-8	- No prognostic accuracy measures reported - Not relevant to post-concussion syndrome
Bagnato, S., Minafra, L., Bravata, V. et al. (2012) Brain-derived neurotrophic factor (Val66Met) polymorphism does not influence recovery from a post-traumatic vegetative state: a blinded retrospective multi-centric study. Journal of Neurotrauma 29(11): 2050-9	- No relevant prognostic factors
Bai, G., Bai, L., Cao, J. et al. (2019) Sex differences in cerebral perfusion changes after mild traumatic brain injury: Longitudinal investigation and correlation with outcome. Brain Research 1708: 93-99	- No prognostic accuracy measures reported
Baker, J. G., Willer, B. S., Dwyer, M. G. et al. (2020) A preliminary investigation of cognitive intolerance and neuroimaging among adolescents returning to school after concussion. Brain Injury 34(6): 818-827	- Data not reported in an extractable format or a format that can be analysed
Ballesteros, M. A., Rubio-Lopez, M. I., San Martin, M. et al. (2018) Serum levels of S100B from jugular bulb as a biomarker of poor prognosis in patients with severe acute brain injury. Journal of the Neurological Sciences 385: 109-114	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Bandyopadhyay, S., Hennes, H., Gorelick, M. H. et al. (2005) Serum neuron-specific enolase as a predictor of short-term outcome in children with closed traumatic brain injury. Academic Emergency Medicine 12(8): 732-8	- Time-point not relevant to post-concussion syndrome which is usually diagnosed at least a few weeks following injury
Bansal, M.; Sinha, V. D.; Bansal, J. (2018) Diagnostic and Prognostic Capability of Newer Magnetic Resonance Imaging Brain Sequences in Diffuse Axonal Injury Patient. Asian Journal of Neurosurgery 13(2): 348-356	- No prognostic accuracy measures reported

Study	Code [Reason]
Barlow, K. M., Marcil, L. D., Dewey, D. et al. (2017) Cerebral Perfusion Changes in Post-Concussion Syndrome: A Prospective Controlled Cohort Study. Journal of Neurotrauma 34(5): 996-1004	- No prognostic accuracy measures reported
Bartnik-Olson, B., Holshouser, B., Ghosh, N. et al. (2021) Evolving White Matter Injury following Pediatric Traumatic Brain Injury. Journal of Neurotrauma 38(1): 111-121	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - No prognostic accuracy measures reported
Bavetta, S., Nimmon, C. C., White, J. et al. (1994) A prospective study comparing SPET with MRI and CT as prognostic indicators following severe closed head injury. Nuclear Medicine Communications 15(12): 961-8	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Bazarian, J. J., Zhong, J., Blyth, B. et al. (2007) Diffusion tensor imaging detects clinically important axonal damage after mild traumatic brain injury: a pilot study. Journal of Neurotrauma 24(9): 1447-59	- No prognostic accuracy measures reported
Beauchamp, M. H., Beare, R., Ditchfield, M. et al. (2013) Susceptibility weighted imaging and its relationship to outcome after pediatric traumatic brain injury. Cortex 49(2): 591-8	- No prognostic accuracy measures reported
Beauchamp, M. H., Degeilh, F., Yeates, K. et al. (2020) Kids' Outcomes And Long-term Abilities (KOALA): protocol for a prospective, longitudinal cohort study of mild traumatic brain injury in children 6 months to 6 years of age. BMJ Open 10(10): e040603	- Study protocol only
Beers, S. R.; Berger, R. P.; Adelson, P. D. (2007) Neurocognitive outcome and serum biomarkers in inflicted versus non-inflicted traumatic brain injury in young children. Journal of Neurotrauma 24(1): 97-105	- No prognostic accuracy measures reported
Begaz, T., Kyriacou, D. N., Segal, J. et al. (2006) Serum biochemical markers for post-concussion syndrome in patients with mild traumatic brain injury. Journal of Neurotrauma 23(8): 1201-10	- Systematic review used as source of primary studies

Study	Code [Reason]
Bendlin, B. B., Ries, M. L., Lazar, M. et al. (2008) Longitudinal changes in patients with traumatic brain injury assessed with diffusion-tensor and volumetric imaging. Neuroimage 42(2): 503-14	- No prognostic accuracy measures reported
Berger, R. P., Adelson, P. D., Pierce, M. C. et al. (2005) Serum neuron-specific enolase, S100B, and myelin basic protein concentrations after inflicted and noninflicted traumatic brain injury in children. Journal of Neurosurgery 103(1suppl): 61-8	- Prognostic accuracy measures reported but not for outcomes relevant to the review protocol
Berger, R. P., Pierce, M. C., Wisniewski, S. R. et al. (2002) Neuron-specific enolase and S100B in cerebrospinal fluid after severe traumatic brain injury in infants and children. Pediatrics 109(2): e31	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Biagianti, B., Stocchetti, N., Brambilla, P. et al. (2020) Brain dysfunction underlying prolonged post-concussive syndrome: A systematic review. Journal of Affective Disorders 262: 71-76	- Systematic review used as source of primary studies
Blackman, J. A., Rice, S. A., Matsumoto, J. A. et al. (2003) Brain imaging as a predictor of early functional outcome following traumatic brain injury in children, adolescents, and young adults. Journal of Head Trauma Rehabilitation 18(6): 493-503	- No prognostic accuracy measures reported
Blatter, D. D., Bigler, E. D., Gale, S. D. et al. (1997) MR-based brain and cerebrospinal fluid measurement after traumatic brain injury: correlation with neuropsychological outcome. Ajnr: American Journal of Neuroradiology 18(1): 1-10	- No prognostic accuracy measures reported
Bogoslovsky, T., Wilson, D., Chen, Y. et al. (2017) Increases of Plasma Levels of Glial Fibrillary Acidic Protein, Tau, and Amyloid beta up to 90 Days after Traumatic Brain Injury. Journal of Neurotrauma 34(1): 66-73	- Study design not relevant to this review protocol
Bonnier, C., Marique, P., Van Hout, A. et al. (2007) Neurodevelopmental outcome after severe traumatic brain injury in very young children: role for subcortical lesions. Journal of Child Neurology 22(5): 519-29	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome

Study	Code [Reason]
Bonnier, C., Nassogne, M. C., Saint-Martin, C. et al. (2003) Neuroimaging of intraparenchymal lesions predicts outcome in shaken baby syndrome. Pediatrics 112(4): 808-14	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - No prognostic accuracy measures reported
Bonow, R. H., Friedman, S. D., Perez, F. A. et al. (2017) Prevalence of Abnormal Magnetic Resonance Imaging Findings in Children with Persistent Symptoms after Pediatric Sports-Related Concussion. Journal of Neurotrauma 34(19): 2706-2712	- Study design not relevant to this review protocol
Bouvier, D., Fournier, M., Dauphin, J. B. et al. (2012) Serum S100B determination in the management of pediatric mild traumatic brain injury. Clinical Chemistry 58(7): 1116-22	- No relevant outcomes
Braga, L. W., Souza, L. N., Najjar, Y. J. et al. (2007) Magnetic resonance imaging (MRI) findings and neuropsychological sequelae in children after severe traumatic brain injury: the role of cerebellar lesion. Journal of Child Neurology 22(9): 1084-9	- No prognostic accuracy measures reported
Brandstack, N., Kurki, T., Hiekkanen, H. et al. (2011) Diffusivity of normal-appearing tissue in acute traumatic brain injury. Clinical Neuroradiology 21(2): 75-82	- No prognostic accuracy measures reported
Brenner, T., Freier, M. C., Holshouser, B. A. et al. (2003) Predicting neuropsychologic outcome after traumatic brain injury in children. Pediatric Neurology 28(2): 104-14	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Brezova, V., Moen, K. G., Skandsen, T. et al. (2014) Prospective longitudinal MRI study of brain volumes and diffusion changes during the first year after moderate to severe traumatic brain injury. NeuroImage Clinical 5: 128-40	- No prognostic accuracy measures reported
Caeyenberghs, K., Leemans, A., Geurts, M. et al. (2010) Brain-behavior relationships in young traumatic brain injury patients: DTI metrics are highly correlated with postural control. Human Brain Mapping 31(7): 992-1002	- No prognostic accuracy measures reported
Calvi, M. R., Beretta, L., Dell'Acqua, A. et al. (2011) Early prognosis after severe traumatic	- The population is those with moderate or severe TBI or is mixed and<60% of the

Study	Code [Reason]
brain injury with minor or absent computed tomography scan lesions. Journal of Trauma-Injury Infection & Critical Care 70(2): 447-51	population has mild TBI - not relevant to post-concussion syndrome
Caplain, S., Blancho, S., Marque, S. et al. (2017) Early Detection of Poor Outcome after Mild Traumatic Brain Injury: Predictive Factors Using a Multidimensional Approach a Pilot Study. Frontiers in neurology [electronic resource]. 8: 666	- No relevant prognostic factors
Carpentier, A., Galanaud, D., Puybasset, L. et al. (2006) Early morphologic and spectroscopic magnetic resonance in severe traumatic brain injuries can detect "invisible brain stem damage" and predict "vegetative states". Journal of Neurotrauma 23(5): 674-85	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - No prognostic accuracy measures reported
Castano Leon, A. M., Cicuendez, M., Navarro, B. et al. (2018) What Can Be Learned from Diffusion Tensor Imaging from a Large Traumatic Brain Injury Cohort?: White Matter Integrity and Its Relationship with Outcome. Journal of Neurotrauma 35(20): 2365-2376	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Castano-Leon, A. M., Cicuendez, M., Navarro, B. et al. (2019) Longitudinal Analysis of Corpus Callosum Diffusion Tensor Imaging Metrics and Its Association with Neurological Outcome. Journal of Neurotrauma 36(19): 2785-2802	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Castano-Leon, A. M., Cicuendez, M., Navarro-Main, B. et al. (2020) Sixto Obrador SENEC prize 2019: Utility of diffusion tensor imaging as a prognostic tool in moderate to severe traumatic brain injury. Part I. Analysis of DTI metrics performed during the early subacute stage. Neurocirugia (Astur : Engl Ed) 31(3): 132-145	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Castano-Leon, A. M., Cicuendez, M., Navarro-Main, B. et al. (2020) SIXTO OBRADOR SENEC PRIZE 2019: Utility of diffusion tensor imaging as a prognostic tool in moderate to severe traumatic brain injury. Part II: Longitudinal analysis of DTI metrics and its association with patient's outcome. Neurocirugia (Astur : Engl Ed) 31(5): 231-248	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome

Study	Code [Reason]
Castellani, C., Bimbashi, P., Ruttenstock, E. et al. (2009) Neuroprotein s-100B -- a useful parameter in paediatric patients with mild traumatic brain injury?. Acta Paediatrica 98(10): 1607-12	- Prognostic accuracy measures reported but not for outcomes relevant to the review protocol
Chabok, S. Y., Moghadam, A. D., Saneei, Z. et al. (2012) Neuron-specific enolase and S100BB as outcome predictors in severe diffuse axonal injury. The Journal of Trauma and Acute Care Surgery 72(6): 1654-7	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Chamard, E., Henry, L., Boulanger, Y. et al. (2014) A follow-up study of neurometabolic alterations in female concussed athletes. Journal of Neurotrauma 31(4): 339-45	- Study design not relevant to this review protocol
Chastain, C. A., Oyoyo, U. E., Zipperman, M. et al. (2009) Predicting outcomes of traumatic brain injury by imaging modality and injury distribution. Journal of Neurotrauma 26(8): 1183-96	- No prognostic accuracy measures reported
Chelly, H., Chaari, A., Daoud, E. et al. (2011) Diffuse axonal injury in patients with head injuries: an epidemiologic and prognosis study of 124 cases. Journal of Trauma-Injury Infection & Critical Care 71(4): 838-46	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Chen, D. Y., Hsu, H. L., Kuo, Y. S. et al. (2016) Effect of Age on Working Memory Performance and Cerebral Activation after Mild Traumatic Brain Injury: A Functional MR Imaging Study. Radiology 278(3): 854-62	- No prognostic accuracy measures reported
Chen, J. K., Johnston, K. M., Collie, A. et al. (2007) A validation of the post concussion symptom scale in the assessment of complex concussion using cognitive testing and functional MRI. Journal of Neurology, Neurosurgery & Psychiatry 78(11): 1231-8	- No prognostic accuracy measures reported
Cheng, F., Yuan, Q., Yang, J. et al. (2014) The prognostic value of serum neuron-specific enolase in traumatic brain injury: systematic review and meta-analysis. PLoS ONE [Electronic Resource] 9(9): e106680	- Systematic review used as source of primary studies
Chiaretti, A., Barone, G., Riccardi, R. et al. (2009) NGF, DCX, and NSE upregulation	- The population is those with moderate or severe TBI or is mixed and<60% of the

Study	Code [Reason]
correlates with severity and outcome of head trauma in children. Neurology 72(7): 609-16	population has mild TBI - not relevant to post-concussion syndrome
Chiou, K. S., Jiang, T., Chiaravalloti, N. et al. (2019) Longitudinal examination of the relationship between changes in white matter organization and cognitive outcome in chronic TBI. Brain Injury 33(7): 846-853	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Choi, J. I., Kim, B. J., Ha, S. K. et al. (2014) Comparison of subgroups based on hemorrhagic lesions between SWI and FLAIR in pediatric traumatic brain injury. Childs Nervous System 30(6): 1011-9	- No prognostic accuracy measures reported
Churchill, N. W., Hutchison, M. G., Graham, S. J. et al. (2019) Mapping brain recovery after concussion: From acute injury to 1 year after medical clearance. Neurology 93(21): e1980-e1992	- No prognostic accuracy measures reported
Churchill, N. W., Hutchison, M. G., Graham, S. J. et al. (2021) Long-term changes in the small-world organization of brain networks after concussion. Scientific reports 11(1): 6862	- No prognostic accuracy measures reported
Cicuendez, M., Castano-Leon, A., Ramos, A. et al. (2017) Prognostic value of corpus callosum injuries in severe head trauma. Acta Neurochirurgica 159(1): 25-32	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Colbert, C. A., Holshouser, B. A., Aaen, G. S. et al. (2010) Value of cerebral microhemorrhages detected with susceptibility-weighted MR Imaging for prediction of long-term outcome in children with nonaccidental trauma. Radiology 256(3): 898-905	- No prognostic accuracy measures reported
Cole, J. H., Jolly, A., de Simoni, S. et al. (2018) Spatial patterns of progressive brain volume loss after moderate-severe traumatic brain injury. Brain 141(3): 822-836	- Study design not relevant to this review protocol
Crichton, A., Ignjatovic, V., Babl, F. E. et al. (2021) Interleukin-8 Predicts Fatigue at 12 Months Post-Injury in Children with Traumatic Brain Injury. Journal of Neurotrauma 38(8): 1151-1163	- No prognostic accuracy measures reported

Study	Code [Reason]
Czeiter, E., Mondello, S., Kovacs, N. et al. (2012) Brain injury biomarkers may improve the predictive power of the IMPACT outcome calculator. Journal of Neurotrauma 29(9): 1770-8	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
D'Souza M, M., Trivedi, R., Singh, K. et al. (2015) Traumatic brain injury and the post-concussion syndrome: A diffusion tensor tractography study. Indian Journal of Radiology & Imaging 25(4): 404-14	- No prognostic accuracy measures reported
D'Souza, M. M., Kumar, M., Choudhary, A. et al. (2020) Alterations of connectivity patterns in functional brain networks in patients with mild traumatic brain injury: A longitudinal resting-state functional magnetic resonance imaging study. Neuroradiology Journal 33(2): 186-197	- No prognostic accuracy measures reported
Dall'Acqua, P., Johannes, S., Mica, L. et al. (2017) Functional and Structural Network Recovery after Mild Traumatic Brain Injury: A 1-Year Longitudinal Study. Frontiers in Human Neuroscience 11: 280	- No prognostic accuracy measures reported
Dall'Acqua, P., Johannes, S., Mica, L. et al. (2017) Prefrontal Cortical Thickening after Mild Traumatic Brain Injury: A One-Year Magnetic Resonance Imaging Study. Journal of Neurotrauma 34(23): 3270-3279	- No prognostic accuracy measures reported
Daoud, H., Alharfi, I., Alhelali, I. et al. (2014) Brain injury biomarkers as outcome predictors in pediatric severe traumatic brain injury. Neurocritical Care 20(3): 427-35	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
de Boussard, C. N., Lundin, A., Karlstedt, D. et al. (2005) S100 and cognitive impairment after mild traumatic brain injury. Journal of Rehabilitation Medicine 37(1): 53-7	- No prognostic accuracy measures reported
De Kruijk, J. R., Leffers, P., Menheere, P. P. et al. (2002) Prediction of post-traumatic complaints after mild traumatic brain injury: early symptoms and biochemical markers. Journal of Neurology, Neurosurgery & Psychiatry 73(6): 727-32	- No prognostic accuracy measures reported
de Kruijk, J. R., Leffers, P., Menheere, P. P. et al. (2003) Olfactory function after mild traumatic brain injury. Brain Injury 17(1): 73-8	- No relevant outcomes

Study	Code [Reason]
	- No prognostic accuracy measures reported
Delano-Wood, L., Bangen, K. J., Sorg, S. F. et al. (2015) Brainstem white matter integrity is related to loss of consciousness and postconcussive symptomatology in veterans with chronic mild to moderate traumatic brain injury. Brain Imaging & Behavior 9(3): 500-12	- No prognostic accuracy measures reported
Dennis, E. L., Babikian, T., Alger, J. et al. (2018) Magnetic resonance spectroscopy of fiber tracts in children with traumatic brain injury: A combined MRS - Diffusion MRI study. Human Brain Mapping 39(9): 3759-3768	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Dennis, E. L., Caeyenberghs, K., Hoskinson, K. R. et al. (2021) White Matter Disruption in Pediatric Traumatic Brain Injury: Results from ENIGMA Pediatric Moderate to Severe Traumatic Brain Injury. Neurology 28: 28	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Dettwiler, A., Murugavel, M., Putukian, M. et al. (2014) Persistent differences in patterns of brain activation after sports-related concussion: a longitudinal functional magnetic resonance imaging study. Journal of Neurotrauma 31(2): 180-8	- No prognostic accuracy measures reported
Dey, S., Gangadharan, J., Deepika, A. et al. (2017) Correlation of ubiquitin C terminal hydrolase and S100beta with cognitive deficits in young adults with mild traumatic brain injury. Neurology India 65(4): 761-766	- No prognostic accuracy measures reported
Di Battista, A. P., Buonora, J. E., Rhind, S. G. et al. (2015) Blood Biomarkers in Moderate-To-Severe Traumatic Brain Injury: Potential Utility of a Multi-Marker Approach in Characterizing Outcome. Frontiers in neurology [electronic resource]. 6: 110	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Dimitriadis, S. I., Zouridakis, G., Rezaie, R. et al. (2015) Functional connectivity changes detected with magnetoencephalography after mild traumatic brain injury. NeuroImage Clinical 9: 519-31	- Study design not relevant to this review protocol
Ding, K., Marquez de la Plata, C., Wang, J. Y. et al. (2008) Cerebral atrophy after traumatic white	- No prognostic accuracy measures reported

Study	Code [Reason]
matter injury: correlation with acute neuroimaging and outcome. Journal of Neurotrauma 25(12): 1433-40	
Dodd, A. B., Lu, H., Wertz, C. J. et al. (2020) Persistent alterations in cerebrovascular reactivity in response to hypercapnia following pediatric mild traumatic brain injury. Journal of Cerebral Blood Flow & Metabolism 40(12): 2491-2504	- No prognostic accuracy measures reported
Du, Q., Weng, J. F., Luo, L. F. et al. (2018) Serum ST2 as a potential prognostic biomarker for traumatic brain injury. Clinica Chimica Acta 487: 145-152	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Edalatfar, M., Piri, S. M., Mehrabinejad, M. M. et al. (2021) Biofluid Biomarkers in Traumatic Brain Injury: A Systematic Scoping Review. Neurocritical Care 05: 05	- Systematic review used as source of primary studies
Edlow, B. L., Copen, W. A., Izzy, S. et al. (2016) Diffusion tensor imaging in acute-to-subacute traumatic brain injury: a longitudinal analysis. BMC Neurology 16: 2	- No prognostic accuracy measures reported
Einarsen, C. E., Moen, K. G., Haberg, A. K. et al. (2019) Patients with Mild Traumatic Brain Injury Recruited from Both Hospital and Primary Care Settings: A Controlled Longitudinal Magnetic Resonance Imaging Study. Journal of Neurotrauma 36(22): 3172-3182	- No prognostic accuracy measures reported
Eisele, A., Hill-Strathy, M., Michels, L. et al. (2020) Magnetic Resonance Spectroscopy following Mild Traumatic Brain Injury: A Systematic Review and Meta-Analysis on the Potential to Detect Posttraumatic Neurodegeneration. Neurodegenerative Diseases 20(1): 2-11	- No relevant prognostic factors
Esbjornsson, E., Skoglund, T., Mitsis, M. K. et al. (2013) Cognitive impact of traumatic axonal injury (TAI) and return to work. Brain Injury 27(5): 521-8	- No prognostic accuracy measures reported
Espana, L. Y., Lee, R. M., Ling, J. M. et al. (2017) Serial Assessment of Gray Matter Abnormalities after Sport-Related Concussion. Journal of Neurotrauma 34(22): 3143-3152	- Study design not relevant to this review protocol

Study	Code [Reason]
Evans, E., Asuzu, D., Cook, N. E. et al. (2018) Traumatic Brain Injury-Related Symptoms Reported by Parents: Clinical, Imaging, and Host Predictors in Children with Impairments in Consciousness Less than 24 Hours. Journal of Neurotrauma 35(19): 2287-2297	- No prognostic accuracy measures reported
Failla, M. D., Juengst, S. B., Arenth, P. M. et al. (2016) Preliminary Associations Between Brain-Derived Neurotrophic Factor, Memory Impairment, Functional Cognition, and Depressive Symptoms Following Severe TBI. Neurorehabilitation & Neural Repair 30(5): 419-30	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Fakhran, S.; Qu, C.; Alhilali, L. M. (2016) Effect of the Suboccipital Musculature on Symptom Severity and Recovery after Mild Traumatic Brain Injury. Ajnr: American Journal of Neuroradiology 37(8): 1556-60	- No prognostic accuracy measures reported
Fakhran, S., Yaeger, K., Collins, M. et al. (2014) Sex differences in white matter abnormalities after mild traumatic brain injury: localization and correlation with outcome. Radiology 272(3): 815-23	- No prognostic accuracy measures reported
Farbota, K. D., Sodhi, A., Bendlin, B. B. et al. (2012) Longitudinal volumetric changes following traumatic brain injury: a tensor-based morphometry study. Journal of the International Neuropsychological Society 18(6): 1006-18	- No prognostic accuracy measures reported
Ferrazzano, P., Yeske, B., Mumford, J. et al. (2021) Brain Magnetic Resonance Imaging Volumetric Measures of Functional Outcome after Severe Traumatic Brain Injury in Adolescents. Journal of Neurotrauma 38(13): 1799-1808	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Finnanger, T. G., Olsen, A., Skandsen, T. et al. (2015) Life after Adolescent and Adult Moderate and Severe Traumatic Brain Injury: Self-Reported Executive, Emotional, and Behavioural Function 2-5 Years after Injury. Behavioural Neurology 2015: 329241	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome

Study	Code [Reason]
Firsching, R., Roehl, F. W., Woischneck, D. H. et al. (2008) The predictive value of ICP as compared to magnetic resonance imaging in comatose patients after head injury. Acta Neurochirurgica - Supplement 102: 237-40	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Firsching, R., Woischneck, D., Klein, S. et al. (2001) Classification of severe head injury based on magnetic resonance imaging. Acta Neurochirurgica 143(3): 263-71	- No prognostic accuracy measures reported
Forouzan, A., Barzegari, H., Hosseini, O. et al. (2021) The Diagnostic Competence of Glial Fibrillary Acidic Protein in Mild Traumatic Brain Injury and Its Prognostic Value in Patient Recovery. Turkish Neurosurgery 31(3): 355-360	- Prognostic accuracy measures reported but not for outcomes relevant to the review protocol
Frankel, M., Fan, L., Yeatts, S. D. et al. (2019) Association of Very Early Serum Levels of S100B, Glial Fibrillary Acidic Protein, Ubiquitin C-Terminal Hydrolase-L1, and Spectrin Breakdown Product with Outcome in ProTECT III. Journal of Neurotrauma 36(20): 2863-2871	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Fraser, D. D., Close, T. E., Rose, K. L. et al. (2011) Severe traumatic brain injury in children elevates glial fibrillary acidic protein in cerebrospinal fluid and serum. Pediatric Critical Care Medicine 12(3): 319-24	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Fridriksson, T., Kini, N., Walsh-Kelly, C. et al. (2000) Serum neuron-specific enolase as a predictor of intracranial lesions in children with head trauma: a pilot study. Academic Emergency Medicine 7(7): 816-20	- No relevant outcomes
Galanaud, D., Perlbarg, V., Gupta, R. et al. (2012) Assessment of white matter injury and outcome in severe brain trauma: a prospective multicenter cohort. Anesthesiology 117(6): 1300-10	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Galloway, N. R., Tong, K. A., Ashwal, S. et al. (2008) Diffusion-weighted imaging improves outcome prediction in pediatric traumatic brain injury. Journal of Neurotrauma 25(10): 1153-62	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome

Study	Code [Reason]
Gan, Z. S., Stein, S. C., Swanson, R. et al. (2019) Blood Biomarkers for Traumatic Brain Injury: A Quantitative Assessment of Diagnostic and Prognostic Accuracy. Frontiers in neurology [electronic resource]. 10: 446	- Systematic review used as source of primary studies
Gao, J. and Zheng, Z. (2015) Development of prognostic models for patients with traumatic brain injury: a systematic review. International journal of clinical and experimental medicine 8(11): 19881-5	- Review article but not a systematic review
Genc, S., Anderson, V., Ryan, N. P. et al. (2017) Recovery of White Matter following Pediatric Traumatic Brain Injury Depends on Injury Severity. Journal of Neurotrauma 34(4): 798-806	- No prognostic accuracy measures reported
Gencturk, M., Tore, H. G., Nascene, D. R. et al. (2019) Various Cranial and Orbital Imaging Findings in Pediatric Abusive and Non-abusive Head trauma, and Relation to Outcomes. Clinical Neuroradiology 29(2): 253-261	- No prognostic accuracy measures reported
Gerber, D. J., Weintraub, A. H., Cusick, C. P. et al. (2004) Magnetic resonance imaging of traumatic brain injury: relationship of T2 SE and T2GE to clinical severity and outcome. Brain Injury 18(11): 1083-97	- No prognostic accuracy measures reported
Gerring, J., Brady, K., Chen, A. et al. (2000) Neuroimaging variables related to development of Secondary Attention Deficit Hyperactivity Disorder after closed head injury in children and adolescents. Brain Injury 14(3): 205-18	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Geyer, C., Ulrich, A., Grafe, G. et al. (2009) Diagnostic value of S100B and neuron-specific enolase in mild pediatric traumatic brain injury. Journal of Neurosurgery. Pediatrics. 4(4): 339-44	- No prognostic accuracy measures reported - No relevant outcomes
Ghonemi, M. O., Rabah, A. A., Saber, H. M. et al. (2013) Role of Phosphorylated Neurofilament H as a diagnostic and prognostic marker in traumatic brain injury. Egyptian Journal of Critical Care Medicine 1(3): 139-144	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome

Study	Code [Reason]
Goyal, A., Failla, M. D., Niyonkuru, C. et al. (2013) S100b as a prognostic biomarker in outcome prediction for patients with severe traumatic brain injury. Journal of Neurotrauma 30(11): 946-57	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Gozt, A. K., Hellewell, S. C., Thorne, J. et al. (2021) Predicting outcome following mild traumatic brain injury: protocol for the longitudinal, prospective, observational Concussion Recovery (CREST) cohort study. BMJ Open 11(5): e046460	- Study protocol only
Gozt, A., Licari, M., Halstrom, A. et al. (2020) Towards the Development of an Integrative, Evidence-Based Suite of Indicators for the Prediction of Outcome Following Mild Traumatic Brain Injury: Results from a Pilot Study. Brain Sciences 10(1): 02	- No prognostic accuracy measures reported
Gradisek, P., Carrara, G., Antiga, L. et al. (2021) Prognostic Value of a Combination of Circulating Biomarkers in Critically Ill Patients with Traumatic Brain Injury: Results from the European CREACTIVE Study. Journal of Neurotrauma 11: 11	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Gradisek, P., Osredkar, J., Kremzar, B. et al. (2011) Biochemical markers of traumatic brain injury. Zdravniski Vestnik 80(4): 293-301	- Study not reported in English
Grados, M. A., Slomine, B. S., Gerring, J. P. et al. (2001) Depth of lesion model in children and adolescents with moderate to severe traumatic brain injury: use of SPGR MRI to predict severity and outcome. Journal of Neurology, Neurosurgery & Psychiatry 70(3): 350-8	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Graham, N. S. N., Zimmerman, K. A., Bertolini, G. et al. (2020) Multicentre longitudinal study of fluid and neuroimaging BIOmarkers of AXonal injury after traumatic brain injury: the BIO-AX-TBI study protocol. BMJ Open 10(11): e042093	- Study protocol only - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome

Study	Code [Reason]
Griffin, A. D., Turtzo, L. C., Parikh, G. Y. et al. (2019) Traumatic microbleeds suggest vascular injury and predict disability in traumatic brain injury. Brain 142(11): 3550-3564	- No prognostic accuracy measures reported
Grossman, E. J., Jensen, J. H., Babb, J. S. et al. (2013) Cognitive impairment in mild traumatic brain injury: a longitudinal diffusional kurtosis and perfusion imaging study. Ajnr: American Journal of Neuroradiology 34(5): 951-7, S1	- Study design not relevant to this review protocol
Guan, W., Yang, Y. L., Xia, W. M. et al. (2003) Serum neuron-specific enolase in predicating outcome of patients with severe traumatic brain injury. Chinese Journal of Clinical Rehabilitation 7(19): 2718-2720	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Guan, W., Yang, Y. L., Xia, W. M. et al. (2003) Significance of serum neuron-specific enolase in patients with acute traumatic brain injury. Chinese Journal of Traumatology 6(4): 218-21	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Haghbayan, H., Boutin, A., Laflamme, M. et al. (2017) The Prognostic Value of MRI in Moderate and Severe Traumatic Brain Injury: A Systematic Review and Meta-Analysis. Critical Care Medicine 45(12): e1280-e1288	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Haghbayan, H., Boutin, A., Laflamme, M. et al. (2016) The prognostic value of magnetic resonance imaging in moderate and severe traumatic brain injury: a systematic review and meta-analysis protocol. Systematic Reviews 5: 10	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - Study protocol only
Hammeke, T. A., McCrea, M., Coats, S. M. et al. (2013) Acute and subacute changes in neural activation during the recovery from sport-related concussion. Journal of the International Neuropsychological Society 19(8): 863-72	- Study design not relevant to this review protocol
Hanten, G., Li, X., Ibarra, A. et al. (2013) Updating memory after mild traumatic brain injury and orthopedic injuries. Journal of Neurotrauma 30(8): 618-24	- No prognostic accuracy measures reported
Heidari, K., Asadollahi, S., Jamshidian, M. et al. (2015) Prediction of neuropsychological outcome after mild traumatic brain injury using clinical parameters, serum S100B protein and	- No prognostic accuracy measures reported

Study	Code [Reason]
findings on computed tomography. Brain Injury 29(1): 33-40	
Hellewell, S. C., Conquest, A., Little, L. et al. (2020) EPO treatment does not alter acute serum profiles of GFAP and S100B after TBI: A brief report on the Australian EPO-TBI clinical trial. Journal of Clinical Neuroscience 76: 5-8	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Hellstrom, T., Kaufmann, T., Andelic, N. et al. (2017) Predicting Outcome 12 Months after Mild Traumatic Brain Injury in Patients Admitted to a Neurosurgery Service. Frontiers in neurology [electronic resource]. 8: 125	- No prognostic accuracy measures reported
Herskovits, E. H., Gerring, J. P., Davatzikos, C. et al. (2002) Is the spatial distribution of brain lesions associated with closed-head injury in children predictive of subsequent development of posttraumatic stress disorder?. Radiology 224(2): 345-51	- Not relevant to post-concussion syndrome
Herskovits, E. H., Megalooikonomou, V., Davatzikos, C. et al. (1999) Is the spatial distribution of brain lesions associated with closed-head injury predictive of subsequent development of attention-deficit/hyperactivity disorder? Analysis with brain-image database. Radiology 213(2): 389-94	- Not relevant to post-concussion syndrome
Hiekkanen, H., Kurki, T., Brandstack, N. et al. (2009) Association of injury severity, MRI-results and ApoE genotype with 1-year outcome in mainly mild TBI: a preliminary study. Brain Injury 23(5): 396-402	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Hilario, A., Ramos, A., Millan, J. M. et al. (2012) Severe traumatic head injury: prognostic value of brain stem injuries detected at MRI. Ajnr: American Journal of Neuroradiology 33(10): 1925-31	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Ho, K. M.; Honeybul, S.; Ambati, R. (2018) Prognostic Significance of Magnetic Resonance Imaging in Patients with Severe Nonpenetrating Traumatic Brain Injury Requiring Decompressive Craniectomy. World Neurosurgery 112: 277-283	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Hofman, P. A., Stapert, S. Z., van Kroonenburgh, M. J. et al. (2001) MR imaging,	- No prognostic accuracy measures reported

Study	Code [Reason]
single-photon emission CT, and neurocognitive performance after mild traumatic brain injury. Ajnr: American Journal of Neuroradiology 22(3): 441-9	
Holshouser, B. A.; Tong, K. A.; Ashwal, S. (2005) Proton MR spectroscopic imaging depicts diffuse axonal injury in children with traumatic brain injury. Ajnr: American Journal of Neuroradiology 26(5): 1276-85	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Holshouser, B. A., Tong, K. A., Ashwal, S. et al. (2006) Prospective longitudinal proton magnetic resonance spectroscopic imaging in adult traumatic brain injury. Journal of Magnetic Resonance Imaging 24(1): 33-40	- No prognostic accuracy measures reported
Holshouser, B., Pivonka-Jones, J., Nichols, J. G. et al. (2019) Longitudinal Metabolite Changes after Traumatic Brain Injury: A Prospective Pediatric Magnetic Resonance Spectroscopic Imaging Study. Journal of Neurotrauma 36(8): 1352-1360	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Homolkova, H.; Prchlik, M.; Tomek, P. (2012) The relationship between S100B protein serum levels, injury severity and Glasgow Outcome Scale values in children with CNS injuries. Neuroendocrinology Letters 33(2): 207-11	- No prognostic accuracy measures reported - Average GCS score consistent with moderate/severe TBI
Hou, D. J., Tong, K. A., Ashwal, S. et al. (2007) Diffusion-weighted magnetic resonance imaging improves outcome prediction in adult traumatic brain injury. Journal of Neurotrauma 24(10): 1558-69	- No prognostic accuracy measures reported
Huebschmann, N. A., Luoto, T. M., Karr, J. E. et al. (2020) Comparing Glial Fibrillary Acidic Protein (GFAP) in Serum and Plasma Following Mild Traumatic Brain Injury in Older Adults. Frontiers in neurology [electronic resource]. 11: 1054	- Time-point not relevant to post-concussion syndrome which is usually diagnosed at least a few weeks following injury
Hughes, D. G., Jackson, A., Mason, D. L. et al. (2004) Abnormalities on magnetic resonance imaging seen acutely following mild traumatic brain injury: correlation with neuropsychological tests and delayed recovery. Neuroradiology 46(7): 550-8	- No prognostic accuracy measures reported
Humble, S. S., Wilson, L. D., Wang, L. et al. (2018) Prognosis of diffuse axonal injury with	- No prognostic accuracy measures reported

Study	Code [Reason]
traumatic brain injury. The Journal of Trauma and Acute Care Surgery 85(1): 155-159	
Ilves, P., Lintrop, M., Talvik, I. et al. (2010) Predictive value of clinical and radiological findings in inflicted traumatic brain injury. Acta Paediatrica 99(9): 1329-36	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - No prognostic accuracy measures reported
Imagawa, K. K., Hamilton, A., Ceschin, R. et al. (2014) Characterization of microstructural injury: a novel approach in infant abusive head trauma-initial experience. Journal of Neurotrauma 31(19): 1632-8	- No prognostic accuracy measures reported - No relevant prognostic factors
Ingebrigtsen, T., Romner, B., Marup-Jensen, S. et al. (2000) The clinical value of serum S-100 protein measurements in minor head injury: a Scandinavian multicentre study. Brain Injury 14(12): 1047-55	- Prognostic accuracy measures reported but not for outcomes relevant to the review protocol
Ingebrigtsen, T., Waterloo, K., Jacobsen, E. A. et al. (1999) Traumatic brain damage in minor head injury: relation of serum S-100 protein measurements to magnetic resonance imaging and neurobehavioral outcome. Neurosurgery 45(3): 468-75; discussion 475	- Full text paper not available
Iraji, A., Chen, H., Wiseman, N. et al. (2016) Compensation through Functional Hyperconnectivity: A Longitudinal Connectome Assessment of Mild Traumatic Brain Injury. Neural Plasticity 2016: 4072402	- Study design not relevant to this review protocol
Iwamura, A., Taoka, T., Fukusumi, A. et al. (2012) Diffuse vascular injury: convergent-type hemorrhage in the supratentorial white matter on susceptibility-weighted image in cases of severe traumatic brain damage. Neuroradiology 54(4): 335-43	- Study not reported in English
Izzy, S., Mazwi, N. L., Martinez, S. et al. (2017) Revisiting Grade 3 Diffuse Axonal Injury: Not All Brainstem Microbleeds are Prognostically Equal. Neurocritical Care 27(2): 199-207	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome

Study	Code [Reason]
Jain, B., Das, A. K., Agrawal, M. et al. (2021) Implications of DTI in mild traumatic brain injury for detecting neurological recovery and predicting long-term behavioural outcome in paediatric and young population-a systematic review. Childs Nervous System 37(8): 2475-2486	- Systematic review used as source of primary studies
Jeong, J. H., Kim, Y. Z., Cho, Y. W. et al. (2010) Negative effect of hypopituitarism following brain trauma in patients with diffuse axonal injury. Journal of Neurosurgery 113(3): 532-8	- Full text paper not available
Johnson, C. P., Juranek, J., Kramer, L. A. et al. (2011) Predicting behavioral deficits in pediatric traumatic brain injury through uncinate fasciculus integrity. Journal of the International Neuropsychological Society 17(4): 663-73	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Jolly, A. E., Balaet, M., Azor, A. et al. (2021) Detecting axonal injury in individual patients after traumatic brain injury. Brain 144(1): 92-113	- Prognostic accuracy measures reported but not for outcomes relevant to the review protocol - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Jorge, R. E., Acion, L., Starkstein, S. E. et al. (2007) Hippocampal volume and mood disorders after traumatic brain injury. Biological Psychiatry 62(4): 332-8	- No prognostic accuracy measures reported
Jorge, R. E., Acion, L., White, T. et al. (2012) White matter abnormalities in veterans with mild traumatic brain injury. American Journal of Psychiatry 169(12): 1284-91	- Study design not relevant to this review protocol - No prognostic accuracy measures reported
Jorge, R. E., Robinson, R. G., Moser, D. et al. (2004) Major depression following traumatic brain injury. Archives of General Psychiatry 61(1): 42-50	- No prognostic accuracy measures reported
Kaplan, A. D., Cheng, Q., Mohan, K. A. et al. (2021) Mixture Model Framework for Traumatic Brain Injury Prognosis Using Heterogeneous	- No prognostic accuracy measures reported

Study	Code [Reason]
Clinical and Outcome Data. IEEE Journal of Biomedical & Health Informatics. PP 26: 26	
Karlsen, R. H., Einarsen, C., Moe, H. K. et al. (2019) Diffusion kurtosis imaging in mild traumatic brain injury and postconcussional syndrome. Journal of Neuroscience Research 97(5): 568-581	- No prognostic accuracy measures reported
Karthikeyan, Y. R.; Purohit, D.; Sinha, V. D. (2017) Role of Magnetic Resonance Imaging in Unconscious Patients due to Diffuse Axonal Injury and Its Prognostic Value. Indian Journal of Neurotrauma 14(1): 15-20	- Systematic review used as source of primary studies
Kellermann, I., Kleindienst, A., Hore, N. et al. (2016) Early CSF and Serum S100B Concentrations for Outcome Prediction in Traumatic Brain Injury and Subarachnoid Hemorrhage. Clinical Neurology & Neurosurgery 145: 79-83	- Not relevant to post-concussion syndrome *Not predicting post-concussion syndrome.*
Khong, E., Odenwald, N., Hashim, E. et al. (2016) Diffusion Tensor Imaging Findings in Post-Concussion Syndrome Patients after Mild Traumatic Brain Injury: A Systematic Review. Frontiers in neurology [electronic resource]. 7: 156	- Systematic review used as source of primary studies
Kim, D. S., Choi, H. J., Yang, J. S. et al. (2015) Radiologic Determination of Corpus Callosum Injury in Patients with Mild Traumatic Brain Injury and Associated Clinical Characteristics. Journal of Korean Neurosurgical Society 58(2): 131-6	- Study design not relevant to this review protocol
King, D. J., Seri, S., Beare, R. et al. (2020) Developmental divergence of structural brain networks as an indicator of future cognitive impairments in childhood brain injury: Executive functions. Developmental Cognitive Neuroscience 42: 100762	- No prognostic accuracy measures reported
Koch, K. M., Nencka, A. S., Swearingen, B. et al. (2021) Acute Post-Concussive Assessments of Brain Tissue Magnetism Using Magnetic Resonance Imaging. Journal of Neurotrauma 38(7): 848-857	- No relevant outcomes
Kuceyeski, A. F., Jamison, K. W., Owen, J. P. et al. (2019) Longitudinal increases in structural connectome segregation and functional	- No prognostic accuracy measures reported

Study	Code [Reason]
connectome integration are associated with better recovery after mild TBI. Human Brain Mapping 40(15): 4441-4456	
Kuchta, J., Wedekind, C., Ernestus, R. I. et al. (2009) The hour-glass model of corpus callosum injury. Central European neurosurgery 70(3): 125-9	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Kumar, R. G.; Boles, J. A.; Wagner, A. K. (2015) Chronic Inflammation After Severe Traumatic Brain Injury: Characterization and Associations With Outcome at 6 and 12 Months Postinjury. Journal of Head Trauma Rehabilitation 30(6): 369-81	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - No relevant prognostic factors
Kumar, R., Saksena, S., Husain, M. et al. (2010) Serial changes in diffusion tensor imaging metrics of corpus callosum in moderate traumatic brain injury patients and their correlation with neuropsychometric tests: a 2-year follow-up study. Journal of Head Trauma Rehabilitation 25(1): 31-42	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Lagares, A., Ramos, A., Perez-Nunez, A. et al. (2009) The role of MR imaging in assessing prognosis after severe and moderate head injury. Acta Neurochirurgica 151(4): 341-56	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Lancaster, M. A., Meier, T. B., Olson, D. V. et al. (2018) Chronic differences in white matter integrity following sport-related concussion as measured by diffusion MRI: 6-Month follow-up. Human Brain Mapping 39(11): 4276-4289	- No prognostic accuracy measures reported
Lancaster, M. A., Olson, D. V., McCrea, M. A. et al. (2016) Acute white matter changes following sport-related concussion: A serial diffusion tensor and diffusion kurtosis tensor imaging study. Human Brain Mapping 37(11): 3821-3834	- No prognostic accuracy measures reported
Lange, R. T., Panenka, W. J., Shewchuk, J. R. et al. (2015) Diffusion tensor imaging findings and postconcussion symptom reporting six	- No prognostic accuracy measures reported

Study	Code [Reason]
weeks following mild traumatic brain injury. Archives of Clinical Neuropsychology 30(1): 7-25	
Lannsjo, M., Raininko, R., Bustamante, M. et al. (2013) Brain pathology after mild traumatic brain injury: an exploratory study by repeated magnetic resonance examination. Journal of Rehabilitation Medicine 45(8): 721-8	- Study design not relevant to this review protocol
Laouchedi, M., Galanaud, D., Delmaire, C. et al. (2015) Deafferentation in thalamic and pontine areas in severe traumatic brain injury. Journal of Neuroradiology. Journal de Neuroradiologie 42(4): 202-11	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Lee, S. Y., Kim, S. S., Kim, C. H. et al. (2012) Prediction of outcome after traumatic brain injury using clinical and neuroimaging variables. Journal of Clinical Neurology 8(3): 224-9	- No prognostic accuracy measures reported
Lei, J., Gao, G., Feng, J. et al. (2015) Glial fibrillary acidic protein as a biomarker in severe traumatic brain injury patients: a prospective cohort study. Critical Care (London, England) 19: 362	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Lesko, M. M., O'Brien, S. J., Childs, C. et al. (2014) Comparison of several prognostic tools in traumatic brain injury including S100B. Brain Injury 28(7): 987-94	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Levin, H. S., Fletcher, J. M., Kusnerik, L. et al. (1996) Semantic memory following pediatric head injury: relationship to age, severity of injury, and MRI. Cortex 32(3): 461-78	- No prognostic accuracy measures reported
Levin, H. S., Mendelsohn, D., Lilly, M. A. et al. (1997) Magnetic resonance imaging in relation to functional outcome of pediatric closed head injury: a test of the Ommaya-Gennarelli model. Neurosurgery 40(3): 432-40; discussion 440	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Levin, H. S., Wilde, E. A., Chu, Z. et al. (2008) Diffusion tensor imaging in relation to cognitive and functional outcome of traumatic brain injury in children. Journal of Head Trauma Rehabilitation 23(4): 197-208	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome

Study	Code [Reason]
Levin, H. S., Wilde, E., Troyanskaya, M. et al. (2010) Diffusion tensor imaging of mild to moderate blast-related traumatic brain injury and its sequelae. Journal of Neurotrauma 27(4): 683-94	- No prognostic accuracy measures reported
Lewis, J. M., Dhawan, S., Obirieze, A. C. et al. (2020) Plasma Biomarker for Post-concussive Syndrome: A Pilot Study Using an Alternating Current Electro-Kinetic Platform. Frontiers in Neurology 11 (no pagination)	- Prognostic accuracy measures reported but not for outcomes relevant to the review protocol
Lewis, L. M., Papa, L., Bazarian, J. J. et al. (2020) Biomarkers May Predict Unfavorable Neurological Outcome after Mild Traumatic Brain Injury. Journal of Neurotrauma 37(24): 2624-2631	- No prognostic accuracy measures reported
Li, N., Shen, J. K., Zhao, W. G. et al. (2004) S-100B and neuron specific enolase in outcome prediction of severe head injury. Chinese Journal of Traumatology 7(3): 156-8	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Lima, D. P., Simao Filho, C., Abib Sde, C. et al. (2008) Quality of life and neuropsychological changes in mild head trauma. Late analysis and correlation with S100B protein and cranial CT scan performed at hospital admission. Injury 39(5): 604-11	- No prognostic accuracy measures reported
Lindblad, C., Pin, E., Just, D. et al. (2021) Fluid proteomics of CSF and serum reveal important neuroinflammatory proteins in blood-brain barrier disruption and outcome prediction following severe traumatic brain injury: a prospective, observational study. Critical Care (London, England) 25(1): 103	- No prognostic accuracy measures reported
Lindsey, H. M., Hodges, C. B., Greer, K. M. et al. (2021) Diffusion-Weighted Imaging in Mild Traumatic Brain Injury: A Systematic Review of the Literature. Neuropsychology Review 15: 15	- Systematic review used as source of primary studies
Lippa, S. M., Gill, J., Brickell, T. A. et al. (2021) Blood Biomarkers Relate to Cognitive Performance Years after Traumatic Brain Injury in Service Members and Veterans. Journal of the International Neuropsychological Society 27(5): 508-514	- Biomarkers measured only at 1 year post-injury

Study	Code [Reason]
Little, D. M., Kraus, M. F., Joseph, J. et al. (2010) Thalamic integrity underlies executive dysfunction in traumatic brain injury. Neurology 74(7): 558-64	- No prognostic accuracy measures reported
Liu, H. and Zhang, X. (2020) Correlation between platelet parameters, platelet/lymphocyte ratio, the severity and prognosis of patients with traumatic brain injury. International Journal of Clinical and Experimental Medicine 13(7): 5187-5192	- No prognostic accuracy measures reported
Ljungqvist, J., Nilsson, D., Ljungberg, M. et al. (2017) Longitudinal changes in diffusion tensor imaging parameters of the corpus callosum between 6 and 12 months after diffuse axonal injury. Brain Injury 31(3): 344-350	- No prognostic accuracy measures reported
Lo, T. Y.; Jones, P. A.; Minns, R. A. (2010) Combining coma score and serum biomarker levels to predict unfavorable outcome following childhood brain trauma. Journal of Neurotrauma 27(12): 2139-45	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Lo, T. Y.; Jones, P. A.; Minns, R. A. (2009) Pediatric brain trauma outcome prediction using paired serum levels of inflammatory mediators and brain-specific proteins. Journal of Neurotrauma 26(9): 1479-87	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Lohani, S., Bhandari, S., Ranabhat, K. et al. (2020) Does Diffuse Axonal Injury MRI Grade Really Correlate with Functional Outcome?. World Neurosurgery 135: e424-e426	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Lomas, J. P. and Dunning, J. (2005) Best evidence topic report. S-100b protein levels as a predictor for long-term disability after head injury. Emergency Medicine Journal 22(12): 889-91	- Systematic review used as source of primary studies
Lotze, M., Grodd, W., Rodden, F. A. et al. (2006) Neuroimaging patterns associated with motor control in traumatic brain injury. Neurorehabilitation & Neural Repair 20(1): 14-23	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - No prognostic accuracy measures reported
Lu, W., Jiang, C., Wang, Z. et al. (2020) Lactic acid, neuron-specific enolase, and blood-brain	- The population is those with moderate or severe TBI or is mixed and<60% of the

Study	Code [Reason]
barrier index after a severe traumatic brain injury: a prospective study. British Journal of Neurosurgery: 1-5	population has mild TBI - not relevant to post-concussion syndrome
Lugones, M., Parkin, G., Bjelosevic, S. et al. (2018) Blood biomarkers in paediatric mild traumatic brain injury: a systematic review. Neuroscience & Biobehavioral Reviews 87: 206-217	- Systematic review used as source of primary studies
Luoto, T. M., Silverberg, N. D., Kataja, A. et al. (2014) Sport concussion assessment tool 2 in a civilian trauma sample with mild traumatic brain injury. Journal of Neurotrauma 31(8): 728-38	- Prognostic accuracy measures reported but not for outcomes relevant to the review protocol
Lutkenhoff, E. S., Wright, M. J., Shrestha, V. et al. (2020) The subcortical basis of outcome and cognitive impairment in TBI: A longitudinal cohort study. Neurology 95(17): e2398-e2408	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Lv, L. Q., Hou, L. J., Yu, M. K. et al. (2011) Risk factors related to dysautonomia after severe traumatic brain injury. Journal of Trauma-Injury Infection & Critical Care 71(3): 538-42	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Maas, A. I., Menon, D. K., Steyerberg, E. W. et al. (2015) Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. Neurosurgery 76(1): 67-80	- Study protocol only
Mac Donald, C. L., Barber, J., Wright, J. et al. (2019) Longitudinal Clinical and Neuroimaging Evaluation of Symptomatic Concussion in 10- to 14-year-old Youth Athletes. Journal of Neurotrauma 36(2): 264-274	- No prognostic accuracy measures reported
Madaan, P., Gupta, D., Agrawal, D. et al. (2021) Neurocognitive Outcomes and Their Diffusion Tensor Imaging Correlates in Children With Mild Traumatic Brain Injury. Journal of Child Neurology 36(8): 664-672	- No prognostic accuracy measures reported *No relevant prognostic accuracy measures. Study evaluated co-relation between neurocognitive outcomes and diffusion tensor parameters in acute phase of mild TBI.*
Madhavan, R., Joel, S. E., Mullick, R. et al. (2019) Longitudinal Resting State Functional Connectivity Predicts Clinical Outcome in Mild Traumatic Brain Injury. Journal of Neurotrauma 36(5): 650-660	- No prognostic accuracy measures reported

Study	Code [Reason]
Manning, K. Y., Schranz, A., Bartha, R. et al. (2017) Multiparametric MRI changes persist beyond recovery in concussed adolescent hockey players. Neurology 89(21): 2157-2166	- No prognostic accuracy measures reported
Mannion, R. J., Cross, J., Bradley, P. et al. (2007) Mechanism-based MRI classification of traumatic brainstem injury and its relationship to outcome. Journal of Neurotrauma 24(1): 128-35	- No prognostic accuracy measures reported *study evaluated MRI changes after concussion compared to healthy non-concussed controls.*
Mannix, R., Eisenberg, M., Berry, M. et al. (2014) Serum biomarkers predict acute symptom burden in children after concussion: a preliminary study. Journal of Neurotrauma 31(11): 1072-5	- No prognostic accuracy measures reported
Mannix, R., Levy, R., Zemek, R. et al. (2020) Fluid Biomarkers of Pediatric Mild Traumatic Brain Injury: A Systematic Review. Journal of Neurotrauma 37(19): 2029-2044	- Systematic review- screened for relevant references
Manzano, S., Holzinger, I. B., Kellenberger, C. J. et al. (2016) Diagnostic performance of S100B protein serum measurement in detecting intracranial injury in children with mild head trauma. Emergency Medicine Journal 33(1): 42-6	- No relevant outcomes
Mao, Y., Zhuang, Z., Chen, Y. et al. (2019) Imaging of glutamate in acute traumatic brain injury using chemical exchange saturation transfer. Quantitative Imaging in Medicine & Surgery 9(10): 1652-1663	- No relevant prognostic factors
Marino, S., Zei, E., Battaglini, M. et al. (2007) Acute metabolic brain changes following traumatic brain injury and their relevance to clinical severity and outcome. Journal of Neurology, Neurosurgery & Psychiatry 78(5): 501-7	- No prognostic accuracy measures reported
Marquez de la Plata, C. D., Garces, J., Shokri Kojori, E. et al. (2011) Deficits in functional connectivity of hippocampal and frontal lobe circuits after traumatic axonal injury. Archives of Neurology 68(1): 74-84	- No prognostic accuracy measures reported
Masiero, S., Cerrel Bazo, H. A., Rattazzi, M. et al. (2021) Developing an instrument for an early prediction model of long-term functional outcomes in people with acquired injuries of the	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome

Study	Code [Reason]
central nervous system: protocol and methodological aspects. Neurological Sciences 42(6): 2441-2446	- No prognostic accuracy measures reported
Matsukawa, H., Shinoda, M., Fujii, M. et al. (2012) Intraventricular hemorrhage on computed tomography and corpus callosum injury on magnetic resonance imaging in patients with isolated blunt traumatic brain injury. Journal of Neurosurgery 117(2): 334-9	- No prognostic accuracy measures reported
Matsushita, M., Hosoda, K., Naitoh, Y. et al. (2011) Utility of diffusion tensor imaging in the acute stage of mild to moderate traumatic brain injury for detecting white matter lesions and predicting long-term cognitive function in adults. Journal of Neurosurgery 115(1): 130-9	- No prognostic accuracy measures reported
Max, J. E., Castillo, C. S., Bokura, H. et al. (1998) Oppositional defiant disorder symptomatology after traumatic brain injury: a prospective study. Journal of Nervous & Mental Disease 186(6): 325-32	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - No prognostic accuracy measures reported
Max, J. E., Keatley, E., Wilde, E. A. et al. (2011) Anxiety disorders in children and adolescents in the first six months after traumatic brain injury. Journal of Neuropsychiatry & Clinical Neurosciences 23(1): 29-39	- No relevant prognostic factors *Study objective was to assess the nature, rate, predictive factors, and neuroimaging correlates of new onset definite anxiety disorders in children after traumatic brain injury (TBI).*
Max, J. E., Keatley, E., Wilde, E. A. et al. (2012) Depression in children and adolescents in the first 6 months after traumatic brain injury. International Journal of Developmental Neuroscience 30(3): 239-45	- No prognostic accuracy measures reported
Max, J. E., Lopez, A., Wilde, E. A. et al. (2015) Anxiety disorders in children and adolescents in the second six months after traumatic brain injury. Journal of Pediatric Rehabilitation Medicine 8(4): 345-55	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - No prognostic accuracy measures reported
Max, J. E., Schachar, R. J., Landis, J. et al. (2013) Psychiatric disorders in children and adolescents in the first six months after mild traumatic brain injury. Journal of	- No prognostic accuracy measures reported - No relevant prognostic factors

Study	Code [Reason]
Neuropsychiatry & Clinical Neurosciences 25(3): 187-97	
Max, J. E., Wilde, E. A., Bigler, E. D. et al. (2012) Neuroimaging correlates of novel psychiatric disorders after pediatric traumatic brain injury. Journal of the American Academy of Child & Adolescent Psychiatry 51(11): 1208-17	- No prognostic accuracy measures reported *study evaluates magnetic resonance imaging correlates of novel new-onset psychiatric disorders following traumatic brain injury (TBI) and orthopaedic injury.*
Mayer, A. R., Kaushal, M., Dodd, A. B. et al. (2018) Advanced biomarkers of pediatric mild traumatic brain injury: Progress and perils. Neuroscience & Biobehavioral Reviews 94: 149-165	- Systematic review- screened for relevant references
Mayer, A. R., Mannell, M. V., Ling, J. et al. (2011) Functional connectivity in mild traumatic brain injury. Human Brain Mapping 32(11): 1825-35	- Prognostic accuracy measures reported but not for outcomes relevant to the review protocol
Mayer, A. R., Stephenson, D. D., Wertz, C. J. et al. (2019) Proactive inhibition deficits with normal perfusion after pediatric mild traumatic brain injury. Human Brain Mapping 40(18): 5370-5381	- No prognostic accuracy measures reported
McInnis, C., Garcia, M. J. S., Widjaja, E. et al. (2021) Magnetic Resonance Imaging Findings Are Associated with Long-Term Global Neurological Function or Death after Traumatic Brain Injury in Critically Ill Children. Journal of Neurotrauma 13: 13	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Meier, T. B., Bergamino, M., Bellgowan, P. S. et al. (2016) Longitudinal assessment of white matter abnormalities following sports-related concussion. Human Brain Mapping 37(2): 833-45	- No relevant outcomes - No prognostic accuracy measures reported
Meier, T. B., Giraldo-Chica, M., Espana, L. Y. et al. (2020) Resting-State fMRI Metrics in Acute Sport-Related Concussion and Their Association with Clinical Recovery: A Study from the NCAA-DOD CARE Consortium. Journal of Neurotrauma 37(1): 152-162	- No prognostic accuracy measures reported
Mercier, E., Boutin, A., Lauzier, F. et al. (2013) Predictive value of S-100beta protein for prognosis in patients with moderate and severe traumatic brain injury: systematic review and meta-analysis. BMJ 346: f1757	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome

Study	Code [Reason]
	- Systematic review- screened for relevant references
Mercier, E., Boutin, A., Shemilt, M. et al. (2016) Predictive value of neuron-specific enolase for prognosis in patients with moderate or severe traumatic brain injury: a systematic review and meta-analysis. CMAJ open 4(3): E371-E382	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Mercier, E., Tardif, P. A., Cameron, P. A. et al. (2018) Prognostic Value of S-100beta Protein for Prediction of Post-Concussion Symptoms after a Mild Traumatic Brain Injury: Systematic Review and Meta-Analysis. Journal of Neurotrauma 35(4): 609-622	- Systematic review- screened for relevant references
Mercier, E., Tardif, P. A., Cameron, P. A. et al. (2018) Prognostic value of neuron-specific enolase (NSE) for prediction of post-concussion symptoms following a mild traumatic brain injury: a systematic review. Brain Injury 32(1): 29-40	- Systematic review used as source of primary studies
Mercier, E., Tardif, P. A., Emond, M. et al. (2017) Characteristics of patients included and enrolled in studies on the prognostic value of serum biomarkers for prediction of postconcussion symptoms following a mild traumatic brain injury: a systematic review. BMJ Open 7(9): e017848	- Systematic review used as source of primary studies
Meric, E., Gunduz, A., Turedi, S. et al. (2010) The prognostic value of neuron-specific enolase in head trauma patients. Journal of Emergency Medicine 38(3): 297-301	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Meshcheryakov, S. V., Semenova, Z. B., Lukianov, V. I. et al. (2018) Prognosis of Severe Traumatic Brain Injury Outcomes in Children. Acta Neurochirurgica - Supplement 126: 11-16	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Messori, A., Polonara, G., Carle, F. et al. (2005) Predicting posttraumatic epilepsy with MRI: prospective longitudinal morphologic study in adults. Epilepsia 46(9): 1472-81	- Population not relevant to this review protocol *Predicting Posttraumatic Epilepsy with MRI*
Miles, L., Grossman, R. I., Johnson, G. et al. (2008) Short-term DTI predictors of cognitive dysfunction in mild traumatic brain injury. Brain Injury 22(2): 115-22	- No prognostic accuracy measures reported

Study	Code [Reason]
Moe, H. K., Follestad, T., Andelic, N. et al. (2020) Traumatic axonal injury on clinical MRI: association with the Glasgow Coma Scale score at scene of injury or at admission and prolonged posttraumatic amnesia. Journal of Neurosurgery: 1-12	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Moen, K. G., Brezova, V., Skandsen, T. et al. (2014) Traumatic axonal injury: the prognostic value of lesion load in corpus callosum, brain stem, and thalamus in different magnetic resonance imaging sequences. Journal of Neurotrauma 31(17): 1486-96	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Moen, K. G., Haberg, A. K., Skandsen, T. et al. (2014) A longitudinal magnetic resonance imaging study of the apparent diffusion coefficient values in corpus callosum during the first year after traumatic brain injury. Journal of Neurotrauma 31(1): 56-63	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Moen, K. G., Skandsen, T., Folvik, M. et al. (2012) A longitudinal MRI study of traumatic axonal injury in patients with moderate and severe traumatic brain injury. Journal of Neurology, Neurosurgery & Psychiatry 83(12): 1193-200	- No prognostic accuracy measures reported
Molteni, E., Pagani, E., Strazzer, S. et al. (2019) Fronto-temporal vulnerability to disconnection in paediatric moderate and severe traumatic brain injury. European Journal of Neurology 26(9): 1183-1190	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Mondello, S., Papa, L., Buki, A. et al. (2011) Neuronal and glial markers are differently associated with computed tomography findings and outcome in patients with severe traumatic brain injury: a case control study. Critical Care (London, England) 15(3): r156	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Moreira da Silva, N., Cowie, C. J. A., Blamire, A. M. et al. (2020) Investigating Brain Network Changes and Their Association With Cognitive Recovery After Traumatic Brain Injury: A Longitudinal Analysis. Frontiers in neurology [electronic resource]. 11: 369	- No prognostic accuracy measures reported - No relevant prognostic factors
Muftuler, L. T., Meier, T. B., Keith, M. et al. (2020) Serial Diffusion Kurtosis Magnetic Resonance Imaging Study during Acute, Subacute, and Recovery Periods after Sport-	- No prognostic accuracy measures reported

Study	Code [Reason]
Related Concussion. Journal of Neurotrauma 37(19): 2081-2092	- Comparator in study does not match that specified in this review protocol *concussed American football players vs matched group of uninjured players*
Muller, K., Ingebrigtsen, T., Wilsgaard, T. et al. (2009) Prediction of time trends in recovery of cognitive function after mild head injury. Neurosurgery 64(4): 698-704; discussion 704	- No prognostic accuracy measures reported
Munivenkatappa, A., Bhagavatulaula, I. D., Shukla, D. P. et al. (2017) Alongitudinal study of changes in Diffusion Tensor Value and their association with cognitive sequelae among patients with mild head injury. Journal of Neurosurgical Sciences 61(3): 283-290	- No prognostic accuracy measures reported
Munivenkatappa, A., Devi, B. I., Shukla, D. P. et al. (2016) Role of the thalamus in natural recovery of cognitive impairment in patients with mild traumatic brain injury. Brain Injury 30(4): 388-392	- No prognostic accuracy measures reported
Murdaugh, D. L., King, T. Z., Sun, B. et al. (2018) Longitudinal Changes in Resting State Connectivity and White Matter Integrity in Adolescents With Sports-Related Concussion. Journal of the International Neuropsychological Society 24(8): 781-792	- No relevant prognostic factors
Murillo-Cabezas, F., Munoz-Sanchez, M. A., Rincon-Ferrari, M. D. et al. (2010) The prognostic value of the temporal course of S100beta protein in post-acute severe brain injury: A prospective and observational study. Brain Injury 24(4): 609-19	- People with severe TBI. Not relevant to PCS.
Mussack, T., Biberthaler, P., Kanz, K. G. et al. (2002) Serum S-100B and interleukin-8 as predictive markers for comparative neurologic outcome analysis of patients after cardiac arrest and severe traumatic brain injury. Critical Care Medicine 30(12): 2669-74	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Nakhjavan-Shahraki, B., Yousefifard, M., Oraii, A. et al. (2017) Meta-analysis of neuron specific enolase in predicting pediatric brain injury outcomes. Excli Journal 16: 995-1008	- Systematic review- screened for relevant references
Narayanan, V., Veeramuthu, V., Ahmad-Annuar, A. et al. (2016) Missense Mutation of Brain	- No prognostic accuracy measures reported

Study	Code [Reason]
Derived Neurotrophic Factor (BDNF) Alters Neurocognitive Performance in Patients with Mild Traumatic Brain Injury: A Longitudinal Study. PLoS ONE [Electronic Resource] 11(7): e0158838	
Nayak, R.; Attry, S.; Ghosh, S. N. (2018) Serum Magnesium as a Marker of Neurological Outcome in Severe Traumatic Brain Injury Patients. Asian Journal of Neurosurgery 13(3): 685-688	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Newcombe, V., Chatfield, D., Outtrim, J. et al. (2011) Mapping traumatic axonal injury using diffusion tensor imaging: correlations with functional outcome. PLoS ONE [Electronic Resource] 6(5): e19214	- Not relevant to post-concussion syndrome
Niogi, S. N., Luther, N., Kutner, K. et al. (2020) Increased sensitivity to traumatic axonal injury on postconcussion diffusion tensor imaging scans in national football league players by using premorbid baseline scans. Journal of Neurosurgery 133(4): 1063-1071	- No prognostic accuracy measures reported
Niu, X., Bai, L., Sun, Y. et al. (2020) Mild traumatic brain injury is associated with effect of inflammation on structural changes of default mode network in those developing chronic pain. Journal of Headache & Pain 21(1): 135	- No prognostic accuracy measures reported
Nordhaug, L. H., Linde, M., Follestad, T. et al. (2019) Change in Headache Suffering and Predictors of Headache after Mild Traumatic Brain Injury: A Population-Based, Controlled, Longitudinal Study with Twelve-Month Follow-Up. Journal of Neurotrauma 36(23): 3244-3252	- Comparator in study does not match that specified in this review protocol *Inappropriate comparison. Three groups: people with mild TBI; people with minor orthopedic injuries but no head injury (trauma controls), and community controls not exposed to any injury.*
Nylen, K., Ost, M., Csajbok, L. Z. et al. (2006) Increased serum-GFAP in patients with severe traumatic brain injury is related to outcome. Journal of the Neurological Sciences 240(12): 85-91	- People with severe TBI. Not relevant to PCS.
Olivecrona, M., Rodling-Wahlstrom, M., Naredi, S. et al. (2009) S-100B and neuron specific enolase are poor outcome predictors in severe traumatic brain injury treated by an intracranial pressure targeted therapy. Journal of Neurology, Neurosurgery & Psychiatry 80(11): 1241-7	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome

Study	Code [Reason]
Olivecrona, Z.; Bobinski, L.; Koskinen, L. O. (2015) Association of ICP, CPP, CT findings and S-100B and NSE in severe traumatic head injury. Prognostic value of the biomarkers. Brain Injury 29(4): 446-54	- People with severe TBI. Not relevant to PCS.
Oni, M. B., Wilde, E. A., Bigler, E. D. et al. (2010) Diffusion tensor imaging analysis of frontal lobes in pediatric traumatic brain injury. Journal of Child Neurology 25(8): 976-84	- Population not relevant to this review protocol *Includes moderate-to-severe traumatic brain injury and with orthopaedic injury.*
Oris, C., Pereira, B., Durif, J. et al. (2018) The Biomarker S100B and Mild Traumatic Brain Injury: A Meta-analysis. Pediatrics 141(6): 06	- No relevant outcomes
Osier, N. D., Conley, Y. P., Okonkwo, D. O. et al. (2018) Variation in Candidate Traumatic Brain Injury Biomarker Genes Are Associated with Gross Neurological Outcomes after Severe Traumatic Brain Injury. Journal of Neurotrauma 35(22): 2684-2690	- People with severe TBI. Not relevant to PCS.
Ostberg, A., Ledig, C., Katila, A. et al. (2020) Volume Change in Frontal Cholinergic Structures After Traumatic Brain Injury and Cognitive Outcome. Frontiers in neurology [electronic resource]. 11: 832	- No prognostic accuracy measures reported *Study compared people with all severities of TBI and controls with acute orthopaedic injuries.*
Otani, N., Morimoto, Y., Kinoshita, M. et al. (2020) Serial changes in serum phosphorylated neurofilament and value for prediction of clinical outcome after traumatic brain injury. Surgical neurology international 11: 387	- No prognostic accuracy measures reported
Pal, D., Gupta, R. K., Agarwal, S. et al. (2012) Diffusion tensor tractography indices in patients with frontal lobe injury and its correlation with neuropsychological tests. Clinical Neurology & Neurosurgery 114(6): 564-71	- No prognostic accuracy measures reported
Palacios, E. M., Owen, J. P., Yuh, E. L. et al. (2020) The evolution of white matter microstructural changes after mild traumatic brain injury: A longitudinal DTI and NODDI study. Science Advances 6(32): eaaz6892	- Comparator in study does not match that specified in this review protocol *People with mild TBS vs orthopaedic trauma control subjects and healthy controls*
Palacios, E. M., Yuh, E. L., Chang, Y. S. et al. (2017) Resting-State Functional Connectivity Alterations Associated with Six-Month Outcomes in Mild Traumatic Brain Injury. Journal of Neurotrauma 34(8): 1546-1557	- No prognostic accuracy measures reported

Study	Code [Reason]
Papa, L., Brophy, G. M., Welch, R. D. et al. (2016) Time Course and Diagnostic Accuracy of Glial and Neuronal Blood Biomarkers GFAP and UCH-L1 in a Large Cohort of Trauma Patients With and Without Mild Traumatic Brain Injury. JAMA Neurology 73(5): 551-60	- No relevant outcomes *diagnostic accuracy of Glial and Neuronal Blood Biomarkers GFAP and UCH-L1 for detecting TBI, CT lesions, and neurosurgical intervention.*
Park, S. H. and Hwang, S. K. (2018) Prognostic Value of Serum Levels of S100 Calcium-Binding Protein B, Neuron-Specific Enolase, and Interleukin-6 in Pediatric Patients with Traumatic Brain Injury. World Neurosurgery 118: e534-e542	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Parkin, G. M., Clarke, C., Takagi, M. et al. (2019) Plasma Tumor Necrosis Factor Alpha Is a Predictor of Persisting Symptoms Post-Concussion in Children. Journal of Neurotrauma 36(11): 1768-1775	- No prognostic accuracy measures reported
Pattinson, C. L., Meier, T. B., Guedes, V. A. et al. (2020) Plasma Biomarker Concentrations Associated With Return to Sport Following Sport-Related Concussion in Collegiate Athletes-A Concussion Assessment, Research, and Education (CARE) Consortium Study. JAMA Network Open 3(8): e2013191	- Comparator in study does not match that specified in this review protocol *No reference standard. No appropriate comparison. Study aimed to examine whether plasma biomarkers can differentiate collegiate athletes who return to sports in less than 14 days or 14 days or more following sports related concussion.*
Pelinka, L. E., Kroepfl, A., Leixnering, M. et al. (2004) GFAP versus S100B in serum after traumatic brain injury: relationship to brain damage and outcome. Journal of Neurotrauma 21(11): 1553-61	- People with severe TBI. Not relevant to PCS.
Pelinka, L. E., Kroepfl, A., Schmidhammer, R. et al. (2004) Glial fibrillary acidic protein in serum after traumatic brain injury and multiple trauma. Journal of Trauma-Injury Infection & Critical Care 57(5): 1006-12	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Peng, C., Xing, Y., Tao, H. et al. (2021) Role of diffusion tensor imaging combined with neuron-specific enolase and s100 calcium-binding protein b detection in predicting the prognosis of moderate and severe traumatic brain injury. Iranian Red Crescent Medical Journal 23 (4)	- No prognostic accuracy measures reported
Perlbarg, V., Puybasset, L., Tollard, E. et al. (2009) Relation between brain lesion location	- People with severe TBI. Not relevant to PCS.

Study	Code [Reason]
and clinical outcome in patients with severe traumatic brain injury: a diffusion tensor imaging study using voxel-based approaches. Human Brain Mapping 30(12): 3924-33	
Personnier, C., Crosnier, H., Meyer, P. et al. (2014) Prevalence of pituitary dysfunction after severe traumatic brain injury in children and adolescents: a large prospective study. Journal of Clinical Endocrinology & Metabolism 99(6): 2052-60	- Not relevant to post-concussion syndrome
Peters, M. E., Rao, V., Bechtold, K. T. et al. (2017) Head injury serum markers for assessing response to trauma: Design of the HeadSMART study. Brain Injury 31(3): 370-378	- Design/methods paper of a study
Piazza, O., Storti, M. P., Cotena, S. et al. (2007) S100B is not a reliable prognostic index in paediatric TBI. Pediatric Neurosurgery 43(4): 258-64	- No prognostic accuracy measures reported
Pineda, J. A., Lewis, S. B., Valadka, A. B. et al. (2007) Clinical significance of alphaII-spectrin breakdown products in cerebrospinal fluid after severe traumatic brain injury. Journal of Neurotrauma 24(2): 354-66	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - No prognostic accuracy measures reported
Posti, J. P., Hossain, I., Takala, R. S. K. et al. (2017) Glial Fibrillary Acidic Protein and Ubiquitin C-Terminal Hydrolase-L1 Are Not Specific Biomarkers for Mild CT-Negative Traumatic Brain Injury. Journal of Neurotrauma 34(7): 1427-1438	- Population not relevant to this review protocol *patients with acute orthopaedic injuries without central nervous system involvement*
Prasad, M. R., Ewing-Cobbs, L., Swank, P. R. et al. (2002) Predictors of outcome following traumatic brain injury in young children. Pediatric Neurosurgery 36(2): 64-74	- No prognostic accuracy measures reported
Puig, J., Ellis, M. J., Kornelsen, J. et al. (2020) Magnetic Resonance Imaging Biomarkers of Brain Connectivity in Predicting Outcome after Mild Traumatic Brain Injury: A Systematic Review. Journal of Neurotrauma 37(16): 1761-1776	- Systematic review used as source of primary studies
Raabe, A., Grolms, C., Keller, M. et al. (1998) Correlation of computed tomography findings and serum brain damage markers following	- No prognostic accuracy measures reported

Study	Code [Reason]
severe head injury. Acta Neurochirurgica 140(8): 787-91; discussion 791	
Raabe, A.; Grolms, C.; Seifert, V. (1999) Serum markers of brain damage and outcome prediction in patients after severe head injury. British Journal of Neurosurgery 13(1): 56-9	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Raabe, A., Grolms, C., Sorge, O. et al. (1999) Serum S-100B protein in severe head injury. Neurosurgery 45(3): 477-83	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Raabe, A. and Seifert, V. (2000) Protein S-100B as a serum marker of brain damage in severe head injury: preliminary results. Neurosurgical Review 23(3): 136-8	- People with severe TBI. Not relevant to PCS.
Rabinowitz, A. R., Hart, T., Whyte, J. et al. (2018) Neuropsychological Recovery Trajectories in Moderate to Severe Traumatic Brain Injury: Influence of Patient Characteristics and Diffuse Axonal Injury. Journal of the International Neuropsychological Society 24(3): 237-246	- No prognostic accuracy measures reported
Raheja, A., Sinha, S., Samson, N. et al. (2016) Serum biomarkers as predictors of long-term outcome in severe traumatic brain injury: analysis from a randomized placebo-controlled Phase II clinical trial. Journal of Neurosurgery 125(3): 631-41	- People with severe TBI. Not relevant to PCS.
Rainey, T., Lesko, M., Sacho, R. et al. (2009) Predicting outcome after severe traumatic brain injury using the serum S100B biomarker: results using a single (24h) time-point. Resuscitation 80(3): 341-5	- People with severe TBI. Not relevant to PCS.
Rao, V., Mielke, M., Xu, X. et al. (2012) Diffusion tensor imaging atlas-based analyses in major depression after mild traumatic brain injury. Journal of Neuropsychiatry & Clinical Neurosciences 24(3): 309-15	- No prognostic accuracy measures reported
Rausa, V. C., Shapiro, J., Seal, M. L. et al. (2020) Neuroimaging in paediatric mild traumatic brain injury: a systematic review. Neuroscience & Biobehavioral Reviews 118: 643-653	- Systematic review used as source of primary studies

Study	Code [Reason]
Ressel, V., O'Gorman Tuura, R., Scheer, I. et al. (2017) Diffusion tensor imaging predicts motor outcome in children with acquired brain injury. Brain Imaging & Behavior 11(5): 1373-1384	- Population not relevant to this review protocol *children with stroke or TBI following rehabilitation therapy.*
Rhine, T., Babcock, L., Zhang, N. et al. (2016) Are UCH-L1 and GFAP promising biomarkers for children with mild traumatic brain injury?. Brain Injury 30(10): 1231-8	- No prognostic accuracy measures reported
Rhine, T., Wade, S. L., Makoroff, K. L. et al. (2012) Clinical predictors of outcome following inflicted traumatic brain injury in children. The Journal of Trauma and Acute Care Surgery 73(4suppl3): S248-53	- No prognostic accuracy measures reported
Rostami, E., Krueger, F., Zoubak, S. et al. (2011) BDNF polymorphism predicts general intelligence after penetrating traumatic brain injury. PLoS ONE [Electronic Resource] 6(11): e27389	- No relevant prognostic factors - No prognostic accuracy measures reported
Rothoerl, R. D.; Woertgen, C.; Brawanski, A. (2000) S-100 serum levels and outcome after severe head injury. Acta Neurochirurgica - Supplement 76: 97-100	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Roy, Z., Subhash, S., Bui, L. A. et al. (2020) Exploratory Analysis of Concussion Recovery Trajectories using Multi-modal Assessments and Serum Biomarkers. Annual International Conference Of The IEEE Engineering In Medicine And Biology Society 2020: 5514-5518	- Study design not relevant to this review protocol *case control study*
Ryan, N. P., Beauchamp, M. H., Beare, R. et al. (2016) Uncovering cortico-striatal correlates of cognitive fatigue in pediatric acquired brain disorder: Evidence from traumatic brain injury. Cortex 83: 222-30	- No prognostic accuracy measures reported
Ryan, N. P., Catroppa, C., Beare, R. et al. (2015) Predictors of longitudinal outcome and recovery of pragmatic language and its relation to externalizing behaviour after pediatric traumatic brain injury. Brain & Language 142: 86-95	- No prognostic accuracy measures reported
Ryan, N. P., Catroppa, C., Beare, R. et al. (2017) Uncovering the neuroanatomical correlates of cognitive, affective and conative theory of mind in paediatric traumatic brain	- No prognostic accuracy measures reported

Study	Code [Reason]
injury: a neural systems perspective. Social Cognitive & Affective Neuroscience 12(9): 1414-1427	
Ryan, N. P., Catroppa, C., Cooper, J. M. et al. (2015) The emergence of age-dependent social cognitive deficits after generalized insult to the developing brain: a longitudinal prospective analysis using susceptibility-weighted imaging. Human Brain Mapping 36(5): 1677-91	- No relevant prognostic factors *This study aimed to examine the differential influence of age-at-insult and brain pathology on complex social and emotional behaviour including Theory of Mind in children and adolescents with traumatic brain injury.*
Ryan, N. P., Catroppa, C., Cooper, J. M. et al. (2015) Relationships between acute imaging biomarkers and theory of mind impairment in post-acute pediatric traumatic brain injury: A prospective analysis using susceptibility weighted imaging (SWI). Neuropsychologia 66: 32-8	- No prognostic accuracy measures reported
Ryan, N. P., Catroppa, C., Hughes, N. et al. (2021) Executive function mediates the prospective association between neurostructural differences within the central executive network and anti-social behavior after childhood traumatic brain injury. Journal of Child Psychology & Psychiatry & Allied Disciplines 24: 24	- No prognostic accuracy measures reported
Ryan, N. P., Genc, S., Beauchamp, M. H. et al. (2018) White matter microstructure predicts longitudinal social cognitive outcomes after paediatric traumatic brain injury: a diffusion tensor imaging study. Psychological Medicine 48(4): 679-691	- No prognostic accuracy measures reported
Ryan, N. P., van Bijnen, L., Catroppa, C. et al. (2016) Longitudinal outcome and recovery of social problems after pediatric traumatic brain injury (TBI): Contribution of brain insult and family environment. International Journal of Developmental Neuroscience 49: 23-30	- No prognostic accuracy measures reported
Saksvik, S. B., Karaliute, M., Kallestad, H. et al. (2020) The Prevalence and Stability of Sleep-Wake Disturbance and Fatigue throughout the First Year after Mild Traumatic Brain Injury. Journal of Neurotrauma 37(23): 2528-2541	- No prognostic accuracy measures reported *Study aimed to determine the prevalence and stability of sleep-wake disturbance and fatigue in people with mild TBI compared to matched trauma controls with orthopedic injuries, and matched community controls* - No relevant prognostic factors

Study	Code [Reason]
Salehpoor, F., Meshkini, A., Razmgiri, A. et al. (2016) Prognostic serum factors in patients with traumatic brain injury: A systematic review. Neurosurgery Quarterly 26(1): 19-36	- Population not relevant to this review protocol
Salorio, C. F., Slomine, B. S., Grados, M. A. et al. (2005) Neuroanatomic correlates of CVLT-C performance following pediatric traumatic brain injury. Journal of the International Neuropsychological Society 11(6): 686-96	- No prognostic accuracy measures reported
Salvato, G., Berlingeri, M., De Maio, G. et al. (2020) Autonomic responses to emotional linguistic stimuli and amplitude of low-frequency fluctuations predict outcome after severe brain injury. NeuroImage Clinical 28: 102356	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Sanchez-Carrion, R., Fernandez-Espejo, D., Junque, C. et al. (2008) A longitudinal fMRI study of working memory in severe TBI patients with diffuse axonal injury. Neuroimage 43(3): 421-9	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Sandhu, S., Soule, E., Fiester, P. et al. (2019) Brainstem Diffuse Axonal Injury and Consciousness. Journal of Clinical Imaging Science 9: 32	- No prognostic accuracy measures reported
Savola, O., Pyhtinen, J., Leino, T. K. et al. (2004) Effects of head and extracranial injuries on serum protein S100B levels in trauma patients. Journal of Trauma-Injury Infection & Critical Care 56(6): 1229-34; discussion 1234	- No prognostic accuracy measures reported
Scheid, R., Walther, K., Guthke, T. et al. (2006) Cognitive sequelae of diffuse axonal injury. Archives of Neurology 63(3): 418-24	- Study design not relevant to this review protocol - No prognostic accuracy measures reported
Schmidt, A. T., Hanten, G., Li, X. et al. (2013) Emotional prosody and diffusion tensor imaging in children after traumatic brain injury. Brain Injury 27(1314): 1528-35	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome

Study	Code [Reason]
Sener, S., Van Hecke, W., Feyen, B. F. et al. (2016) Diffusion Tensor Imaging: A Possible Biomarker in Severe Traumatic Brain Injury and Aneurysmal Subarachnoid Hemorrhage?. Neurosurgery 79(6): 786-793	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Shahim, P., Gren, M., Liman, V. et al. (2016) Serum neurofilament light protein predicts clinical outcome in traumatic brain injury. Scientific Reports 6: 36791	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Shahim, P., Politis, A., van der Merwe, A. et al. (2020) Time course and diagnostic utility of NfL, tau, GFAP, and UCH-L1 in subacute and chronic TBI. Neurology 95(6): e623-e636	- Prognostic accuracy measures reported but not for outcomes relevant to the review protocol
Shahim, P., Tegner, Y., Marklund, N. et al. (2018) Neurofilament light and tau as blood biomarkers for sports-related concussion. Neurology 90(20): e1780-e1788	- Prognostic accuracy measures reported but not for outcomes relevant to the review protocol
Shahim, P., Tegner, Y., Wilson, D. H. et al. (2014) Blood biomarkers for brain injury in concussed professional ice hockey players. JAMA Neurology 71(6): 684-92	- Prognostic accuracy measures reported but not for outcomes relevant to the review protocol
Shahim, P., Zetterberg, H., Tegner, Y. et al. (2017) Serum neurofilament light as a biomarker for mild traumatic brain injury in contact sports. Neurology 88(19): 1788-1794	- Study design not relevant to this review protocol
Sharma, B., Changoor, A., Monteiro, L. et al. (2020) Prognostic-factors for neurodegeneration in chronic moderate-to-severe traumatic brain injury: a systematic review protocol. Systematic Reviews 9(1): 23	- Study protocol only - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Shemilt, M., Boutin, A., Lauzier, F. et al. (2019) Prognostic Value of Glial Fibrillary Acidic Protein in Patients With Moderate and Severe Traumatic Brain Injury: A Systematic Review and Meta-Analysis. Critical Care Medicine 47(6): e522-e529	- Population not relevant to this review protocol
Shetty, T., Nguyen, J. T., Cogsil, T. et al. (2018) Clinical Findings in a Multicenter MRI Study of	- No prognostic accuracy measures reported

Study	Code [Reason]
Mild TBI. Frontiers in neurology [electronic resource]. 9: 836	
Shibahashi, K., Doi, T., Tanaka, S. et al. (2016) The Serum Phosphorylated Neurofilament Heavy Subunit as a Predictive Marker for Outcome in Adult Patients after Traumatic Brain Injury. Journal of Neurotrauma 33(20): 1826-1833	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Shore, P. M., Berger, R. P., Varma, S. et al. (2007) Cerebrospinal fluid biomarkers versus glasgow coma scale and glasgow outcome scale in pediatric traumatic brain injury: the role of young age and inflicted injury. Journal of Neurotrauma 24(1): 75-86	- No relevant prognostic factors - No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Sidaros, A., Engberg, A. W., Sidaros, K. et al. (2008) Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: a longitudinal study. Brain 131(pt2): 559-72	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - No prognostic accuracy measures reported
Sidaros, A., Skimminge, A., Liptrot, M. G. et al. (2009) Long-term global and regional brain volume changes following severe traumatic brain injury: a longitudinal study with clinical correlates. Neuroimage 44(1): 1-8	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Sigmund, G. A., Tong, K. A., Nickerson, J. P. et al. (2007) Multimodality comparison of neuroimaging in pediatric traumatic brain injury. Pediatric Neurology 36(4): 217-26	- No prognostic accuracy measures reported
Silva, P. P., Bhatnagar, S., Herman, S. D. et al. (2015) Predictors of Hypopituitarism in Patients with Traumatic Brain Injury. Journal of Neurotrauma 32(22): 1789-95	- No relevant prognostic factors - No relevant outcomes
Siman, R., Shahim, P., Tegner, Y. et al. (2015) Serum SNTF Increases in Concussed Professional Ice Hockey Players and Relates to	- Time-point not relevant to post-concussion syndrome which is usually diagnosed at least a few weeks following injury

Study	Code [Reason]
the Severity of Postconcussion Symptoms. Journal of Neurotrauma 32(17): 1294-300	
Simon-Pimmel, J., Lorton, F., Guiziou, N. et al. (2015) Serum S100beta Neuroprotein Reduces Use of Cranial Computed Tomography in Children After Minor Head Trauma. Shock 44(5): 410-6	- No relevant outcomes
Singh, A., Singh, K., Sahu, A. et al. (2021) Serum Concentration of Myelin Basic Protein as a Prognostic Marker in Mild-to-moderate Head Injury Patients: A Prospective Study in a Tertiary Care Center. Indian Journal of Neurosurgery: 1-5	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - No relevant outcomes
Skandsen, T., Kvistad, K. A., Solheim, O. et al. (2011) Prognostic value of magnetic resonance imaging in moderate and severe head injury: a prospective study of early MRI findings and one-year outcome. Journal of Neurotrauma 28(5): 691-9	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Skandsen, T., Kvistad, K. A., Solheim, O. et al. (2010) Prevalence and impact of diffuse axonal injury in patients with moderate and severe head injury: a cohort study of early magnetic resonance imaging findings and 1-year outcome. Journal of Neurosurgery 113(3): 556-63	- Full text paper not available
Slavoaca, D., Birle, C., Stan, A. et al. (2020) Prediction of Neurocognitive Outcome after Moderate-Severe Traumatic Brain Injury Using Serum Neuron-Specific Enolase and S100 biomarkers. Journal of Medicine & Life 13(3): 306-313	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Smitherman, E., Hernandez, A., Stavinoha, P. L. et al. (2016) Predicting Outcome after Pediatric Traumatic Brain Injury by Early Magnetic Resonance Imaging Lesion Location and Volume. Journal of Neurotrauma 33(1): 35-48	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Sojka, P., Stalnacke, B. M., Bjornstig, U. et al. (2006) One-year follow-up of patients with mild traumatic brain injury: occurrence of post-	- No prognostic accuracy measures reported

Study	Code [Reason]
traumatic stress-related symptoms at follow-up and serum levels of cortisol, S-100B and neuron-specific enolase in acute phase. Brain Injury 20(6): 613-20	
Sours, C., Zhuo, J., Roys, S. et al. (2015) Disruptions in Resting State Functional Connectivity and Cerebral Blood Flow in Mild Traumatic Brain Injury Patients. PLoS ONE [Electronic Resource] 10(8): e0134019	- No prognostic accuracy measures reported
Spinella, P. C., Dominguez, T., Drott, H. R. et al. (2003) S-100beta protein-serum levels in healthy children and its association with outcome in pediatric traumatic brain injury. Critical Care Medicine 31(3): 939-45	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Stalnacke, B. M., Bjornstig, U., Karlsson, K. et al. (2005) One-year follow-up of mild traumatic brain injury: post-concussion symptoms, disabilities and life satisfaction in relation to serum levels of S-100B and neurone-specific enolase in acute phase. Journal of Rehabilitation Medicine 37(5): 300-5	- No prognostic accuracy measures reported
Stapert, S., de Kruijk, J., Houx, P. et al. (2005) S-100B concentration is not related to neurocognitive performance in the first month after mild traumatic brain injury. European Neurology 53(1): 22-6	- No prognostic accuracy measures reported
Stefanovic, B., Duric, O., Stankovic, S. et al. (2017) Elevated Serum Protein S100B and Neuron Specific Enolase Values as Predictors of Early Neurological Outcome After Traumatic Brain Injury. Journal of Medical Biochemistry 36(4): 314-321	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Stenberg, J., Eikenes, L., Moen, K. G. et al. (2021) Acute Diffusion Tensor and Kurtosis Imaging and Outcome following Mild Traumatic Brain Injury. Journal of Neurotrauma 10: 10	- No prognostic accuracy measures reported
Stephenson, D. D., Meier, T. B., Pabbathi Reddy, S. et al. (2020) Resting-State Power and Regional Connectivity After Pediatric Mild Traumatic Brain Injury. Journal of Magnetic Resonance Imaging 52(6): 1701-1713	- No prognostic accuracy measures reported
Stewan Feltrin, F., Zaninotto, A. L., Guirado, V. M. P. et al. (2018) Longitudinal changes in brain volumetry and cognitive functions after	- The population is those with moderate or severe TBI or is mixed and<60% of the

Study	Code [Reason]
moderate and severe diffuse axonal injury. Brain Injury 32(10): 1208-1217	population has mild TBI - not relevant to post-concussion syndrome
Stokum, J. A., Sours, C., Zhuo, J. et al. (2015) A longitudinal evaluation of diffusion kurtosis imaging in patients with mild traumatic brain injury. Brain Injury 29(1): 47-57	- No prognostic accuracy measures reported
Strangman, G. E., O'Neil-Pirozzi, T. M., Supelana, C. et al. (2012) Fractional anisotropy helps predicts memory rehabilitation outcome after traumatic brain injury. Neurorehabilitation 31(3): 295-310	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Stranjalis, G., Korfias, S., Papapetrou, C. et al. (2004) Elevated serum S-100B protein as a predictor of failure to short-term return to work or activities after mild head injury. Journal of Neurotrauma 21(8): 1070-5	- Time-point not relevant to post-concussion syndrome which is usually diagnosed at least a few weeks following injury
Strauss, S. B., Kim, N., Branch, C. A. et al. (2016) Bidirectional Changes in Anisotropy Are Associated with Outcomes in Mild Traumatic Brain Injury. Ajnr: American Journal of Neuroradiology 37(11): 1983-1991	- No prognostic accuracy measures reported
Studer, M., Goeggel Simonetti, B., Heinks, T. et al. (2015) Acute S100B in serum is associated with cognitive symptoms and memory performance 4 months after paediatric mild traumatic brain injury. Brain Injury 29(1314): 1667-73	- No prognostic accuracy measures reported
Studerus-Germann, A. M., Gautschi, O. P., Bontempi, P. et al. (2018) Central nervous system microbleeds in the acute phase are associated with structural integrity by DTI one year after mild traumatic brain injury: A longitudinal study. Neurologia i Neurochirurgia Polska 52(6): 710-719	- No prognostic accuracy measures reported
Stukas, S., Higgins, V., Frndova, H. et al. (2019) Characterisation of serum total tau following paediatric traumatic brain injury: a case-control study. The Lancet Child & Adolescent Health 3(8): 558-567	- No relevant prognostic factors
Sun, Y., Wang, S., Gan, S. et al. (2021) Serum Neuron-Specific Enolase Levels Associated with Connectivity Alterations in Anterior Default	- No prognostic accuracy measures reported

Study	Code [Reason]
Mode Network after Mild Traumatic Brain Injury. Journal of Neurotrauma 38(11): 1495-1505	
Takagi, M., Babl, F. E., Anderson, N. et al. (2019) Protocol for a prospective, longitudinal, cohort study of recovery pathways, acute biomarkers and cost for children with persistent postconcussion symptoms: the Take CARe Biomarkers study. BMJ Open 9(2): e022098	- Study protocol only
Takala, R. S., Posti, J. P., Runtti, H. et al. (2016) Glial Fibrillary Acidic Protein and Ubiquitin C-Terminal Hydrolase-L1 as Outcome Predictors in Traumatic Brain Injury. World Neurosurgery 87: 8-20	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Takanashi, Y., Shinonaga, M., Naitoh, M. et al. (2000) Magnetic resonance imaging with gadolinium DTPA enhancement in patients with acute head injury. Journal of Neurotrauma 17(4): 359-65	- Not relevant to post-concussion syndrome
Tanoue, K., Matsui, K., Nozawa, K. et al. (2012) Predictive value of early radiological findings in inflicted traumatic brain injury. Acta Paediatrica 101(6): 614-7	- No relevant prognostic factors
Taylor, H. G., Dietrich, A., Nuss, K. et al. (2010) Post-concussive symptoms in children with mild traumatic brain injury. Neuropsychology 24(2): 148-59	- No prognostic accuracy measures reported
Taylor, H. G., Orchinik, L. J., Minich, N. et al. (2015) Symptoms of Persistent Behavior Problems in Children With Mild Traumatic Brain Injury. Journal of Head Trauma Rehabilitation 30(5): 302-10	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Terpstra, A. R., Girard, T. A., Colella, B. et al. (2017) Higher Anxiety Symptoms Predict Progressive Hippocampal Atrophy in the Chronic Stages of Moderate to Severe Traumatic Brain Injury. Neurorehabilitation & Neural Repair 31(12): 1063-1071	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Thelin, E. P., Jeppsson, E., Frostell, A. et al. (2016) Utility of neuron-specific enolase in traumatic brain injury; relations to S100B levels, outcome, and extracranial injury severity. Critical Care (London, England) 20: 285	- Study design not relevant to this review protocol

Study	Code [Reason]
Thelin, E. P., Johannesson, L., Nelson, D. et al. (2013) S100B is an important outcome predictor in traumatic brain injury. Journal of Neurotrauma 30(7): 519-28	- Study design not relevant to this review protocol
Thelin, E., Al Nimer, F., Frostell, A. et al. (2019) A Serum Protein Biomarker Panel Improves Outcome Prediction in Human Traumatic Brain Injury. Journal of Neurotrauma 36(20): 2850-2862	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Thomas, D. G.; Palfreyman, J. W.; Ratcliffe, J. G. (1978) Serum-myelin-basic-protein assay in diagnosis and prognosis of patients with head injury. Lancet 1(8056): 113-5	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - No prognostic accuracy measures reported
Thompson, W. H., Thelin, E. P., Lilja, A. et al. (2016) Functional resting-state fMRI connectivity correlates with serum levels of the S100B protein in the acute phase of traumatic brain injury. NeuroImage Clinical 12: 1004-1012	- No prognostic accuracy measures reported
Tollard, E., Galanaud, D., Perlbarg, V. et al. (2009) Experience of diffusion tensor imaging and 1H spectroscopy for outcome prediction in severe traumatic brain injury: Preliminary results. Critical Care Medicine 37(4): 1448-55	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Tolli, A., Hoybye, C., Bellander, B. M. et al. (2019) Impact of pituitary dysfunction on cognitive and global outcome after traumatic brain injury and aneurysmal subarachnoid haemorrhage. Journal of Rehabilitation Medicine 51(4): 264-272	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Tong, K. A., Ashwal, S., Holshouser, B. A. et al. (2004) Diffuse axonal injury in children: clinical correlation with hemorrhagic lesions. Annals of Neurology 56(1): 36-50	- No relevant prognostic factors
Treble-Barna, A., Patronick, J., Uchani, S. et al. (2020) Epigenetic Effects on Pediatric Traumatic Brain Injury Recovery (EETR): An Observational, Prospective, Longitudinal Concurrent Cohort Study Protocol. Frontiers in neurology [electronic resource]. 11: 460	- Study protocol only

Study	Code [Reason]
Treble-Barna, A., Pilipenko, V., Wade, S. L. et al. (2020) Cumulative Influence of Inflammatory Response Genetic Variation on Long-Term Neurobehavioral Outcomes after Pediatric Traumatic Brain Injury Relative to Orthopedic Injury: An Exploratory Polygenic Risk Score. Journal of Neurotrauma 37(13): 1491-1503	- No relevant prognostic factors
Ucar, T., Baykal, A., Akyuz, M. et al. (2004) Comparison of serum and cerebrospinal fluid protein S-100b levels after severe head injury and their prognostic importance. Journal of Trauma-Injury Infection & Critical Care 57(1): 95-8	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
van der Horn, H. J., Mangina, N. R., Rakers, S. E. et al. (2021) White matter microstructure of the neural emotion regulation circuitry in mild traumatic brain injury. European Journal of Neuroscience 53(10): 3463-3475	- No prognostic accuracy measures reported
van der Horn, H. J., Scheenen, M. E., de Koning, M. E. et al. (2017) The Default Mode Network as a Biomarker of Persistent Complaints after Mild Traumatic Brain Injury: A Longitudinal Functional Magnetic Resonance Imaging Study. Journal of Neurotrauma 34(23): 3262-3269	- No prognostic accuracy measures reported
van der Horn, H. J., Vergara, V. M., Espinoza, F. A. et al. (2020) Functional outcome is tied to dynamic brain states after mild to moderate traumatic brain injury. Human Brain Mapping 41(3): 617-631	- No prognostic accuracy measures reported
van der Naalt, J., Hew, J. M., van Zomeren, A. H. et al. (1999) Computed tomography and magnetic resonance imaging in mild to moderate head injury: early and late imaging related to outcome. Annals of Neurology 46(1): 70-8	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
van der Naalt, J., van Zomeren, A. H., Sluiter, W. J. et al. (2000) Acute behavioural disturbances related to imaging studies and outcome in mild-to-moderate head injury. Brain Injury 14(9): 781-8	- No relevant prognostic factors
van Eijck, M. M., Herklots, M. W., Peluso, J. et al. (2020) Accuracy in prediction of long-term functional outcome in patients with traumatic	- Study design not relevant to this review protocol

Study	Code [Reason]
axonal injury: a comparison of MRI scales. Brain Injury 34(5): 595-601	
van Eijck, M. M., Schoonman, G. G., van der Naalt, J. et al. (2018) Diffuse axonal injury after traumatic brain injury is a prognostic factor for functional outcome: a systematic review and meta-analysis. Brain Injury 32(4): 395-402	- Systematic review used as source of primary studies
Varma, S., Janesko, K. L., Wisniewski, S. R. et al. (2003) F2-isoprostane and neuron-specific enolase in cerebrospinal fluid after severe traumatic brain injury in infants and children. J Neurotrauma 20(8): 781-6	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - No prognostic accuracy measures reported
Vasa, R. A., Grados, M., Slomine, B. et al. (2004) Neuroimaging correlates of anxiety after pediatric traumatic brain injury. Biological Psychiatry 55(3): 208-16	- No prognostic accuracy measures reported - The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Veeramuthu, V., Narayanan, V., Kuo, T. L. et al. (2015) Diffusion Tensor Imaging Parameters in Mild Traumatic Brain Injury and Its Correlation with Early Neuropsychological Impairment: A Longitudinal Study. Journal of Neurotrauma 32(19): 1497-509	- No prognostic accuracy measures reported
Venkatesan, U. M.; Dennis, N. A.; Hillary, F. G. (2015) Chronology and chronicity of altered resting-state functional connectivity after traumatic brain injury. Journal of Neurotrauma 32(4): 252-64	- Study design not relevant to this review protocol
Vijayakumari, A. A., Parker, D., Osmanlioglu, Y. et al. (2021) Free Water Volume Fraction: An Imaging Biomarker to Characterize Moderate-to-Severe Traumatic Brain Injury. Journal of Neurotrauma 20: 20	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Vinjamuri, S. and O'Driscoll, K. (2000) Significance of white matter abnormalities in patients with closed head injury. Nuclear Medicine Communications 21(7): 645-9	- No prognostic accuracy measures reported
Volpe, D. S. J., Oliveira, Ncac, Santos, A. C. et al. (2017) Neuropsychological outcome of	- The population is those with moderate or severe TBI or is mixed and<60% of the

Study	Code [Reason]
children with traumatic brain injury and its association with late magnetic resonance imaging findings: A cohort study. Brain Injury 31(12): 1689-1694	population has mild TBI - not relevant to post-concussion syndrome
Vos, P. E., Jacobs, B., Andriessen, T. M. et al. (2010) GFAP and S100B are biomarkers of traumatic brain injury: an observational cohort study. Neurology 75(20): 1786-93	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Vos, P. E., Lamers, K. J., Hendriks, J. C. et al. (2004) Glial and neuronal proteins in serum predict outcome after severe traumatic brain injury. Neurology 62(8): 1303-10	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Walder, B., Robin, X., Rebetez, M. M. et al. (2013) The prognostic significance of the serum biomarker heart-fatty acidic binding protein in comparison with s100b in severe traumatic brain injury. Journal of Neurotrauma 30(19): 1631-7	- People with severe TBI. Not relevant to PCS.
Wang, J. Y., Bakhadirov, K., Abdi, H. et al. (2011) Longitudinal changes of structural connectivity in traumatic axonal injury. Neurology 77(9): 818-26	- No prognostic accuracy measures reported
Wang, J. Y., Bakhadirov, K., Devous, M. D., Sr. et al. (2008) Diffusion tensor tractography of traumatic diffuse axonal injury. Archives of Neurology 65(5): 619-26	- People with severe TBI. Not relevant to PCS.
Wang, X. H. and Zhang, X. D. (2006) Evaluating the prognosis and degree of brain injury by combined S-100 protein and neuron specific enolase determination. Neural Regeneration Research 1(7): 649-652	- Full text paper not available
Wang, Y., Nelson, L. D., LaRoche, A. A. et al. (2016) Cerebral Blood Flow Alterations in Acute Sport-Related Concussion. Journal of Neurotrauma 33(13): 1227-36	- No prognostic accuracy measures reported
Wang, Z., Zhang, M., Sun, C. et al. (2021) Single Mild Traumatic Brain Injury Deteriorates Progressive Interhemispheric Functional and Structural Connectivity. Journal of Neurotrauma 38(4): 464-473	- No prognostic accuracy measures reported
Ward, M. D., Weber, A., Merrill, V. D. et al. (2020) Predictive Performance of Traumatic Brain Injury Biomarkers in High-Risk Elderly	- Erratum - original article not included

Study	Code [Reason]
Patients. The Journal of Applied Laboratory Medicine 5(3): 608	
Ware, A. L., Goodrich-Hunsaker, N. J., Lebel, C. et al. (2020) Post-Acute Cortical Thickness in Children with Mild Traumatic Brain Injury versus Orthopedic Injury. Journal of Neurotrauma 37(17): 1892-1901	- No prognostic accuracy measures reported
Ware, A. L., Shukla, A., Goodrich-Hunsaker, N. J. et al. (2020) Post-acute white matter microstructure predicts post-acute and chronic post-concussive symptom severity following mild traumatic brain injury in children. NeuroImage Clinical 25: 102106	- No prognostic accuracy measures reported
Ware, J. B., Biester, R. C., Whipple, E. et al. (2016) Combat-related Mild Traumatic Brain Injury: Association between Baseline Diffusion-Tensor Imaging Findings and Long-term Outcomes. Radiology 280(1): 212-9	- Study design not relevant to this review protocol
Ware, J. B., Dolui, S., Duda, J. et al. (2020) Relationship of Cerebral Blood Flow to Cognitive Function and Recovery in Early Chronic Traumatic Brain Injury. Journal of Neurotrauma 37(20): 2180-2187	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Ware, J. B., Hart, T., Whyte, J. et al. (2017) Inter-Subject Variability of Axonal Injury in Diffuse Traumatic Brain Injury. Journal of Neurotrauma 34(14): 2243-2253	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Warner, M. A., Youn, T. S., Davis, T. et al. (2010) Regionally selective atrophy after traumatic axonal injury. Archives of Neurology 67(11): 1336-44	- No prognostic accuracy measures reported
Watt, S. E., Shores, E. A., Baguley, I. J. et al. (2006) Protein S-100 and neuropsychological functioning following severe traumatic brain injury. Brain Injury 20(10): 1007-17	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Wedekind, C., Fischbach, R., Pakos, P. et al. (1999) Comparative use of magnetic resonance imaging and electrophysiologic investigation for the prognosis of head injury. Journal of Trauma-Injury Infection & Critical Care 47(1): 44-9	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Weiss, N., Galanaud, D., Carpentier, A. et al. (2008) A combined clinical and MRI approach	- People with severe TBI. Not relevant to PCS.

Study	Code [Reason]
for outcome assessment of traumatic head injured comatose patients. Journal of Neurology 255(2): 217-23	
Whyte, J., Katz, D., Long, D. et al. (2005) Predictors of outcome in prolonged posttraumatic disorders of consciousness and assessment of medication effects: A multicenter study. Archives of Physical Medicine & Rehabilitation 86(3): 453-62	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - No prognostic accuracy measures reported
Wiesmann, M., Steinmeier, E., Magerkurth, O. et al. (2010) Outcome prediction in traumatic brain injury: comparison of neurological status, CT findings, and blood levels of S100B and GFAP. Acta Neurologica Scandinavica 121(3): 178-85	- No prognostic accuracy measures reported
Wilde, E. A., Hunter, J. V., Newsome, M. R. et al. (2005) Frontal and temporal morphometric findings on MRI in children after moderate to severe traumatic brain injury. Journal of Neurotrauma 22(3): 333-44	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Wilde, E. A., McCauley, S. R., Hunter, J. V. et al. (2008) Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. Neurology 70(12): 948-55	- No prognostic accuracy measures reported
Wilkinson, A. A., Dennis, M., Simic, N. et al. (2017) Brain biomarkers and pre-injury cognition are associated with long-term cognitive outcome in children with traumatic brain injury. BMC Pediatrics 17(1): 173	- No prognostic accuracy measures reported
Wilkinson, A. A., Simic, N., Frndova, H. et al. (2016) Serum Biomarkers Help Predict Attention Problems in Critically Ill Children With Traumatic Brain Injury. Pediatric Critical Care Medicine 17(7): 638-48	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Wilson, J. T., Hadley, D. M., Wiedmann, K. D. et al. (1995) Neuropsychological consequences of two patterns of brain damage shown by MRI in survivors of severe head injury. Journal of Neurology, Neurosurgery & Psychiatry 59(3): 328-31	- No prognostic accuracy measures reported
Wilson, J. T., Wiedmann, K. D., Hadley, D. M. et al. (1988) Early and late magnetic resonance imaging and neuropsychological outcome after	- No prognostic accuracy measures reported

Study	Code [Reason]
head injury. Journal of Neurology, Neurosurgery & Psychiatry 51(3): 391-6	
Woertgen, C.; Rothoerl, R. D.; Brawanski, A. (2002) Early S-100B serum level correlates to quality of life in patients after severe head injury. Brain Injury 16(9): 807-16	- People with severe TBI. Not relevant to PCS.
Woertgen, C., Rothoerl, R. D., Holzschuh, M. et al. (1997) Comparison of serial S-100 and NSE serum measurements after severe head injury. Acta Neurochirurgica 139(12): 1161-4; discussion 1165	- People with severe TBI. Not relevant to PCS.
Woertgen, C., Rothoerl, R. D., Metz, C. et al. (1999) Comparison of clinical, radiologic, and serum marker as prognostic factors after severe head injury. Journal of Trauma-Injury Infection & Critical Care 47(6): 1126-30	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Woischneck, D.; Schmitz, B.; Kapapa, T. (2017) MRI detection of cerebral lesions in post-traumatic anisocoria: specificity and prognostic significance. Clinical Radiology 72(5): 426.e7-426.e15	- No prognostic accuracy measures reported
Wozniak, G., Georgoulias, P., Iliadis, C. et al. (2010) Serotonin and neuron-specific enolase: Serum acute and mid-term levels and their association with posttraumatic depression. Neurosurgery Quarterly 20(4): 297-303	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Wu, X., Zou, Q., Hu, J. et al. (2015) Intrinsic Functional Connectivity Patterns Predict Consciousness Level and Recovery Outcome in Acquired Brain Injury. Journal of Neuroscience 35(37): 12932-46	- Population not relevant to this review protocol
Wu, Y. C., Harezlak, J., Elsaid, N. M. H. et al. (2020) Longitudinal white-matter abnormalities in sports-related concussion: A diffusion MRI study. Neurology 95(7): e781-e792	- No prognostic accuracy measures reported
Wylie, G. R., Freeman, K., Thomas, A. et al. (2015) Cognitive Improvement after Mild Traumatic Brain Injury Measured with Functional Neuroimaging during the Acute Period. PLoS ONE [Electronic Resource] 10(5): e0126110	- No prognostic accuracy measures reported
Xiong, K., Zhu, Y., Zhang, Y. et al. (2014) White matter integrity and cognition in mild traumatic	- No prognostic accuracy measures reported

Study	Code [Reason]
brain injury following motor vehicle accident. Brain Research 1591: 86-92	
Xu, H., Wang, X., Chen, Z. et al. (2018) Longitudinal Changes of Caudate-Based Resting State Functional Connectivity in Mild Traumatic Brain Injury. Frontiers in neurology [electronic resource]. 9: 467	- No prognostic accuracy measures reported
Xu, L., Ware, J. B., Kim, J. J. et al. (2021) Arterial Spin Labeling Reveals Elevated Cerebral Blood Flow with Distinct Clusters of Hypo- and Hyperperfusion after Traumatic Brain Injury. Journal of Neurotrauma 10: 10	- No prognostic accuracy measures reported
Yakoub, K. M., Davies, D. J., Su, Z. et al. (2019) Investigation into repetitive concussion in sport (RECOS): study protocol of a prospective, exploratory, observational cohort study. BMJ Open 9(7): e029883	- Study protocol only
Yakoub, K. M., O'Halloran, P., Davies, D. J. et al. (2018) Study of Concussion in Rugby Union through MicroRNAs (SCRUM): a study protocol of a prospective, observational cohort study. BMJ Open 8(11): e024245	- Study protocol only
Yan, E. B., Satgunaseelan, L., Paul, E. et al. (2014) Post-traumatic hypoxia is associated with prolonged cerebral cytokine production, higher serum biomarker levels, and poor outcome in patients with severe traumatic brain injury. Journal of Neurotrauma 31(7): 618-29	- People with severe TBI. Not relevant to PCS.
Yang, T., Song, J., Bu, X. et al. (2016) Elevated serum miR-93, miR-191, and miR-499 are noninvasive biomarkers for the presence and progression of traumatic brain injury. Journal of Neurochemistry 137(1): 122-9	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - Prognostic accuracy measures reported but not for outcomes relevant to the review protocol - No relevant prognostic factors
Yeates, K. O., Beauchamp, M., Craig, W. et al. (2017) Advancing Concussion Assessment in Pediatrics (A-CAP): a prospective, concurrent cohort, longitudinal study of mild traumatic brain injury in children: protocol study. BMJ Open 7(7): e017012	- Study protocol only

Study	Code [Reason]
Yeates, K. O., Kaizar, E., Rusin, J. et al. (2012) Reliable change in postconcussive symptoms and its functional consequences among children with mild traumatic brain injury. Archives of Pediatrics & Adolescent Medicine 166(7): 615-22	- No prognostic accuracy measures reported
Yin, B., Li, D. D., Huang, H. et al. (2019) Longitudinal Changes in Diffusion Tensor Imaging Following Mild Traumatic Brain Injury and Correlation With Outcome. Frontiers in Neural Circuits 13: 28	- No prognostic accuracy measures reported
Yu, M. K. and Ye, W. (2012) The imaging diagnosis and prognosis assessment of patients with midbrain injury in the acute phase of craniocerebral injury. Acta Neurochirurgica - Supplement 114: 317-21	- No prognostic accuracy measures reported
Yu, Y., Meng, F., Zhang, L. et al. (2020) A multi-domain prognostic model of disorder of consciousness using resting-state fMRI and laboratory parameters. Brain Imaging & Behavior 11: 11	- Population not relevant to this review protocol
Yuan, L., Wei, X., Xu, C. et al. (2015) Use of multisequence 3.0-T MRI to detect severe traumatic brain injury and predict the outcome. British Journal of Radiology 88(1052): 20150129	- People with severe TBI. Not relevant to PCS.
Yuh, E. L., Cooper, S. R., Mukherjee, P. et al. (2014) Diffusion tensor imaging for outcome prediction in mild traumatic brain injury: a TRACK-TBI study. Journal of Neurotrauma 31(17): 1457-77	- No prognostic accuracy measures reported
Yuh, E. L., Mukherjee, P., Lingsma, H. F. et al. (2013) Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury. Annals of Neurology 73(2): 224-35	- No prognostic accuracy measures reported
Zaninotto, A. L., Grassi, D. C., Duarte, D. et al. (2021) DTI-derived parameters differ between moderate and severe traumatic brain injury and its association with psychiatric scores. Neurological Sciences 15: 15	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Zhan, S., Li, N., Cai, Y. et al. (2003) Correlation of neuron specific enolase serum concentration and prognosis in patients with severe head	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome

Study	Code [Reason]
injury. Chinese Journal of Clinical Rehabilitation 7(2): 312-313	
Zhang, J., Tian, L., Zhang, L. et al. (2019) Relationship between white matter integrity and post-traumatic cognitive deficits: a systematic review and meta-analysis. Journal of Neurology, Neurosurgery & Psychiatry 90(1): 98-107	- Systematic review used as source of primary studies
Zhang, Z. Y., Li, J., Ye, Q. et al. (2019) Usefulness of serum interleukin-33 as a prognostic marker of severe traumatic brain injury. Clinica Chimica Acta 497: 6-12	- People with severe TBI. Not relevant to PCS.
Zhang, Z. Y., Zhang, L. X., Dong, X. Q. et al. (2014) Comparison of the performances of copeptin and multiple biomarkers in long-term prognosis of severe traumatic brain injury. Peptides 60: 13-7	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Zheng, P., He, B., Guo, Y. et al. (2015) Decreased apparent diffusion coefficient in the pituitary and correlation with hypopituitarism in patients with traumatic brain injury. Journal of Neurosurgery 123(1): 75-80	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome - Prognostic accuracy measures reported but not for outcomes relevant to the review protocol
Zhou, F., Zhan, J., Gong, T. et al. (2021) Characterizing Static and Dynamic Fractional Amplitude of Low-Frequency Fluctuation and its Prediction of Clinical Dysfunction in Patients with Diffuse Axonal Injury. Academic Radiology 28(3): e63-e70	- Study design not relevant to this review protocol
Zhu, D. C., Covassin, T., Nogle, S. et al. (2015) A potential biomarker in sports-related concussion: brain functional connectivity alteration of the default-mode network measured with longitudinal resting-state fMRI over thirty days. Journal of Neurotrauma 32(5): 327-41	- Comparator in study does not match that specified in this review protocol
Zhu, J.; Ling, J.; Ding, N. (2019) Association between Diffusion Tensor Imaging Findings and Cognitive Outcomes Following Mild Traumatic Brain Injury: A PRISMA-Compliant Meta-Analysis. Acs Chemical Neuroscience 10(12): 4864-4869	- Systematic review used as source of primary studies

Study	Code [Reason]
Zurek, J.; Bartlova, L.; Fedora, M. (2011) Hyperphosphorylated neurofilament NF-H as a predictor of mortality after brain injury in children. Brain Injury 25(2): 221-6	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Zurek, J., Bartlova, L., Marek, L. et al. (2010) Serum S100B protein as a molecular marker of severity in traumatic brain injury in children. Ceska a Slovenska Neurologie a Neurochirurgie 73(1): 37-44	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome
Zurek, J. and Fedora, M. (2012) The usefulness of S100B, NSE, GFAP, NF-H, secretagogin and Hsp70 as a predictive biomarker of outcome in children with traumatic brain injury. Acta Neurochirurgica 154(1): 93-103; discussion 103	- No prognostic accuracy measures reported
Zurek, J. and Fedora, M. (2011) Dynamics of glial fibrillary acidic protein during traumatic brain injury in children. Journal of Trauma-Injury Infection & Critical Care 71(4): 854-9	- The population is those with moderate or severe TBI or is mixed and<60% of the population has mild TBI - not relevant to post-concussion syndrome

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10 **Table 37: Studies excluded from the clinical review – <u>prognostic test and treat</u>**

Study	Code [Reason]
Bandyopadhyay, S., Hennes, H., Gorelick, M. H. et al. (2005) Serum neuron-specific enolase as a predictor of short-term outcome in children with closed traumatic brain injury. Academic Emergency Medicine 12(8): 732-738	- Study design not relevant to this review protocol - no comparison of two strategies/interventions
Bogoslovsky, T., Wilson, D., Chen, Y. et al. (2017) Increases of plasma levels of glial fibrillary acidic protein, tau, and amyloid beta up to 90 days after traumatic brain injury. Journal of Neurotrauma 34(1): 66-73	- Study design not relevant to this review protocol - no comparison of two strategies/interventions
Bouvier, D., Balayssac, D., Durif, J. et al. (2019) Assessment of the advantage of the serum S100B protein biomonitoring in the management of paediatric mild traumatic brain injury-PROS100B: protocol of a multicentre unblinded stepped wedge cluster randomised trial. BMJ Open 9(5): e027365	- Protocol only
Bulut, M., Koksal, O., Dogan, S. et al. (2006) Tau protein as a serum marker of brain damage	- Study design not relevant to this review protocol - no comparison of two strategies/interventions

Study	Code [Reason]
in mild traumatic brain injury: Preliminary results. Advances in Therapy 23(1): 12-22	- No relevant prognostic factors
Chen, H., Ding, V., Zhu, G. et al. (2022) Association between Blood and CT Imaging Biomarkers in a Cohort of Mild Traumatic Brain Injury Patients. Journal of neurotrauma	- Duplicate reference
Chen, Hui, Ding, Victoria Y, Zhu, Guangming et al. (2022) Association between Blood and Computed Tomographic Imaging Biomarkers in a Cohort of Mild Traumatic Brain Injury Patients. Journal of neurotrauma	- Population not relevant to this review protocol
Cheng, F., Yuan, Q., Yang, J. et al. (2014) The prognostic value of serum neuron-specific enolase in traumatic brain injury: systematic review and meta-analysis. PLoS ONE [Electronic Resource] 9(9): e106680	- Systematic review does not contain studies relevant to this review protocol - no comparison of two strategies/interventions
Elting, J. W., De Jager, A. E. J., Teelken, A. W. et al. (2000) Comparison of serum S-100 protein levels following stroke and traumatic brain injury. Journal of the Neurological Sciences 181(12): 104-110	- Study design not relevant to this review protocol - no comparison of two strategies/interventions
Filippidis, A. S., Papadopoulos, D. C., Kapsalaki, E. Z. et al. (2010) Role of the S100B serum biomarker in the treatment of children suffering from mild traumatic brain injury. Neurosurgical Focus 29(5): e2	- Review article but not a systematic review
Fraser, D. D., Close, T. E., Rose, K. L. et al. (2011) Severe traumatic brain injury in children elevates glial fibrillary acidic protein in cerebrospinal fluid and serum. Pediatric Critical Care Medicine 12(3): 319-24	- Population limited to those with severe head injury - not relevant to post-concussion syndrome - Study design not relevant to this review protocol - no comparison of two strategies/interventions
Hakiminia, B., Alikiaie, B., Khorvash, F. et al. (2022) Targeting Mitochondrial and Brain Injury Markers in Acquired Brain Injuries: A Randomized, Double-Blind, Placebo-Controlled Study with Melatonin. Advanced Pharmaceutical Bulletin 12(1): 118-127	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
John, J.A., Sajan, J.E., Oommen, A. et al. (2022) Predicting functional outcomes in severe traumatic brain injury: Role of S100B along with other clinical and imaging parameters. Current Medical Issues 20(2): 74-81	- Population limited to those with severe head injury - not relevant to post-concussion syndrome
Kovesdi, E., Luckl, J., Bukovics, P. et al. (2010) Update on protein biomarkers in traumatic brain injury with emphasis on clinical use in adults and pediatrics. Acta Neurochirurgica 152(1): 1-17	- Systematic review does not contain studies relevant to this review protocol - no comparison of two strategies/interventions
Li, Ying, Ding, Victoria Y, Chen, Hui et al. (2022) Comparing blood biomarkers to clinical decision rules to select patients suspected of traumatic brain injury for head computed tomography. The neuroradiology journal: 19714009221101306	- Population not relevant to this review protocol
Mercier, E., Tardif, P. A., Cameron, P. A. et al. (2018) Prognostic value of neuron-specific enolase (NSE) for prediction of post-concussion symptoms following a mild traumatic brain injury: a systematic review. Brain Injury 32(1): 29-40	- Systematic review does not contain studies relevant to this review protocol - no comparison of two strategies/interventions
Nakhjavan-Shahraki, B., Yousefifard, M., Oraii, A. et al. (2017) Meta-analysis of neuron specific enolase in predicting pediatric brain injury outcomes. Excli Journal 16: 995-1008	- Systematic review does not contain studies relevant to this review protocol - no comparison of two strategies/interventions
Pandor, A., Goodacre, S., Harnan, S. et al. (2011) Diagnostic management strategies for adults and children with minor head injury: a systematic review and an economic evaluation. Health Technology Assessment (Winchester, England) 15(27): 1-202	- Systematic review does not contain studies relevant to this review protocol - no comparison of two strategies/interventions
Studer, M., Goeggel Simonetti, B., Heinks, T. et al. (2015) Acute S100B in serum is associated with cognitive symptoms and memory performance 4 months after paediatric mild traumatic brain injury. Brain injury 29(1314): 1667-1673	- Study design not relevant to this review protocol - no comparison of two strategies/interventions
Wozniak, G., Georgoulias, P., Iliadis, C. et al. (2010) Serotonin and neuron-specific enolase: Serum acute and mid-term levels and their association with posttraumatic depression. Neurosurgery Quarterly 20(4): 297-303	- Study design not relevant to this review protocol - no comparison of two strategies/interventions - Population limited to those with severe head injury - not relevant to post-concussion syndrome

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.

Appendix J – Research recommendations – full details

J.1 Research recommendation

J.1.1 What is the prognostic accuracy of brain injury biomarkers and/or MRI for predicting post-concussion syndrome?

J.1.2 Why this is important

Head injury is a common reason for presentation to the emergency department. Most injuries are classed as minor, and most people make a full recovery. However, a significant number will go on to develop persistent and disabling symptoms including headaches, dizziness, cognitive difficulties and difficulty sleeping. This constellation of symptoms is known as post-concussion syndrome.

At present, there are no clinical or other predictive tools that would enable clinicians to determine which people with apparently minor head injury are at risk of post-concussion syndrome. Inability to identify people most at risk precludes the design of clinical trials of intervention aimed at preventing or reducing post-concussion symptoms.

J.1.3 Rationale for research recommendation

Importance to 'patients' or the population	The ability to identify head injured people most at risk of post-concussion syndrome would enable appropriate follow up and support to be put into place at any early stage. This would reduce the risk of the symptoms being unrecognised and becoming intractable and would improve health-related quality of life, which has been shown to be poor in this group of people. The ability to identify head injured people most at risk of post-concussion syndrome would also facilitate the design of clinical trials of interventions designed to prevent or reduce post-concussion symptoms. Identification of effective treatment of post-concussion syndrome and the ability to target this appropriately would improve health-related quality of life, reduce demands on other services and facilitate return of patients to education and employment.
Relevance to NICE guidance	Future NICE guidance would be able to recommend use of evidence-based methods of identifying people most at risk from post-concussion syndrome and would in the future potentially be able to recommend evidence-based methods of treating post-concussion syndrome.
Relevance to the NHS	Head injury is a common condition. People with post-concussion syndrome currently access services from a range of speciality group. Design of a dedicated and effective care pathway for people at risk would not only improve patient outcomes but would also represent an efficient use of NHS resources. Use of biomarkers and/or MRI to predict outcome in people with apparently minor head injury is not currently part of standard

	management in the emergency department. Because of the large number of people who present with apparently minor head injuries, the costs of introduction of such investigations would be considerable. It is therefore essential that the evidence base underpinning any such change in practice is secure.
National priorities	None identified
Current evidence base	The recent NICE systematic review of the currently available evidence identified a number of studies, but all had associated limitations. Study populations varied, with varying proportions of mild traumatic brain injury (TBI) subjects. Some studies had a mixed population of adults and children, and the proportions were unclear. Some studies had looked at multiple biomarker and/or MRI factors, making it difficult to disentangle the influence of individual factors. There was no consistency about the definition of post-concussion syndrome; various outcome measures had been used, including the Glasgow Outcome Scale, which includes patients with more severe outcomes. Most studies had collected sample for biomarkers within 48 hours of injury, but in two studies samples were obtained up to 14 days after head injury. Differences between studies prevented meta-analysis. Results for each study were therefore considered alongside each other, for each biomarker and MRI finding. Data for each combination of prognostic factor, outcome & statistical measure based on small numbers (<200, some <50) Most evidence was graded low or very low on QUIPs checklist, due to attrition; incomplete reporting of results; concerns about study participation – doubt in some studies if all eligible subjects included; unclear definition of prognostic factor(s); unclear or variable time point of measurement; and lack of clarity about method of clinical outcome measurement. Imprecision was an issue for most of data reported, due to small numbers. The Guidelines Committee concluded that no clinical recommendations could be made at the present time about the use of biomarkers or MRI in prediction of post-concussion syndrome due to lack of good quality evidence.
Equality considerations	People who develop post-concussion syndrome following head injury can be of both sexes and all ages. The condition affects people from a range of ethnicities. Investigative methods and treatment interventions would need to be designed to be suitable for all groups.

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J.154 Modified PICO table

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Population	Inclusion: Infants, children and adult with suspected head injury • Strata: o Adults (aged ≥16 years) o Children and babies (aged 0 to <16 years)
Prognostic variables under consideration	1. Biomarkers Blood biomarkers - S100 calcium binding protein B (S100B) -Ubiquitin C-terminal Hydrolase-L1 (UCHL1) -Neuron Specific Enolase (NSE) -Brain-derived neurotrophic factor (BDNF) -Neurofilament light (NFL) - Neurofilament Heavy (NF-H) - αII-Spectrin breakdown products (SBDP) - Myelin basic protein (MBP) - glial fibrillary acidic protein (GFAP) Salivary biomarkers -salivary microRNAs (miRNAs) -Extracellular vesicles (EVs) -S100B Urine biomarkers -Extracellular vesicles (EVs) Biomarkers are used within 48 hrs of head injury. Measurements of biomarkers in CSF not relevant as usually only access to this in those with severe head injury, while most people with post-concussion syndrome have mild head injury (GCS 13-15) and lumbar puncture to analyse CSF biomarkers is not indicated here.

	2. MRI MRI to be left open for signs (and sequences) used to predict post-concussion syndrome. MRI is booked during acute presentation (it could be done 3 weeks to a month after injury) 3. Combination of MRI and blood/salivary biomarkers
Reference standard	Post-concussion syndrome confirmed by constellation of symptoms • Range of symptoms including cognitive, physical, emotional and sleep related. Reference standard to include symptoms as reported in the studies. In adults, diagnosis of post-concussion syndrome is based on: 1. Glasgow Coma outcome scale (GOS) and GOSE (Glasgow Outcome Score Extended 2. Rivermead Post-Concussion Score 3. Other symptoms commonly used to define include: o Duration of post-traumatic amnesia o Abnormalities in cognition – most common include: Rey Auditory Verbal Learning Test (RAVLT), Trails Making Test Part A/B, WAIS IV Processing Speed Index, NIH Toolbox Cognitive Battery, CANTAB o Patient reported outcomes - Quality of Life After Brain Injury – Overall Scale (QOLIBRI-OS) and SF-12/SF-36 o Markers of mental health problems - PTSD Checklist (PCL-5), Participant Health Questionnarie-9 (PHQ-9), Generalised Anxiety Disorder-7 (GAD-7), Brief Symptom Inventory (BSI), Hospital Anxiety and Depression Scale (HADS) o Scales of sleep disturbance and fatigue In children diagnosis is based on symptoms, The Rivermead Post-concussion Symptoms Questionnaire (RPQ) and acute stress response. Post- concussion syndrome definition: Post-concussion syndrome occurs when concussion symptoms last beyond the expected recovery period after the initial injury. The usual recovery period is weeks to months. These symptoms could be physical, cognitive, emotional or sleep related. This may include

	multiple physical symptoms such as headaches, dizziness, nausea, balance and co-ordination problems, changes in appetite, sleep, vision, and hearing; and cognitive and behavioural symptoms such as fatigue, anxiety, depression, irritability; problems with memory, concentration, and decision-making. In some people these symptoms may persist from 2 weeks to longer than 3 months post injury. GCS in such patients will be 14-15.
Outcome	Prognostic accuracy of listed prognostic factors for predicting post-concussion syndrome Sensitivity/specificity
Study design	Prospective cohort studies
Timeframe	Medium – required for when the guidance is updated
Additional information	None

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