National Institute for Health and Care Excellence

NICE COVID-19 rapid guideline: managing COVID-19

[I] Evidence reviews for COVID-19 Associated Pulmonary Aspergillosis (CAPA) – Risk Factors and Signs and Symptoms

NICE guideline NG191

December 2021

Guideline version (Final)

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Review question A1: Risk factors

Background

COVID-19 disease is known to have a range of potential complications and co-infections. Secondary fungal infections (aspergillus) have been reported in patients following hospitalisation (Chong et al, 2021a). Although the incidence is low, the mortality rate is high. Recommendations on identifying, diagnosing and treating secondary fungal infections are required to ensure consistent practice and help improve outcomes for people with these infections (Chong et al., 2021b).

Objective

This review aims to identify what risk factors are associated with developing CAPA in people with COVID-19.

Review question 1: Risk factors

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review question for this evidence review is:

1. What risk factors in people who have or, as part of their acute illness, have had confirmed COVID-19 are associated with developing CAPA?

Methodology

The evidence review was developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

A recent taskforce report was identified, which is highly relevant to the reviews being undertaken on CAPA (Verweij et al., 2021). In addition to the evidence review, relevant information from this document was presented to the panel and considered when making recommendations.

Summary of included studies

A literature search for CAPA identified 466 references (see appendix B for full details). These references were screened using their titles and abstracts and 44 full text references were obtained and assessed for relevance.

42 studies were excluded. Details of the excluded studies are in appendix C.

2 studies are included in this evidence review (Chong 2021a and Prattes 2021). A summary of the included studies and their quality assessment is shown in appendices D and E. Meta-analysis was not undertaken for this review as Chong (2021) reported risk ratios and Prattes (2021) reported hazard ratios. Therefore no forest plots were produced.

Study characteristics

Study characteristic	Chong 2021a	Prattes 2021
Location and setting	China, France, Greece, Italy, Mexico, Netherlands, Spain	Austria, Belgium, France, Germany, Italy, Pakistan, Spain, UK, USA
Study design	Systematic review containing 8 cohort studies (3 retrospective, 5 prospective)	Retrospective observational cohort study
No. of patients (N)	729	592
Follow-up	NA	NA
Age (years)	Range 59 – 71	Range 54 - 75
Gender (% female)	28.5%	29.2%
Baseline characteristics	Adults aged 18 and over, hospitalised with COVID-19. Baseline characteristics were varied, however the majority of the participants were male, with varying comorbidities and a BMI >26 kg/m^2 on average	Adults aged 18 and over, hospitalised in ICU* for COVID-19. Baseline characteristics varied, however, the majority of participants were male, and had underlying cardiovascular disease
COVID-19 infection	Confirmed SARS-CoV-2 infection with RT-PCR*	Confirmed SARS-CoV-2 infection with RT-PCR
CAPA infection	Participants were diagnosed with invasive fungal infection using bronchoalveolar lavage and assay of sample.	Participants were diagnosed with invasive fungal infection as per ECMM* criteria (proven, probable, possible)

Study characteristic	Chong 2021a	Prattes 2021
Inclusion criteria	1. Studies that contain comparative data describing the clinical characteristics, risk factors and outcomes of hospitalised COVID-19 patients with CAPA* and without CAPA 2. Studies that confirmed diagnosis of CAPA using several diagnostic criteria from current literature (AspICU*, CAPA-ECMM*, Modified AspICU*, EORTC/MSG*) 3. Studies where the diagnosis of COVID-19 was confirmed by RT-PCR as well as nasal, pharyngeal, sputum, tracheal aspirate, non-directed bronchial lavage, and bronchial lavage 4. Studies published between 1st January 2020 and August 2021 in peer-reviewed journals	1. Adults aged 18 years and above, with confirmed PCR SARS-CoV-2 infection 2. ICU admission for COVID-19 acute respiratory failure

Study characteristic	Chong 2021a	Prattes 2021
Main exclusion criteria	1. Studies that did not meet the specific diagnostic criteria for CAPA diagnosis (e.g. if they described aspergillus colonisation from BAL/NBL*, the authors did not specify if it was invasive pulmonary aspergillosis or colonisation, and the data provided were not sufficient to make any distinction) 2. Systematic reviews, literature reviews, editorials, conference abstracts, opinion articles, meta-analysis, case reports or studies with fewer than 30 participants 3. Studies involving COVID-19 patients less than 18 years of age 4. Studies that did not have comparative data between CAPA and non-CAPA patients 5. Articles where pulmonary aspergillosis was concurrently diagnosed with other micro-organisms like bacteria/viruses 6. Articles that described aspergillosis obtained from non-respiratory tract cultures 7. Studies published in languages besides English and there was no translated version available 8. Studies where the CAPA diagnosis was made during post-mortem examination	ICU admission due to other conditions besides COVID-19 acute respiratory failure
Other notes	None	The CAPA group comprised 109 patients. Of these 11 had histologically proven CAPA, 80 had probable CAPA and 18 had possible CAPA.
***Abbreviations: AspICU:** Aspergillus Intensive Care Unit Algorithm**; BAL:** bronchoalveolar lavage**; CAPA:** COVID-19-associated pulmonary aspergillosis; **ECMM:** European Confederation of Medical Mycology; **EORTC/MSG:** European Organisation for Research and Treatment of Cancer/Mycoses Study Group; **ICU:** Intensive Care Unit; **Modified Asp-ICU:** Modified Aspergillus Intensive Care Unit algorithm; **RT-PCR:** Reverse transcription polymerase chain reaction.		

Results

Review question: What risk factors in people who have or, as part of their acute illness, have had confirmed COVID-19 are associated with developing CAPA?

There remains a high degree of uncertainty over possible risk factors that are associated with people developing COVID-19-associated pulmonary aspergillosis.

What is the evidence informing this conclusion?

Evidence comes from 2 studies. The first (Chong 2021) was a systematic review and meta-analysis of cohort studies comparing the clinical characteristics of people with CAPA to people without CAPA. The systematic review included cohort studies that investigated the clinical characteristics and outcomes of people who are hospitalised with proven or probable CAPA and confirmed COVID-19 (Bartoletti 2020; Delliere 2021; Gangneux 2020; Lahmer 2021; Segrelles-Calvo 2021; Van Biesen 2021; Velez Pintado 2021; Wang 2020).

The second study identified in this review (Prattes 2021) was a multinational cohort study that evaluated the risk factors associated with developing CAPA in people hospitalised and admitted to the intensive care for COVID-19 acute respiratory failure.

Publication status

The two studies included in this review were full publications (Chong 2021 and Prattes 2021). All 8 of the studies included in the systematic review (Chong 2021) were full publications as well.

Study characteristics

The Chong 2021 systematic review included 8 cohort studies, with 729 participants and ages ranging from 59-71 years. It included people who developed COVID-19 and were admitted to hospitals and later diagnosed with CAPA. The included studies

collected data from participants during the early surges of COVID-19 in March-August 2020.

Prattes 2021 evaluated 592 participants, with 109/592 with proven, probable or possible CAPA who were admitted to ICU for COVID-19 acute respiratory failure. Participants in Prattes 2021 were aged between 54-75 years and were admitted between March 2020 – April 2021.

Both studies compared the clinical characteristics, or risk factors, of people with COVID-19 and confirmed CAPA with those without CAPA. The majority of participants in both studies were male (Chong 2021- 71.5% male and Prattes 2021 - 70.8% male), and were adults who were hospitalised with confirmed COVID-19. Participants were diagnosed with CAPA as defined by the ECMM criteria and the AspICU algorithm criteria.

What are the main results?

The results from the studies indicated that there is a possible association between CAPA incidence and increasing age, long-term corticosteroid treatment, higher sequential organ failure assessment (SOFA) score, progression to invasive mechanical ventilation and COVID-19 treatment with tocilizumab. There is an association of borderline significance between the presence of underlying chronic obstructive pulmonary disease (COPD) and CAPA.

Our confidence in the results

The certainty of the evidence for these risk factors was rated as very low, due to serious risk of bias with the studies controlling variables, due to serious indirectness (Prattes 2021) from the inclusion of people with possible CAPA (not proven or probable) and due to serious inconsistency as Chong 2021 analysed studies that varied methodologically.

The risk factors in the systematic review and the single cohort study are reported in general terms and not in detail. Details on confounding variables, such as diagnostic

criteria and treatment regimens were not clearly defined. It was also unclear how these different variables were controlled in both the CAPA and non-CAPA groups, and how they were accounted for throughout data collection and analysis.

As both studies evaluated people from different waves of the COVID-19 pandemic, it is possible that changes in practice (e.g. treatments for COVID-19 in different centres, different diagnostic criteria for CAPA) throughout the COVID-19 pandemic context (e.g. surges and recovery periods in COVID-19 waves, take-up of vaccinations), may affect the number of people who contracted COVID-19 and CAPA.

Currently, there is limited evidence that identifies the associations between patient characteristics and CAPA development in COVID-19 disease and the current evidence base is small.

References

Bartoletti, M., Pascale, R., Cricca, M., Rinaldi, M., Maccaro, A., Bussini, L., Fornaro, G., Tonetti, T., Pizzilli, G., Francalanci, E. and Giuntoli, L., 2020. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. *Clinical Infectious Diseases*.

Chong, W.H., Saha, B.K. and Neu, K.P., 2021a. Comparing the clinical characteristics and outcomes of COVID-19-associate pulmonary aspergillosis (CAPA): a systematic review and meta-analysis. *Infection*, pp.1-14.

Chong, W.H., Saha, B.K., Ramani, A. and Chopra, A., 2021b. State-of-the-art review of secondary pulmonary infections in patients with COVID-19 pneumonia. *Infection*, pp.1-15.

Dellière, S., Dudoignon, E., Fodil, S., Voicu, S., Collet, M., Oillic, P.A., Salmona, M., Dépret, F., Ghelfenstein-Ferreira, T., Plaud, B. and Chousterman, B., 2021. Risk factors associated with COVID-19-associated pulmonary aspergillosis in ICU patients: a French multicentric retrospective cohort. *Clinical Microbiology and Infection*, *27*(5), pp.790-e1.

Gangneux, J.P., Reizine, F., Guegan, H., Pinceaux, K., Le Balch, P., Prat, E., Pelletier, R., Belaz, S., Le Souhaitier, M., Le Tulzo, Y. and Seguin, P., 2020. Is the COVID-19 pandemic a good time to include aspergillus molecular detection to categorize aspergillosis in ICU patients? A monocentric experience. *Journal of Fungi*, *6*(3), p.105.

Lahmer, T., Kriescher, S., Herner, A., Rothe, K., Spinner, C.D., Schneider, J., Mayer, U., Neuenhahn, M., Hoffmann, D., Geisler, F. and Heim, M., 2021. Invasive pulmonary aspergillosis in critically ill patients with severe COVID-19 pneumonia: Results from the prospective AspCOVID-19 study. *PloS one*, *16*(3), p.e0238825.

Pintado, M.V., Camiro-Zúñiga, A., Soto, M.A., Cuenca, D., Mercado, M. and Crabtree-Ramirez, B., 2021. COVID-19-associated invasive pulmonary aspergillosis in a tertiary care center in Mexico City. *Medical mycology*.

Review question A2: Signs and symptoms

Background

COVID-19 disease is known to have a range of potential complications and co-infections. Secondary fungal infections (aspergillus) have been reported in patients following hospitalisation (Chong et al., 2021a). Although the incidence is low, mortality rate is high. Recommendations on identifying, diagnosing, and treating secondary fungal infections are required to ensure consistent practice and help improve outcomes for people with these infections (Chong et al., 2021b).

Objective

This evidence review aims to identify the prevalence of the signs and symptoms of COVID-19 associated pulmonary aspergillosis (CAPA) experienced by people who have or, as part of their acute illness, have had confirmed COVID-19 and have diagnosed CAPA.

Review question

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review question for this evidence review is:

1. What is the prevalence of signs and symptoms among people who have or, as part of their acute illness, have had confirmed COVID-19 and have diagnosed CAPA?

Methodology

The evidence review was developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

A recent taskforce report was identified, which is highly relevant to the reviews being undertaken on CAPA (Verweij et al., 2021). In addition to the evidence review, relevant information from this document was presented to the panel and considered when making recommendations.

Summary of included studies

A literature search for CAPA identified 466 references (see appendix B for full details). These references were screened using their titles and abstracts and 22 full text references were obtained and assessed for relevance.

21 studies were excluded. Details of excluded studies are in appendix C.

One study is included in this evidence summary. A summary of the included study and its quality assessment is shown in appendices D and E. Meta-analysis was not undertaken for this review as only one study was identified. Therefore no forest plots were produced.

Study characteristics

Study characteristic	Segrelles-Calvo 2021
Location and setting	Madrid, Spain. Respiratory ICU ward.
No. of patients (N)	7
Follow-up	NA
Age (years)	Range 42 – 75
Gender (% female)	2 (29%)
Baseline characteristics	6 (86%) had orotracheal intubation. No other relevant characteristics reported.
COVID infection	All had confirmed diagnosis of severe pneumonia caused by SARS-CoV-2 (confirmed by PCR)
CAPA infection	Participants were diagnosed with invasive fungal infections using bronchoalveolar lavage (BAL) sample using an Aspergillus EIA assay.
Inclusion criteria	Patients admitted to the respiratory ICU, with a positive PCR test for COVID-19 and diagnosed with invasive fungal infection (the detection of the Aspergillus galactomannan antigen was carried out in the BAL sample by using the Platelia™ Aspergillus EIA assay).
Main exclusion criteria	Not reported
Other notes	None

Results

Research question: What is the prevalence of signs and symptoms among people who have or, as part of their acute illness, have had confirmed COVID-19 and have diagnosed CAPA?

There is very limited evidence on symptoms of invasive pulmonary aspergillosis (IPA) in people who have or, as part of their acute illness, have had confirmed COVID-19.

What is the evidence informing this conclusion?

Evidence comes from one small, retrospective cohort study aiming to determine the prevalence of IPA and risk factors for IPA in people admitted to ICU due to severe SARS-CoV-2 infection (Segrellos-Calvo 2021).

Publication status

The included study has been published and peer-reviewed.

Study characteristics

The included study had seven participants. Their ages ranged from 42 to 75. Two participants (29%) were female. All had PCR-confirmed COVID-19. They were diagnosed with IPA using bronchoalveolar lavage using an Aspergillus EIA assay. All participants had been admitted to respiratory ICU.

What are the main results?

Critical outcomes

Fever, dyspnoea and cough were the most common symptoms among the participants (affecting 100%, 86% and 86% respectively).

Important outcomes

All outcomes for this review were classified as critical outcomes.

Our confidence in the results

The evidence is extremely sparse and the results could be due to chance. The study was at high risk of bias due to a lack of detail about how outcomes were measured. There could also be variation over time or between people assessing symptoms, potentially introducing bias.

Outcomes were also downgraded twice for imprecision, as the precision of the result was not reported and could not be calculated.

The symptoms reported are also associated with COVID-19, and therefore it is not possible to attribute the symptoms to COVID-19 associated pulmonary aspergillosis (CAPA) alone.

References

Blot SI, Taccone FS, Van den Abeele AM, *et al.* AspICU Study Investigators. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. Am J Respir Crit Care Med. 2012 Jul 1;186(1):56-64. doi: 10.1164/rccm.201111-1978OC. Epub 2012 Apr 19. Erratum in: Am J Respir Crit Care Med. 2012 Oct 15;186(8):808. PMID: 22517788.

Chong, W.H., Saha, B.K. and Neu, K.P., 2021a. Comparing the clinical characteristics and outcomes of COVID-19-associate pulmonary aspergillosis (CAPA): a systematic review and meta-analysis. Infection, pp.1-14.

Chong, W.H., Saha, B.K., Ramani, A. and Chopra, A., 2021b. State-of-the-art review of secondary pulmonary infections in patients with COVID-19 pneumonia. Infection, pp.1-15.

Segrelles-Calvo, G, Araújo, G R S, Llopis-Pastor, E et al. (2021) Prevalence of opportunistic invasive aspergillosis in COVID-19 patients with severe pneumonia. Mycoses 64(2): 144-151

Verweij, P.E., Brüggemann, R.J., Azoulay, E., Bassetti, M., Blot, S., Buil, J.B., Calandra, T., Chiller, T., Clancy, C.J., Cornely, O.A. and Depuydt, P., 2021. Taskforce report on the diagnosis and clinical management of COVID-19 associated pulmonary aspergillosis. *Intensive Care Medicine*, pp.1-16.

Evidence to decision

Benefits and harms

The panel were presented with evidence from one systematic review (Chong 2021) and two primary studies (Prattes 2021 and Segrelles-Calvo 2021). The studies presented evidence on the risk factors and signs and symptoms associated with people developing CAPA.

The panel agreed that there was insufficient evidence to define specific risk factors or signs and symptoms of CAPA. Although the studies suggest that increasing age and chronic lung disease may increase the risk of developing CAPA, the panel considered that the evidence was not strong enough to include these specific risk factors in a diagnostic recommendation. They also agreed that, while studies suggest that people who receive invasive mechanical ventilation are at increased risk of CAPA, the thresholds for mechanical ventilation vary across centres and invasive mechanical ventilation may not be considered an independent risk factor for CAPA. The panel also considered the evidence around whether taking long-term immunosuppressants can increase the risk of CAPA, but concluded that the evidence was not strong enough to list ‘long-term immunosuppressants’ as an independent risk factor for CAPA.

The panel highlighted the need to use clinical judgement and assess the individual needs of people who are suspected to have CAPA, before progressing further with their diagnosis and management.

The panel considered whether existing clinical algorithms for the diagnosis of invasive pulmonary aspergillosis could be applied to CAPA. In particular, the panel discussed the AspICU algorithm, which is a clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. However, the panel agreed not to recommend use of the AspICU algorithm for CAPA because of a lack of evidence of its use in this condition and meaningful differences between the people for which the AspICU algorithm is typically used and the people who are at risk of developing CAPA.

The panel discussed that from their experience, a diagnosis of CAPA should usually be made as part of a multidisciplinary team, with input from infection specialists (for example, medical microbiologists or infectious disease specialists).

Certainty of the evidence

The certainty of the evidence was rated as low to very low for all outcomes. This was due to serious risk of bias, serious indirectness, and serious inconsistency. The panel discussed that heterogeneity of the study participants, and the variations in local practice in reporting and case definitions of CAPA also reduced their certainty in the results.

In particular, the panel discussed that the association shown between invasive mechanical ventilation and CAPA is likely to be at risk of bias from confounding due to the difference in diagnostic approach between those who are invasively mechanically ventilated and those who are not.

Values and preferences

The panel were not aware of any systematically collected data about the preferences and values in people who are suspected to have CAPA.

Resources

No formal analysis of resource impact has been carried out. The panel recommended that decisions about whether to suspect CAPA should be made as part of a multidisciplinary team which includes infection specialists, which may not currently be in place in all settings where people who are critically ill are cared for.

Equity

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but that assessments should take place in the same way for all people who are critically ill and have, or have had, COVID-19 as part of their acute illness.

No other equity issues were identified.

Acceptability

The panel were not aware of any systematically collected evidence about the acceptability of assessing for suspicion of CAPA.

Feasibility

The panel were not aware of any systematically collected evidence about feasibility, but agreed that this approach should be feasible, particularly where a multidisciplinary team which includes infection specialists is already in place.

Appendix A: PICO table

Question A1: What risk factors in people who have or, as part of their acute illness, have had confirmed COVID-19 are associated with developing CAPA?

Criteria	Notes
Population	Adults, young people and children who are critically ill and have or, as part of their acute illness, have had confirmed COVID-19, and who have diagnosed CAPA.
Exposure	Any
Outcomes	Risk factors or factors that are associated with CAPA (as defined by the study). Examples may include: • Age • Sex • Comorbidities • Other medications received (either in the long or short term e.g. for treatment of COVID-19)
Settings	ICU in hospital settings
Subgroups	None
Study types	Any The following study design types for this question are preferred. Where these studies are not identified, other study designs will be considered. Preferred: • Systematic reviews of cohort studies with non-CAPA control groups • Cohort studies (prospective or retrospective) with non-CAPA control groups • Cross-sectional studies
Countries	Any
Timepoints	From 2020 onwards
Other exclusions	The scope sets out what the guideline will and will not include (exclusions). Further exclusions specific to this guideline include:

	• non-English language papers, studies that are only available as abstracts, and narrative reviews • animal studies • editorials, letters, news items, case reports and commentaries, conference abstracts and posters • theses and dissertations
Equality issues	Sex, age, ethnicity, religion or beliefs, people with a learning disability and disabled people, socioeconomic status, people who are pregnant or breastfeeding, people whose first language isn't English, refugees, asylum seekers, migrant workers and people who are homeless.

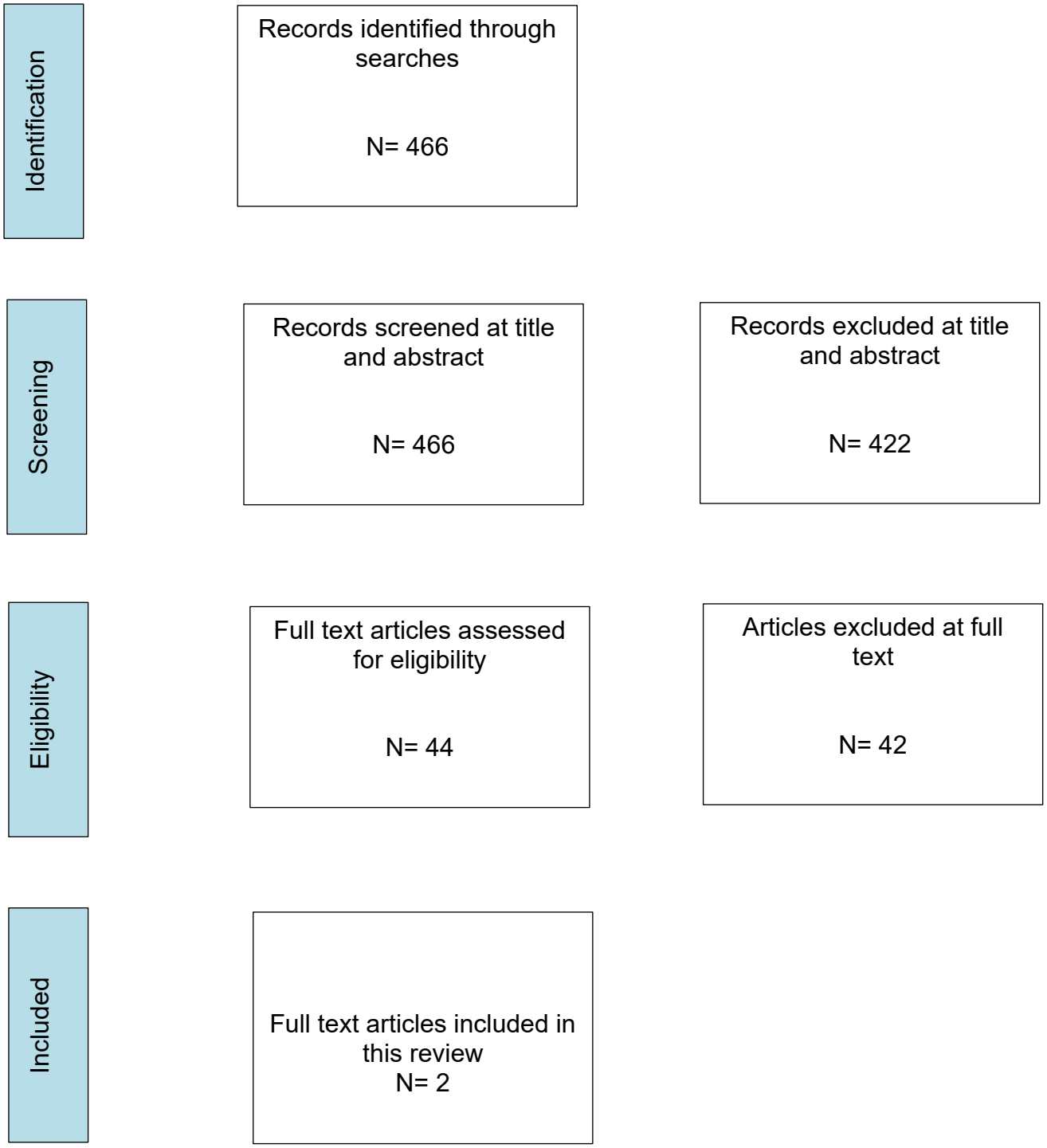
Question A2: What is the prevalence of signs and symptoms among people who have or, as part of their acute illness, have had confirmed COVID-19 and have diagnosed CAPA?

Criteria	Notes
Population	Adults, young people and children who have or, as part of their acute illness, have had confirmed COVID-19, and who have diagnosed CAPA. They should be currently critically ill.
Interventions	Not applicable
Comparators	Not applicable
Outcomes	Prevalence of signs and symptoms in people with diagnosed CAPA. Signs and symptoms as reported by studies, including but not limited to those identified in the AspICU algorithm.
Settings	Hospital settings (ICU)
Subgroups	• Adults > 50 years • Children <12 years of age • Gender • Ethnic background • Pregnant women • Comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity)
Study types	Any The following study design types for this question are preferred. Where these studies are not identified, other study designs will be considered. Preferred: • Systematic reviews of cohort studies • Cohort studies (prospective or retrospective) • Cross-sectional studies
Countries	Any
Timepoints	From 2020 onwards

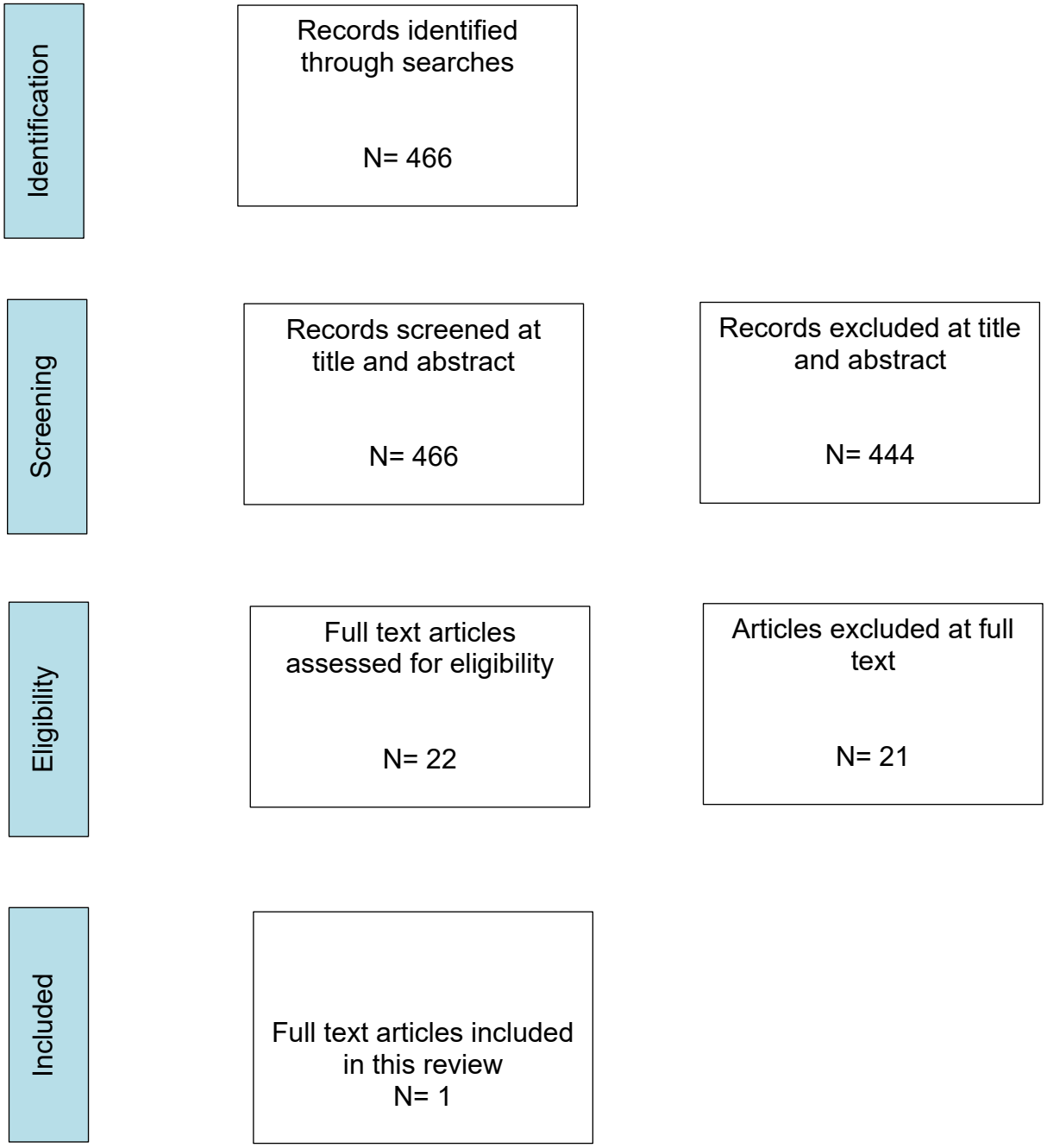
Other exclusions	The scope sets out what the guideline will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts, and narrative reviews • animal studies • editorials, letters, news items, case reports and commentaries, conference abstracts and posters • theses and dissertations
Equality issues	Sex, age, ethnicity, religion or beliefs, people with a learning disability and disabled people, socioeconomic status, people who are pregnant or breastfeeding, people whose first language isn't English, refugees, asylum seekers, migrant workers and people who are homeless.

Appendix B: Literature search strategy/Data source

PRISMA flow chart: Risk factors



PRISMA flow chart: Signs and symptoms



Search history methods

The searches for the effectiveness evidence were run on 12 10 2021. The following databases were searched: Central Register of Controlled Trials (Wiley), Cochrane Database of Systematic Reviews (Wiley), Embase (Ovid), MEDLINE ALL (Ovid), NICE Evidence Search and the World Health Organisation Covid-19 database. Full search strategies for each database are provided in Appendix B. Pre-prints were searched via EPPI reviewer v5.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

Search design and peer review

This search was developed in compliance with Appendix L of NICE's manual on developing guidelines.

A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 12/10/2021. This search report is compliant with the requirements of PRISMA-S.

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

NICE's approach to retrieving preprints has evolved throughout the pandemic:

- Prior to 20th April 2020 MedRxiv and BioRxiv were searched directly.
- From 20th April 2020 an automated process was used to download the entire MedRxiv and BioRxiv COVID-19 and SARS-COV-2 collection into EPPI Reviewer 5 and update the results daily. Individual topic searches were

conducted within EPPI Reviewer to get round the limitations of the native search functionality in MedRxiv and BioRxiv.

- From 19th August 2021, results from additional preprint servers were added to the EPPI Reviewer database on a weekly basis. The additional results were sourced from the aggregator sites Europe PMC and the NIH Office of Portfolio Analysis COVID-19 database. These sites index multiple preprint servers, including Arxiv, MedRxiv, BioRxiv, Research Square, SSRN and preprints.org. The NIH database is pre-sifted for COVID-19 related references. Europe PMC is broader, and so we initially used their stock strategy to narrow the results down to a subset that were related to COVID-19. References added to the aggregator sites from the 10th August 2021 were downloaded, but searches of these sources were not backdated further.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

The search was limited from 2020 to date as defined in the review protocol.

Search filters

- Covid-19 filter

The development of NICE's main database search strategy for Covid-19 is covered in: Levay P and Finnegan A (2021) The NICE COVID-19 search strategy for Ovid MEDLINE and Embase: developing and maintaining a strategy to support rapid guidelines. MedRxiv preprint. https://doi.org/10.1101/2021.06.11.21258749

- Systematic reviews filters

The MEDLINE SR filter was “Health-evidence.ca Systematic review search filter” from Lee et al. (2012). The standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

The Embase SR filter was “Health-evidence.ca Systematic review search filter” from Lee et al. (2012). The standard NICE modifications were used: pubmed.tw added to line medline.tw.

Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

- RCT filters

The MEDLINE RCT filter was McMaster Therapy – Medline - “best balance of sensitivity and specificity” version. The standard NICE modifications were used: randomized.mp changed to randomi?ed.mp.
Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.
The Embase RCT filter was McMaster Therapy – Embase “best balance of sensitivity and specificity” version.
Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association*, 94(1), 41-47.

Main search – Databases

Database	Date searched	Database platform	Database segment or version	No. of results downloaded
MEDLINE ALL	12/10/21	Ovid	Ovid MEDLINE(R) ALL 1946 to October 11, 2021	170
Embase	12/10/21	Ovid	Embase 1974 to 2021 October 11	167
Cochrane - Cochrane Database of Systematic Reviews	12/10/21	Wiley	Cochrane Database of Systematic Reviews Issue 10 of 12, October 2021	0

Cochrane - CENTRAL	12/10/21	Wiley	*Cochrane* Central Register of Controlled Trials Issue 10 of 12, October 2021	4
MedRxiv/BioRxiv/Europe PMC/NIH Portfolio Preprints [EPPI review]	12/10/21	Wiley	pre-prints v3 09:29	12
WHO Covid-19 Database	12/10/21	N/A	N/A	0 (Searched but nothing unique found)
NICE Evidence Search	12/10/21	N/A	N/A	0 (Searched but nothing unique found)

Search strategy history

Database name: MEDLINE ALL

1 SARS-CoV-2/ or COVID-19/ (112571)

2 (corona* adj1 (virus* or viral*)).ti,ab,kw,kf. (4214)

3 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab,kw,kf. (64038)

4 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw,kf. (196275)

5 or/1-4 (201655)

6 limit 5 to yr="2020-Current" (188328)

7 (6 and english.lg.) not (letter or historical article or comment or editorial or news or case reports).pt. not (Animals/ not humans/) (138128)

8 exp Aspergillosis/ (17174)

9 aspergill*.ti,ab,kw,kf. (56403)

10 CAPA.ti,ab,kw,kf. (538)

11 azole-resist*.ti,ab,kw,kf. (1672)

12 or/8-11 (60368)

13 7 and 12 (170)

Database name: Embase

1 exp severe acute respiratory syndrome coronavirus 2/ or coronavirus disease 2019/ or experimental coronavirus disease 2019/ (161779)

2 (corona* adj1 (virus* or viral*)).ti,ab,kw. (3898)

3 (CoV not (Coefficien* or co-efficien* or covalent* or covington or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk" or CoVR or CoVS)).ti,ab,kw. (56317)

4 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw. (198000)

5 or/1-4 (212228)

6 limit 5 to yr="2020-Current" (197095)

7 (6 and english.lg.) not (letter or editorial or conference).pt. not (nonhuman/ not human/) not "case report".sh. not medline*.db. (89410)

8 exp aspergillosis/ (28021)

9 aspergill*.ti,ab,kw. (71121)

10 CAPA.ti,ab,kw. (689)

11 azole-resist*.ti,ab,kw. (2043)

12 or/8-11 (80048)

13 7 and 12 (167)

14 (conference abstract or conference paper or conference proceeding or "conference review").pt. (4991938)

15 13 not 14 (167)

Database name: Cochrane Database of Systematic Reviews / Central Register of Controlled Trials

#1 MeSH descriptor: [SARS-CoV-2] this term only 479

#2 MeSH descriptor: [COVID-19] this term only 657

#3 (corona* near/1 (virus* or viral*)):ti,ab,kw 262

#4 (CoV NOT (Coefficien* or "co-efficient" or “co-efficiency” or “co-efficiencies” or covalent* or Covington* or covariant* or covarianc* or "cut-off value" or "cut-off values" or "cutoff value" or "cutoff values" or "cut-off volume" or "cut-off volumes" or "cutoff volume" or "cutoff volumes" or "combined optimisation value" or "combined optimisation values" or "combined optimization value" or "combined optimization values" or "central vessel trunk" or "central vessel trunks" or CoVR or CoVS)):ti,ab,kw 528

#5 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel" or Ncov* or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or SARSCoV2* or "SARS-CoV2" or "severe acute respiratory syndrome" or "severe acute respiratory syndromes" or covid19 or covid-19 or covid):ti,ab,kw 7869

#6 {or #1-#5} with Cochrane Library publication date Between Jan 2020 and Dec 2021, in Cochrane Reviews 43

#7 {or #1-#5} with Publication Year from 2020 to 2021, in Trials 7644

#8 #6 OR #7 7687

#9 MeSH descriptor: [Aspergillosis] explode all trees 148

#10 aspergill*:ti,ab,kw 882

#11 CAPA:ti,ab,kw 140

#12 azole-resist*:ti,ab,kw 22

#13 {or #9-#12} 1038

#14 #8 and #13 4

Database name: Pre-print - medRxiv and bioRxiv/ Europe PMC/NIH Portfolio

These were searched via EPPI reviewer v5 using filters Title and Abstract HAS ALL and AND Title and Abstract HAS ANY.

Search term Aspergill*

Database name: World Health Organisation Covid-19 database

This was searched by using search term Aspergill*

Database name: NICE Evidence Search

This was searched by using search terms Aspergill*

Appendix C: Excluded studies at full text screening

Review question A1: Risk factors

Study	Reason for exclusion
Afzal Prof., Saira and Nasir, Mehreen Aspergillosis and Mucormycosis in COVID-19 Patients; a Systematic Review and Meta-analysis. medrxiv preprint	- Not a relevant study design *Systematic review and meta-analysis of case reports/case series*
Alanio, Alexandre, Delliere, Sarah, Fodil, Sofiane et al. High prevalence of putative invasive pulmonary aspergillosis in critically ill COVID-19 patients. medrxiv preprint	- Not a relevant study design
Apostolopoulou, Anna, Esquer Garrigos, Zerelda, Vijayvargiya, Prakhar et al. (2020) Invasive Pulmonary Aspergillosis in Patients with SARS-CoV-2 Infection: A Systematic Review of the Literature. Diagnostics (Basel, Switzerland) 10(10)	- SR and meta-analysis of case reports/case series *Includes case reports and case series. From 2021 so more recent systematic reviews are available.*
Bartoletti, Michele, Pascale, Renato, Cricca, Monica et al. (2020) Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	- Covered by an included systematic review
Borman, Andrew M, Palmer, Michael D, Fraser, Mark et al. (2020) COVID-19-Associated Invasive Aspergillosis: Data from the UK National Mycology Reference Laboratory. Journal of clinical microbiology 59(1): e02136-20-	- Study does not report any of the results specified in the protocol *Study does not report on risk factors or any relevant outcomes*
Chauvet, Paul, Mallat, Jihad, Arumadura, Clothilde et al. (2020) Risk Factors for Invasive Pulmonary Aspergillosis in Critically Ill Patients With Coronavirus Disease 2019-Induced Acute Respiratory Distress Syndrome. Critical care explorations 2(11): e0244	- Not a relevant study design *Case series*
Chong, Woon H and Neu, Kristoffer P (2021) The Incidence, Diagnosis, and Outcomes of COVID-19-associated Pulmonary Aspergillosis (CAPA): A Systematic Review. The Journal of hospital infection	- Supporting information -*Study does not contain extractable data*
Dellière, Sarah, Dudoignon, Emmanuel, Fodil, Sofiane et al. (2021) Risk factors associated with COVID-19-associated pulmonary aspergillosis in ICU patients: a French multicentric retrospective cohort. Clinical Microbiology and Infection 27(5): 790-e1	- Covered by an included systematic review
Dimopoulos, George, Almyroudi, Maria-Panagiota, Myrianthefs, Pavlos, Rello, Jordi (2021) COVID-19-associated pulmonary aspergillosis (CAPA). Journal of Intensive Medicine	- Not a relevant study design *Review article but not a systematic review*

Dupont, Damien, Menotti, Jean, Turc, Jean et al. (2021) Pulmonary aspergillosis in critically ill patients with Coronavirus Disease 2019 (COVID-19). Med Mycol 59(1): 110-114	- Does not contain a population of people with proven CAPA *Participants with putative IPA only*
Falces-Romero, Iker, Ruiz-Bastian, Mario, Diaz-Pollan, Beatriz et al. (2020) Isolation of Aspergillus spp. in respiratory samples of patients with COVID-19 in a Spanish Tertiary Care Hospital. Mycoses	- Does not contain a population of people with proven CAPA *The majority of the patients included had putative/probable CAPA only and not proven CAPA*
Fekkar, Arnaud, Lampros, Alexandre, Mayaux, Julien et al. (2021) Occurrence of Invasive Pulmonary Fungal Infections in Patients with Severe COVID-19 Admitted to the ICU. American journal of respiratory and critical care medicine 203(3): 307-317	- Does not contain a population of people with proven CAPA – *The majority of patients included had putative/probable CAPA only and not proven CAPA*
Helleberg, Marie; Steensen, Morten; Arendrup, Maiken Cavling (2021) Invasive aspergillosis in patients with severe COVID-19 pneumonia. Clinical Microbiology and Infection 27(1): 147-148	- Not a relevant study design
Janssen, Nico A F, Nyga, Remy, Vanderbeke, Lore et al. (2021) Multinational Observational Cohort Study of COVID-19-Associated Pulmonary Aspergillosis1. Emerging infectious diseases 27(11)	- Does not contain a population of people with proven CAPA - *Patients with possible, probable and diagnosed CAPA all grouped together and can't be separated; data is not extractable*
Kariyawasam Ruwandi, M., Dingle Tanis, C., Kula Brittany, E. et al. COVID-19 Associated Pulmonary Aspergillosis: Systematic Review and Patient-Level Meta-Analysis. medrxiv preprint	- Study does not report any of the results specified in the protocol *Does not report risk factors*
Khan, M. S. (2021) The urge for early detection and effective therapy against COVID-19 fungal co-infection: A retrospective study. Annals of Phytomedicine-an International Journal 10(1): 77-s84	- Not a relevant study design *A review, not including patients*
Koehler, Philipp, Cornely, Oliver A., B?ttiger, Bernd W. et al. (2020) COVID-19 Associated Pulmonary Aspergillosis. Mycoses na(na)	- Not a relevant study design *No non-CAPA group for comparison; case series*
Lamoth, Frederic, Glampedakis, Emmanouil, Boillat-Blanco, Noémie et al. (2020) Incidence of invasive pulmonary aspergillosis among critically ill COVID-19 patients. Clinical Microbiology and Infection 26(12): 1706-1708	- Not a relevant study design
Lv, Longxian, Jiang, Huiyong, Chen, Yanfei et al. (2021) The faecal metabolome in COVID-19 patients is altered and associated with clinical features and gut microbes. Analytica chimica acta 1152: 338267	- Supporting information *Study does not contain extractable data*
Marr, Kieren A, Platt, Andrew, Tornheim, Jeffrey A et al. (2021) Aspergillosis Complicating Severe Coronavirus Disease. Emerging infectious diseases 27(1)	- Not a relevant study design
Meawed, Takwa E, Ahmed, Sherweet M, Mowafy, Sherif M S et al. (2021) Bacterial and fungal ventilator associated pneumonia in critically ill COVID-19 patients during the second wave. Journal of infection and public health 14(10): 1375-1380	- Supporting information *Study does not contain extractable data*

Mitaka, Hayato, Kuno, Toshiki, Takagi, Hisato et al. (2021) Incidence and mortality of COVID-19-associated pulmonary aspergillosis: A systematic review and meta-analysis. Mycoses 64(9): 993-1001	- Study does not report any of the results specified in the protocol *Reports incidence and mortality, not risk factors.*
Mitaka, Hayato, Perlman, David C, Javaid, Waleed et al. (2020) Putative invasive pulmonary aspergillosis in critically ill patients with COVID-19: An observational study from New York City. Mycoses 63(12): 1368-1372	- Does not contain a population of people with proven CAPA - *All of the participants were not diagnosed with CAPA (possible CAPA only)*
Montrucchio, G, Lupia, T, Lombardo, D et al. (2021) Risk factors for invasive aspergillosis in ICU patients with COVID-19: current insights and new key elements. Annals of intensive care 11(1): 136	- Not a relevant study design
Mulet Bayona, Juan Vicente, Tormo Palop, Nuria, Salvador Garcia, Carme et al. (2021) Impact of the SARS-CoV-2 Pandemic in Candidaemia, Invasive Aspergillosis and Antifungal Consumption in a Tertiary Hospital. Journal of fungi (Basel, Switzerland) 7(6)	- Study does not report any of the results specified in the protocol
Nasir, Nosheen, Farooqi, Joveria, Mahmood, Syed Faisal et al. (2020) COVID-19-associated pulmonary aspergillosis (CAPA) in patients admitted with severe COVID-19 pneumonia: An observational study from Pakistan. Mycoses 63(8): 766-770	- Not a relevant study design *No non-CAPA group for comparison*
Nebreda-Mayoral, Teresa, Miguel-Gomez, Maria Antonia, March-Rossello, Gabriel Alberto et al. (2020) Bacterial/fungal infection in hospitalized patients with COVID-19 in a tertiary hospital in the Community of Castilla y Leon, Spain. Enfermedades infecciosas y microbiologia clinica (English ed.)	- Study not reported in English *In Spanish*
Paramythiotou, Elisabeth, Dimopoulos, George, Koliakos, Nikolaos et al. (2021) Epidemiology and Incidence of COVID-19-Associated Pulmonary Aspergillosis (CAPA) in a Greek Tertiary Care Academic Reference Hospital. Infect Dis Ther 10(3): 1779-1792	- Study does not report any of the results specified in the protocol *Does not report risk factors for CAPA*
Permpalung, Nitipong, Chiang, Teresa Po-Yu, Massie, Allan B et al. (2021) COVID-19 Associated Pulmonary Aspergillosis in Mechanically Ventilated Patients. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	- Does not contain a population of people with proven CAPA – *Participants were not diagnosed with CAPA (possible CAPA only)*
Razazi, Keyvan, Arrestier, Romain, Haudebourg, Anne Fleur et al. (2020) Risks of ventilator-associated pneumonia and invasive pulmonary aspergillosis in patients with viral acute respiratory distress syndrome related or not to Coronavirus 19 disease. Critical care (London, England) 24(1): 699	- Data and outcomes not reported in an extractable format
Saeed, Nermin Kamal, Al-Khawaja, Safaa, Alsalman, Jameela et al. (2021) Bacterial co-infection in patients with SARS-CoV-2 in the Kingdom of Bahrain. World journal of virology 10(4): 168-181	- Does not contain a population of people with proven CAPA *Participants not diagnosed with CAPA*

Salmanton-Garcia, Jon, Sprute, Rosanne, Stemler, Jannik et al. (2021) COVID-19-Associated Pulmonary Aspergillosis, March-August 2020. Emerging infectious diseases 27(4): 1077-1086	- Not a relevant study design *Report of multiple case series*
Sarrazyn, Camille, Dhaese, Sofie, Demey, Birgit et al. (2021) Incidence, risk factors, timing, and outcome of influenza versus COVID-19-associated putative invasive aspergillosis. Infection control and hospital epidemiology 42(9): 1149-1150	- Not a relevant study design
Segrelles-Calvo, Gonzalo, Araújo, Glauber R S, Llopis-Pastor, Estefanía et al. (2021) Prevalence of opportunistic invasive aspergillosis in COVID-19 patients with severe pneumonia. Mycoses 64(2): 144-151	- Covered by an included SR
Singh, Shreya, Verma, Nipun, Kanaujia, Rimjhim et al. (2021) Mortality in critically ill patients with coronavirus disease 2019-associated pulmonary aspergillosis: A systematic review and meta-analysis. Mycoses 64(9): 1015-1027	- Study does not report any of the results specified in the protocol *Only reports mortality, not risk factors*
Sung, Anita H. and Martin, Stephan, Phan, Bryant, Benigno, Michael, Stephens, Jennifer, Chambers, Richard, Aram, Jalal A. (2021) Patient Characteristics and Risk Factors in Invasive Mold Infections: Comparison from a Systematic Review and Database Analysis. ClinicoEconomics and Outcomes Research 13: 593-602	- Supporting information *Study does not contain extractable data*
Velez Pintado, Mariana, Camiro-Zuniga, Antonio, Aguilar Soto, Mercedes et al. (2021) COVID-19-associated invasive pulmonary aspergillosis in a tertiary care center in Mexico City. Medical mycology 59(8): 828-833	- Covered by an included systematic review
Versyck, Maaike, Zarrougui, Wafa, Lambiotte, Fabien et al. (2021) Invasive pulmonary aspergillosis in COVID-19 critically ill patients: Results of a French monocentric cohort. Journal de mycologie medicale 31(2): 101122	- Does not report any of the results specified in the protocol *Does not report risk factors, and no comparison group*
Wasylyshyn, Anastasia I, Wasylyshyn, G Rostyslaw, Linder, Kathleen A et al. (2021) COVID-19-Associated Pulmonary Aspergillosis at an Academic Medical Center in the Midwestern United States. Mycopathologia 186(4): 499-505	- Does not contain a population of people with non-CAPA - *Study does not report on a comparison group (non-CAPA)*
White, P Lewis, Dhillon, Rishi, Cordey, Alan et al. (2021) A National Strategy to Diagnose Coronavirus Disease 2019-Associated Invasive Fungal Disease in the Intensive Care Unit. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 73(7): e1634-e1644	- Not a relevant study design *Strategy document*
Yusuf, Erlangga, Vonk, Alieke, van den Akker, Johannes P C et al. (2021) Frequency of Positive Aspergillus Tests in COVID-19 Patients in Comparison to Other Patients with Pulmonary	- Does not contain a population of people with non-CAPA *Study does not compare risk factors between CAPA and non-CAPA*

Infections Admitted to the Intensive Care Unit. Journal of clinical microbiology 59(3)	
Zia, Mohammadali and Goli, Mohammad (2021) Predisposing factors of important invasive fungal coinfections in COVID-19 patients: a review article. The Journal of international medical research 49(9): 3000605211043413	- Supporting information *Study does not contain extractable data*

Review question A2: Signs and symptoms

Study reference	Reason for exclusion
Apostolopoulou, Anna, Esquer Garrigos, Zerelda, Vijayvargiya, Prakhar et al. (2020) Invasive Pulmonary Aspergillosis in Patients with SARS-CoV-2 Infection: A Systematic Review of the Literature. Diagnostics (Basel, Switzerland) 10(10)	- Not a relevant study design *A systematic review of case series, which are not an included study design.*
Chong, Woon H and Neu, Kristoffer P (2021) The Incidence, Diagnosis, and Outcomes of COVID-19-associated Pulmonary Aspergillosis (CAPA): A Systematic Review. The Journal of hospital infection	- Study does not contain outcomes of interest *Does not report symptoms of CAPA*
Dimopoulos, George, Almyroudi, Maria-Panagiota, Myrianthefs, Pavlos, Rello, Jordi (2021) COVID-19-associated pulmonary aspergillosis (CAPA). Journal of Intensive Medicine	- Study does not contain outcomes of interest *Does not report symptoms of CAPA*
El-Kholy, Noha Ahmed; El-Fattah, Ahmed Musaad Abd; Khafagy, Yasser W (2021) Invasive Fungal Sinusitis in Post COVID-19 Patients: A New Clinical Entity. The Laryngoscope	- Does not contain a population of people with CAPA *Participants have acute invasive fungal rhinosinusitis, not CAPA.*
Frias-De-Leon, Maria Guadalupe, Pinto-Almazan, Rodolfo, Hernandez-Castro, Rigoberto et al. (2021) Epidemiology of Systemic Mycoses in the COVID-19 Pandemic. Journal of fungi (Basel, Switzerland) 7(7)	- Study does not contain outcomes of interest *Study does not report symptoms of CAPA*
Hoenigl, Martin, Egger, Matthias, Boyer, Johannes et al. (2021) Serum Lateral Flow assay with digital reader for the diagnosis of invasive pulmonary aspergillosis: A two-centre mixed cohort study. Mycoses 64(10): 1197-1202	- Study does not contain outcomes of interest *Reports accuracy of serum lateral flow assay for diagnosis of CAPA, not symptoms of CAPA.*
Iqbal, Ahtesham, Ramzan, Moazma, Akhtar, Aftab et al. (2021) COVID-Associated Pulmonary Aspergillosis and Its Related Outcomes: A Single-Center Prospective Observational Study. Cureus 13(8): e16982	- Study does not contain outcomes of interest *Study does not report symptoms of CAPA*
Janssen, Nico A F, Nyga, Remy, Vanderbeke, Lore et al. (2021) Multinational Observational Cohort Study of COVID-19-Associated Pulmonary Aspergillosis1. Emerging infectious diseases 27(11)	- Study does not contain outcomes of interest *Study does not report symptoms of CAPA*
Kariyawasam Ruwandi, M., Dingle Tanis, C., Kula Brittany, E. et al. COVID-19 Associated Pulmonary Aspergillosis: Systematic Review and Patient-Level Meta-Analysis. medrxiv preprint	- Study does not contain outcomes of interest *Does not report symptoms of CAPA*
Lahmer, Tobias, Kriescher, Silja, Herner, Alexander et al. (2021) Invasive pulmonary aspergillosis in critically ill patients with severe COVID-19 pneumonia: Results from the	- Study does not contain outcomes of interest *Does not report symptoms of CAPA*

Study reference	Reason for exclusion
prospective AspCOVID-19 study. PloS one 16(3): e0238825	
Lv, Longxian, Jiang, Huiyong, Chen, Yanfei et al. (2021) The faecal metabolome in COVID-19 patients is altered and associated with clinical features and gut microbes. Analytica chimica acta 1152: 338267	- Does not contain a population of people with CAPA *Participants are not diagnosed with CAPA*
Meawed, Takwa E, Ahmed, Sherweet M, Mowafy, Sherif M S et al. (2021) Bacterial and fungal ventilator associated pneumonia in critically ill COVID-19 patients during the second wave. Journal of infection and public health 14(10): 1375-1380	- Does not contain a population of people with CAPA *Study includes bacterial and fungal ventilator associated pneumonia, not patients diagnosed with CAPA.*
Mercier, Toine, Dunbar, Albert, Veldhuizen, Vincent et al. (2020) Point of care aspergillus testing in intensive care patients. Crit Care 24(1): 642-642	- Study does not contain outcomes of interest *Evaluates the performance of a lateral flow assay for diagnosis, does not report symptoms of CAPA.*
Nebreda-Mayoral, Teresa, Miguel-Gomez, Maria Antonia, March-Rossello, Gabriel Alberto et al. (2020) Bacterial/fungal infection in hospitalized patients with COVID-19 in a tertiary hospital in the Community of Castilla y Leon, Spain. Enfermedades infecciosas y microbiologia clinica (English ed.)	- Study not reported in English *Study is in Spanish*
Paramythiotou, Elisabeth, Dimopoulos, George, Koliakos, Nikolaos et al. (2021) Epidemiology and Incidence of COVID-19-Associated Pulmonary Aspergillosis (CAPA) in a Greek Tertiary Care Academic Reference Hospital. Infect Dis Ther 10(3): 1779-1792	- Not a relevant study design *Case series. Reviews the symptom criteria, so useful for information.*
Prattes, Juergen, Wauters, Joost, Giacobbe, Daniele Roberto et al. (2021) Risk factors and outcome of pulmonary aspergillosis in critically ill coronavirus disease 2019 patients-a multinational observational study by the European Confederation of Medical Mycology. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases	- Study does not contain outcomes of interest *Does not report symptoms of CAPA*
Rajendra Santosh, Arvind Babu; Muddana, Keerthi; Bakki, Shobha Rani (2021) Fungal Infections of Oral Cavity: Diagnosis, Management, and Association with COVID-19. SN comprehensive clinical medicine: 1-12	- Does not contain a population of people with CAPA *Study looks at oral fungal infections, not participants diagnosed with CAPA*
Singh, Shreya, Verma, Nipun, Kanaujia, Rimjhim et al. (2021) Mortality in critically ill patients with coronavirus disease 2019-associated pulmonary aspergillosis: A systematic review and meta-analysis. Mycoses 64(9): 1015-1027	- Study does not contain outcomes of interest *Reports on mortality of CAPA, not symptoms*
Velez Pintado, Mariana, Camiro-Zuniga, Antonio, Aguilar Soto, Mercedes et al. (2021) COVID-19-associated invasive pulmonary	- Study does not contain outcomes of interest *Study does not report symptoms of CAPA*

Study reference	Reason for exclusion
aspergillosis in a tertiary care center in Mexico City. Medical mycology 59(8): 828-833	
Versyck, Maaike, Zarrougui, Wafa, Lambiotte, Fabien et al. (2021) Invasive pulmonary aspergillosis in COVID-19 critically ill patients: Results of a French monocentric cohort. Journal de mycologie medicale 31(2): 101122	- Does not contain a population of people with CAPA *Participants not diagnosed with CAPA*
Zuo, Tao, Zhan, Hui, Zhang, Fen et al. (2020) Alterations in Fecal Fungal Microbiome of Patients With COVID-19 During Time of Hospitalization until Discharge. Gastroenterology 159(4): 1302-1310e5	- Does not contain a population of people with CAPA *Participants have not been diagnosed with CAPA.*

Appendix D: Data extraction

Chong, 2021

Bibliographic Reference	Chong, Woon Hean; Saha, Biplab K; Neu, Kristoffer P; Comparing the clinical characteristics and outcomes of COVID-19-associate pulmonary aspergillosis (CAPA): a systematic review and meta-analysis.; Infection; 2021

Study details

Study design	Systematic review
Trial registration (if reported)	PROSPERO: CRD42021247177
Aims/ review questions	To examine and discuss the incidence of secondary invasive pulmonary aspergillosis in COVID-19 patients (i.e. CAPA), clinical characteristics, diagnostic criteria, biomarkers and associated outcomes
Search date	01-August-2021
Country/ Geographical location	China, France, Greece, Italy, Mexico, Netherlands, Spain
Setting(s)	Patients hospitalised with COVID-19
Population description	All patients with confirmed COVID-19 diagnosis and proven CAPA diagnosis
Inclusion criteria	1. Studies that contain comparative data describing the clinical characteristics, risk factors and outcomes of hospitalised COVID-19 with CAPA and without CAPA 2. Studies that confirmed diagnosis of CAPA using several diagnostic criteria from current literature (AspICU, CAPA-ECMM, Modified AspICU, EORTC/MSG 3. Studies where the diagnosis of COVID-19 was confirmed by RT-PCR as well as nasal, pharyngeal, sputum, tracheal aspirate, non-directed bronchial lavage, and bronchial lavage 4. Articles published between 1st January 2020 and August 2021 in peer-reviewed journals
Exclusion criteria	1. Studies that did not meet the specific diagnostic criteria for CAPA diagnosis outlined in this study's inclusion criteria (i.e. studies that did not describe aspergillus colonisation from bronchoalveolar lavage (BAL)/non-directed bronchoalveolar lavage (NBL), the studies where the authors did not specify if it were invasive pulmonary aspergillosis or colonisation and studies where the data provided was not sufficient to make any diagnostic distinction were all excluded)

	2. Systematic reviews, literature reviews, editorials, conference abstracts, opinion articles, meta-analysis, case reports or studies with fewer than 30 participants 3. Studies involving COVID-19 patients of less than 18 years of age 4. Studies that did not have comparative data between CAPA and non-CAPA patients 5. Studies where pulmonary aspergillosis was concurrently diagnosed with other micro-organisms like bacteria/viruses 6. Studies that described aspergillosis obtained from non-respiratory tract cultures 7. Studies published in languages besides English that were not translatable 8. Studies where the diagnosis was made during post-mortem examination.
Intervention/test/approach	People diagnosed with CAPA
Comparator (where applicable)	People not diagnosed with CAPA
Searching methods	A literature search of PubMed and Web of Science for keywords like: COVID-19, SARS-CoV-2, CAPA, fungal infections, secondary infections, fungal pneumonia, mycosis, aspergillosis, aspergillus, IPA.
Methods of data analysis	A meta-analysis was performed for clinical characteristics and outcomes using Review manager (RevMan) software. Dichotomous outcomes were assessed using Mantel–Haenszel statistical method and measured in odds ratios (ORs) and their 95% confidence intervals (CIs). Continuous outcomes were evaluated by inverse variance method and measured in mean difference (MDs). Using DerSimonian and Laird's random-effects model, pooled ORs, MDs, and 95% CIs were calculated, and extracted outcomes were pooled by weighted averages.
Methods to investigate heterogeneity	The authors recognised that heterogeneity would be present, and so used a random effects model. Statistical heterogeneity among the studies was assessed by the I^2 statistic, where I^2 >50 was classified as high heterogeneity.
Risk of bias assessment	Risk of bias was assessed using the Newcastle-Ottawa Scale. Two researchers performed this assessment of the included studies and any disagreements were resolved by discussion.
Summary of findings	CAPA patients are likely to be older with underlying COPD. Long-term use of corticosteroids may predispose to CAPA and patients with CAPA have a more significant disease severity based on their SOFA scores, the onset of ICU admission and in-hospital mortality rates.
Source of funding	None
Study limitations (Author)	The author reported on the difficulties of diagnosing CAPA. As there is no agreed case definition, and there aren't any clear

	non-invasive diagnostic procedures it is difficult to identify CAPA in these patients. This limits the sample sizes in all studies, and may explain the lack of analysable data. The included studies report varying rates of CAPA, and the characteristics of people with CAPA vary, meaning that combining them in a meta-analysis has limitations. Lastly, the majority of patient recruitment for the included studies was conducted in the first wave of the COVID-19 pandemic and as such may not reflect actual risk factors and outcomes due to the changing management and treatment landscape for COVID-19.
Study limitations (Reviewer)	A major limitation includes the fact that this study only included cohort studies with over 30 participants, thus limiting the evidence base but potentially reducing bias by not including smaller studies. The review also included studies conducted in the first wave of the pandemic and as such may not represent current practice and associations/understanding of the disease. Lastly, as reported by the author, there was some heterogeneity between the included studies in terms of treatment regimens, clinical characteristics and outcomes and as such this may limit the ability to perform appropriate and accurate meta-analysis and pool results from all centres.
Other details	Study only included patients with confirmed/proven CAPA.

Study arms

CAPA (N = 109)

Non-CAPA (N = 620)

Characteristics

Characteristics	Study (N = 625)
Age Mean (SD)	62.92 (3.99)
Male No of events	n = 365/514; % = 71.00
COPD No of events	n = 39/514; % = 7.60
Diabetes	n = 121/506; % = 23.91

Characteristics	Study (N = 625)
No of events	
Cancer No of events	n = 15/332; % = 4.52
Long-term corticosteroids No of events	n = 19/250; % = 7.60
Long-term immunosuppressants No of events	n = 11/142; % = 7.75

Outcomes

Risk factors

Outcomes	Study (N = 625)
Age Mean (SD)	66.58 (4.55)
Male Odds ratio/95% CI	0.82 (0.43 to 1.55)
COPD Odds ratio/95% CI	2.75 (1 to 7.52)
Diabetes Odds ratio/95% CI	1.2 (0.71 to 2.01)
Cancer Odds ratio/95% CI	2.25 (0.68 to 5.07)
Long-term corticosteroids Odds ratio/95% CI	3.53 (1.16 to 10.69)
Long-term immunosuppressants Odds ratio/95% CI	1.97 (0.28 to 12.29)
Initial antibiotic treatment for COVID-19 Odds ratio/95% CI	0.88 (0.39 to 1.97)
Initial corticosteroid treatment for COVID-19	0.69 (0.19 to 2.58)

Outcomes	Study (N = 625)
Odds ratio/95% CI	
Tocilizumab treatment for COVID-19 Odds ratio/95% CI	1.85 (0.88 to 3.89)
Hydroxychloroquine treatment for COVID-19 Odds ratio/95% CI	0.43 (0.07 to 2.68)
SOFA score Mean difference/95% CI	2.57 (1.46 to 3.68)

Prattes, 2021

Bibliographic Reference	Prattes, Juergen; Wauters, Joost; Giacobbe, Daniele Roberto; Salmanton-Garcia, Jon; Maertens, Johan; Bourgeois, Marc; Reynders, Marijke; Rutsaert, Lynn; Van Regenmortel, Niels; Lormans, Piet; Feys, Simon; Reisinger, Alexander Christian; Cornely, Oliver A; Lahmer, Tobias; Valerio, Maricela; Delhaes, Laurence; Jabeen, Kauser; Steinmann, Joerg; Chamula, Mathilde; Bassetti, Matteo; Hatzl, Stefan; Rautemaa-Richardson, Riina; Koehler, Philipp; Lagrou, Katrien; Hoenigl, Martin; ECMM-CAPA Study, Group; Risk factors and outcome of pulmonary aspergillosis in critically ill coronavirus disease 2019 patients-a multinational observational study by the European Confederation of Medical Mycology.; Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases; 2021

Study details

Study design	Cohort study
Trial registration (if reported)	Not reported
Study start date	01-Mar-2020
Study end date	01-May-2021
COVID-19 prevalence at the time of the study	Unclear
Aim of the study	To determine the prevalence of CAPA in patients with COVID-19 in ICU and to investigate risk factors for CAPA as well as outcomes
Country/ Geographical location	Austria, Belgium, France, Germany, Italy, Pakistan, Spain, UK, USA
Study setting	Hospitalised patients with COVID-19 in ICU
Population description	Hospitalised adults with COVID-19, with varying demographics, clinical presentations and comorbidities
Inclusion criteria	1. Adults aged 18 years and above, with confirmed PCR SARS-CoV-2 infection 2. ICU admission for COVID-19 acute respiratory failure
Exclusion criteria	ICU admission due to other conditions beside COVID-19 acute respiratory failure
Intervention/test/approach	People diagnosed with CAPA (n=11 with proven CAPA; n=80 with probable CAPA, n=18 with possible CAPA)
Comparator (where applicable)	People not diagnosed with CAPA (n=483)
Methods for population selection/allocation	Retrospective observational study from ICU admission notes

Methods of data analysis	Fischer's exact test, Schemper and Smith/Kaplan-Meier estimators. Risk factors were investigated using Cox models to estimate the association of risk factors with survival.
Attrition/loss to follow-up	NA
Summary of findings	CAPA was more prevalent in older patients, who required invasive ventilation and patients who received tocilizumab as part of their treatment for COVID-19.
Source of funding	NIHR Manchester Biomedical Research Centre, German Federal Ministry of Research and Education and State of North Rhine-Westphalia.
Study limitations (Author)	No predefined CAPA screening, fungal diagnostics strategies or treatment protocols across study centres. Data entry between March 2020 and May 2021 was variable and inconsistent as there was no clear case definition for disease. Data on dosages and administration of treatments were varied and there is incomplete data reported for some patients.
Study limitations (Reviewer)	Wide inclusion/exclusion criteria make it difficult to pinpoint disease epidemiology. The study was conducted over a year and so data may not reflect current best practices or the current evolution of COVID-19 disease and associated infections.
Other details	18/109 patients in the CAPA group had possible CAPA

Study arms

CAPA (N = 109)

Non-CAPA (N = 483)

Characteristics

Study-level characteristics

Characteristic	Study (N = 592)
Age Range	55 to 73
Female No of events	n = 173; % = 29.2
Cardiovascular disease No of events	n = 329; % = 55.6

Characteristic	Study (N = 592)
Diabetes No of events	n = 160; % = 27.0
Active malignant disease No of events	n = 43; % = 7.3
Obesity (BMI >30 kg/m^2) No of events	n = 168/544; % = 30.9
Pulmonary disease No of events	n = 113; % = 19.1
Solid organ transplantation No of events	n = 14; % = 2.4
Smoking No of events	n = 66/587; % = 11.2

Outcomes

Risk factors

Outcomes	Study (N = 592)
Age Hazard ratio/95% CI	1.18 (1.08 to 1.28)
Gender Female Hazard ratio/95% CI	0.68 (0.42 to 1.09)
Number of coexisting conditions Hazard ratio/95% CI	0.92 (0.76 to 1.10)
Cardiovascular disease Hazard ratio/95% CI	1.2 (0.81 to 1.78)
Diabetes Hazard ratio/95% CI	1.12 (0.73 to 1.73)
Active malignant disease	1.56 (0.81 to 3)

Outcomes	Study (N = 592)
Hazard ratio/95% CI	
Obesity (BMI >30 kg) Hazard ratio/95% CI	0.89 (0.54 to 1.44)
Pulmonary disease Hazard ratio/95% CI	1.42 (0.89 to 2.24)
Solid organ transplantation Hazard ratio/95% CI	2.2 (0.9 to 5.42)
Smoking Hazard ratio/95% CI	1.36 (0.76 to 2.44)
ECMO Hazard ratio/95% CI	0.8 (0.37 to 1.7)
Invasive ventilation Hazard ratio/95% CI	2.53 (1.53 to 4.17)
Non-invasive ventilation Hazard ratio/95% CI	0.08 (0.02 to 0.33)
Any invasive ventilation Hazard ratio/95% CI	2.93 (1.6 to 5.35)
Treatment with Glucocorticoids Hazard ratio/95% CI	1.01 (0.68 to 1.5)
Treatment with Tocilizumab Hazard ratio/95% CI	2.34 (1.35 to 4.06)
Treatment with Azithromycin Hazard ratio/95% CI	0.63 (0.33 to 1.21)

Segrelles-Calvo, 2021

Bibliographic Reference	Segrelles-Calvo, Gonzalo; Araújo, Glauber R S; Llopis-Pastor, Estefanía; Carrillo, Javier; Hernández-Hernández, Marta; Rey, Laura; Rodríguez Melean, Nestor; Escribano, Inés; Antón, Esther; Zamarro, Celia; García-Salmones, Mercedes; Frases, Susana; Prevalence of opportunistic invasive aspergillosis in COVID-19 patients with severe pneumonia.; Mycoses; 2021; vol. 64 (no. 2); 144-151

Study details

Trial registration (if reported)	Not reported
Study start date	Feb-2020
Study end date	Apr-2020
Aim of the study	Not reported
Country/ Geographical location	Madrid, Spain
Study setting	ICU in Rey Juan Carlos University Hospital
Population description	People with a confirmed diagnosis of severe pneumonia caused by SARS-CoV-2 (confirmed by PCR). Participants were also diagnosed with invasive fungal infections using bronchoalveolar lavage (BAL) sample using an Aspergillus EIA assay.
Inclusion criteria	Patients admitted to the respiratory ICU, with a positive PCR test for COVID-19 and diagnosed with invasive fungal infection (the detection of the Aspergillus galactomannan antigen was carried out in the BAL sample by using the Platelia™ Aspergillus EIA assay).
Exclusion criteria	Not reported.
Intervention/test/approach	No intervention
Comparator (where applicable)	No comparator
Methods for population selection/allocation	Allocation: NA Population selection: people admitted to ICU
Methods of data analysis	Descriptive
Attrition/loss to follow-up	NA
Summary of findings	Symptoms are similar to symptoms of COVID-19.
Source of funding	Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro; Conselho Nacional de Desenvolvimento Científico e Tecnológico
Study limitations (Author)	Symptoms experienced by the participants could not differentiate between COVID-19 and invasive pulmonary aspergillosis.

Study limitations (Reviewer)	The sample size is very small, so results could be due to chance alone. There is no comparison group of people with COVID-19 and without CAPA to compare symptoms between. Symptoms experienced by the participants are described by study as COVID-19 symptoms, reflecting the uncertainty about whether the symptoms are related to COVID-19 or to CAPA. Symptoms are not reported in detail.

Study arms

CAPA (N = 7)

People diagnosed with infection by Aspergillus spp. isolated from respiratory samples (mainly bronchoalveolar lavage).

Characteristics

Study-level characteristics

Characteristic	Study (N = 7)
Age Range	42 to 75
Female No of events	n = 2; % = 29
Male No of events	n = 5; % = 71
Ethnicity Custom value	Not reported
Orotracheal intubation (number) No of events	n = 6; % = 86

Outcomes

Symptoms

Outcome	CAPA (N = 7)
Fever No of events	n = 7; % = 100
Dyspnoea No of events	n = 6; % = 86
Cough No of events	n = 6; % = 86
Sputum No of events	n = 1; % = 14
Malaise No of events	n = 3; % = 43
Diarrhoea No of events	n = 1; % = 14
Headache No of events	n = 1; % = 14

Appendix E: Risk of bias

Chong, 2021

Bibliographic Reference	Chong, Woon Hean; Saha, Biplab K; Neu, Kristoffer P; Comparing the clinical characteristics and outcomes of COVID-19-associate pulmonary aspergillosis (CAPA): a systematic review and meta-analysis.; Infection; 2021

Critical appraisal - GUT ROBIS checklist

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
Study eligibility criteria	Were the eligibility criteria appropriate for the review question?	Yes
Study eligibility criteria	Were eligibility criteria unambiguous?	Yes
Study eligibility criteria	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
Study eligibility criteria	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Yes
Identification and selection of studies	Were methods additional to database searching used to identify relevant reports?	No information
Identification and selection of studies	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably yes
Identification and selection of studies	Were restrictions based on date, publication format, or language appropriate?	Yes
Identification and selection of studies	Were efforts made to minimise error in selection of studies?	Yes
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Were efforts made to minimise error in data collection?	Yes
Data collection and study appraisal	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Probably yes

Section	Question	Answer
Data collection and study appraisal	Were all relevant study results collected for use in the synthesis?	No
Data collection and study appraisal	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably yes
Data collection and study appraisal	Were efforts made to minimise error in risk of bias assessment?	Probably yes
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Did the synthesis include all studies that it should?	Yes
Synthesis and findings	Were all pre-defined analyses reported or departures explained?	No information
Synthesis and findings	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes
Synthesis and findings	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Yes
Synthesis and findings	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably yes
Synthesis and findings	Were biases in primary studies minimal or addressed in the synthesis?	Probably yes
Synthesis and findings	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Moderate
Overall study ratings	Applicability as a source of data	Partially applicable

Prattes, 2021

Bibliographic Reference	Prattes, Juergen; Wauters, Joost; Giacobbe, Daniele Roberto; Salmanton-Garcia, Jon; Maertens, Johan; Bourgeois, Marc; Reynders, Marijke; Rutsaert, Lynn; Van Regenmortel, Niels; Lormans, Piet; Feys, Simon; Reisinger, Alexander Christian; Cornely, Oliver A; Lahmer, Tobias; Valerio, Maricela; Delhaes, Laurence; Jabeen, Kauser; Steinmann, Joerg; Chamula, Mathilde; Bassetti, Matteo; Hatzl, Stefan; Rautemaa-Richardson, Riina; Koehler, Philipp; Lagrou, Katrien; Hoenigl, Martin; ECMM-CAPA Study, Group; Risk factors and outcome of pulmonary aspergillosis in critically ill coronavirus disease 2019 patients-a multinational observational study by the European Confederation of Medical Mycology.; Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases; 2021

Critical appraisal - ROBINS-I Checklist

Age

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	No
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information

Section	Question	Answer
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

Gender - Female

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	No
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No

Section	Question	Answer
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No

Section	Question	Answer
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes

Section	Question	Answer
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

Number of co-existing conditions

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	No
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information

Section	Question	Answer
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate

Section	Question	Answer
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

Obesity

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	No
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate

Section	Question	Answer
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes

Section	Question	Answer
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

Active malignant disease

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	No
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable

Section	Question	Answer
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information

Section	Question	Answer
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

Solid organ transplantation

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	No

Section	Question	Answer
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes

Section	Question	Answer
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No

Section	Question	Answer
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

Cardiovascular disease

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	No
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable

Section	Question	Answer
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes

Section	Question	Answer
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

Pulmonary disease

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	No
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes

Section	Question	Answer
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

Diabetes

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	No
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable

Section	Question	Answer
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes

Section	Question	Answer
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

History of smoking

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	No
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information

Section	Question	Answer
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

Non-invasive ventilation

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	No
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No

Section	Question	Answer
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No

Section	Question	Answer
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes

Section	Question	Answer
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

ECMO

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	No
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information

Section	Question	Answer
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate

Section	Question	Answer
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

Invasive ventilation

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	No
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate

Section	Question	Answer
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes

Section	Question	Answer
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

Any invasive respiratory support

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	No
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable

Section	Question	Answer
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes

Section	Question	Answer
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	No
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate

Section	Question	Answer
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Low

Section	Question	Answer
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

COVID-19 treatment with tocilizumab

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Probably yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information

Section	Question	Answer
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Probably yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Yes
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes

Section	Question	Answer
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

COVID-19 treatment with azithromycin

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Probably yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information

Section	Question	Answer
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate

Section	Question	Answer
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Partially Applicable

Segrelles-Calvo, 2021

Bibliographic Reference	Segrelles-Calvo, Gonzalo; Araújo, Glauber R S; Llopis-Pastor, Estefanía; Carrillo, Javier; Hernández-Hernández, Marta; Rey, Laura; Rodríguez Melean, Nestor; Escribano, Inés; Antón, Esther; Zamarro, Celia; García-Salmones, Mercedes; Frases, Susana; Prevalence of opportunistic invasive aspergillosis in COVID-19 patients with severe pneumonia.; Mycoses; 2021; vol. 64 (no. 2); 144-151

Critical appraisal - RoB (JBI checklist)

Outcome: All CAPA symptoms

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Yes *(Exposure to CAPA (i.e. diagnosis with CAPA) measured using BAL)*
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Not applicable *(No comparator group)*
Assessment questions	Were strategies to deal with confounding factors stated?	Not applicable *(No comparison group)*
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear *(No detail given about how the outcomes (symptoms of CAPA) were measured.)*
Assessment questions	Was appropriate statistical analysis used?	No *(Descriptive only, not possible to attribute the symptoms to CAPA)*
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

Appendix F: Forest Plots

No forest plots have been produced for this review.

Appendix G: GRADE profiles

Risk factors for people hospitalised with confirmed COVID-19 and CAPA

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With People without CAPA	With People with CAPA		Risk with People without CAPA	Risk difference with People with CAPA
Risk factor - Age											
592 (1 observational study)	serious[a]	not serious	serious[b]	not serious	none	Very low	NR	NR	**HR 1.18** (1.08 to 1.29)		
Risk factor - Gender (Female)											
592 (1 observational study)	serious[a]	not serious	serious[b]	serious[c]	none	Very low	23/109 (21.1%)	23/483 (4.8%)	**HR 0.68** (0.42 to 1.10)	211 per 1,000	**62 fewer per 1,000** (from 116 fewer to 18 more)
Risk factor - Sex (Male)											
514 (7 observational studies)	serious[a]	serious[d]	not serious	serious[c]	none	Very low	291/412 (70.6%)	74/102 (72.5%)	**OR 0.82** (0.43 to 1.56)	706 per 1,000	**43 fewer per 1,000** (from 198 fewer to 83 more)
Risk factor - Number of coexisting conditions											

Certainty assessment							Summary of findings				
592 (1 observational study)	serious[a]	not serious	serious[b]	serious[c]	none	Very low			**HR 0.92** (0.76 to 1.10)	0 per 1,000	**1 fewer per 1,000** (from 1 fewer to 1 fewer)
Risk factor - History of smoking											
587 (1 observational study)	serious[a]	not serious	serious[b]	serious[c]	none	Very low	52/482 (10.8%)	14/105 (13.3%)	**HR 1.36** (0.76 to 2.43)	108 per 1,000	**36 more per 1,000** (from 25 fewer to 134 more)
Risk factor - Obesity											
544 (1 observational study)	serious[a]	not serious	serious[b]	serious[c]	none	Very low	24/85 (28.2%)	144/459 (31.4%)	**HR 0.89** (0.54 to 1.47)	282 per 1,000	**27 fewer per 1,000** (from 118 fewer to 104 more)
Risk factor - Diabetes											
506 (7 observational studies)	serious[a]	serious[d]	not serious	serious[c]	none	Very low	94/404 (23.3%)	27/102 (26.5%)	**OR 1.20** (0.71 to 2.03)	233 per 1,000	**34 more per 1,000** (from 56 fewer to 148 more)
Risk factor - Diabetes											
592 (1 observational study)	serious[a]	not serious	serious[b]	serious[c]	none	Very low	128/483 (26.5%)	32/109 (29.4%)	**HR 1.12** (0.73 to 1.72)	265 per 1,000	**27 more per 1,000** (from 64 fewer to 146 more)
Risk factor - Cancer											

Certainty assessment							Summary of findings				
332 (4 observational studies)	serious[a]	serious[d]	not serious	serious[c]	none	Very low	10/271 (3.7%)	5/61 (8.2%)	**OR 2.25** (0.68 to 7.44)	37 per 1,000	**42 more per 1,000** (from 12 fewer to 185 more)

Risk factor - Active malignant disease

592 (1 observational study)	serious[a]	not serious	serious[b]	serious[c]	none	Very low	32/483 (6.6%)	11/109 (10.1%)	**HR 1.56** (0.81 to 3.00)	66 per 1,000	**35 more per 1,000** (from 12 fewer to 120 more)

Risk factor - COPD

514 (7 observational studies)	serious[a]	serious[d]	not serious	not serious	none	Very low	25/412 (6.1%)	14/102 (13.7%)	**OR 2.75** (1.00 to 7.56)	61 per 1,000	**90 more per 1,000** (from 0 fewer to 267 more)

Risk factor - Cardiovascular disease

592 (1 observational study)	serious[a]	not serious	serious[b]	serious[c]	none	Very low	63/483 (13.0%)	68/109 (62.4%)	**HR 1.20** (0.81 to 1.78)	130 per 1,000	**24 more per 1,000** (from 23 fewer to 90 more)

Risk factor - Pulmonary disease

592 (1 observational study)	serious[a]	not serious	serious[b]	serious[c]	none	Very low	26/109 (23.9%)	87/483 (18.0%)	**HR 1.42** (0.89 to 2.27)	239 per 1,000	**82 more per 1,000** (from 23 fewer to 223 more)

Risk factor - Solid organ transplant

Certainty assessment							Summary of findings				
592 (1 observational study)	serious[a]	not serious	serious[b]	not serious	none	Very low	9/483 (1.9%)	23/109 (21.1%)	**HR 2.20** (0.90 to 5.38)	19 per 1,000	**22 more per 1,000** (from 2 fewer to 78 more)

Risk factor - Long term corticosteroid

250 (3 observational studies)	serious[a]	serious[d]	not serious	not serious	none	Very low	10/190 (5.3%)	9/60 (15.0%)	**OR 3.53** (1.16 to 10.74)	53 per 1,000	**111 more per 1,000** (from 8 more to 321 more)

Risk factor - Long term immunosuppressants

142 (2 observational studies)	serious[a]	serious[d]	serious[e]	serious[c]	none	Very low	8/112 (7.1%)	3/30 (10.0%)	**OR 1.87** (0.28 to 12.49)	71 per 1,000	**54 more per 1,000** (from 50 fewer to 419 more)

Risk factors - Non-invasive ventilation

584 (1 observational study)	serious[a]	not serious	serious[b]	not serious	none	Very low	204/481 (42.4%)	14/103 (13.6%)	**HR 0.08** (0.02 to 0.32)	424 per 1,000	**381 fewer per 1,000** (from 413 fewer to 262 fewer)

Risk factor - Extracorporeal Membrane Oxygenation (ECMO)

587 (1 observational study)	serious[a]	not serious	serious[b]	not serious	none	Very low	41/481 (8.5%)	8/106 (7.5%)	**HR 0.80** (0.37 to 1.73)	85 per 1,000	**16 fewer per 1,000** (from 53 fewer to 58 more)

Risk factors - Invasive mechanical ventilation

Certainty assessment							Summary of findings				
591 (1 observational study)	serious[a]	not serious	serious[b]	not serious	none	Very low	322/482 (66.8%)	96/109 (88.1%)	**HR 2.53** (1.53 to 4.18)	668 per 1,000	**271 more per 1,000** (from 147 more to 322 more)

Risk factor - Any invasive respiratory support

587 (1 observational study)	serious[a]	not serious	serious[b]	not serious	none	Very low	326/481 (67.8%)	93/106 (87.7%)	**HR 2.93** (1.60 to 5.37)	678 per 1,000	**286 more per 1,000** (from 159 more to 320 more)

Risk factor - COVID-19 treatment with Tocilizumab

514 (4 observational studies)	serious[a]	serious[d]	not serious	serious[c]	none	Very low	171/440 (38.9%)	41/74 (55.4%)	**OR 1.85** (0.88 to 3.89)	389 per 1,000	**152 more per 1,000** (from 30 fewer to 323 more)

Risk factor - COVID-19 treatment with Tocilizumab

581 (1 observational study)	serious[a]	not serious	serious[b]	not serious	none	Very low	24/477 (5.0%)	15/104 (14.4%)	**HR 2.34** (1.35 to 4.06)	50 per 1,000	**63 more per 1,000** (from 17 more to 139 more)

Risk factor - COVID-19 treatment with corticosteroid

510 (4 observational studies)	serious[a]	serious[d]	serious[e]	serious[c]	none	Very low	300/449 (66.8%)	30/61 (49.2%)	**OR 0.69** (0.19 to 2.51)	668 per 1,000	**87 fewer per 1,000** (from 391 fewer to 167 more)

Risk factor - COVID-19 treatment with glucocorticoids

Certainty assessment							Summary of findings				
592 (1 observational study)	serious[a]	not serious	not serious	serious[c]	none	Very low	-/483	-/109	**HR 1.01** (0.68 to 1.50)	0 per 1,000	**-- per 1,000** (from -- to --)

Risk factor - COVID19 treatment with antibiotic

542 (5 observational studies)	serious[a]	serious[d]	serious[e]	serious[c]	none	Very low	391/479 (81.6%)	52/63 (82.5%)	**OR 0.88** (0.39 to 1.99)	816 per 1,000	**20 fewer per 1,000** (from 182 fewer to 82 more)

Risk factor - COVID19 treatment with Hydroxychloroquine

514 (4 observational studies)	serious[a]	serious[d]	not serious	serious[c]	none	Very low	359/440 (81.6%)	52/74 (70.3%)	**OR 0.43** (0.07 to 2.64)	816 per 1,000	**160 fewer per 1,000** (from 579 fewer to 105 more)

Risk factor - COVID19 treatment with azithromycin

358 (1 observational study)	serious[a]	not serious	not serious	serious[c]	none	Very low	75/296 (25.3%)	11/62 (17.7%)	**HR 0.63** (0.33 to 1.20)	253 per 1,000	**85 fewer per 1,000** (from 161 fewer to 42 more)

Risk factor - Age

729 (8 observational studies)	serious[a]	serious[d]	not serious	not serious	none	Very low	NR	NR	-		MD **7.52 SD higher** (2.02 higher to 13.02 higher)

Risk factor - BMI >27 kg/m2

Certainty assessment							Summary of findings				
729 (4 observational studies)	serious[a]	serious[d]	not serious	serious[c]	none	Very low	NR	NR	-		MD **0.46 SD lower** (1.93 lower to 1.01 higher)

Sequential Organ Failure Assessment (SOFA) Score

NR (3 observational studies)	serious[a]	serious[d]	not serious	not serious	none	Very low	NR	NR	-		MD **2.57 higher** (1.46 higher to 3.68 higher)

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **OR:** odds ratio

Explanations

a. Unclear how variables were controlled throughout the study
b. Study analysed patients with possible CAPA with those with proven and probable CAPA
c. CI crosses line of no effect
d. Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA.
e. Differences amongst the populations included within the study

Signs and symptoms of people hospitalised with COVID-19 and with CAPA

Certainty assessment							Summary of findings	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)	Impact
							With [comparison] / With [intervention]	
Symptom: Fever (During ICU admission)								
7 (1 observational study)	serious[a]	not serious	not serious	very serious[b]	none	Very low	7/7 (100%) of participants with CAPA had fever. No comparator group.	
Symptom: Diarrhoea (During ICU admission)								
7 (1 observational study)	serious[a]	not serious	not serious	very serious[b]	none	Very low	1/7 (14%) of participants with CAPA had diarrhoea. No comparator group.	
Symptom: Headache (During ICU admission)								
7 (1 observational study)	serious[a]	not serious	not serious	very serious[b]	none	Very low	1/7 (14%) of participants with CAPA had headache. No comparator group.	
Symptom: Dyspnoea (During ICU admission)								
7 (1 observational study)	serious[a]	not serious	not serious	very serious[b]	none	Very low	6/7 (86%) of participants with CAPA had dyspnoea. No comparator group.	
Symptom: Cough (During ICU admission)								
7 (1 observational study)	serious[a]	not serious	not serious	very serious[b]	none	Very low	6/7 (86%) of participants with CAPA had cough. No comparator group.	

Certainty assessment							Summary of findings
Symptom: Malaise (During ICU admission)							
7 (1 observational study)	serious[a]	not serious	not serious	very serious[b]	none	Very low	3/7 (43%) of participants with CAPA had malaise. No comparator group.
Symptom: Sputum (During ICU admission)							
7 (1 observational study)	serious[a]	not serious	not serious	very serious[b]	none	Very low	1/7 (14%) of participants with CAPA had sputum. No comparator group.

CI: confidence interval

Explanations

a. The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19.
b. No CIs could be reported

Appendix H: Recommendations for research

Question	**What are the possible outcomes for people who are critically ill and have COVID-19-associated pulmonary aspergillosis (CAPA)?**
Population	Adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness, and who have CAPA. Subgroups of particular interest: young people and children, pregnant women, ethnicity, immunosuppression and subgroups who have higher rates of COVID-19
Outcomes	• presence of fungal serum biomarkers (for example galactomannan and beta-D-glucan) • measures of inflammation (for example C-reactive protein) • need for respiratory support (for example, invasive mechanical ventilation or extracorporeal membrane oxygenation [ECMO]) • hospitalisation metrics (for example, mortality, length of hospital stay, admission to and length of stay in intensive care) • long-term morbidity outcomes, functional measures and patient outcomes • results may be stratified (for example, disease severity, use of ECMO)

Question	**What risk factors in people who are critically ill and have, or have had, COVID-19 as part of their acute illness are associated with developing COVID-19-associated pulmonary aspergillosis (CAPA)?**

Evidence review: Risk factors and signs and symptoms for COVID-19 associated pulmonary aspergillosis

Population	Adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness. Subgroups of particular interest include children and young people, and pregnant women.
Exposure	Any
Outcomes	• association of CAPA with individual factors (for example, age, sex, ethnicity, comorbidities, COVID-19 vaccination status,) • association of CAPA with COVID-19 treatments (for example, respiratory support for COVID-19, high-dose corticosteroids, interleukin-6 inhibition) • association of CAPA with length of stay in hospital