NICE advice

SYNE-COV for predicting COVID-19 outcomes

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is SYNE-COV. It is a cloud-based software designed to help manage COVID-19 in hospitals. It does this by predicting the chance of people with COVID-19 being admitted for intensive care, having mechanical ventilation, or dying while in hospital.
- The **innovative aspect** is that it is a prediction tool using machine-learning algorithms that analyse data from electronic health records to help clinicians' decision making in real time.
- The intended **place in therapy** would be alongside existing early warning scores in hospitals for monitoring deterioration in people with COVID-19.

- The **main points from the evidence** summarised in this briefing are from 1 published study and 1 unpublished study. The published study retrospectively analysed data from a cohort of people with COVID-19 who were admitted to an NHS hospital trust (n=879). Machine-learning algorithms were used to predict the chance of 3 clinical outcomes. Results suggest that the best model using one of 3 algorithms showing area under the receiver operating characteristic scores were 0.76 for hospital mortality, 0.84 for intensive care admission and 0.87 for having mechanical ventilation. The unpublished validation study assessed the performance of the SYNE-COV algorithm and reported the accuracy of risk prediction compared with existing clinical risk scores as a reference standard.
- The **key uncertainty** around the evidence is that it is from only 1 peer reviewed study, which included anonymised patient data from 1 NHS hospital trust during a 5-month period. Further large studies at multiple sites would be useful to validate the machine-learning algorithms, and to provide further evidence for predicting key clinical outcomes when managing COVID-19. The experts considered there to be uncertainty around the potential benefits to clinical practice.
- The **cost** of SYNE-COV used in addition to standard care ranges from £18,000 to £30,000 per year, depending on the number of beds and patients in each NHS trust.

The technology

SYNE-COV (Sensyne Health) is a cloud-based software. It uses a machine-learning algorithm to analyse clinical data in electronic health records to estimate the chance of health deteriorating in a person with COVID-19. This is measured by 3 clinical outcomes:

- having invasive mechanical ventilation
- being admitted for intensive care
- the risk of people with COVID-19 dying in hospital.

SYNE-COV uses clinical data including demographics, vital signs, blood biochemistry and respiratory physiology to provide a real-time risk estimation. This helps clinician manging patients' symptoms and to help make clinical decisions about treatment. Each risk estimation ranges from 0% to 100%. The lower the score the less likelihood an outcome occurs.

The company states that the algorithm is a supporting tool and its risk prediction should be used along with other relevant patient data for clinical decision making.

Innovations

SYNE-COV is developed as a clinical algorithm for predicting clinical outcomes in people with COVID-19 who are admitted to hospital.

In the UK, there have been methods developed for predicting COVID-19 related outcomes such as the OpenSAFELY platform (Williamson et al. 2021). Soltan et al. (2021) used linear and non-linear machine-learning classifiers to predict hospital admission in people presenting to hospital, comparing prediction between people with and without COVID-19. The company notes that there is no commercial, UK Conformity Assessed marked technology similar to SYNE-COV.

Current care pathway

NICE has published a guideline on managing COVID-19. There is no recommendation on predicting the risk of condition progression for people admitted to hospitals. The guideline recommends ensuring healthcare professionals have access to resources to support discussions about treatment plans. Hospitals should review management for people who are deteriorating, and use the track-and-trigger system (National Early Warning Score 2 [NEWS2]) for managing COVID-19 in hospitals. The recommendation is in line with the guidance by the Royal College of Physicians (RCP), which emphasises using NEWS2 in managing COVID-19. The RCP guidance states that using NEWS2 will ensure that people who are deteriorating, or at risk of deteriorating, have a timely initial assessment by a competent clinical decision maker. NEWS2 should supplement clinical judgement in assessing the patient's condition.

The NICE guideline on acutely ill adults in hospital: recognising and responding to deterioration gives best practice advice on the care of adult patients admitted to hospital. It recommends that adult patients in acute hospital settings should have physiological observations recorded at the time of their admission or initial assessment. After the admission, these measurements for physiological signs should be regularly monitored regularly with predetermined response criteria to changes to identify patients whose physiological status is deteriorating or is at risk of deterioration. NICE recommends using a tool (NEWS) based on an aggregate score made up of the measures of respiratory rate,

oxygen saturations, blood pressure, pulse rate, levels of consciousness and temperature to improve the detection and response to patients' physiological deterioration.

The following publications have been identified as relevant to this care pathway:

- NICE's COVID-19 rapid guideline on managing COVID-19
- NICE's guideline on acutely ill adults in hospital: recognising and responding to deterioration
- Royal College of Physicians guideline on National Early Warning Score (NEWS) 2.

Population, setting and intended user

SYNE-COV is intended to help clinical management for people aged between 18 and 100 years with COVID-19 being assessed in hospitals.

The company states that SYNE-COV should be used by senior clinicians, for instance healthcare professionals who are at consultant level in acute or secondary care settings.

Costs

Technology costs

The cost of SYNE-COV ranges from £18,000 to £30,000 per year depending on the number of beds and patients in each NHS trust.

Costs of standard care

National track-and-trigger systems can be automated or paper based. Paper-based early warning score (EWS) charts are available for free to download from the Royal College of Physicians website.

A study reported that, on average, it took 3 minutes 35 seconds nursing time to do manual vital signs observations and EWS calculations (Wong et al. 2017). Current hourly pay of a band 5 nurse ranges from £12.74 to £15.66 depending on the length of service. Wong et al. (2017) also reported that the using automated EWS systems reduced nursing time to

2 minutes 30 seconds. The cost of the automated system ranges from £30,000 to £90,000 for system installation, configuration and set up, and costs a further £0.35 to £0.70 per acute bed, every day.

Resource consequences

The technology was developed in collaboration with 1 NHS hospital trust, and has not yet been widely used in the NHS.

SYNE-COV is intended to be used as a supporting tool along with current EWS for monitoring deterioration in COVID-19. As an add-on intervention, the resource impact of using SYNE-COV would result in additional costs to standard care. However, it has the potential to be resource releasing if using the results to improve COVID-19 management that could reduce hospital stay and mortality. There is currently no evidence to support these claims.

No changes to facilities or infrastructure are needed to adopt the technology because SYNE-COV is compatible with existing NHS IT infrastructure. It can be integrated into existing hospital systems and dashboards with no need for a separate application to view the risk prediction. The company provides training on how to use and interpret the results given by the predictor, and the training cost is included in the cost of the technology.

Regulatory information

SYNE-COV has obtained UK Conformity Assessed (UKCA) marking.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

People over 65, men and people from black, Asian, and ethnic minority groups are disproportionally affected by COVID-19 (Office for National Statistics, 2020). Age, sex and race are protected characteristics under the Equality Act (2010).

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement for medtech innovation briefings. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

A search identified a total of 415 references. Of these, 19 references were reviewed in detail and 1 study (Heldt et al. 2021) is included in this briefing.

The company noted additional 2 studies: Abu-Jamous et al. (2020) examined the associations of comorbidities and medications with COVID-19 presentation and hospital mortality in people with confirmed COVID-19. Fletcher et al. (2020) explored any risk factors associated with progression to severe disease in people with COVID-19. Both studies analysed data from electronic health records using regression models and included people who were admitted to hospitals between January and May 2020. The study cohorts overlapped with that in Heldt et al. (2021). Therefore, Heldt et al. (2021) is summarised in this briefing.

The company also provided an unpublished clinical validation study which assessed the performance of the SYNE-COV algorithm.

The clinical evidence and its strengths and limitations is summarised in the overall assessment of the evidence.

Overall assessment of the evidence

Overall, the quantity of evidence for SYNE-COV is limited. The published study was a retrospective study analysing a cohort of people with COVID-19 who were admitted to the emergency department of 1 NHS hospital trust during a 5-month period. The prediction models in both studies used limited data that was collected over a few hours after people were admitted to the emergency department. Further studies at multiple sites are needed to validate the machine-learning algorithms, and to provide evidence for predicting key clinical outcomes when managing COVID-19.

Heldt et al. (2021)

Study size, design and location

A retrospective study analysed a cohort of 879 people with a confirmed COVID-19 using viral polymerase chain reaction swab tests. Anonymised patient data was obtained from the Chelsea and Westminster Hospital NHS foundation trust between 1 January and 26 May 2020.

Intervention and comparator

Three machine-learning algorithms were benchmarked to predict patient outcomes from electronic health records:

- logistic regression, predicting the probability of a clinical end point as a linear function of the feature space, was used as a baseline algorithm
- random forest
- extreme gradient boosted trees (XGBoost).

No comparator.

Predictive accuracy was measured in terms of area under curve (AUC) of the receiver operating characteristic (ROC) and precision-recall curves are provided to assess expected real-world performance relative to random classifiers. F1 scores were calculated to measure of the accuracy of an algorithm based on 2 factors: precision and recall. The higher the F1 score, the better the accuracy.

Key outcomes

Of 1,235 people in the analysis, 630 people had data available from their hospital admissions to discharges. This included 629 people (99.8%) admitted to the hospital through the emergency department and 1 person (0.2%) who was admitted directly to the intensive care unit. Considering the study inclusion criteria, a total of 129 out of 879 people (15%) were admitted for intensive care, 62 of 878 people (7%) had mechanical ventilation, and 193 of 619 people (31%) died in hospital.

Intensive care unit admission: the XGBoost machine-learning algorithm reached an

AUC-ROC of 0.84 and an F1 score of 0.52. This was followed by prediction using the random forest algorithm (AUC-ROC=0.83; F1 score=0.49) and the logic regression algorithm (AUC-ROC=0.72, F1 score=0.40). Patient age and measures of oxygenation status were strong indicators for intensive care unit admission, with advanced age decreasing the probability of intensive care admission.

Having mechanical ventilation: both random forest and XGBoost algorithms reached AUC-ROC of 0.87. F1 scores were 0.42 and 0.31 for XGBoost and random forest algorithm, respectively. The logistic regression reached an AUC-ROC of 0.74 and an F1 score of 0.23. Patient age and oxygenation status were most predictive of having mechanical ventilation, with additional contributions from blood test values, such as lactate and deoxyhaemoglobin levels.

Hospital mortality: the random forest machine-learning algorithm reached an AUC-ROC of 0.76 and an F1 score of 0.61. This was followed by prediction by the XGBoot algorithm (AUC-ROC=0.76; F1 score=0.60) and the logic regression algorithm (AUC-ROC=0.70, F1 score=0.56). Age was an important predictor, with older age contributing to increased risk of hospital mortality.

Strengths and limitations

The study analysed data set from 2 hospitals from 1 NHS hospital trust. The cohort included people who were admitted to hospitals in a 5-month period. The authors noted that data used for risk predications was limited to the first few hours of a person in the emergency department, and some information such as medical history or primary care were not included for predicting patient outcomes. Several study authors are employees of the company (Sensyne Health).

Clinical validation study (unpublished)

Study size, design and location

A clinical validation study evaluating performance of SYNE-COV based on a total of 2,315 people with COVID-19 admitted to 2 hospitals in 1 NHS hospital trust between 1 January and 25 December 2020. The validation study assessed included study population, demographics of the study population and performance of the SYNE-COV algorithm.

Intervention and comparator

SYNE-COV, a machine-learning algorithm uses electronic medical records of patients who have tested positive for COVID-19. This is to predict each individual's risk of 3 clinical outcomes:

- admission to an adult intensive care unit
- having invasive mechanical ventilation
- dying while in hospital.

No comparator.

Key outcomes

Study population

Over 10,000 people were admitted to 2 hospitals in 1 NHS hospital trust during the study period. People were included in the study cohort if they met all the inclusion criteria and did not met a single exclusion criterion. Of people included, 3 cohorts were constructed by clinical outcomes: need for intensive care admission and invasive mechanical ventilation, and in-hospital mortality. Each dataset of the cohorts was tested against data quality criteria such as the sample size and the completeness of clinical data for individuals. A total of 2,315 people met the criteria and were included in the study.

Demographics of study population

Of 2,315 people with confirmed COVID-19 in the study, a statistical analysis was done to examine demographic characteristics of people admitted to the 2 hospitals. The analysis found that age, sex and ethnicity of people differed by hospitals. Age and ethnicity also varied significantly by each calendar month in 2020. Such variability in the study population suggested the population could be generalisable to people with COVID-19 admitted to NHS hospitals.

SYNE-COV algorithm

The SYNE-COV algorithm was used to generate a risk prediction for each of the 3 clinical outcomes for each patient. The performance of risk predictions is evaluated using metrics including AUC-ROC. This shows the probability that the model assigns a higher risk to a

randomly chosen positive outcome than to a randomly chosen negative outcome. The higher the AUC, the better the model is at predicting a risk of needing intensive care admission, ventilation or hospital mortality.

Predictions by SYNE-COV are compared with those made by standard clinical risk scores including the National Early Warning Score 2 (NEWS2), Sequential Organ Failure Assessment (SOFA) score and the Acute Physiology as well as Chronic Health Evaluation II (APACHEII) score. Based on data collected during a patient's attendance at the emergency department, the accuracy of predictions were:

- Intensive care unit admission: SYNE-COV reached AUC-ROC values of 0.88 and 0.78 in 2 hospitals, respectively. It had sensitivity of 84% and 70% respectively in 2 hospitals, and specificity of 78% and 75%.
- Having mechanical ventilation: SYNE-COV reached AUC-ROC values of 0.91 and 0.68 in 2 hospitals, respectively. It had sensitivity of 74% and 47% respectively in 2 hospitals, and specificity of 94% and 84%.
- Hospital mortality: SYNE-COV reached AUC-ROC values of 0.85 and 0.77 in 2 hospitals, respectively. It had sensitivity of 75% and 88% respectively in 2 hospitals, and specificity of 79% and 51%.

Strengths and limitations

This is an unpublished validation report that has not been peer reviewed. It was based on real-world data obtained from 2 hospitals in 1 NHS hospital trust during a 1-year period. The performance of algorithms was compared with other clinical risk scores including NEWS2.

Sustainability

This is a digital health technology.

Recent and ongoing studies

One expert noted that there were some preliminary discussions about setting up a prospective clinical study after adoption. The company confirmed the prospective study and also an ongoing study that would extend the retrospective validation to 2 additional

NHS Trusts.

Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

All 4 experts were familiar with machine-learning algorithms for prediction or the principles of the use of clinical prediction tools in acutely unwell patients.

Level of innovation

All 4 experts thought that SYNE-COV is novel. The innovative aspects of the technology were using data collected across time points to predict potential risks, short calculation time, and using artificial intelligence for a real-time risk estimate. One expert added that using machine learning to refine the prediction model was innovative.

Potential patient impact

The potential benefits identified by 4 experts included improved prediction of COVID-19 outcomes and earlier interventions that may lead to improved patient care. One expert thought collating provision of information about patients' prognosis in their hospital stay would help shared decision making for treatment at an early stage. One expert noted that the clinical algorithm has been used in the research setting as a part of the regulatory process and has not yet been used in clinical practice. Therefore, there is uncertainty around its potential benefits to clinical practice. The company noted that the technology has been deployed in the NHS and is starting to be used in live prediction at Chelsea and Westminster hospital. Another expert said that the technology was developed based on a limited patient data set from early in the pandemic. This means it is unclear how the model would perform its prediction as the pandemic evolves (that is, the emergent variants of SARS-CoV-2).

Potential system impact

The main system benefits identified by experts were improving the management of

COVID-19. This could be resource releasing by shortening people's hospital stays and reducing the need for expensive care when patients are admitted to the intensive care unit. Two experts thought that earlier identification of people at risk of deterioration and needing mechanical ventilation could potentially allow an earlier transfer to a critical-care setting or avoid escalating their care in hospitals. There might be a significant cost saving. Two experts thought it was too early to say what the system benefits would be because of lack of evidence. The experts said that the software was designed specifically for COVID-19, and it could change the current pathway for managing COVID-19 if evidence supports its benefits in clinical practice.

Three experts thought using SYNE-COV would need changes in hospital IT systems to enable clinicians to see the prediction scores in hospitals. The experts agreed that training is needed to use the technology. Overreliance on the SYNE-COV results was identified as a main risk, which may lead to inappropriate clinical management. Other potential risks identified by the experts including failure to identify people at a high risk of deterioration, misinterpretation of the SYNE-COV results, delayed or inaccuracy of data and the technology being used inexperienced or unqualified clinicians.

General comments

The experts said that currently NEWS scores are standard care to predict deterioration and clinical observation. There are some scoring systems that are used in intensive care units to estimate the severity of diseases and risk of death such as APACHE II SOFA. One expert noted that SYNE-COV is not intended for use in children. The experts agreed that evidence is important to understand SYNE-COV's clinical and cost effectiveness in the NHS.

Expert commentators

The following clinicians contributed to this briefing:

- Professor Andrew Beggs, professor of cancer genetics and surgery, University of Birmingham/University Hospitals Birmingham NHS Foundation Trust. Professor Beggs is chief investigator of a trial on using an artificial intelligence algorithm commissioned by NHS Test and Trace and written by Sensyne Plc.

- Dr Gary Davies, hospital medical director, Chelsea and Westminster Hospital. SYNE-COV is trialled in Chelsea and Westminster Hospital. Declared no financial or direct conflicts of interest.
- Dr Matthew C Frise, Consultant in Acute Medicine and Intensive Care, Royal Berkshire NHS Foundation Trust. Declared no direct conflicts of interest.
- Professor Pallav Shah, consultant physician in respiratory medicine, Royal Brompton and Harefield Hospitals and Chelsea and Westminster Hospital. Did not declare any interests.

Dr Lucy Mackillop (Chief Medical Officer, Sensyne Health plc) and Dr Marcela Vizcaychipi (one of the inventors of SYNE-COV) contributed to this briefing.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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