Supplementing the National Early Warning Score (NEWS2) for anticipating early
deterioration among patients with COVID-19 infection

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Abstract

Importance
An early minimally symptomatic phase is often followed by deterioration in patients with COVID-19 infection. This study shows that the addition of age and a minimal set of common blood tests taken in patients on admission to hospital significantly improves the National Early Warning Score (NEWS2) for risk-stratification of severe COVID disease.

Objective
To supplement the NEWS2 score with a small number of easily obtained additional demographic, physiological and blood variables indicative of severity of COVID-19 infection.

Design
Retrospective observational cohort with internal and temporal held-out external validation.

Setting
Acute secondary care.

Participants
708 patients admitted to an acute multi-site UK NHS hospital with confirmed COVID-19 disease from 1st March to 5th April 2020.

Intervention
Not applicable.

Main outcome and measures
The primary outcome was patient status at 14 days after symptom onset categorised as severe disease (WHO-COVID-19 Outcomes Scales 6-8: i.e. transferred to intensive care unit or death). 218 of the 708 patients reached the primary end point. A range of physiological and blood biomarkers were assessed for their association with the primary outcome. Adjustments included age, gender, ethnicity and comorbidities (hypertension, diabetes, heart, respiratory and kidney diseases).

Results
NEWS2 total score was a weak predictor for severity of COVID-19 infection at 14 days (internally validated AUC = 0.628). The addition of age and common blood tests (CRP, neutrophil count, estimated GFR and albumin) provided substantial improvements to a risk stratification model but performance was still only moderate (AUC = 0.75). Common comorbidities hypertension, diabetes, heart, respiratory and kidney diseases have minor additional predictive value.

Conclusions and relevance
Adding age and a minimal set of common blood parameters to NEWS2 improves the risk stratification of patients likely to develop severe COVID-19 outcomes. The addition of a few common parameters is likely to be much easier to implement in a short time-scale than a novel risk-scoring system.
Introduction

While approximately 80% of individuals with COVID-19 infection have mild or no symptoms\(^1\), some develop severe COVID-19 disease requiring hospital admission. As of 23rd April 2020, there have been >2.5 million confirmed cases worldwide\(^2\). Within the subset of those requiring hospitalisation, early identification of those who deteriorate and require transfer to an intensive care unit (ICU) for organ support or may die is invaluable\(^12\).

Currently available risk scores for deterioration of acutely ill patients include (1) widely-used generic ward-based risk indices such as the National Early Warning Score (NEWS2)\(^3\) or modified sequential organ failure assessment (mSOFA)\(^4\); and (2) the pneumonia-specific risk index, CURB-65\(^5\) which usefully capture a combination of physiological observations with limited blood markers and comorbidities. The NEWS2 is a summary score of six physiological parameters or ‘vital signs’ (respiratory rate, oxygen saturation, systolic blood pressure, heart rate, level of consciousness, temperature and supplemental oxygen dependency), used to identify patients at risk of early clinical deterioration in the UK NHS hospitals\(^6,7\). The physiological parameters assessed in the NEWS2 score - particularly patient temperature, oxygen saturations and the supplemental oxygen dependency - have been associated with COVID-19 outcomes\(^1\); however, little is known about their predictive value for the severity of COVID-19 disease. Additionally, a number of COVID-19-specific risk indices are being developed\(^8–10\) as well as unvalidated online calculators\(^11\) but generalisability is not yet known\(^10\). A Chinese study has suggested a modified version of NEWS2 with addition of age only\(^12\) but without any data on performance. With near universal usage of NEWS2 in UK NHS Trusts since March 2019\(^13\), minor adaptation to NEWS2 would be relatively easy to implement.

As the SARS-Cov2 pandemic has progressed, evidence has emerged regarding potentially useful blood biomarkers\(^1,14–17\). Although most of these early reports contain data from small numbers of patients, a number of markers have been found to be associated with severity. These include neutrophilia and lymphopenia, particularly in older adults\(^9,16,18,19\), neutrophil-to-lymphocyte ratio\(^20\), raised C-Reactive Protein (CRP) and lymphocyte-to-CRP ratio\(^20\), markers of liver and cardiac injury such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and cardiac troponin\(^21\) and elevated D-dimers, ferritin and fibrinogen\(^2,5,7\). Furthermore, plasma levels of cytokines such as IL-6 have been found to be higher in COVID-19 patients compared to controls\(^1\).

Our aim is to understand the performance of NEWS2 and identify a supplemental combination of simple clinical and blood biomarkers routinely measured in hospitals to supplement the NEWS2 score to improve prediction of a severe disease outcome at 14 days from symptom onset. To reach this aim, our specific objectives were:

1. To explore independent associations of routinely measured physiological and blood parameters (including NEWS2 parameters) at or near hospital admission with disease
severity (i.e., ICU admission or death), adjusting for socio-demographics and comorbidities.

2. To examine which minimal combination of these potential determinants of disease severity (physiological and blood parameters, sociodemographics and comorbidities) are the best predictors of disease severity at 14 days since symptom onset; and

3. To compare the predictive value of the resulting model with a model based on the NEWS2 total score alone.

Methods

Patients

The study cohort was defined as all adult inpatients testing positive for SARS-Cov2 by reverse transcription polymerase chain reaction (RT-PCR) between 1st March to 5th April 2020 at a multi-site acute NHS hospital in South East London (UK). The catchment area of King’s College Hospital NHS Foundation Trust includes the most severely affected part of the UK during the current pandemic. All patients included in the study had symptoms consistent with COVID-19 disease (e.g. cough, fever, dyspnoea, myalgia, delirium). We excluded subjects who were seen in the emergency department but not admitted. For purposes of temporal external validation, detailed below, patients were split into training and temporal external validation samples, with those tested positive before 31st March 2020 assigned to training, and those tested positive on/after 31st March 2020 assigned to validation.

This project operated under London South East Research Ethics Committee (reference 18/LO/2048) approval granted to the King’s Electronic Records Research Interface (KERRI); specific work on COVID-19 research was reviewed with expert patient input on a virtual committee with Caldicott Guardian oversight.

Data Processing

The data (demographics, emergency department letters, discharge summaries, clinical notes, lab results, vital signs) were retrieved and analyzed in near real-time from the structured and unstructured components of the electronic health record (EHR) using a variety of natural language processing (NLP) informatics tools belonging to the CogStack ecosystem, namely MedCAT and MedCATTrainer. The CogStack NLP pipeline captures negation, synonyms, and acronyms for medical SNOMED-CT concepts as well as surrounding linguistic context using deep learning and long short-term memory networks. MedCAT produces unsupervised annotations for all SNOMED-CT concepts under parent terms Clinical Finding, Disorder, Organism, and Event with disambiguation, pre-trained on MIMIC-III. The annotated SNOMED-CT terms are summarised in Supplementary Table 1.

Starting from our previous model, further supervised training improved detection of annotations and meta-annotations such as experiencer (is the concept annotated experienced by the patient or other), negation (is the concept annotated negated or not) and temporality (is
the concept annotated in the past or present) with MedCATTrainer. Meta-annotations for hypothetical, historical and experiencer were merged into “Irrelevant” allowing us to exclude any mentions of a concept that do not directly relate to the patient currently. Performance of the MedCAT NLP pipeline for disorders mentioned in the text was evaluated on 4343 annotations in 146 clinical documents by a clinician (JT). F1 scores, precision, and recall are presented in Supplementary Table 2.

Measures

Outcome. The primary outcome was patient status at 14 days after symptom onset, or admission to hospital where symptom onset was missing, categorised as transfer to ICU/death (WHO-COVID-19 Outcomes Scales 6-8) vs. not ICU/death (Scales 3-5). The WHO-COVID-19 Outcome Scales 6-7 incorporate admission to an ICU while Outcome Scale 8 indicates death. Date of symptom onset, date of ICU transfer and date of death were ascertained and verified manually by a clinician.

Blood parameters. We focused on biomarkers that were routinely obtained at or shortly after admission and were therefore available for the vast majority of patients. These comprised: albumin (g/L), alanine aminotransferase (ALT; IU/L), creatinine (µmol/L), C-reactive protein (CRP; mg/L), estimated Glomerular Filtration Rate (eGFR; mL/min), Haemoglobin (g/L), lymphocyte count (x 10⁹/L), neutrophil count (x 10⁹/L), and platelet count (PLT; x 10⁹/L). We also derived the neutrophil-to-lymphocyte ratio (NLR) and the lymphocyte-to-CRP ratio. Troponin-T (ng/L) and Ferritin (ug/L) were included, although these measures were only available for a subset of participants. D-dimers and HbA1c were excluded since they were measured in very few patients at admission and insufficient samples were available for analysis.

Physiological parameters. We included the six physiological parameters that form the basis of the NEWS2 score, namely, respiratory rate (breaths per minute), oxygen saturation (%), systolic blood pressure (mmHg), heart rate (beats/min), temperature (°C), and consciousness (measured by Glasgow Coma Scale (GCS) total score). All were measured at or shortly after admission. We assessed these parameters individually as well as a NEWS2 total score. Diastolic blood pressure, which is not part of the NEWS2 score, was also included in the analyses.

Demographics and comorbidities. Age, sex, ethnicity and comorbidities were considered. Where ethnicity data was available this was categorised as caucasian vs. BAME (Black, Asian and minority ethnic). For supplementary models adjusting for ethnicity, patients with ethnicity reported as ‘unknown/mixed/other’ were excluded. We included binary measures (present vs. not present) of relevant comorbid chronic health conditions derived from the NLP pipeline described above: hypertension, diabetes, heart disease (heart failure and ischemic heart disease), respiratory disease (asthma and chronic obstructive pulmonary disease, COPD) and chronic kidney disease.
Statistical analyses

Preliminary descriptive and exploratory analyses were performed. To address our first objective – exploring independent associations of physiological and blood parameters with 14-day death/ICU – we used penalised maximum likelihood logistic regression which reduces bias due to small sample size\(^27\). Each parameter was tested independently, adjusted for age and sex (Model 1) and then additionally adjusted for comorbidities (Model 2). Parameters exhibiting skewed distributions were transformed before modelling with logarithmic or square-root transformations. All parameters were scaled (mean = 0, standard deviation = 1) to improve interpretability. Outlying high values for some blood parameters were retained after individual examination by clinicians who ascertained their plausibility. We used the maximal available sample when testing each parameter. Given the number of tests conducted, \(P\)-values were adjusted using the Benjamini-Hochberg procedure to keep the False discovery rate at 5\%\(^28\). These models were conducted with R 3.6\(^{23}\) using the logistf\(^{24}\) package.

To address our second and third objectives – which combination of parameters performed best in predicting the 14-day outcome over and above NEWS2 – we estimated models combining all parameters using regularized logistic regression with a LASSO (Least Absolute Shrinkage and Selection Operator) estimator which shrinks parameters according to their variance, reduces overfitting and enables automatic variable selection\(^29\). The optimal degree of regularization was determined by identifying a tuning parameter \(\lambda\) using cross-validation\(^30\). LASSO regression provides a sparse, interpretable model, which allows us to predict individual risk scores (i.e. probability of severe outcome). Starting from an initial model with NEWS2 total score only, sets of features were added in order of (i) age and sex, (ii) blood and physiological parameters; (iii) comorbid conditions. A final model was estimated using NEWS2 total score alongside the top five most influential features from previous models. To estimate the predictive performance of our model on new unseen cases of the same underlying population, we performed internal nested cross-validation (10 folds and 20 repeats for the inner loop; 10 folds and 100 repeats for the outer loop). Overall discrimination was assessed based on the area under the curve (AUC). All continuous features were scaled (mean = 0, standard deviation = 1). Missing feature information was imputed (after scaling) using k-Nearest Neighbours imputation (k=5). Scaling and kNN imputation were incorporated within the model development and selection process to avoid data leakage which would otherwise result in optimistic performance measures\(^31\).

To assess whether a more complex machine learning estimator would improve predictive performance, we repeated this set of models using gradient boosted trees implemented in the XGBoost library\(^{32}\). Procedures for internally validating these models were equivalent to those described above for regularized logistic regression except the imputation step was omitted due to the ability of XGBoost to handle missing data.

The predictive performance of the derived regularized logistic regression model was then evaluated by temporal external validation\(^33\) with a hold-out sample of 256 patients who were admitted to hospital after the training sample (see Supplementary Figure 1). This involved
estimating the original model exactly as presented, including scaling and imputation models derived in the training data set. Discrimination performance was assessed using AUC, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Model calibration was assessed using a calibration plot (model predicted probability vs. true probability). These models were estimated in Python 3.6 using NumPy, and Scikit-Learn.

Sensitivity analyses were performed to account for potential demographic variability. Recent evidence suggest sex differences with men more likely to experience worse outcomes. Therefore, in separate models, we tested interactions between each physiological and blood parameter and sex using likelihood-ratio tests (comparing a null model with the main effects only vs. a model additionally including the interaction term). In addition, we replicated all models with adjustment for ethnicity in the subset of individuals with available data for ethnicity (n=285 in training sample).

Results

The initial inpatient cohort comprised 452 inpatients testing positive for COVID-19 of whom 159 (35%) were transferred to ICU or died (COVID-19 WHO Score 6-8) within 14 days of symptom onset. Table 1 describes the clinical characteristics of the cohort: the mean age was 67 years (standard deviation = 18.5); 54% (n=248) were male; 42% (n=120) were categorised as BAME. Patients associated with a more severe outcome were significantly older (71 vs. 65 years; p = 0.004) but there was no evidence of differences by sex or ethnicity. There were some differences between groups in the prevalence of comorbidities but these did not reach statistical significance after multiple testing correction. For example, compared to patients with less severe outcomes, those who transferred to ICU or died had higher rates of hypertension (60% vs. 50%; p = 0.11), diabetes (38% vs. 32%; p = 0.33), heart failure (16% vs. 11%; p = 0.33) and chronic kidney disease (24% vs. 16%; p = 0.11). Rates of other comorbidities were similar between the two groups. There were differences between outcome groups for most blood and physiological parameters. Patients who had transferred to ICU or died within 14 days had, at admission, lower levels of Albumin, ALT, and estimated GFR; and elevated levels of CRP, creatinine, Ferritin, and Neutrophils. Mean NEWS2 total scores were significantly different (3.4 vs 2.1; p < 0.001; corresponding to Cohen’s d of -0.57) in patients who transferred to ICU or died, compared to inpatients experiencing less severe outcomes.

Logistic regression models were used to assess independent associations between each physiological and blood parameter and disease severity measured as transfer to ICU or death (Table 2). Individuals were more likely to have transferred to ICU/died within 14 days of symptom onset if: they had higher CRP, NEWS2 score, heart rate, neutrophils, neutrophil-lymphocyte ratio, respiration rate; or if they had lower lymphocyte/CRP ratios, eGFR, creatinine, and oxygen saturation. These associations remained after adjustment for age, sex and comorbidities. There was no evidence of differences by sex (results not presented) and findings were consistent when additionally adjusting for ethnicity in secondary analyses using the subset of individuals with ethnicity data (Supplementary Table 3).
Combining physiological and blood parameters to assess ability to improve on NEWS2 in predicting 14-day outcome

To identify which minimal set of parameters were best able to improve on NEWS2 in predicting the 14-day outcome (ICU/death vs. not ICU/death), we combined all predictors in a single logistic regression model using LASSO regularisation. Internally validated predictive performance based on the area under the ROC curve (AUC) is presented in Table 3 for different feature sets. NEWS2 shows poor discrimination with an AUC of 0.628. Adding age and sex to a baseline model of NEWS2 total score only increased the AUC by 0.025 to 0.653 (+/- 2SD range: 0.639, 0.667). Further adding in all other blood and physiological parameters (except NEWS2) increased the AUC further by 0.089, to 0.742 (+/- 2SD: 0.726, 0.758). Additionally including comorbidities in this model did not improve performance. A final model was estimated including NEWS2 and the top five most important features taken from Model 4. This simpler model resulted in a slightly larger AUC of 0.751 (+/- 2SD range: 0.737, 0.764) which may indicate some overfitting due to the pre-selection of variables from previous analyses. Results were consistent when repeating these models in the subset of patients with information available on ethnicity (Supplementary Table 5).

Figure 1 summarises feature importances from the LASSO logistic regression models. When adding blood and physiological parameters to NEWS2 (‘NEWS2 + DBP’), 8 features were retained, in order of effect sizes: NEWS2 total score, CRP, neutrophils, estimated GFR, albumin, age, Troponin T, and oxygen saturation. Notably, when additionally considering comorbid conditions (‘NEWS2 + DBPC’), the retained features were similar, and no comorbid conditions were retained. This suggests that most of the variance is already captured by the top 5 parameters.

When these models were repeated using a more complex estimator (gradient boosted trees, using XGBoost\textsuperscript{32}) the pattern of results was consistent with those from regularized logistic regression (Supplementary Table 5). Namely, the internally validated AUC improved from 0.646 for a model with NEWS2 alone, to 0.722 for a model that additionally included the five parameters: CRP, neutrophils, estimated GFR, albumin, and age. Importantly, while the pattern of results was consistent, a more complex machine learning estimator produced no improvements to predictive performance.

Temporal external validation was conducted on a hold-out sample of 256 patients. This sample was similar to the training sample on all parameters (Supplementary Table 6) except the proportion who transferred to ICU or died was lower. Overall, results from the hold-out sample were consistent with those from internal validation. The AUC for NEWS2 alone was 0.700, and this improved to 0.730 when adding all blood and physiological parameters (sensitivity = 0.441; specificity = 0.873). The AUC for the simplified final model including NEWS2 and the top five features (CRP, neutrophils, estimated GFR, albumin and age) was similar (AUC = 0.730; sensitivity = 0.458; specificity = 0.873) (Supplementary Table 7). Calibration for these models
(Supplementary Figure 2) was acceptable but showed some consistent overestimation of risk probabilities.

**Discussion**

To our knowledge our study is the first to systematically attempt to improve performance of NEWS2 specifically for COVID-19. We found that the NEWS2 score shows overall poor discrimination with high specificity but poor sensitivity for severe outcomes in COVID-19 infection (transfer to ICU or death). However, its value for risk stratification (especially sensitivity) can be significantly improved by adding age and a small number of additional blood parameters (CRP, neutrophils, estimated GFR and albumin). A number of blood measures previously linked with more severe outcomes – such as lymphocyte and ALT – did not provide additional value to the model over and above the existing features despite being more common in those individuals with more severe outcomes. Moreover, cardiac disease and myocardial injury has been described to be commonly seen in the severe COVID-19 cases in China. In our model, blood Troponin-T, a marker of myocardial injury, had additional salient signal but was only measured in a subset of our cohort at admission, so it was not included in our final model. This would have to be explored further in larger datasets. A systematic review of 10 prediction models for mortality in COVID-19 infection found broad similarities with the features retained in our models, particularly regarding CRP and neutrophil levels. However, existing prediction models suffer several methodological weaknesses including over-fitting, selection bias, and reliance on cross-sectional data without accounting for censoring. Additionally, almost all existing studies have relied on ethnically homogenous Chinese cohorts and thus may be unrepresentative of other global populations.

With regards to pre-existing disease comorbidities (hypertension, diabetes mellitus, heart failure, ischaemic heart disease, COPD, asthma and chronic kidney disease), these were more common in patients with severe outcomes but had minimal contribution to the risk prediction and were not retained in the final model. This was unexpected and suggests potential shared variance between pre-existing health conditions and some of the included blood or physiological markers. Future research should explore further the potential underlying shared mechanisms that can predict deterioration.

NEWS2 is a summary score derived from six physiological parameters, including oxygen saturation. While NEWS2 total score was one of the most influential parameters in our models, the oxygen saturation sub-parameter remained influential and was retained following regularisation (i.e. model ‘NEWS + DBP’). This suggests some residual association over and above what is captured by the NEWS2 score between oxygen saturation and more severe outcomes, and reinforces Royal College of Physicians guidance that the NEWS2 score ceilings with respect to respiratory function.
Strengths and limitations

Our study included data from a large sample of patients admitted to hospital with high rates of the primary outcome (transfer to ICU or death) and considered a large number of potential predictors including demographics, physiological and blood parameters and comorbidities. However, some limitations should be acknowledged. First, there are likely to be other parameters not measured in this study that could improve the risk stratification model substantially (e.g. radiological features, other comorbidities or comorbidity load). This could be addressed by future work to introduce additional data modalities, but these were not considered in the present study to avoid limiting the real-world implementation of the risk stratification model; a complex model with many parameters will be harder to implement in clinical practice. Second, we used a 14-day time window from the symptom onset date as this provides a balance between medium-term prognostication and actionable risk stratification at the usual period of deterioration. Longer timeframes may be useful for prognostication but are harder to generalise due to the greater number of factors affecting outcomes, including institutional, regional or national policies. Since NEWS2 score is optimised for very near-term deterioration at 24 hours⁷, a 14-day window was used as a compromise. Third, while the hold-out sample used for temporal external validation was similar in terms of demographics, blood and physiological parameters, the rate of more severe outcomes differed significantly. Perhaps due to changes in hospital procedures over time, this again suggests the need to validate these models in other hospitals or regions. Finally, while the model was derived from two hospital sites providing a mixed population, this study highlights that initial prediction models still have poor sensitivity and recalibration would be required before implementation as a risk model in clinical practice. Validation across datasets from a wider geographical region will be necessary to ensure generalisability.

Conclusion

In conclusion, this study suggests that the simple addition of a limited number of blood parameters to the existing and widely implemented NEWS2 system can contribute to improved risk stratification among COVID-19 patients. Our model can be easily implemented in clinical practice and predicted risk score probabilities of individual patients are easy to communicate. The additional parameters are widely collected on patients at hospital admission, and with near universal usage of NEWS2 in NHS Trusts since March 2019¹³, a minor adaptation to NEWS2 is substantially easier to implement in a variety of health settings than a bespoke risk score.
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### Tables

#### Table 1: Patient characteristics at hospital admission

|                      | N avail. | All patients | Patients by status at 14-day endpoint | FDR-adjusted P-value for test between outcome groups |
|----------------------|----------|--------------|---------------------------------------|------------------------------------------------------|
|                      |          |              | WHO-COVID-19 Outcomes Scales | WHO-COVID-19 Outcomes Scales |
|                      |          |              | 3-5 (no ICU/death) n=393 | 6-8 (ICU/death) n=159 |
| Age                  | 452      | 67.00 [28.00]| 64.87 [30.00] | 70.92 [27.00] | 0.004 |
| Sex (male) N (%)     | 452      | 248 (54.9%)  | 157 (53.6%) | 91 (57.2%) | 0.682 |
| BAME N (%)           | 285      | 120 (42.1%)  | 73 (41.0%) | 47 (43.9%) | 0.770 |
| **Comorbidities**    |          |              |                          |                                      |
| Hypertension         | 452      | 243 (53.8%)  | 147 (50.2%) | 96 (60.4%) | 0.106 |
| Diabetes mellitus    | 452      | 154 (34.1%)  | 93 (31.7%) | 61 (38.4%) | 0.325 |
| Heart Failure        | 452      | 57 (12.6%)   | 32 (10.9%) | 25 (15.7%) | 0.325 |
| Ischaemic Heart Diseases | 452 | 85 (18.8%) | 55 (18.8%) | 30 (18.9%) | 1.000 |
| COPD                 | 452      | 48 (10.6%)   | 27 (9.2%) | 21 (13.2%) | 0.366 |
| Asthma               | 452      | 65 (14.4%)   | 44 (15.0%) | 21 (13.2%) | 0.770 |
| Chronic Kidney Disease | 452 | 84 (18.6%) | 46 (15.7%) | 38 (23.9%) | 0.105 |
| **Blood biomarkers** |          | Mean [IQR]   |                          |                                      |
| Albumin              | 322      | 37.11 [7.00]| 38.05 [7.00] | 35.48 [7.00] | <0.001 |
| Alanine aminotransferase (ALT) | 184 | 54.83 [33.00] | 60.34 [30.50] | 46.45 [34.00] | 0.386 |
| C-reactive protein (CRP) | 419 | 93.55 [106.70] | 72.99 [84.90] | 130.41 [135.62] | <0.001 |
| Creatinine           | 420      | 121.67 [49.00]| 105.86 [40.50] | 150.42 [72.00] | 0.001 |
| Estimated GFR        | 334      | 63.75 [40.00]| 68.01 [36.00] | 56.05 [44.50] | <0.001 |
| Ferritin             | 122      | 1356.01 [1165.25]| 1272.35 [1149.75] | 1442.45 [902.50] | 0.016 |
| Parameter                        | N avail. | Mean [IQR]          | P-value |
|---------------------------------|----------|---------------------|---------|
| **Haemoglobin**                 | 419      | 125.05 [30.00]      | 125.52 [30.00] | 124.21 [28.75] | 0.770 |
| Lymphocyte count                | 419      | 1.45 [0.67]         | 1.10 [0.69]   | 2.09 [0.67]   | 0.695 |
| Neutrophil count                | 418      | 5.72 [3.53]         | 5.06 [3.01]   | 6.91 [5.31]   | <0.001 |
| Neutrophil/lymphocyte ratio    | 418      | 6.80 [5.01]         | 5.81 [4.22]   | 8.58 [6.26]   | <0.001 |
| Lymphocyte/CRP ratio            | 416      | 0.07 [0.04]         | 0.08 [0.05]   | 0.05 [0.02]   | <0.001 |
| Platelet count                  | 421      | 226.68 [103.00]     | 228.34 [102.50] | 223.69 [104.25] | 0.958 |
| Troponin T                      | 141      | 33.92 [29.00]       | 30.40 [26.00] | 37.92 [38.50] | 0.351 |
| **Physiological parameters**    |          |                     |         |
| NEWS2 Total Score               | 401      | 2.51 [3.00]         | 2.10 [3.00]   | 3.40 [4.00]   | <0.001 |
| Heart rate                      | 405      | 85.35 [20.00]       | 84.49 [19.00] | 87.15 [23.50] | 0.359 |
| Oxygen saturation               | 404      | 96.22 [3.00]        | 96.54 [2.00]  | 95.56 [3.00]  | 0.008 |
| Respiration rate                | 405      | 19.84 [2.00]        | 19.42 [2.00]  | 20.72 [3.00]  | 0.008 |
| GCS score                       | 172      | 14.12 [1.00]        | 14.20 [1.00]  | 13.95 [1.00]  | 0.117 |
| Systolic blood pressure         | 405      | 127.39 [29.00]      | 127.09 [26.50] | 128.00 [32.00] | 0.770 |
| Diastolic blood pressure        | 405      | 72.69 [18.00]       | 73.20 [18.00] | 71.63 [19.00] | 0.325 |
| Temperature                     | 405      | 37.12 [0.90]        | 37.12 [0.90]  | 37.11 [1.00]  | 0.682 |

**Notes.**

1 Wilcoxon test for continuous variables; \( \chi^2 \) test for binary variables. FDR-corrected P-values based on the Benjamini–Hochberg correction.
Table 2: Logistic regression models for each blood and physiological measure tested separately, sorted by effect size

| Measure                          | N avail. | Model 1: Age, sex only | Model 2: + all comorbidities |
|----------------------------------|----------|------------------------|-----------------------------|
|                                  |          | Odds Ratio [95% C.I.]   | FDR-adjusted P-value<sup>1</sup> | Odds Ratio [95% C.I.] | FDR-adjusted P-value<sup>1</sup> |
| CRP                              | 419      | 2.04 [1.64, 2.57]      | <0.001                      | 2.06 [1.65, 2.60]    | <0.001                      |
| NEWS2 Total Score                | 401      | 1.82 [1.46, 2.30]      | <0.001                      | 1.83 [1.46, 2.31]    | <0.001                      |
| Lymphocyte/CRP ratio             | 416      | 0.56 [0.44, 0.71]      | <0.001                      | 0.56 [0.44, 0.71]    | <0.001                      |
| Troponin T                       | 141      | 1.51 [1.02, 2.30]      | 0.119                       | 1.69 [1.08, 2.78]    | 0.073                       |
| Neutrophil count                 | 418      | 1.66 [1.33, 2.09]      | <0.001                      | 1.68 [1.35, 2.12]    | <0.001                      |
| Ferritin                         | 122      | 1.55 [1.05, 2.40]      | 0.098                       | 1.60 [1.07, 2.54]    | 0.073                       |
| Estimated GFR                    | 334      | 0.65 [0.51, 0.83]      | 0.004                       | 0.66 [0.49, 0.87]    | 0.023                       |
| Respiration rate                 | 405      | 1.47 [1.19, 1.83]      | 0.002                       | 1.46 [1.19, 1.82]    | 0.003                       |
| Albumin                          | 322      | 0.68 [0.53, 0.87]      | 0.010                       | 0.69 [0.53, 0.89]    | 0.024                       |
| Oxygen saturation                | 404      | 0.72 [0.57, 0.89]      | 0.010                       | 0.71 [0.56, 0.88]    | 0.013                       |
| Neutrophil/lymphocyte ratio     | 418      | 1.35 [1.09, 1.70]      | 0.026                       | 1.36 [1.09, 1.72]    | 0.028                       |
| Creatinine                       | 420      | 1.35 [1.09, 1.69]      | 0.024                       | 1.35 [1.04, 1.76]    | 0.073                       |
| Heart rate                       | 405      | 1.30 [1.05, 1.62]      | 0.068                       | 1.32 [1.06, 1.65]    | 0.050                       |
| ALT                              | 184      | 1.17 [0.86, 1.60]      | 0.923                       | 1.22 [0.88, 1.68]    | 0.682                       |
| Temperature                      | 405      | 1.09 [0.88, 1.36]      | 1.000                       | 1.10 [0.88, 1.36]    | 0.999                       |
| Diastolic blood pressure         | 405      | 0.90 [0.73, 1.11]      | 0.952                       | 0.92 [0.74, 1.13]    | 0.999                       |
| Platelet count                   | 421      | 0.95 [0.77, 1.16]      | 1.000                       | 0.94 [0.76, 1.15]    | 0.999                       |
| Lymphocyte count                 | 419      | 1.05 [0.86, 1.29]      | 1.000                       | 1.05 [0.86, 1.29]    | 0.999                       |
GCS score | 172 | 0.95 [0.70, 1.31] | 1.000 | 0.96 [0.70, 1.32] | 0.999
---|---|---|---|---|---
Hemoglobin | 419 | 0.98 [0.79, 1.20] | 1.000 | 1.03 [0.83, 1.27] | 0.999
Systolic blood pressure | 405 | 0.97 [0.78, 1.20] | 1.000 | 0.98 [0.78, 1.21] | 0.999

**Notes.**

1FDR-corrected P-values based on the Benjamini–Hochberg correction.

Odds ratios represent a one standard deviation change in the respective blood and clinical measure at admission (tested in separate models). Model 1 adjusted for age and sex. Model 2 additionally adjusted for comorbidities (hypertension, diabetes, heart diseases, respiratory diseases, and chronic kidney disease).

**Table 3: Internally validated predictive performance (n=452)**

**Notes.** AUC based on repeated, nested cross-validation (inner loop: 10-fold, 20 repeats; outer loop = 10-fold, 100 repeats). Missing values imputed at each outer loop with K-Nearest Neighbours (KNN) imputation.

| Included features | Internally validated AUC | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|
| | Mean | -2SD | +2SD |
| 1 | NEWS2 | 0.628 | 0.619 | 0.637 | 0.180 | 0.950 | 0.664 | 0.681 |
| 2 | NEWS2 + D | 0.653 | 0.639 | 0.667 | 0.189 | 0.929 | 0.597 | 0.678 |
| 3 | NEWS2 + DBP | 0.742 | 0.726 | 0.758 | 0.400 | 0.857 | 0.585 | 0.723 |
| 4 | NEWS2 + DBPC | 0.737 | 0.721 | 0.753 | 0.385 | 0.854 | 0.588 | 0.719 |
| 5 | NEWS2 + CRP + Neutrophil + eGFR + Albumin + Age | 0.751 | 0.737 | 0.764 | 0.415 | 0.842 | 0.589 | 0.727 |

D = Age, sex
C = comorbidities (8 features)
B = bloods (10 features)
P = physiological parameters (7 features)
Figures

Figure 1: Feature importances from LASSO logistic regression in training sample (n=452)

Notes. Feature importances refer to absolute values of standardised coefficients from logistic regression, sorted by effect size in model ‘NEWS2 + DBPC’. Where a feature is labelled on the y-axis, it was entered into the model. Features retained following LASSO regularisation are represented by a coloured bar; the absence of a bar indicates that this feature was omitted during regularisation.
Supplementary Materials

Supplementary Figure 1: Timing of 14-day endpoints for training (n=452) and validation (n=256) samples
Supplementary Figure 2: Calibration plot from temporal external validation
Supplementary Table 1: SNOMED terms

| SNOMED concept name | SNOMED concept IDs                                      |
|---------------------|--------------------------------------------------------|
| Diabetes            | S-230572002, S-44054006, S-237599002, S-49455004       |
| Heart Failure       | S-42343007, S-426263006, S-48447003, S-418304008, S-10633002 |
| IHD                 | S-401314000, S-194828000, S-233839009, S-414545008 S-394659003, S-1755008, S-413838009 |
| Hypertension        | S-59621000                                             |
| COPD                | S-13645005, S-313297008                                |
| Asthma              | S-195967001                                            |
| CKD                 | S-433144002, S-90688005, S-709044004                    |

Supplementary Table 2: F1, precision and recall for NLP co-morbidity detection

MedCATTrainer was used to collect manual annotations for 146 clinical documents totalling 4343 annotations. Each co-morbidity is defined using one or more SNOMED terms. Predicted true positive labels (TP), precision (P), recall (R), F1-score (F1) are shown for these aggregated concepts. These results only consider entity detection and not meta annotation.

|              | TP | F1  | P    | R    | SNOMED terms                                      |
|--------------|----|-----|------|------|--------------------------------------------------|
| Diabetes mellitus | 73 | 0.936 | 0.924 | 0.948 | S-230572002, S-44054006, S-237599002, S-49455004 |
| Heart Failure | 11 | 0.893 | 0.786 | 1.000 | S-42343007, S-426263006, S-48447003, S-418304008 S-10633002 |
| IHD          | 23 | 0.979 | 0.958 | 1.000 | S-401314000, S-194828000, S-233839009, S-414545008 S-394659003, S-1755008 S-413838009 |
| Hypertension | 84 | 0.883 | 0.988 | 0.778 | S-59621000                                       |
| COPD         | 14 | 0.967 | 0.933 | 1.000 | S-13645005, S-313297008                          |
Supplementary Table 3: Logistic regression models for each blood measure tested separately, adjusted for ethnicity for patients with information on ethnicity

| Measure                  | N avail. | Model 1: Age, sex, ethnicity | Model 2: + all comorbidities |
|--------------------------|----------|------------------------------|------------------------------|
|                          |          | N                            | OR [95% C.I.]                | FDR-adjusted P-value | OR [95% C.I.]                | FDR-adjusted P-value |
| CRP                      | 263      | 2.15 [1.63, 2.91]            | <0.001                       | 2.24 [1.68, 3.07]     | <0.001                       |
| NEWS2 Total Score        | 250      | 2.06 [1.56, 2.79]            | <0.001                       | 2.04 [1.54, 2.77]     | <0.001                       |
| Troponin T               | 84       | 1.62 [0.94, 2.99]            | 0.394                        | 1.86 [1.01, 3.60]     | 0.210                        |
| Lymphocyte/CRP ratio     | 260      | 0.57 [0.41, 0.76]            | 0.001                        | 0.56 [0.41, 0.76]     | 0.001                        |
| Neutrophil count         | 262      | 1.57 [1.20, 2.12]            | 0.007                        | 1.56 [1.19, 2.10]     | 0.009                        |
| Oxygen saturation        | 252      | 0.63 [0.47, 0.83]            | 0.009                        | 0.66 [0.49, 0.87]     | 0.022                        |
| Heart rate               | 253      | 1.46 [1.12, 1.93]            | 0.029                        | 1.45 [1.11, 1.92]     | 0.037                        |
| Respiration rate         | 253      | 1.46 [1.15, 1.90]            | 0.012                        | 1.44 [1.14, 1.87]     | 0.021                        |
| GCS score                | 109      | 0.70 [0.43, 1.11]            | 0.440                        | 0.70 [0.42, 1.14]     | 0.527                        |
| Albumin                  | 191      | 0.71 [0.51, 0.97]            | 0.162                        | 0.71 [0.51, 0.99]     | 0.210                        |
| Creatinine               | 264      | 1.24 [0.95, 1.65]            | 0.440                        | 1.33 [0.97, 1.87]     | 0.341                        |
| Estimated GFR            | 199      | 0.81 [0.58, 1.11]            | 0.594                        | 0.77 [0.53, 1.12]     | 0.553                        |
| ALT                      | 130      | 1.14 [0.73, 1.80]            | 1.000                        | 1.26 [0.79, 2.04]     | 0.950                        |
| Neutrophil/lymphocyte ratio | 262    | 1.24 [0.95, 1.65]            | 0.440                        | 1.22 [0.94, 1.62]     | 0.527                        |
| Temperature              | 253      | 1.18 [0.92, 1.52]            | 0.594                        | 1.18 [0.92, 1.53]     | 0.573                        |
|                | 81  | 1.08 [0.64, 1.81] | 1.000 | 1.17 [0.69, 2.00] | 1.000 |
|----------------|-----|------------------|-------|------------------|-------|
| Ferritin       | 265 | 0.89 [0.67, 1.15] | 1.000 | 0.89 [0.67, 1.15] | 1.000 |
| Platelet count | 253 | 0.89 [0.67, 1.17] | 1.000 | 0.91 [0.68, 1.20] | 1.000 |
| Diastolic blood pressure | 263 | 1.08 [0.85, 1.37] | 1.000 | 1.08 [0.85, 1.38] | 1.000 |
| Lymphocyte count | 265 | 1.07 [0.83, 1.38] | 1.000 | 1.07 [0.83, 1.40] | 1.000 |
| Hemoglobin     | 253 | 0.90 [0.69, 1.17] | 1.000 | 0.93 [0.71, 1.21] | 1.000 |

**Notes.**
Odds ratios for 1 SD change in each blood measure at admission (tested in separate models)
Model 1 adjusted for age and sex and ethnicity. Model 2 additionally adjusted for comorbidities (hypertension, diabetes, heart diseases, respiratory diseases and chronic kidney disease)

**Supplementary Table 4:** Internally validated predictive performance, adjusted for ethnicity for patients with information on ethnicity (n=285)

| Included features | Internally validated AUC | Sensitivity | Specificity | PPV | NPV  |
|-------------------|-------------------------|-------------|-------------|-----|------|
|                   | Mean        | -2SD | +2SD |        |     |     |
| 1 NEWS2           | 0.663       | 0.641 | 0.648 | 0.256 | 0.889 | 0.582 | 0.665 |
| 2 NEWS2 + D       | 0.654       | 0.628 | 0.680 | 0.283 | 0.878 | 0.585 | 0.671 |
| 3 NEWS2 + DBP     | 0.722       | 0.693 | 0.750 | 0.432 | 0.805 | 0.571 | 0.702 |
| 4 NEWS2 + DBPC    | 0.710       | 0.681 | 0.740 | 0.434 | 0.794 | 0.559 | 0.700 |
| 5 NEWS2 + CRP + Neutrophil + eGFR + Albumin + Age | 0.734       | 0.713 | 0.756 | 0.414 | 0.797 | 0.549 | 0.693 |

D = Age, sex
C = comorbidities (8 features)
B = bloods (10 features)
P = physiological parameters (7 features)
Supplementary Table 5: Internally validated predictive performance using XGBoost (Gradient Boosting Trees) (n=452)

AUC based on repeated, nested cross-validation (inner loop: 10-fold, 20 repeats; outer loop = 10-fold, 100 repeats).

| Included features | Internally validated AUC | Sensitivity | Specificity | PPV | NPV |
|-------------------|--------------------------|-------------|-------------|-----|-----|
|                   | Mean | -2SD | +2SD |       |     |     |
| 1 NEWS2           | 0.646 | 0.626 | 0.666 | 0.364 | 0.880 | 0.624 | 0.718 |
| 2 NEWS2 + D       | 0.667 | 0.652 | 0.682 | 0.344 | 0.910 | 0.680 | 0.719 |
| 3 NEWS2 + DBP     | 0.728 | 0.700 | 0.755 | 0.452 | 0.837 | 0.601 | 0.739 |
| 4 NEWS2 + DBPC    | 0.719 | 0.693 | 0.745 | 0.428 | 0.839 | 0.591 | 0.731 |
| 5 NEWS2 + CRP     | 0.722 | 0.660 | 0.785 | 0.480 | 0.836 | 0.615 | 0.748 |

D = Age, sex
C = comorbidities (8 features)
B = bloods (10 features)
P = physiological parameters (7 features)
Supplementary Table 6: Comparison of training and held-out validation samples

| 14-day outcome                      | Training sample (n=452) | Validation sample (n=256) | P-value for test of difference between samples¹ |
|------------------------------------|-------------------------|---------------------------|-----------------------------------------------|
| COVID-19 WHO Score 6-8 (ICU/death) | 452 N avail. 159 (35.2%) | 256 N avail. 59 (23.0%) | 0.001                                         |

Demographics

| Age | Training sample (n=452) | Validation sample (n=256) | P-value |
|-----|-------------------------|---------------------------|---------|
| Age | 452 67.0 [28.0]         | 256 67.9 [25.5]           | 0.822   |

| Sex (male) N (%) | Training sample (n=452) | Validation sample (n=256) | P-value |
|-----------------|-------------------------|---------------------------|---------|
| 452 248 (54.9%) | 256 137 (53.5%)          | 0.788                     |

| BAME N (%) | Training sample (n=452) | Validation sample (n=256) | P-value |
|------------|-------------------------|---------------------------|---------|
| 285 120 (42.1%) | 206 86 (41.7%) | 0.999                     |

Comorbidities

| Comorbidities | Training sample (n=452) | Validation sample (n=256) | P-value |
|---------------|-------------------------|---------------------------|---------|
| Hypertension  | 452 243 (53.8%)         | 256 146 (57.0%)           | 0.446   |
| Diabetes      | 452 154 (34.1%)         | 256 85 (33.2%)            | 0.879   |
| Heart Failure | 452 57 (12.6%)          | 256 24 (9.4%)             | 0.239   |
| Ischaemic Heart Diseases | 452 85 (18.8%) | 256 43 (16.8%) | 0.572   |
| COPD          | 452 48 (10.6%)          | 256 30 (11.7%)            | 0.746   |
| Asthma        | 452 65 (14.4%)          | 256 37 (14.5%)            | 0.999   |
| Chronic Kidney Disease | 452 84 (18.6%) | 256 39 (15.2%) | 0.304   |

Blood biomarkers

| Blood biomarkers | Training sample (n=452) | Validation sample (n=256) | P-value |
|-----------------|-------------------------|---------------------------|---------|
| Albumin         | 322 37.1 [7.0]          | 219 36.4 [6.0]            | 0.079   |
| ALT             | 184 54.8 [33.0]         | 105 42.8 [31.0]           | 0.889   |
| CRP             | 419 93.5 [106.7]        | 224 97.7 [94.2]           | 0.341   |
| Creatinine      | 420 121.7 [49.0]        | 226 147.1 [62.8]          | 0.190   |
| Estimated GFR   | 334 63.7 [40.0]         | 225 59.7 [44.0]           | 0.076   |
| Ferritin        | 122 1356.0 [1165.2]     | 78 1668.8 [1258.2]        | 0.702   |
| Haemoglobin     | 419 125.1 [30.0]        | 226 125.3 [31.0]          | 0.919   |
|                               | N avail. | Mean [IQR]          | P-value |
|-------------------------------|----------|---------------------|---------|
| **Lymphocyte count**          | 419      | 1.5 [0.7]           | 226     | 1.3 [0.6]            | 0.247 |
| **Neutrophil count**          | 418      | 5.7 [3.5]           | 226     | 5.7 [3.9]            | 0.952 |
| **Neutrophil/lymphocyte ratio** | 418   | 6.8 [5.0]           | 226     | 6.8 [4.7]            | 0.387 |
| **Lymphocyte/CRP ratio**      | 416      | 0.1 [0.0]           | 224     | 0.0 [0.0]            | 0.191 |
| **Platelet count**            | 421      | 226.7 [103.0]       | 226     | 223.7 [124.2]        | 0.652 |
| **Troponin T**                | 141      | 33.9 [29.0]         | 94      | 87.8 [45.2]          | 0.414 |
| **Physiological parameters**  | N avail. | Mean [IQR]          | P-value |
| NEWS2 Total Score             | 401      | 2.5 [3.0]           | 253     | 2.7 [3.0]            | 0.283 |
| Heart rate                    | 405      | 85.4 [20.0]         | 254     | 85.3 [19.0]          | 0.894 |
| Oxygen saturation             | 404      | 96.2 [3.0]          | 254     | 96.1 [3.0]           | 0.562 |
| Respiration rate              | 405      | 19.8 [2.0]          | 254     | 20.4 [2.0]           | 0.161 |
| GCS score                     | 172      | 14.1 [1.0]          | 103     | 14.3 [1.0]           | 0.432 |
| Systolic blood pressure       | 405      | 127.4 [29.0]        | 254     | 127.4 [25.0]         | 0.834 |
| Diastolic blood pressure      | 405      | 72.7 [18.0]         | 254     | 72.7 [17.0]          | 0.721 |
| Temperature                   | 405      | 37.1 [0.9]          | 254     | 37.0 [0.7]           | 0.101 |

Notes.
1 Wilcoxon test for continuous variables; $\chi^2$ test for binary variables.
Supplementary Table 7: Temporal external validation, using hold-out sample (n=256)

| Included features                        | AUC  | Sensitivity | Specificity | PPV  | NPV  |
|------------------------------------------|------|-------------|-------------|------|------|
| NEWS2                                    | 0.700 | 0.305       | 0.939       | 0.600 | 0.819 |
| NEWS2 + DBP                              | 0.730 | 0.441       | 0.873       | 0.510 | 0.839 |
| NEWS2 + CRP + Neutrophil + eGFR + Albumin + Age | 0.730 | 0.458       | 0.873       | 0.519 | 0.843 |

D = Age, sex  
C = comorbidities (8 features)  
B = bloods (10 features)  
P = physiological parameters (7 features)