Predicting outcomes of COVID-19 from admission biomarkers: a prospective UK cohort study

David T Arnold ,[1] Marie Attwood,[2] Shaney Barratt,[1] Anna Morley,[1] Karen T Elvers,[3] Jorgen McKernon,[4] Charmaine Donald,[5] Adrian Oates,[4] Alan Noel,[2] Alasdair MacGowan,[2] Nick A Maskell,[1] Fergus W Hamilton[6]

Handling editor Richard Body

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/emermed-2020-210380).

[1]Academic Respiratory Unit, University of Bristol, Bristol, UK
[2]Bristol Centre for Antimicrobial Research, North Bristol NHS Trust, Bristol, UK
[3]Medicines Discovery Institute Cardiff, Cardiff University, Cardiff, UK
[4]Biochemistry, North Bristol NHS Trust, Bristol, UK
[5]Immunology, North Bristol NHS Trust, Bristol, UK
[6]Infection Sciences, North Bristol NHS Trust, Bristol, UK

Correspondence to
Dr David T Arnold, Academic Respiratory Unit, University of Bristol, Bristol BS10 5NB, UK; arnold.dta@gmail.com

Received 11 July 2020
Revised 30 March 2021
Accepted 10 April 2021
Published Online First 21 May 2021

To cite: Arnold DT, Attwood M, Barratt S, *et al*. *Emerg Med J* 2021;**38**:543–548.

ABSTRACT

Introduction COVID-19 has an unpredictable clinical course, so prognostic biomarkers would be invaluable when triaging patients on admission to hospital. Many biomarkers have been suggested using large observational datasets but sample timing is crucial to ensure prognostic relevance. The DISCOVER study prospectively recruited patients with COVID-19 admitted to a UK hospital and analysed a panel of putative prognostic biomarkers on the admission blood sample to identify markers of poor outcome.

Methods Consecutive patients admitted to hospital with proven or clinicoradiological suspected COVID-19 were consented. Admission bloods were extracted from the clinical laboratory. A panel of biomarkers (interleukin-6 (IL-6), soluble urokinase plasminogen activator receptor (suPAR), Krebs von den Lungen 6, troponin, ferritin, lactate dehydrogenase, B-type natriuretic peptide, procalcitonin) were performed in addition to routinely performed markers (C reactive protein (CRP), neutrophils, lymphocytes, neutrophil:lymphocyte ratio). Age, National Early Warning Score (NEWS2), CURB-65 and radiographic severity score on initial chest radiograph were included as comparators. All biomarkers were tested in logistic regression against a composite outcome of non-invasive ventilation, intensive care admission or death, with area under the curve (AUC) (figures calculated).

Results 187 patients had 28-day outcomes at the time of analysis. CRP (AUC: 0.69, 95% CI: 0.59 to 0.78), lymphocyte count (AUC: 0.62, 95% CI: 0.53 to 0.72) and other routine markers did not predict the primary outcome. IL-6 (AUC: 0.77, 0.65 to 0.88) and suPAR (AUC: 0.81, 0.72 to 0.88) showed some promise, but simple clinical features alone such as NEWS2 score (AUC: 0.70, 0.60 to 0.79) or age (AUC: 0.70, 0.62 to 0.77) performed nearly as well.

Discussion Admission blood biomarkers have only moderate predictive value for predicting COVID-19 outcomes, while simple clinical features such as age and NEWS2 score outperform many biomarkers. IL-6 and suPAR had the best performance, and further studies should focus on the additive value of these biomarkers to routine care.

Key messages

What is already known on this subject

► Biomarkers that predict the clinical course of COVID-19 would be invaluable at the point of hospital admission. Several blood-based biomarkers have been suggested but have not been tested in a prospective UK cohort.

What this study adds

► In this prospective UK cohort, routinely performed blood biomarkers at the point of hospital admission had limited ability, in isolation, to predict poor outcomes from COVID-19. Biomarkers of immune activation had the best predictive performance alongside routinely collected clinical information.

INTRODUCTION

COVID-19 causes a wide spectrum of disease, from asymptomatic to severe respiratory failure. The majority of patients who present to hospital will recover but some develop rapidly progressive respiratory compromise requiring ventilatory support. Biomarkers that might predict this deterioration would be invaluable when triaging patients on hospital admission to inform who can be safely discharged versus those who need careful respiratory monitoring.

The rapidly emerging literature base around biomarkers in COVID-19 has mainly extracted data from electronic health records of large cohort studies.[1–4] Far fewer have prospectively recruited and followed up patients. Those that have tested novel biomarkers have often done so at later timepoints in patients limiting extrapolation to hospital admission.[5–7] Few UK studies have assessed the additional value of biomarkers compared with the routinely recorded demographic information and clinical scales (such as National Early Warning Scores or CURB-65).

The DIagnostic and Severity markers of COVID-19 to Enable Rapid triage (DISCOVER) study prospectively recruited patients admitted with COVID-19 to a single UK hospital, with the aim of comparing the ability of various biomarkers and clinical scores to predict mortality, need for non-invasive ventilation (NIV) or intensive care unit (ITU) admission.

METHODS

This study is reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies (see online supplemental material)

Study design

This was a prospective cohort study aimed to assess prognostic clinical and blood biomarkers for COVID-19 disease based on the earliest available clinical and biochemical information.

Outcomes

The primary outcome of prediction was a composite outcome of ITU admission, NIV with continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BIPAP) outside the ITU or death (defined below as 'severe disease').

The secondary outcome was a composite outcome of ITU admission and death.

Patient recruitment

All patients were recruited via the DISCOVER study, a single-centre observational study at North Bristol NHS Trust recruiting patients with COVID-19, from 30 March 2020 until 29 June 2020. Patients were recruited on the basis of a positive PCR result for SARS-CoV-2, using the established PHE assay in use at the time or a clinicoradiological diagnosis of COVID-19 disease. During the pandemic, community testing became widely available, although the results were not available to hospital staff. As such, later patients were often recruited on the basis of a history of positive testing in the community. The only exclusion criteria was an inability to consent. For patients in ITU, family members were able to consent on behalf of them if too unwell to consent as a personel consultee.

Clinical information

Clinical information was recorded on a REDCap (Vanderbilt University) database,[8] by the consenting nurse or physician. Routine demographics were recorded and presence of important comorbidities. Comorbidities were defined either by their recording in the admission notes/hospital record (for hypertension, heart disease and chronic lung disease), the presence of a positive serological result (for HIV) or for requirement for dialysis or an estimated glomerular filtration rate (eGFR) of <30 mL/min (for chronic kidney disease). Ethnicity was also recorded.

The earliest admission National Early Warning Score (NEWS2) was extracted from the clinical record. This is a numeric score (from 0 to 20), reflecting the degree of physiological dysfunction.[9] Higher numbers indicate more severe physiological dysfunction. Routine biochemistry and haematology results were extracted from the clinical record, using the earliest available figure. Outcome data recorded was in line with RECOVERY, the national RCT of therapeutic interventions for COVID-19 (https://www.recoverytrial.net/). This included 28-day mortality, requirement for ITU, ventilation, renal replacement therapy, and inotropes.

NIV was defined by the receipt of NIV by CPAP, BIPAP or High Flow Nasal Oxygen (HFNO) any time during the hospital stay.

The radiological severity score was calculated using the method described by Wong *et al*.[10] A score of 0–4 was assigned to each lung depending on the extent of involvement by consolidation or ground glass opacities: 0=no involvement, 1 =<25%, 2=25%–49%, 3=50–75%, 4 =>75% involvement. The scores for each lung were summed to produce a final severity score ranging from 0 to 8. Radiographs were scored by a respiratory and infectious diseases physician.

Table 1 Demographics of the study cohort

Characteristic	Survivor, N=148	Non-survivor/ITU/NIV, N=39	P value
Age (18+), years	55 (44–71)	66 (60–76)	<0.001
Sex			0.7
Male	79 (53)	22 (56)	
Female	69 (47)	17 (44)	
PCR proven disease			0.6
Proven	111 (75)	31 (79)	
Suspected	37 (25)	8 (21)	
Status at time of consent			0.010
Inpatient	119 (80)	38 (97)	
Outpatient	29 (20)	1 (2.6)	
Diabetes status			0.3
No	115 (78)	34 (87)	
T1DM	3 (2.0)	1 (2.6)	
T2DM	30 (20)	4 (10)	
Heart disease	34 (23)	12 (31)	0.3
Chronic lung disease	26 (18)	20 (51)	<0.001
Severe liver disease	3 (2.0)	2 (5.1)	0.3
Severe kidney impairment (eGFR <30 or dialysis)	16 (11)	6 (15)	0.4
Hypertension	37 (25)	15 (38)	0.10
HIV status	1 (0.7)	1 (2.6)	0.4
Non-white ethnicity	20 (16)	5 (15)	0.9

Median (IQR); n (%).
Wilcoxon rank sum test; Pearson's χ^2 test; Fisher's exact test.
eGFR, estimated glomerular filtration rate; ITU, Intensive Care admission; NIV, non-invasive ventilation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Biomarkers and samples

For conventional biomarkers of infection (namely C reactive protein (CRP), components of the full blood count and routine renal function), data were prospectively recorded. The first result from that admission was taken or, for established inpatients, the result on the day of the diagnosis. These results were available to the clinician and therefore could impact on prognosis (ie, clinicians were not blinded to these results)

For other potential predictive markers (lactate dehydrogenase (LDH), procalcitonin (PCT), interleukin-6 (IL-6), Krebs von den Lungen 6 (KL-6), ferritin, troponin, B-type natriuretic peptide (NT-pro-BNP), soluble urokinase plasminogen activator receptor (suPAR)), analysis was performed on frozen samples in batch analysis as described below. Laboratory staff were unaware of clinical outcome and were therefore functionally blinded.

The earliest initial sample was extracted from the blood sciences laboratory after routine testing had been performed; in admitted cases this was the initial sample taken in the emergency department (ED); in hospitalised cases, this was the sample from the day of diagnosis. suPAR analysis was performed on the suPARnostic ELISA platform; KL-6 and IL-6 were performed on the Fujirebio Lumipulse. CRP, ferritin, LDH, troponin, NT-pro-BNP and PCT were performed on the Roche Diagnostics cobas platform. The specific analytic platforms were spectrophotometric: c701 (CRP) and c501 (LDH), immunoassay: e501 (ferritin, troponin, NT-pro-BNP, PCT). The full blood count was performed on the Sysmex XN (Sysmex Diagnostics).

As the volume of blood available varied and was small, the total number of assays varied slightly; as for some participants only enough blood was available to perform one or two assays, or there was technical failure and an inability to repeat due to lack of sample.

Statistical approach

In this study, we aimed to identify whether any individual biomarker (lymphocyte count, neutrophil count, neutrophil:lymphocyte ratio (NLR), CRP, IL-6, KL-6, suPAR, NT-pro-BNP, LDH, PCT, troponin T, ferritin) had prognostic significance for the primary outcome as an individual marker, when used on the initial blood sample taken.

There was a deliberate focus on relatively simplistic (logistic regression) models: given the sample size, complex models would be at risk of overfitting, and the main target was to identify the additional value of a biomarker, all of which are reported on a linear scale.[11] Complete case analysis was performed for each individual biomarker.

Receiver operating characteristic curve (ROC) curves were generated, and area under the curve (AUC) figures were calculated alongside sensitivity and specificity for each biomarker, at Youden's index. CIs were generated around the AUC by bootstrapping.

All analysis was performed in R (V.4.0.0), using the packages 'tidyverse', 'broom', 'tidymodels' and 'pROC'. Analytic code is available at: https://github.com/gushamilton/discover_prediction/

Patient and public involvement

Given the difficultly of performing PPI during a pandemic, patients were not involved in the design, or conduct, or reporting, or dissemination plans of the DISCOVER study at the time this manuscript was submitted.

RESULTS

One hundred eighty-seven participants had reached 28 days postdiagnosis and were included in the analysis (prespecified timing of the primary outcome). Table 1 shows the demographics of the cohort. One hundred and one patients (54%) were male, and the median age was 58 (IQR: 46–73) years; 76% of the cohort had positive PCR results for SARS-CoV-2, with the remaining clinically suspected.

Comorbidities were relatively common within the cohort with hypertension and diabetes being the most predominant. Patients with severe disease (death, ITU admission or NIV) were generally older and more comorbid than non-severe patients. Thirty-nine patients had the primary outcome. Fifteen patients went to the ITU, of which 4 died and 11 survived. Seven patients required NIV outside the ITU, 4 of whom died (see figure 1).

There was a significant variation in physiological state (eg, NEWS2), with a median NEWS2 score of 4 (IQR 2–6), with the highest NEWS2 score recorded was 13. Patients that had severe disease had higher NEWS2 scores. There was also wide variation in functional status, with many patients having some degree of frailty, with frailer patients more likely to die or require enhanced care. Escalation status was recorded for most patients, with patients who died more likely to have limitations on ceiling of care, recorded in table 2.

Admission blood tests are recorded in table 3. There was no significant difference for many blood tests, with lymphocyte count being slightly lower in those with severe disease

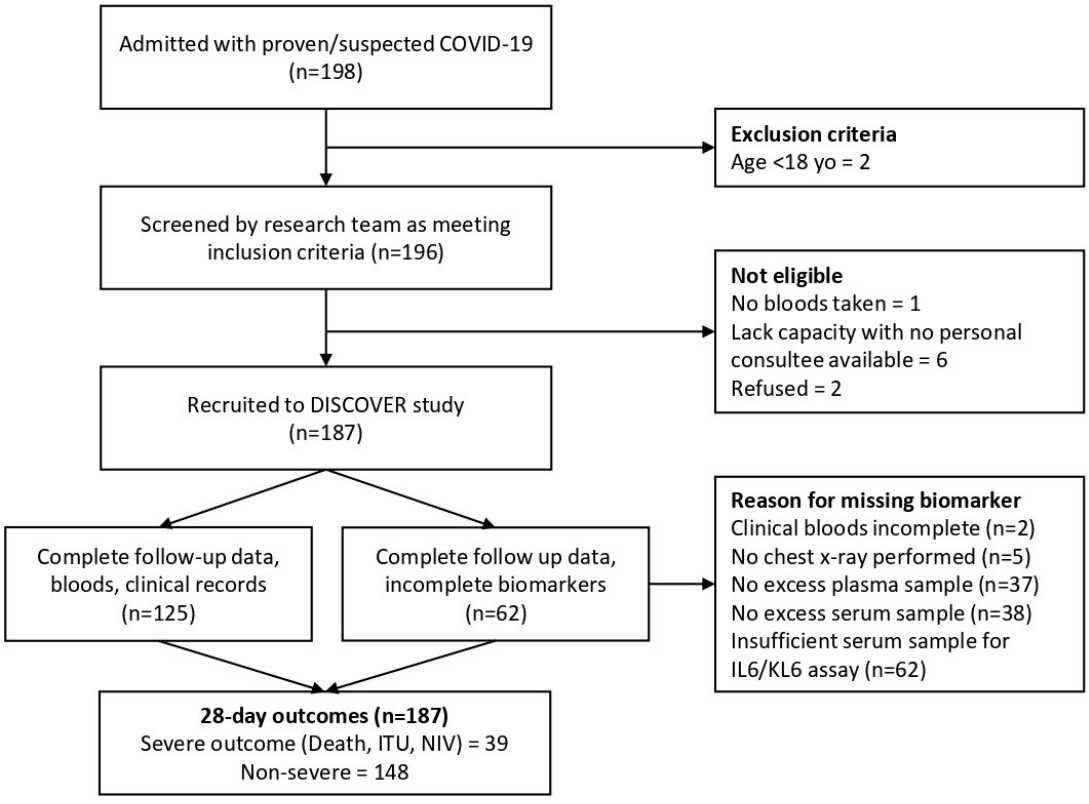


Figure 1 Study flowchart. ITU, intensive care admission; NIV, required non-invasive ventilation.

Table 2 Escalation status

Characteristic	Survivor, N=148	Non-survivor/ITU/NIV, N=39
For full escalation to ITU including intubation and ventilation	104 (83)	18 (55)
Not for invasive ventilation (intubation and ventilation) but would be for NIV or CPAP on ward.	8 (6.3)	11 (33)
Not for ITU or for NIV/CPAP	14 (11)	3 (9.1)
For palliative treatments only	0 (0)	1 (3.0)
Unknown	22	6

Statistics presented: n (%).
CPAP, continuous positive airway pressure; ITU, Intensive Care admission; NIV, non-invasive ventilation.

and NLR being slightly higher. Renal dysfunction was more common in the severe disease.

Logistic regression and AUC calculation

Table 4 shows biomarker performance to predict severe COVID-19 outcomes. Blood was not available for all participants for all tests, with the number included in each model listed. Most biomarkers had modest predictive value, with suPAR (AUC 0.81) and IL-6 (AUC 0.77) having the best performance. Many biomarkers had weak performance (CRP, neutrophils, lymphocytes, KL-6), with AUC figures between 0.5 and 0.65. ROC plots are available in the online supplemental material for all biomarkers. Of note, both age and NEWS2 score performed as well as most biomarkers.

Results of routine biomarkers (CRP, neutrophils, lymphocytes and NLR) are shown in figure 2. Best performing novel biomarkers (IL-6, suPAR, LDH and PCT) box plots are shown in figure 3 (PCT values have been logged prior to plotting to aid visualisation as they had very wide ranges).

Secondary outcomes

For the composite outcome of ITU and mortality, results are reported in the online supplemental material. Due to a small number of events (18 deaths, 15 ITU admissions), CIs were wider, but results were similar although perhaps slightly worse. Again, suPAR and IL-6 were the best performing biomarkers (AUC 0.81 for suPAR, AUC 0.70 for IL-6), with most other biomarkers having an AUC between 0.5 and 0.65.

Table 3 Conventional blood tests

Characteristic	Survivor, N=148	Non-survivor/ITU/NIV, N=39	P value
Haemoglobin (g/L)	135 (126–148)	134 (112–147)	0.4
White cell count (x10^9/L)	7.6 (5.7–9.9)	6.9 (5.0–9.7)	0.7
Neutrophils (x10^9/L)	5.7 (3.9–8.0)	5.8 (3.7–8.4)	0.6
Lymphocytes (x10^9/L)	1.08 (0.68–1.55)	0.86 (0.58–1.16)	0.018
Platelets (x10^9/L)	239 (189–289)	202 (149–258)	0.009
Sodium (mmol/L)	138 (135–140)	137 (136–138)	0.4
Urea (mmol/L)	4.7 (3.6–7.1)	7.0 (5.0–9.4)	<0.001
eGFR (mL/min)	89 (65–90)	64 (50–86)	<0.001
Albumin (mmol/L)	33.5 (31.0–36.8)	32.0 (27.5–34.0)	0.009
CRP (mg/L)	44 (12–86)	87 (54–152)	<0.001
NLR	4.9 (2.8–9.4)	6.3 (4.7–12.3)	0.023

Median (IQR).
Wilcoxon rank-sum test.
CRP, C reactive protein; eGFR, estimated glomerular filtration rate; ITU, Intensive Care admission; NIV, non-invasive ventilation; NLR, neutrophil:lymphocyte ratio.

Table 4 Biomarker/clinical indicator performance to predict severe COVID-19 outcomes

Biomarker/clinical indicator	AUC (95% CI)	Sensitivity at Youden's index	Specificity at Youden's index
CRP (n=179)	0.69 (0.59 to 0.78)	0.77	0.55
Neutrophils (n=185)	0.53 (0.43 to 0.64)	0.44	0.69
Lymphocytes (n=185)	0.62 (0.53 to 0.72)	0.85	0.38
NLR (n=185)	0.62 (0.53 to 0.71)	0.82	0.43
IL-6 (n=125)	0.77 (0.65 to 0.88)	0.70	0.83
KL-6 (n=149)	0.51 (0.38 to 0.65)	0.21	0.92
suPAR (n=150)	0.81 (0.72 to 0.88)	0.82	0.65
Procalcitonin (n=150)	0.72 (0.62 to 0.81)	0.94	0.43
Ferritin (n=149)	0.64 (0.53 to 0.74)	0.59	0.69
LDH (n=149)	0.62 (0.51 to 0.72)	0.55	0.69
Troponin (n=149)	0.70 (0.6 to 0.79)	0.88	0.45
BNP (n=149)	0.64 (0.53 to 0.74)	0.67	0.58
Age (n=187)	0.70 (0.62 to 0.77)	0.95	0.41
NEWS2 score (n=182)	0.70 (0.60 to 0.79)	0.41	0.88
CURB-65 (n=180)	0.65 (0.55 to 0.73)	0.72	0.54
Radiographic severity score (n=182)	0.60 (0.49 to 0.71)	0.36	0.91

AUC, area under the curve; BNP, B-type natriuretic peptide; CRP, C reactive protein; IL-6, interleukin-6; KL-6, Krebs von den Lungen 6; LDH, lactate dehydrogenase; NLR, neutrophil:lymphocyte ratio; suPAR, soluble urokinase plasminogen activator receptor.

DISCUSSION

COVID-19 remains a clinical challenge. The majority of patients who present to hospital will recover but some develop rapidly progressive respiratory failure. Biomarkers that might predict this deterioration would be invaluable when triaging patients on hospital admission to inform who can be safely discharged versus those who might need intensive care support in the near future. This paper presents a prospectively recruited UK cohort of patients with COVID-19 with targeted biomarker sampling at presentation.

Previous literature

A large observational study recruiting from the majority of NHS hospitals (ISARIC) estimates that of the 34 608 patients with

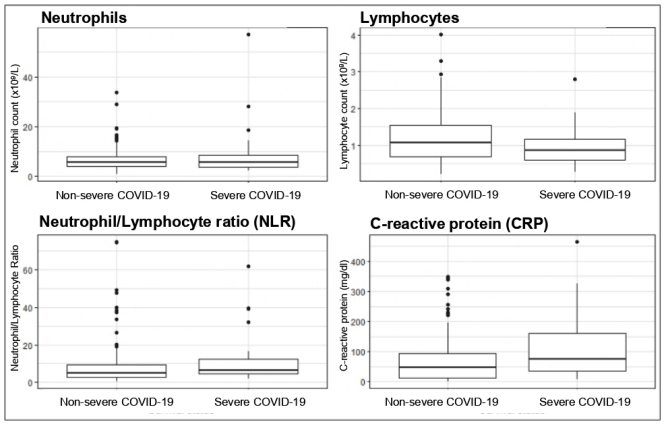


Figure 2 Box plots of routine blood biomarkers.

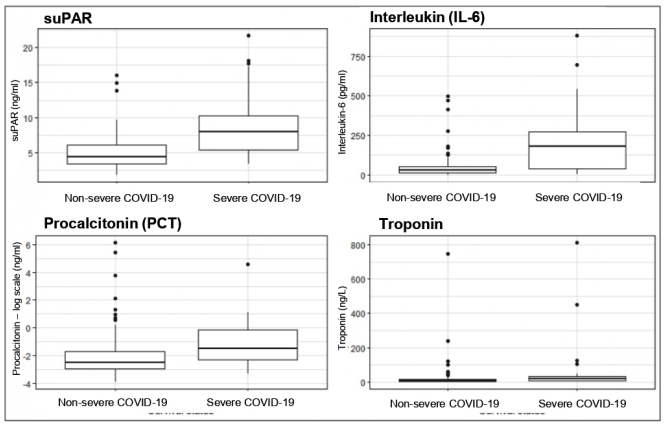


Figure 3 Box plots of best performing novel blood biomarkers. suPAR, soluble urokinase plasminogen activator receptor.

outcome data, 7374 (17%) required admission to ITU and 11 659 (33.7%) died within follow-up.[12] There have been numerous studies and meta-analyses on potential predictors of respiratory decline in COVID-19 pneumonia with the development of a 'cytokine storm' in specific patients cited as a major determinant.[13 14] As a result, there has been a focus on biomarkers that rise in other similar conditions such as ferritin, LDH, IL-6 and suPAR.[15] A rise in cardiovascular events and coagulopathies has also been seen in patients with COVID-19 pneumonia so biomarkers such as troponin, NT-pro-BNP, fibrinogen and D-dimer have been studied.[16–19] Given that mortality from COVID-19 increases with age and frailty, biomarkers of frailty have been shown to be related to worse outcomes (albumin, eGFR).[2 12 20] Finally, given this is a respiratory infection, blood-based biomarkers that prognosticate bacterial pneumonia have been included in treatment guidelines and even entry criteria for clinical trials, including lymphopaenia, neutrophilia, PCT and C reactive protein.[6 21]

Study findings

In this study, conventionally performed blood biomarkers, in isolation, did not predict outcome when performed on admission. Neutrophilia and C reactive protein had AUC close to 0.5, with lymphopaenia and NLR having only marginally better discriminative value. Cardiac markers were on average slightly higher in patients with worse clinical outcomes but should not be relied on to make treatment decisions at baseline. Literature suggests that they may have more utility when measured serially, especially in the very unwell patient.[16]

Markers of immune activation had more promise at the admission timepoint with IL-6 and suPAR the best-performing within this cohort. It has been hypothesised that an exaggerated immune response or 'cytokine storm' plays a significant role in COVID-19 and several immunomodulatory therapies are being trialled. IL-6 is a proinflammatory mediator for the induction of the acute phase response and shown to be a predictive marker of deterioration in other serious lung pathologies. Specific to COVID-19, Han and colleagues[22] assessed the cytokine profile of 102 patients, admitted to a single hospital in Wuhan, by disease severity on admission. From a panel of six cytokines (TNF-α, IFN-γ, IL-2, IL-4, IL-6 and IL-10), serum IL-6 was predictive of disease severity at the time with an AUC of 0.84, although longer term outcomes were not reported. Another prospective study of 89 patients admitted to a German hospital demonstrated that admission IL-6 was superior to other blood-based biomarkers at predicting the need for mechanical ventilation (using a cut-off of 35 pg/mL).[22] Another prospective study of 89 patients admitted to a German hospital demonstrated that admission IL-6 was superior to other blood-based biomarkers at predicting the need for mechanical ventilation (using a cut-off of 35 pg/mL).[6] In our study, the admission IL-6 (at a cut-off of 74.9 pg/mL) had a sensitivity of 0.70 and specificity of 0.84 (AUC 0.77). Randomised trial evidence is emerging showing that treatment with the IL-6 receptor antagonists, tocilizumab and sarilumab, improves outcomes, including survival in severely unwell patients with COVID-19.[23]

suPAR, a marker of immune activation, has been shown to predict deterioration in several infectious and inflammatory disorders. It forms part of the fibrinolysis cascade and increased levels have been shown to predispose to clotting abnormality and renal dysfunction, both of which are important drivers of morbidity and mortality in COVID-19. A prospective study of 57 patients presenting with COVID-19 demonstrated that admission levels of suPAR were significantly greater among patients who eventually required ventilatory support.[15] A cut-off of 6 ng/mL had a sensitivity of 86% and specificity of 92%. A prospective study of 57 patients presenting with COVID-19 demonstrated that admission levels of suPAR were significantly greater among patients who eventually required ventilatory support.[15] A cut-off of 6 ng/mL had a sensitivity of 86% and specificity of 92%. In our study, it performed reasonably compared with other blood biomarkers but at a cut-off of 5.2 ng/dL only had a sensitivity of 82% and specificity of 65%, with lower cutoffs increasing sensitivity at relatively little cost.

Clinical markers

The focus of this study was the additional role of blood biomarkers when initially assessing patients presenting with COVID-19. The DISCOVER cohort also collected routinely recorded clinical data including demographics, baseline observations and initial radiography. It is notable that this easily accessible information outperformed many of the blood-based biomarkers tested.

The NEWS2 is used throughout the UK. There is currently limited evidence supporting its use in COVID-19.[24] In China, Liao and colleagues[25] created a non-validated COVID-19-specific NEWS2 score (where age over 65 added 3 points). We could not find any prospective UK-based studies accessing the utility of NEWS2 in COVID-19 admission.[25] In the DISCOVER cohort, NEWS2 score had an AUC of 0.70. The CURB-65 score is a severity scoring system for community-acquired pneumonia and is often used to make decisions around need for hospital admission. Although previous retrospective literature from our centre has shown that CURB-65 scores are higher in patients with a worse outcome from COVID-19,[26] this prospective study has demonstrated that it cannot be relied on to make treatment decisions on an individual patient level.

Strengths

The DISCOVER cohort was prospectively designed and analysed the earliest ED blood sample, which is a key strength. Clinical metadata was robustly recorded, and novel biomarkers were performed in batch assays, maximising replicability and reducing bias as results could not influence patient care. Unlike other datasets (eg, Electronic Health Record extractions), we included patients who had clinically suspected COVID-19, as the currently available assays still have limited sensitivity. Technicians were employed to extract blood out of autoanalyser machines to get the earliest possible sample, enabling recruitment of patients after admission or even

as outpatients. Missing data around comorbidities was rare, as patients were prospectively recruited by research nurses.

Limitations

The major limitation of this study is the limited sample size, leading to imprecise estimates of biomarker performance. A second limitation is the composite outcome of NIV, ITU admission and death, which has been used in major interventional COVID-19 trials. Although this is clinically useful and may aid differentiation of those who require specialist care, the provision and use of NIV are more clinician and hospital dependent and may be harder to extrapolate from. However, our secondary analysis of ITU admission and death was largely similar, supporting this approach. Finally, although around 80% of patients had blood available, a proportion did not have excess sample available for additional testing, so only the routinely performed biomarkers (CRP, neutrophils, lymphocytes, NLR) are recorded for those patients. It is also important to note that these results were available to clinicians and therefore may have biased the outcome (ie, patients with high CRP may have received more aggressive therapy). At the time of recruitment to this study, there were however no approved therapies for COVID-19 and it is therefore unlikely this strongly biased the results.

CONCLUSION

To our knowledge, this is the largest recruited UK cohort of consecutive patients presenting with COVID-19. Blood biomarkers, when performed on admission bloods, had only moderate predictive value for COVID-19 similar to age and routine clinical scores (eg, NEWS2 score). IL-6 and suPAR had the best performance, and further, large prospective studies should validate the additional value of these biomarkers to routinely collected clinical information.

Twitter David T Arnold @DavidT_Arnold and Marie Attwood @ree19872

Contributors DTA and FWH had the idea for the study. SB, AMG and NAM have a supervisory role. AM led the collection of samples. KTE, JMK, CD, AO and AN were involved in the analysis of samples. FWH led the data analysis. All authors were involved in the writing of the manuscript.

Funding The DISCOVER study was supported by grants from the Southmead Hospital Charity and Elizabeth Blackwell Institute (Grant number: not applicable/NA). DTA is funded by a National Institute for Health Research (NIHR) Doctoral Research Fellowship (DRF-2018-11-ST2-065). FH is funded via the National Institute for Health Academic Clinical Fellowship scheme.The suPARnostic ELISA kits and IL-6/KL-6 assays were gifts from ViroGates (Birkeroed, Denmark) and Fujirebio Europe, respectively, for unrestricted research activity (Grant number: not applicable/NA).

Disclaimer The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethics approval via South Yorkshire REC: 20/YH/0121, CRN approval no: 45469.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Although we are unable to share raw data, the analytic code is available at https://github.com/gushamilton/discover_prediction/

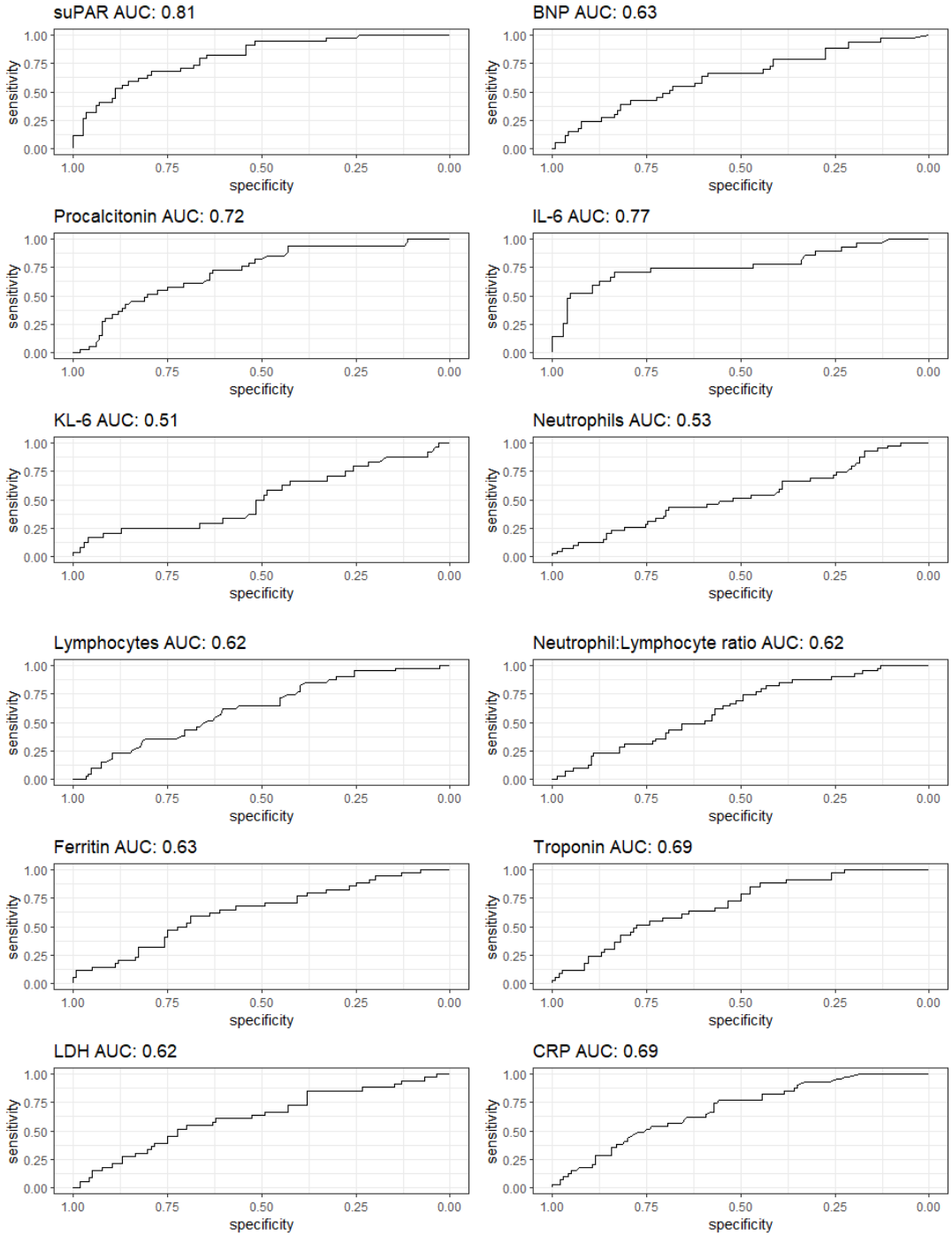
ORCID iD

David T Arnold http://orcid.org/0000-0003-3158-7740

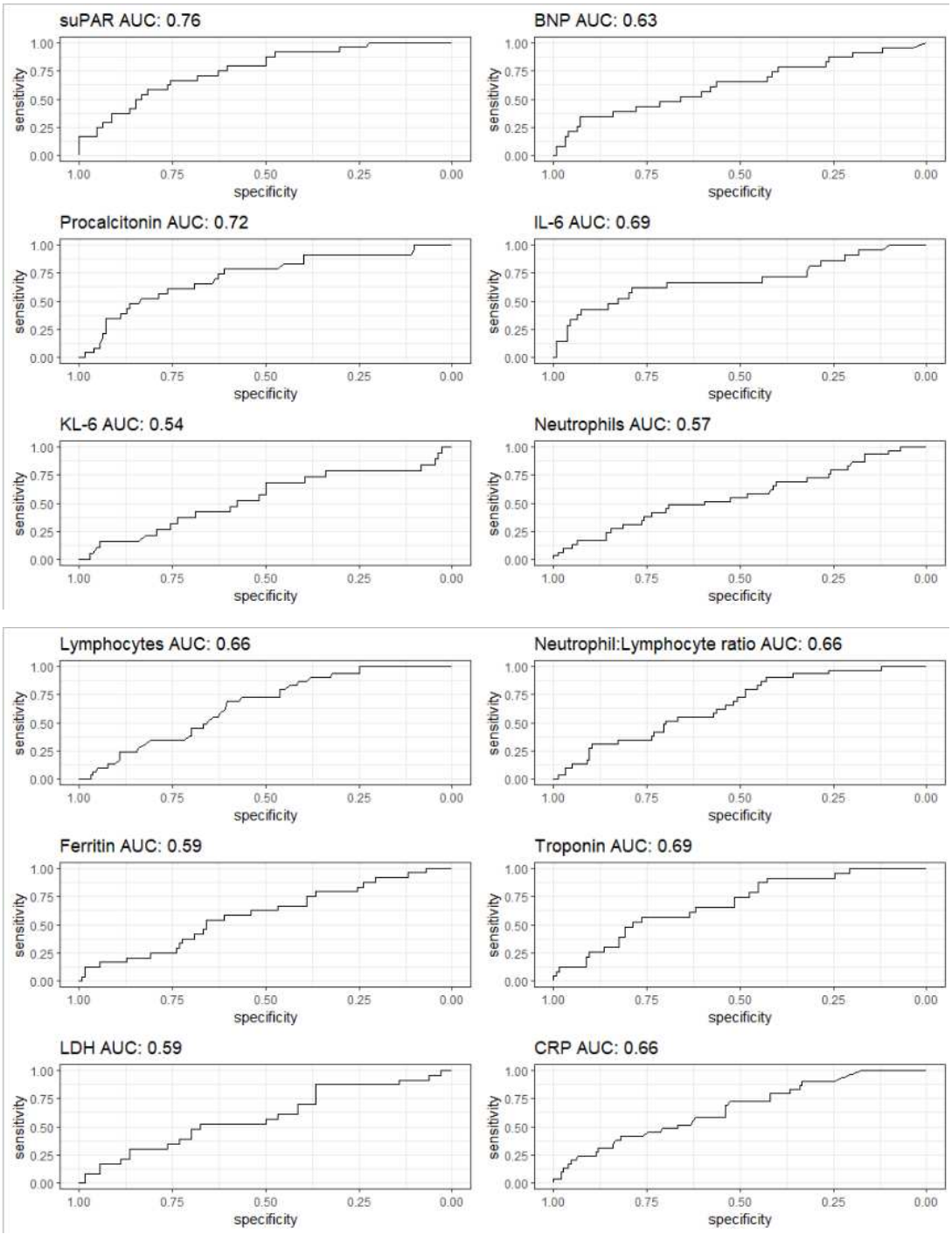
REFERENCES

1 Petrilli CM, Jones SA, Yang J, *et al*. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020;369:m1966.
2 Galloway JB, Norton S, Barker RD, *et al*. A clinical risk score to identify patients with COVID-19 at high risk of critical care admission or death: an observational cohort study. *J Infect* 2020;81:282–8.
3 Liang W, Liang H, Ou L, *et al*. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. *JAMA Intern Med* 2020;180:1081.
4 Shi S, Qin M, Cai Y, *et al*. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J* 2020;41:2070–9.
5 Smadja DM, Guerin CL, Chocron R, *et al*. Angiopoietin-2 as a marker of endothelial activation is a good predictor factor for intensive care unit admission of COVID-19 patients. *Angiogenesis* 2020;23:611–20.
6 Herold T, Jurinovic V, Arnreich C, *et al*. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol* 2020;146:128–36.
7 Rastrelli G, Di Stasi V, Inglese F, *et al*. Low testosterone levels predict clinical adverse outcomes in SARS-CoV-2 pneumonia patients. *Andrology* 2021;9:88–98.
8 Harris PA, Taylor R, Minor BL, *et al*. The REDCap Consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
9 McGinley A, Pearse RM. A national early warning score for acutely ill patients. *BMJ* 2012;345:e5310.
10 Wong HYF, HYS L, Fong AH. Frequency and distribution of chest radiographic findings in COVID-19 positive patients. *Radiology* 2019:201160.
11 Wynants L, Van Calster B, Collins GS, *et al*. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. *BMJ* 2020;369:m1328.
12 ISARIC. *International severe acute respiratory and EmergingvInfections Consortium): COVID-19 report*, 2020.
13 Henry BM, de Oliveira MHS, Benoit S, *et al*. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med* 2020;58:1021–8.
14 Kermali M, Khalsa RK, Pillai K, *et al*. The role of biomarkers in diagnosis of COVID-19 - A systematic review. *Life Sci* 2020;254:117788.
15 Rovina N, Akinosoglou K, Eugen-Olsen J, *et al*. Soluble urokinase plasminogen activator receptor (suPAR) as an early predictor of severe respiratory failure in patients with COVID-19 pneumonia. *Crit Care* 2020;24:187.
16 Vrsalovic M, Vrsalovic Presecki A. Cardiac troponins predict mortality in patients with COVID-19: a meta-analysis of adjusted risk estimates. *J Infect* 2020;81:e99–100.
17 Gao L, Jiang D, Wen X-S, *et al*. Prognostic value of NT-proBNP in patients with severe COVID-19. *Respir Res* 2020;21:83.
18 Artifoni M, Danic G, Gautier G, *et al*. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. *J Thromb Thrombolysis* 2020;50:211–6.
19 Zhang L, Yan X, Fan Q. D-Dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost* 2020.
20 Kato H, Shimizu H, Shibue Y, *et al*. Clinical course of 2019 novel coronavirus disease (COVID-19) in individuals present during the outbreak on the diamond Princess cruise SHIP. *J Infect Chemother* 2020;26:865–9.
21 Luo Z, Wang N, Liu P, *et al*. Association between chest CT features and clinical course of coronavirus disease 2019. *Respir Med* 2020;168:105989.
22 Han H, Ma Q, Li C, *et al*. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. *Emerg Microbes Infect* 2020;9:1123–30.
23 medrxiv. Interleukin-6 receptor antagonists in critically ill patients with Covid-19 – preliminary report. Available: https://www.medrxiv.org/content/10.1101/2021.01.07.21249390v2
24 Ihle-Hansen H, Berge T, Tveita A. COVID-19: symptoms, course of illness and use of clinical scoring systems for the first 42 patients admitted to a Norwegian local Hospital. *Tidsskr Nor Laegeforen* 2020;140. [Epub ahead of print: 05 May 2020]. doi:10.4045/tidsskr.20.0301
25 Liao X, Wang B, Kang Y. Novel coronavirus infection during the 2019–2020 epidemic: preparing intensive care units—the experience in Sichuan Province, China. *Intensive Care Med* 2020;46:357–60.
26 Tomlins J, Hamilton F, Gunning S, *et al*. Clinical features of 95 sequential hospitalised patients with novel coronavirus 2019 disease (COVID-19), the first UK cohort. *J Infect* 2020;81:e59–61.

Supplementary 1: ROC plots for each biomarker for the primary outcome



Supplementary 2: Performance of each biomarker on the composite of ITU admission and mortality; ROC plots and diagnostic performance



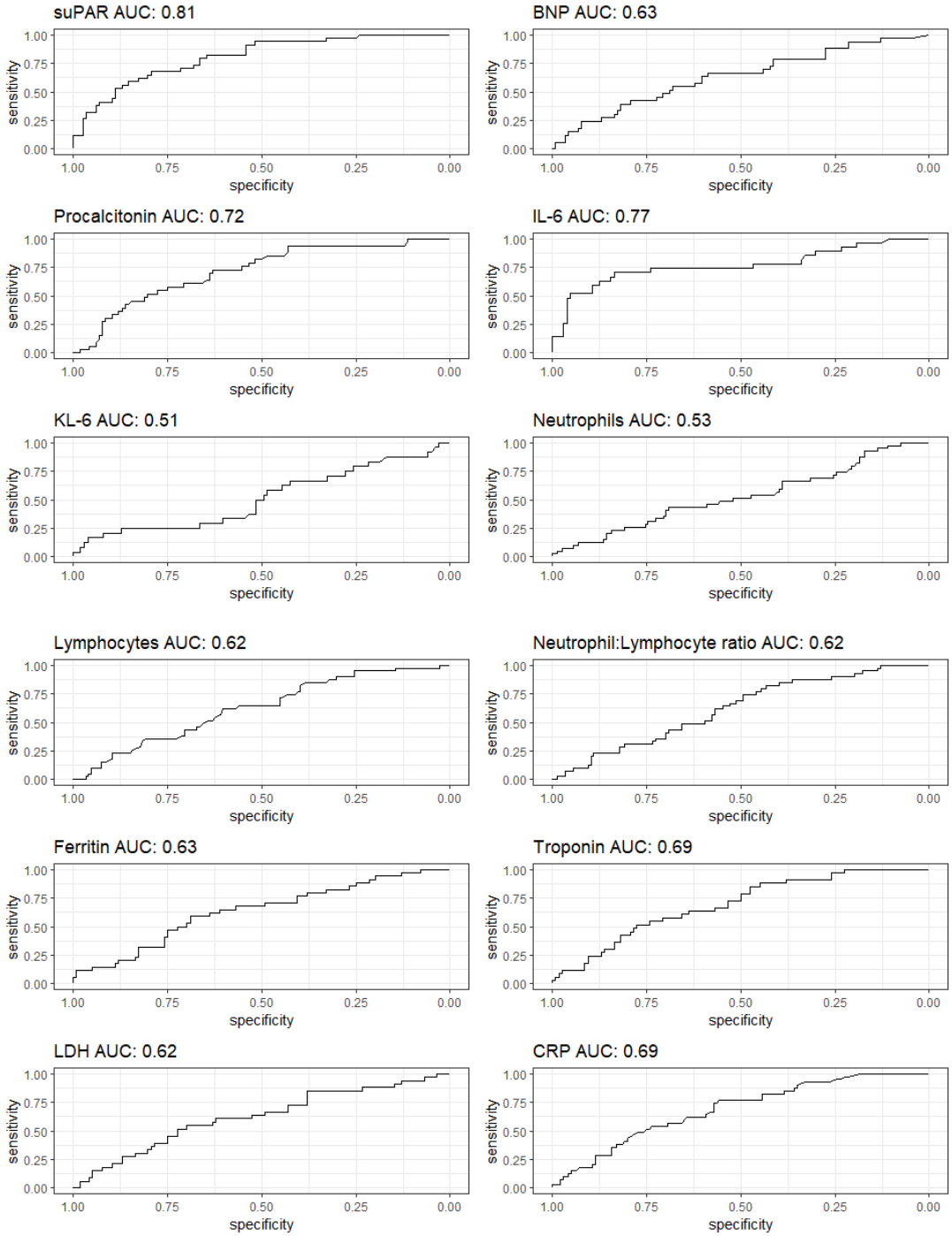
Supplement 3: Proven vs suspected cases – a comparison

Characteristic	Proven, N = 142	Suspected, N = 45	p-value
Age (18+)	61 (47, 75)	53 (41, 62)	0.010
			0.7
Male	78 (55%)	23 (51%)	
Female	64 (45%)	22 (49%)	
			0.049
Inpatient	115 (81%)	42 (93%)	
Outpatient	27 (19%)	3 (6.7%)	
Diabetes status			0.2
None	117 (82%)	32 (71%)	
T1DM	3 (2.1%)	1 (2.2%)	
T2DM	22 (15%)	12 (27%)	
Heart disease	39 (27%)	7 (16%)	0.11
Chronic Lung disease	39 (27%)	7 (16%)	0.11
Severe Liver disease	4 (2.8%)	1 (2.2%)	>0.9
Severe kidney impairment (eGFR< 30 or dialysis)	18 (13%)	4 (8.9%)	0.5
Hypertension	40 (28%)	12 (27%)	0.8
HIV status	2 (1.4%)	0 (0%)	>0.9
Primary outcome:			0.6
Survivor	111 (78%)	37 (82%)	
Non-survivor/ITU/NIV	31 (22%)	8 (18%)	
Non-white ethnicity	21 (18%)	4 (10%)	0.3
Median (IQR); n (%)			

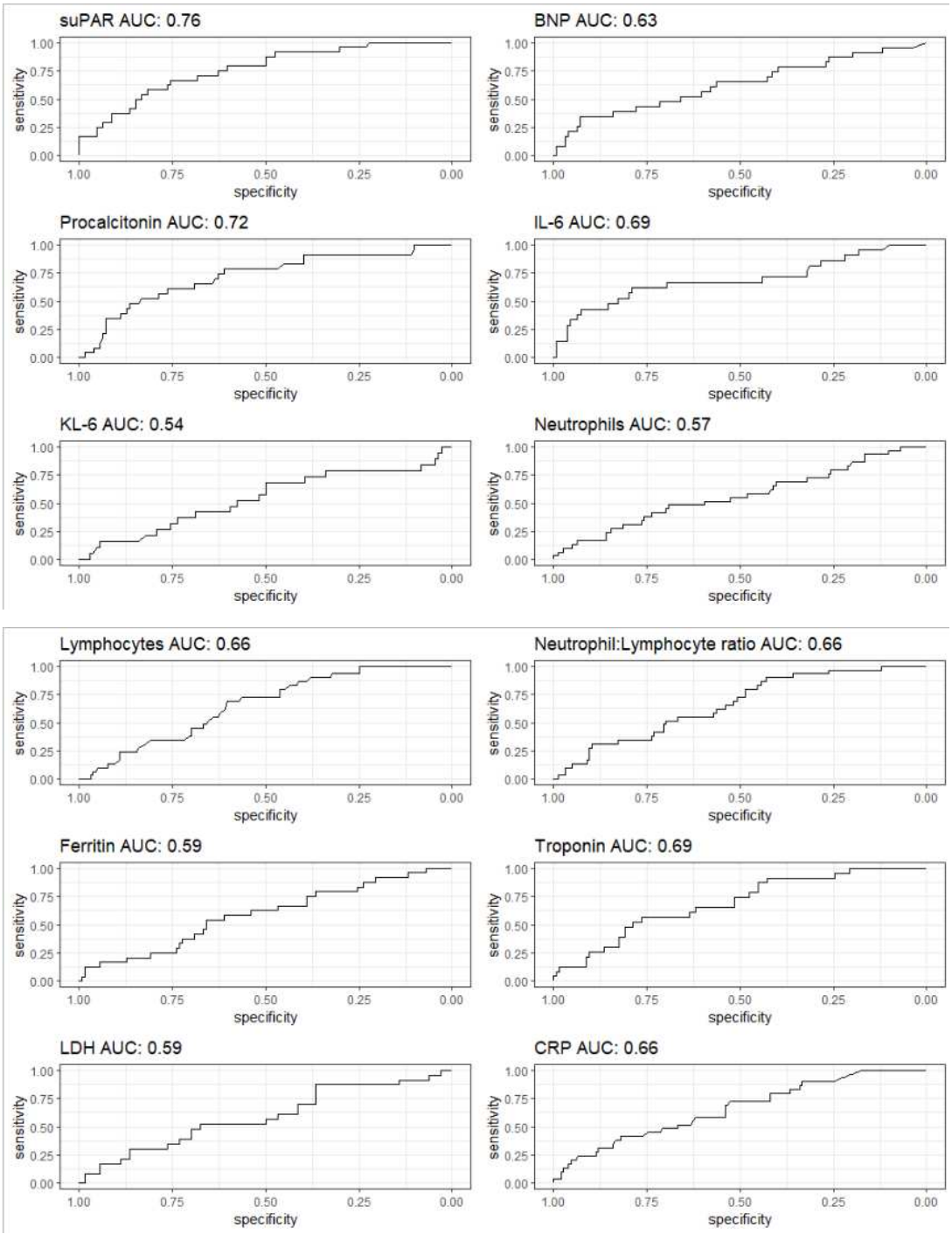
Supplemement 4: Odds ratios (logged) for each predictor

Term	Coefficent	Lower 95% CI	Higher 95% CI	P value
CRP	1.7918	1.3134	2.5712	0.0006
Neutrophils	1.3993	0.7875	2.5014	0.2511
Lymphocytes	0.4988	0.2604	0.9332	0.0316
NLR	1.5346	1.0386	2.2912	0.0327
IL6	2.3320	1.6058	3.5821	0.0000
KL6	1.0008	0.9998	1.0018	0.1291
suPAR	13.9827	5.2240	44.3974	0.0000
LDH	2.8663	1.0115	8.7361	0.0540
Ferritin	1.5478	1.1056	2.2308	0.0142
Troponin T	1.7433	1.2442	2.5218	0.0018
BNP	1.2597	1.0452	1.5305	0.0168
NEWS (unlogged)	1.3068	1.1497	1.4995	0.0001
Age (unlogged)	1.0441	1.0209	1.0701	0.0003

Supplementary 1: ROC plots for each biomarker for the primary outcome



Supplementary 2: Performance of each biomarker on the composite of ITU admission and mortality; ROC plots and diagnostic performance



Supplement 3: Proven vs suspected cases – a comparison

Characteristic	Proven, N = 142	Suspected, N = 45	p-value
Age (18+)	61 (47, 75)	53 (41, 62)	0.010
			0.7
Male	78 (55%)	23 (51%)	
Female	64 (45%)	22 (49%)	
			0.049
Inpatient	115 (81%)	42 (93%)	
Outpatient	27 (19%)	3 (6.7%)	
Diabetes status			0.2
None	117 (82%)	32 (71%)	
T1DM	3 (2.1%)	1 (2.2%)	
T2DM	22 (15%)	12 (27%)	
Heart disease	39 (27%)	7 (16%)	0.11
Chronic Lung disease	39 (27%)	7 (16%)	0.11
Severe Liver disease	4 (2.8%)	1 (2.2%)	>0.9
Severe kidney impairment (eGFR< 30 or dialysis)	18 (13%)	4 (8.9%)	0.5
Hypertension	40 (28%)	12 (27%)	0.8
HIV status	2 (1.4%)	0 (0%)	>0.9
Primary outcome:			0.6
Survivor	111 (78%)	37 (82%)	
Non-survivor/ITU/NIV	31 (22%)	8 (18%)	
Non-white ethnicity	21 (18%)	4 (10%)	0.3
Median (IQR); n (%)			

Supplemement 4: Odds ratios (logged) for each predictor

Term	Coefficent	Lower 95% CI	Higher 95% CI	P value
CRP	1.7918	1.3134	2.5712	0.0006
Neutrophils	1.3993	0.7875	2.5014	0.2511
Lymphocytes	0.4988	0.2604	0.9332	0.0316
NLR	1.5346	1.0386	2.2912	0.0327
IL6	2.3320	1.6058	3.5821	0.0000
KL6	1.0008	0.9998	1.0018	0.1291
suPAR	13.9827	5.2240	44.3974	0.0000
LDH	2.8663	1.0115	8.7361	0.0540
Ferritin	1.5478	1.1056	2.2308	0.0142
Troponin T	1.7433	1.2442	2.5218	0.0018
BNP	1.2597	1.0452	1.5305	0.0168
NEWS (unlogged)	1.3068	1.1497	1.4995	0.0001
Age (unlogged)	1.0441	1.0209	1.0701	0.0003