

Extended laboratory panel testing in the Emergency Department for risk-stratification of patients with COVID-19: a single centre retrospective service evaluation

Mark J Ponsford^{1,2,*†} & Ross J Burton^{1†}, Leitchan Smith³, Palwasha Khan^{4,5}, Robert Andrews¹, Simone Cuff¹, Laura Tan⁷, Matthias Eberl^{1,6}, Ian R Humphreys^{1,6}, Farbod Babolhavaeji⁸, Andreas Artemiou⁹, Manish Pandey⁷, Stephen Jolles² & Jonathan Underwood^{1,10}

† contributed equally

* corresponding author

Affiliations

¹ Division of Infection and Immunity, School of Medicine, Cardiff University, Cardiff, UK

² Immunodeficiency Centre for Wales, University Hospital of Wales, Cardiff, UK

³ Information & Technology Team, Cardiff and Vale University Health Board, Cardiff, UK

⁴ Department of Sexual Health, Cardiff and Vale University Health Board, Cardiff, UK

⁵ Department of Clinical Research, London School of Hygiene & Tropical Medicine, London, UK

⁶ Systems Immunity Research Institute, Cardiff University, Cardiff, UK

⁷ Adult Critical Care Directorate, Cardiff and Vale University Health Board, Cardiff, UK

⁸ Department of Emergency Medicine, Cardiff and Vale University Health Board, Cardiff, UK

⁹ School of Mathematics, Cardiff University, Cardiff, UK

¹⁰ Department of Infectious Diseases, Cardiff and Vale University Health Board, Cardiff, UK

30 **Background**

31 The role of specific blood tests to predict poor prognosis in patients admitted with infection from
 32 SARS-CoV2 virus remains uncertain. During the first wave of the global pandemic, an extended
 33 laboratory testing panel was integrated into the local pathway to guide triage and healthcare
 34 resource utilisation for emergency admissions. We conducted a retrospective service evaluation to
 35 determine the utility of extended tests (D-dimer, ferritin, high-sensitivity troponin I, lactate
 36 dehydrogenase, procalcitonin) compared to the core panel (full blood count, urea & electrolytes,
 37 liver function tests, C-reactive protein).

38 **Methods**

39 Clinical outcomes for adult patients with laboratory-confirmed COVID-19 admitted between 17th
 40 March to 30st June 2020 were extracted, alongside costs estimates for individual tests. Prognostic
 41 performance was assessed using multivariable logistic regression analysis with 28-day mortality used
 42 as the primary endpoint, and a composite of 28-day intensive care escalation or mortality for
 43 secondary analysis.

44 **Results**

45 From 13,500 emergency attendances we identified 391 unique adults admitted with COVID-19. Of
 46 these, 113 died (29%) and 151 (39%) reached the composite endpoint. “Core” test variables adjusted
 47 for age, gender and index of deprivation had a prognostic AUC of 0.79 (95% Confidence Interval, CI:
 48 0.67 to 0.91) for mortality and 0.70 (95% CI: 0.56 to 0.84) for the composite endpoint. Addition of
 49 “extended” test components did not improve upon this.

50 **Conclusion**

51 Our findings suggest use of the extended laboratory testing panel to risk stratify community-
 52 acquired COVID-19-positive patients on admission adds limited prognostic value. We suggest
 53 laboratory requesting should be targeted to patients with specific clinical indications.

54

55 Introduction:

56 In December 2019, a novel coronavirus disease (COVID-19) was reported in China, caused by severe
57 acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). In the first 8 months since its
58 emergence, SARS-CoV-2 has caused over 32 million infections and more than a million deaths
59 worldwide (2). The majority of patients with COVID-19 experience a mild influenza-like illness,
60 however approximately 15-25% of those admitted to hospital develop pneumonia that may evolve
61 into acute respiratory distress syndrome (ARDS) (3-6). Experience from the Italian region of
62 Lombardy highlighted the potential of uncontrolled COVID-19 outbreaks to rapidly overwhelm local
63 intensive care capacity and healthcare systems (5). In the United Kingdom, Wales has one of the
64 lowest number of intensive care beds per head of population in Europe (7, 8), prompting
65 implementation of scoring systems to support patient triage and allocation of healthcare resources.

66 The ability to identify patients at greatest risk of developing life-threatening complications from
67 SARS-CoV-2 infection based on haematological and biochemical laboratory markers was suggested
68 early in the pandemic. A range of admission tests including D-dimer, ferritin, high-sensitivity
69 troponin I (hs-Trop), and lactate dehydrogenase (LDH) have been linked with disease severity and
70 risk of death (9-13). Similar findings have been replicated in meta-analysis (14). Furthermore, use of
71 a broader range of laboratory tests in patients with COVID-19 has been supported by the UK Royal
72 College of Pathologists (15). Accordingly, an extended panel of laboratory tests was integrated
73 within the standard of care pathway for COVID-19 admissions presenting via the Emergency
74 Department (ED) of the University Hospital of Wales. This panel consisted of both “core” (full blood
75 count, FBC; urea & electrolytes, U&E; liver function tests, LFTs; C-reactive protein, CRP) and
76 “extended” test components (D-dimer; LDH; ferritin; hs-Trop; and procalcitonin, PCT).

77 A joint National Health Service (NHS)-University collaboration supporting the rapid creation of an
78 electronic healthcare registry (see extended methods) provided a timely opportunity to
79 retrospectively assess the value and cost of implementing this extended laboratory panel. This is
80 particularly relevant given a recent systematic review of methodological and reporting standards
81 highlighting caution before extrapolating models and decision thresholds derived from prognostic
82 biomarker studies into local clinical practice (18). The role of extended components remains poorly
83 represented in prognostic studies within the UK population to date (4, 16-19). We therefore
84 conducted a service evaluation focusing on the ability of these tests to predict mortality or
85 escalation to intensive care in the first 28-days following admission, in adult patients with PCR-
86 confirmed COVID-19. Our primary aim was to assess how addition of components of the extended
87 panel altered the prognostic performance of the core panel (15). Our secondary aim was to explore
88 the additional cost of extended testing components. Together, this directs refinement of a risk
89 stratification panel with potential cost savings ahead of future waves of COVID-19.

90 Methods

91 Study population

92 We identified patients aged ≥ 18 years admitted between 17th March 2020 to 30th June 2020 via the
 93 Emergency Department (ED) of the University Hospital of Wales (Cardiff, UK). This 1,000-bed
 94 hospital is a tertiary referral centre within the region with the greatest recorded total of COVID-19
 95 case positives in Wales (20). Only patients with SARS-CoV-2 infection confirmed by positive reverse
 96 transcriptase polymerase chain reaction (PCR) on nasopharyngeal swab, and likely community-
 97 acquired disease (defined as swab positive between 14 days prior or 7 days following the date of
 98 initial emergency attendance) were included. Patients transferred in from other hospitals were
 99 excluded.

100 The primary dataset was extracted as part of a service evaluation to assist local care planning. A fully
 101 anonymised dataset was created by a member of the Health Board NHS IT team. Prior to
 102 anonymisation, the postcode was used to extract the Welsh Index of Multiple Deprivation (WIMD)
 103 for each patient, as obtained from <https://wimd.gov.wales/>. As such, ethical approval was not
 104 required for this study.

105 Data fields including admission date, clinical outcomes, and laboratory measurements were
 106 integrated into an electronic healthcare registry “Cardiff Hospital Admissions Database” (CHAD)
 107 using a bespoke software package: CHADBuilder (*see extended methods*). Laboratory test results
 108 from the index presentation reported within the first 72 hours of ED presentation were considered
 109 as candidate variables.

110 Outcomes

111 28-day mortality was chosen as the primary endpoint in accordance with UK COVID-19 mortality
 112 reporting. To support generalisability between studies (4, 16) we performed secondary analysis
 113 using the composite endpoint of 28-day mortality or admission to intensive care.

114 Laboratory testing panel

115 All testing was performed in the United Kingdom Accreditation Service (UKAS)-accredited
 116 Biochemistry, Immunology, and Haematology Laboratories at the University Hospital of Wales. Cost
 117 estimates were obtained from the Health Board Laboratory Medicine Directorate, reflecting
 118 consumables, reagent, analyser running and maintenance costs, and staff time chargeable to NHS
 119 test requestors.

120 Statistical analysis

121 Statistical significance testing was performed according to the data encountered: for categorical
 122 data, such as gender, Fisher’s exact or chi-square testing was performed. For continuous data,
 123 Welch’s t-tests were used if the assumptions of normality were met; otherwise non-parametric

Mann-Whitney U tests were employed. In edge-cases, permutation testing was performed. Two-sided statistical significance was set at $p < 0.05$, with Bonferroni correction for multiple testing.

Model development

Candidate laboratory variables were triaged for inclusion based on their membership of core or extended laboratory test panels, before a data-driven approach was applied. This included assessment of variability, individual p-values corrected for multiple comparisons and multicollinearity with generation of a Spearman's rank correlation matrix.

Logistic regression, support vector machines, random forest, and gradient boosted trees were all considered for multivariate predictive models. Models with complexity greater than logistic regression were found to offer little improvement (data not shown). Multivariate logistic regression was implemented in Python (version 3.7) using the Scikit-Learn package (version 0.23) (21) and Statsmodels (version 0.11). Complete case analysis was conducted to enable meaningful comparison between core and extended tests.

To minimise bias, models were evaluated using cross-validation with 5-folds, with stratification to account for class imbalance. Performance statistics are reported as the average across all folds with binomial proportion 95% confidence intervals. Model discrimination was assessed by area under receiver operating characteristic curve (ROC AUC), accuracy (balanced by support) and weighted F1 score (the average F1 score was calculated for each class and weighted by support). In addition to these performance metrics, threshold-performance curves were generated to assess the effect of the decision threshold on model sensitivity and specificity (22). Source code for all models can be found on GitHub: <https://github.com/burtonrj/CardiffCovidBiomarkers>

Our evaluation is reported using the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidance for Prediction Model development and validation (See Appendix).

Patient involvement

These data were generated as part of a rapid service improvement and as such patients were not involved in the setting of the research question or interpretation of the study.

Results

Definition and overview of service evaluation cohort

We focused on admissions occurring after the operational roll-out of the first extended laboratory test panel components into standard clinical practice. During this 105 day period, over 13,500 ED attendances were recorded. Of these, 391 adults were admitted via ED with a laboratory-confirmed diagnosis of COVID-19 meeting our definition of likely community-acquired COVID-19 (**Figure 1: Study Flowchart**). The median age was 69 years (interquartile range, IQR: 55 - 75 years) with males predominant (52.4%). Within 28-days of index ED attendance, 113 deaths occurred (29% mortality), and 151 patients reached the composite secondary endpoint of intensive care admission/death (39%).

Univariate analysis of laboratory predictors of adverse inpatient course

We next analysed the association between individual candidate variables and patient outcomes to identify important predictors of adverse outcome. Admission clinical variables are presented in **Table 1 (for full dataset, Supplementary S1&S2)**. Advanced age was strongly associated with increased risk of death and the composite of ICU admission and death. In contrast, neither gender nor socio-economic deprivation were associated with 28-day mortality. For laboratory variables, missing data were rare for core test panel components. Within the extended testing panel, hs-Trop and D-dimer were available in 70-80% of patients admitted with COVID-19 within the first 72 hours of ED attendance. An early admission PCT test result was available in 40% of patients, whilst ferritin and LDH levels were recorded in 42-46% of cases. Testing rates were similar between patient survival groups.

In univariate analysis of the core laboratory panel components, increased CRP, neutrophil:lymphocyte ratio, urea, creatinine; or decrease in serum albumin were all strongly associated with risk of death. Within the extended panel, D-dimer, hs-Trop and PCT differed between survivors and non-survivors on univariate analysis (**Figure 2; Supplementary S3**). No extended panel members were associated with development of the composite outcome (**Supplementary S4&S5**). Age was associated with several variables (**Supplementary S6**), indicating it could confound the relationship between a test result and mortality.

Development of prognostic model based on core and extended laboratory admission test panels

We therefore used multivariate logistic regression to adjust for the role of age, whilst controlling for gender and WIMD, based on consistent identification of their contribution to outcomes in COVID-19 cohorts (23, 24). Restricting to cases with complete data (n=130) across core and extended laboratory tests, we found an optimal combination of core test variables to be CRP, albumin, urea, neutrophil:lymphocyte ratio, creatinine, age, gender and WIMD (**Figure 3, Supplementary S7**). This

gave a prognostic AUC of 0.79 (95% confidence interval, CI: 0.67 to 0.91) for 28-day mortality, and 0.70 (95% CI: 0.56 – 0.84) for the composite outcome.

We next assessed the discriminative value associated with inclusion of extended panel components within our multivariate model, relative to this core test set (**Figure 5**). Addition of D-dimer resulted in a marginal increase in mean AUC score to 0.82, but this was not significantly different (95% CI: 0.71 – 0.85) to the performance of core testing alone. Concerning the composite outcome, addition of admission hs-Trop to the core panel resulted in the greatest AUC score: 0.72 (95% CI: 0.60 to 0.83) but again, this did not represent a significant increase in performance to the core panel alone (**Supplementary S7&S8**). Consideration of extended test components individually or in combination did not improve upon this. To internally validate these findings, we performed stratified cross-validation, observing convergence of training and validation curves, thus suggesting a low-risk of over-fitting associated with these models (**Supplementary S9&S10**). Assessing the calibration of these models across a range of performance metrics by varying the decision threshold (the probability at which a patient is predicted to either die or be admitted to intensive care), we found no significant benefit from addition of the extended relative to the core laboratory testing panel (**Supplementary S11&12**).

Patterns of extended panel requesting during the first wave

Local cost estimates for NHS requesting the core laboratory panel totalled £16.44 per patient, with an additional £55.48 incurred for the extended set (**Supplementary S13**). In order to contextualise testing beyond the cohort of community-acquired COVID-19, we constructed a run-chart of test requesting within the first 72 hours of admission via ED and COVID-19-related admissions (**Figure 4**). D-dimer and hs-Trop testing rates rose in line with COVID-19 admissions during March and April, with a 1-2 week delay apparent for LDH, ferritin, and PCT requesting. Strikingly, whilst COVID-19 admissions declined following the April peak, the intensity of extended biomarker panel requesting remained. Using January and June 2020 to represent requesting patterns before and after the first wave of COVID-19, mean monthly requesting increased by 29.7%, 224%, and 588% for hs-Trop, ferritin, and LDH, respectively. In contrast, recorded monthly ED attendance fell by 24.0% over this period. PCT and quantitative D-dimer were specifically introduced in response to the pandemic, but still averaged >50 daily test requests within the early admission period during June. Across the evaluation period, over 6,400 D-dimer and 5,400 PCT requests were made, with an estimated service cost of £246,000.

Discussion

To support the effective and efficient use of resources through evidence-based clinical practice, we conducted a service evaluation determining the prognostic value associated with routinely performed laboratory investigation in 130 adults admitted with community acquired SARS-CoV-2 infection. By leveraging a bespoke electronic healthcare registry, we reveal an extended panel (including D-dimer, LDH, hs-Trop, ferritin, PCT) provided only limited additional prognostic information beyond that provided by components of the core panel (FBC, U&E, LFT, and CRP). Together, this directs refinement of the clinical testing panel employed before and during future potential waves, underlining the relevance of this registry-approach to support cost-utility of investigation pathways.

We identified 5 studies within the peer-reviewed and pre-print literature concerning laboratory biomarker risk stratification of adult COVID-19 admissions in the UK population (4, 16-19). The largest reported, an 8-point pragmatic risk score developed by the ISARIC Consortium, achieved a modest AUC performance score of 0.77 (95% CI 0.76 to 0.77) when predicting 28-day mortality (18). To date, only 1 UK study has considered the prognostic role of variables within our extended laboratory panel (16). In their prospective analysis of 155 patients, Arnold et al. found conventional laboratory biomarkers such as CRP and neutrophil elevation offered limited prognostic performance (with AUC scores of 0.52 and 0.54, respectively), whilst ferritin, PCT, hs-Trop, and LDH performed with AUC scores of 0.65 to 0.71. It is important to note that within this study cohort, the incidence of clinical deterioration was low (overall mortality was only 4% vs 29% for our service evaluation) which may have limited the power of the study (16). This highlights regional variation in rates of hospitalisation and mortality, and further motivated a locally-led assessment of practice.

Consistent with the emerging COVID-19 literature, we observed an association between laboratory markers of acute phase inflammatory response (elevated neutrophil count, CRP; depressed lymphocytes and albumin), cardiac injury, activation of thrombosis, and renal impairment with subsequent adverse outcome (6, 23, 25). We found a combination of CRP, albumin, urea, neutrophil:lymphocyte ratio, and creatinine alongside simple demographics achieved an AUC of 0.79 (95% CI: 0.67 – 0.91) when predicting 28-day mortality, and 0.70 (95% CI: 0.56 – 0.84) for the composite endpoint. We found no evidence that use of this panel at admission significantly improved performance for either outcome. Importantly, we identified use of the extended laboratory panel continued despite falling rates of COVID-19 presentations, indicating a change in routine test requesting patterns. Addition of the extended laboratory test panel equates to £54 per patient (a relative cost increase of over 400% to the core panel alone), with significant cost ramifications when performed at scale.

Our service evaluation has several strengths, notably assessment of the performance of an extended panel of laboratory tests not widely considered in UK prognostic studies to date (4, 16-19). These tests were integrated into routine practice prior to the local peak of the pandemic, based on available literature and national guidelines (15). In contrast with the batched analysis undertaken under research condition in previous studies (16), all tests described here were conducted by accredited laboratories using platforms calibrated to international reference standards, facilitating future data sharing. Our multivariate approach is well-suited to investigate whether specific laboratory tests provide additional prognostic value beyond conventional parameters (26), using inclusion criteria and clinically-relevant endpoints in line with other reported studies (4, 17, 18). Finally, we considered the service costs that accompanied implementing these tests into routine practice (27), a relevant factor often neglected in other publications.

Our evaluation also has a number of limitations, reflecting the challenges of clinical data collection during an epidemic. It represents retrospective experience from a single tertiary referral centre, limiting sample size and the generalisability of our findings. Secondly, availability of extended test panel results during the early admission period was mixed. Admission D-dimer and hs-Trop results were available for 70-80% of patients, comparing favourably to a similar UK registry-based study where D-dimer results were only available at time of admission in 37.2% (17). Conversely, we observed high rates of missing data for LDH, ferritin, and PCT, undermining their relevance as a prognostic tool. This was likely due to operational factors such as a delay in test roll out relative to epidemic peak, and requirement for an additional sample tube. Because it cannot be assumed that data are missing at random, we chose to perform complete case analysis. Although this limits our statistical power, it avoids unfounded assumptions and potentially invalid imputation. In its current form, the CHAD-registry lacks detailed information on patient-level physiological observations, nature of co-morbidities, and therapeutic interventions. Similarly, all registry-linked laboratory values were available to clinicians, and are likely to have influenced management decisions. With advances in clinical care diagnostics, therapeutics are likely to alter the observed performance of the prognostic model. These limitations apply equally to pragmatic risk-scores (4, 16, 18). Finally, we recognise our evaluation consider the index test result and a specific question of inpatient prognosis, and additional indications exist for requesting components of the extended laboratory tests that fall outside of our primary and secondary endpoints. For instance, the use of PCT is often employed to support antibiotic stewardship (28), and was integrated into routine practice locally in early April 2020. There may also be merit in more targeted use of additional testing particularly as therapeutic options evolve. Hence, whilst we highlight the significant associated healthcare costs with implementation of extended laboratory testing, we do not make specific claims concerning the potential savings from discontinuing unnecessary investigations (27).

287 *Implications for practice*

288 Laboratory markers supporting early risk stratification of patients are often used in the ED setting,
 289 and have been shown to benefit patient triage (29). Our data suggest that systematic testing of
 290 COVID-19-positive patients upon admission with an “extended” laboratory panel provide little
 291 additional prognostic information for COVID-19 mortality or intensive care admission “core” tests.
 292 Besides the financial impact, over-requesting of laboratory tests are likely to increase the number of
 293 false-positive results, with the potential to lead to further potentially harmful tests (e.g. computed
 294 tomography pulmonary angiography in patients with marginally elevated D-dimer but no clinical
 295 indication of thromboembolic disease) (30). We suggest that the use of these laboratory markers be
 296 targeted to patients with specific clinical indications for these, such as PCT to guide antibiotic
 297 prescription or hs-Trop in patients with suspected myocardial injury.

298 In conclusion, we report our real-world experience from the use of an extended laboratory
 299 prognostic testing panel in patients hospitalised with community-acquired COVID-19. These findings
 300 directly inform clinical practice, guiding cost-efficient use of resources in potential future waves.

301

Data sharing

Requests for data sharing will be reviewed by a clinical and information regulatory governance panel and considered on an individual basis.

Author contributions

MJP and SJ conceived the service evaluation. MJP wrote the first draft, supervised by SJ, and JU. LS, RA and RJB performed initial data extraction. RJB constructed CHAD, and led data analysis support for multivariate modelling from AA and PK. All authors contributed scientific and clinical guidance regarding design, feature selection, and have reviewed the final draft.

Acknowledgements

We thank James Webb and Philip Clee (NHS IT governance) for their advice and guidance in facilitating the Electronic Healthcare Registry underpinning this service evaluation, and Nigel Roberts and Alun Roderick for assistance in providing costings for laboratory tests. Additional support was provided by Professor Valentina Escott-Price, Dr Martyn Stones and Dr Irina Erchova.

Conflict of interest statement

SJ has participated in advisory boards, trials, projects, and has been a speaker CSL Behring, Takeda, Thermofisher, Swedish Orphan Biovitrum, Biotest, Binding Site, BPL, Octapharma, Sanofi, LFB, Pharming, Biocryst, Zarodex, Weatherden and UCB Pharma.

Sources of funding

This study was supported by UK Research and Innovation (UKRI) and the National Institute for Health Research (NIHR) via the UK Coronavirus Immunology Consortium (UK-CIC). MJP was funded by the Welsh Clinical Academic Training (WCAT) programme, is a participant in the NIH Graduate Partnership Program, and recipient of a Career Development Award from the Association of Clinical Pathologists (ACP). RJB was supported by a School of Medicine PhD Studentship (to R.J.B.); IH was supported by Wellcome Trust Senior Research Fellow; M.E. was supported by the Welsh European Funding Office's Accelerate programme; J.U. was supported by MRC-NIHR Clinical Academic Research Partnership (grant number MR/T023791/1). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Key Messages

During the first wave of the pandemic, the literature and guidance from the UK Royal College of Pathologists supported the use of extended biochemistry and haematology testing upon admission to support risk stratification of patients with COVID-19 infection- however the prognostic performance of these markers remains unclear.

Our service evaluation suggests that systematic testing of COVID-19-positive patients with likely community-acquired disease upon admission with an “extended” laboratory panel (high-sensitivity Troponin I, Ferritin, Lactate Dehydrogenase, procalcitonin, or quantitative D-dimer) provides limited additional prognostic information for 28-day mortality or intensive care admission, relative to conventional “core” tests such as a full blood count, renal function, C-reactive protein combined with simple demographics.

Few clinicians know the cost of the tests they request for their patients. With individual “extended” panel members costing over £20 per test, and thousands of tests requested per month within a single hospital, these costs quickly escalate.

Besides the financial impact, over-requesting of laboratory tests are likely to increase the number of false-positive results, with the potential to lead to further potentially harmful investigations (e.g. computed tomography pulmonary angiography in patients with marginally elevated D-dimer but no clinical indication of thromboembolic disease). We suggest that the use of these laboratory markers be targeted to patients with specific clinical indications for these, such as procalcitonin to guide antibiotic stewardship or hs-Troponin I in patients with suspected myocardial injury.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-33.
2. The Johns Hopkins Coronavirus Resource Center (CRC) <https://coronavirus.jhu.edu/> [accessed 30-SEP-2020]
3. Singer AJ, Morley EJ, Henry MC. Staying Ahead of the Wave. *New England Journal of Medicine*. 2020.
4. Galloway JB, Norton S, Barker RD, Brookes A, Carey I, Clarke BD, 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. *Journal of Infection*. 2020;81(2):282-8.
5. Grasselli G, Pesenti A, Cecconi M. Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response. *JAMA*. 2020;323(16):1545-6.
6. Skevaki C, Fragkou PC, Cheng C, Xie M, Renz H. Laboratory characteristics of patients infected with the novel SARS-CoV-2 virus. *Journal of Infection*. 2020;81(2):205-12.
7. Rhodes A, Ferdinande P, Flaatten H, Guidet B, Metnitz PG, Moreno RP. The variability of critical care bed numbers in Europe. *Intensive Care Medicine*. 2012;38(10):1647-53.
8. Welsh Government: Together for Health – A Delivery Plan for the Critically Ill <http://www.wales.nhs.uk/documents/delivery-plan-for-the-critically-ill.pdf2013>.
9. Gao Y, Li T, Han M, Li X, Wu D, Xu Y, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. *Journal of Medical Virology*. 2020;92(7):791-6.
10. Liu F, Li L, Xu M, Wu J, Luo D, Zhu Y, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *Journal of Clinical Virology*. 2020;127:104370.
11. Yu B, Li X, Chen J, Ouyang M, Zhang H, Zhao X, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis. *Journal of Thrombosis and Thrombolysis*. 2020:1-10.
12. Shi S, Qin M, Cai Y, Liu T, Shen B, Yang F, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *European Heart Journal* 2020;41(22):2070-9.
13. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine*. 2020;382(18):1708-20.
14. Figliozzi S, Masci P-G, Ahmadi N, Tondi L, Koutli E, Aimo A, et al. Predictors of Adverse Prognosis in Covid-19: A Systematic Review and Meta-analysis. *European Journal of Clinical Investigation*. 50:e13362 .
15. Royal College of Pathologists: Guidance on the use and interpretation of clinical biochemistry tests in patients with COVID-19 infection. 17th April 2020. Available: <https://www.rcpath.org/uploads/assets/3f1048e5-22ea-4bda-953af20671771524/G217-RCPath-guidance-on-use-and-interpretation-of-clinical-biochemistry-tests-in-patients-with-COVID-19-infection.pdf>.
16. Arnold DT, Attwood M, Barratt S, Elvers K, Morley A, McKernon J, et al. Blood parameters measured on admission as predictors of outcome for COVID-19; a prospective UK cohort study. *medRxiv*. 2020:2020.06.25.20137935.
17. Gupta RK, Marks M, Samuels THA, Luintel A, Rampling T, Chowdhury H, et al. Systematic evaluation and external validation of 22 prognostic models among hospitalised adults with COVID-19: An observational cohort study. *medRxiv*. 2020:2020.07.24.20149815.
18. Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. *British Medical Journal*. 2020;370:m3339.
19. Abdulaal A, Patel A, Charani E, Denny S, Mughal N, Moore L. Prognostic modelling of COVID-19 using artificial intelligence in a UK population. *Journal of Medical Internet Research*. 2020.
20. Public Health Wales Rapid COVID-19 Surveillance : Confirmed Case Data by Local Authority of Residence online dashboard:

<https://public.tableau.com/profile/public.health.wales.health.protection#!/vizhome/RapidCOVID-19virology-Public/Headlinesummary2020>

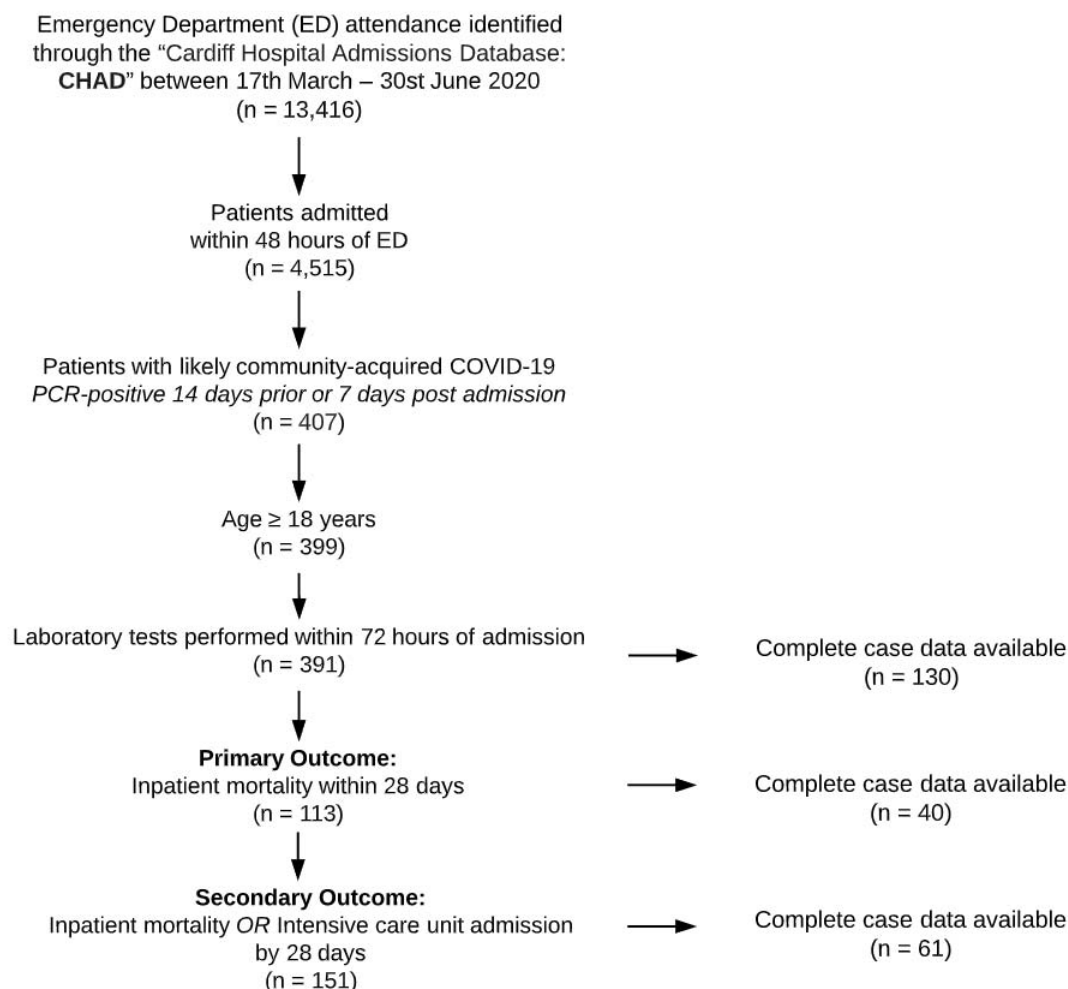
21. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Perrot M, et al. Scikit-learn: Machine Learning in Python. *Journal of Machine Learning Research*. 2011;12(85)(85):2825-30.
22. Singh K. Runway <https://github.com/ML4LHS/runway>: GitHub; 2020 [
23. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. *BMJ*. 2020;369:m1328.
24. Williamson E, Walker AJ, Bhaskaran KJ, Bacon S, Bates C, Morton CE, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. *medRxiv*. 2020:2020.05.06.20092999.
25. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, 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.
26. Moons KGM, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? *BMJ*. 2009;338:b375.
27. Broughton PM, Woodford FP. Benefits of costing in the clinical laboratory. *Journal of Clinical Pathology*. 1983;36(9):1028-35.
28. Han J, Gatheral T, Williams C. Procalcitonin for patient stratification and identification of bacterial co-infection in COVID-19. *Clinical Medicine*. 2020;20(3):e47-e.
29. Kristensen M, Iversen AKS, Gerds TA, Østervig R, Linnet JD, Barfod C, et al. Routine blood tests are associated with short term mortality and can improve emergency department triage: a cohort study of >12,000 patients. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*. 2017;25(1):115.
30. Bindraban RS, Ten Berg MJ, Naaktgeboren CA, Kramer MHH, Van Solinge WW, Nanayakkara PWB. Reducing Test Utilization in Hospital Settings: A Narrative Review. *Ann Lab Med*. 2018;38(5):402-12.

Table 1: Demographic and selected clinical laboratory predictor variables on admission for evaluation cohort.

*Variables captured in the summarised cohort of community-acquired PCR-confirmed COVID-19 cases admitted through the ED between 17th March 2020 and 30th June 2020. Summary statistics are given as the median and range for continuous variables and absolute counts for discrete variables. * Welsh index of multiple deprivation, WIMD, is ranked from 1 (most deprived) to 1,909 (least deprived), and presented as frequencies within each quartile. †Fischer's exact test.*

Variable	Survivors (n= 278)		Non-survivors (n=113)		p-value
	Frequency	% Missing	Frequency	% Missing	
Gender		0		0	
Male	141 (50.7%)	-	64 (56.6%)	-	0.316†
Female	137 (49.3%)	-	49 (44.4%)	-	
WIMD*		2.52		0.885	0.228†
Quartile 1 (< 246)	65 (23.4%)	-	29 (25.6%)	-	
Quartile 2 (246 – 871)	61 (21.9%)	-	35 (31.0%)	-	
Quartile 3 (872 – 1672)	73 (26.3%)	-	23 (20.4%)	-	
Quartile 4 (> 1672)	72 (25.9%)	-	25 (22.1%)	-	
	Median [IQR]		Median [IQR]		
Age, years	63.5 [51.25 - 77.75]	0	81.0 [71.0 - 88.0]	0	< 0.0001
“Core” test component			Median [IQR]		
Albumin, g/L	33.0 [29.0 - 36.0]	3.24	29.0 [26.0 - 32.0]	1.77	< 0.0001
Alkaline phosphatase U/L	80.0 [63.0 - 111.5]	0.04	100.0 [76.0 - 133.5]	0.02	0.0006
Alanine transaminase U/L	27.0 [17.0 - 46.0]	0.04	23.0 [14.0 - 32.0]	0.02	0.256
Bilirubin µmol/L	10.0 [7.0 - 15.0]	0.04	12.0 [8.0 - 17.0]	0.02	0.0018
C-reactive protein, mg/L	70.5 [21.0 - 131.75]	0.00	98.0 [55.75 - 164.75]	2.65	0.005
Creatinine, µmol/L	82.0 [66.0 - 105.0]	0.36	111.0 [79.0 - 192.0]	0.00	< 0.0001
Estimated GFR ml/min/1.73m ²	75.0 [55.0 - 89.0]	0.01	51.0 [25.0 - 74.0]	0.00	< 0.0001
Globulin g/L	38.0 [34.0 - 42.0]	0.07	40.0 [36.0 - 45.75]	0.06	0.0161
Haemoglobin g/L	135.0 [122.0 - 149.0]	0.00	135.0 [122.0 - 149.0]	0.00	0.036
Lymphocyte count x10 ⁹ /L	1.0 [0.7 - 1.4]	0.00	0.9 [0.6 - 1.22]	0.01	0.961
Neutrophil count x10 ⁹ /L	5.4 [3.7 - 7.98]	0.00	7.3 [4.57 - 9.8]	0.01	0.017
Neutrophil : Lymphocyte ratio	5.25 [3.25 - 9.81]	0.36	8.11 [4.34 - 14.53]	0.88	0.011
Platelet count x10 ⁹ /L	234.0 [183.75 - 294.5]	0.00	216.0 [160.0 - 285.0]	0.00	0.210
Potassium mmol/L	3.9 [3.6 - 4.3]	0.01	4.1 [3.73 - 4.6]	0.03	0.0006
Protein g/L	71.0 [67.0 - 76.0]	0.07	70.0 [65.0 - 74.0]	0.06	0.04
Sodium mmol/L	137.0 [134.0 - 139.0]	0.00	138.0 [134.0 - 141.0]	0.00	< 0.0001
Urea mmol/L	5.7 [4.0 - 8.5]	0.36	10.2 [7.2 - 16.2]	0.00	< 0.0001
White blood cell count x10 ⁹ /L	7.35 [5.3 - 9.93]	0.00	9.0 [6.4 - 12.3]	0.00	0.016
“Extended” test component					
Ferritin µg/L	325.0 [125.0 - 828.0]	57.9	482.0 [245.5 - 993.5]	54.9	0.395
High sensitivity D-dimer µg/L	926.5 [587.75 - 1750.0]	28.1	1497.0 [929.0 - 3885.0]	30.1	0.0003
High Sensitivity Troponin I ng/L	7.0 [3.0 - 23.0]	24.8	35.5 [15.75 - 117.0]	22.1	< 0.0001
Lactate dehydrogenase U/L	349.5 [270.25 - 549.75]	53.2	383.5 [290.5 - 501.25]	54.0	0.999
Procalcitonin µg/L	0.14 [0.06 - 0.38]	41.4	0.31 [0.09 - 0.86]	38.9	0.019

Figure 1: Study Flowchart



450

451

Figure 2: Laboratory test results according to survival outcome and grouped by gender

Caption: Box and swarm plots showing the initial laboratory test results from laboratory-confirmed COVID-19 patients, grouped by gender and 28-day mortality. Example variables considered from the components of the core laboratory test panel. * indicates level of significance, assessed by Mann-Whitney U test with correction for multiple testing: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$, **** $p < 0.001$.

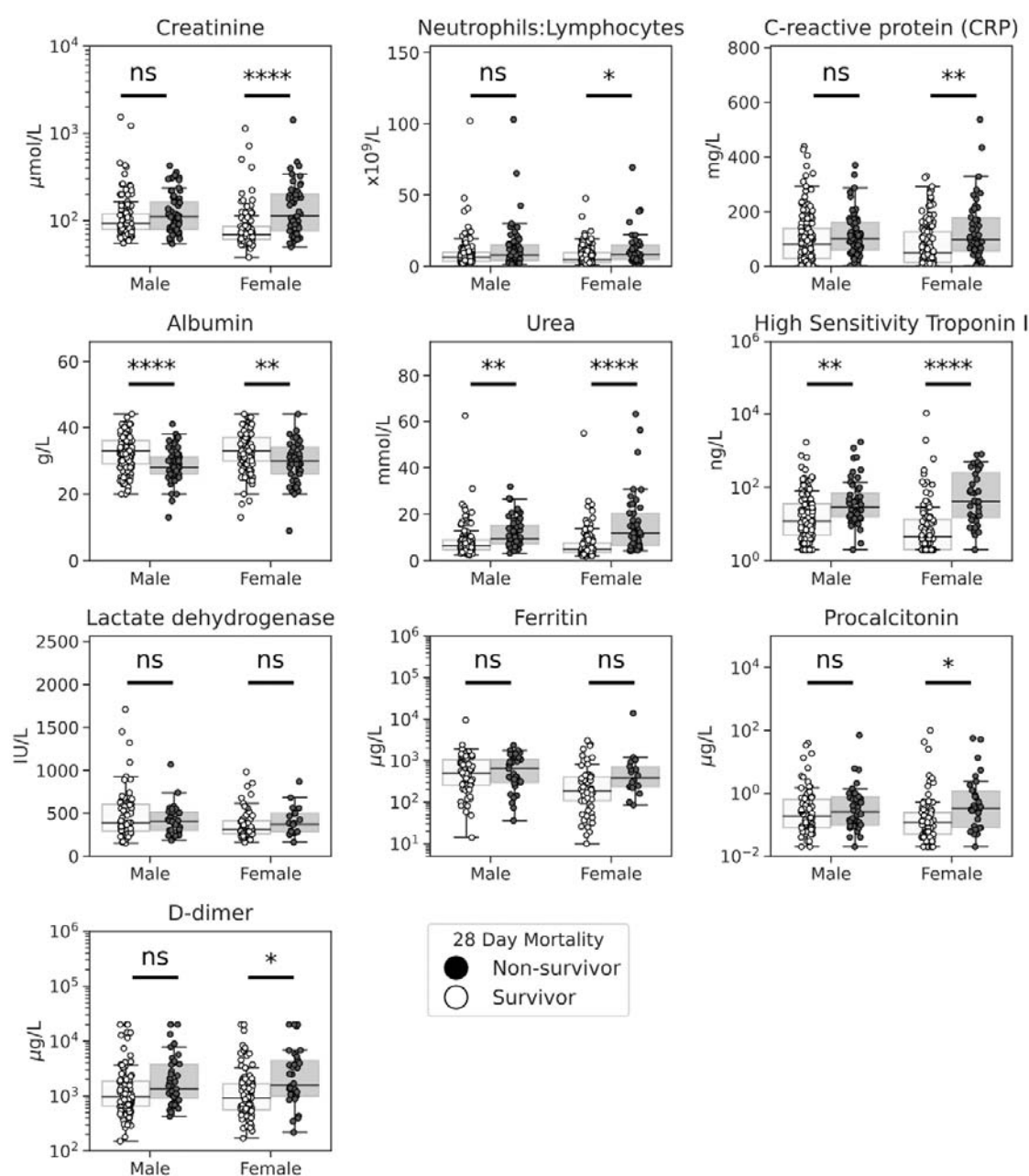
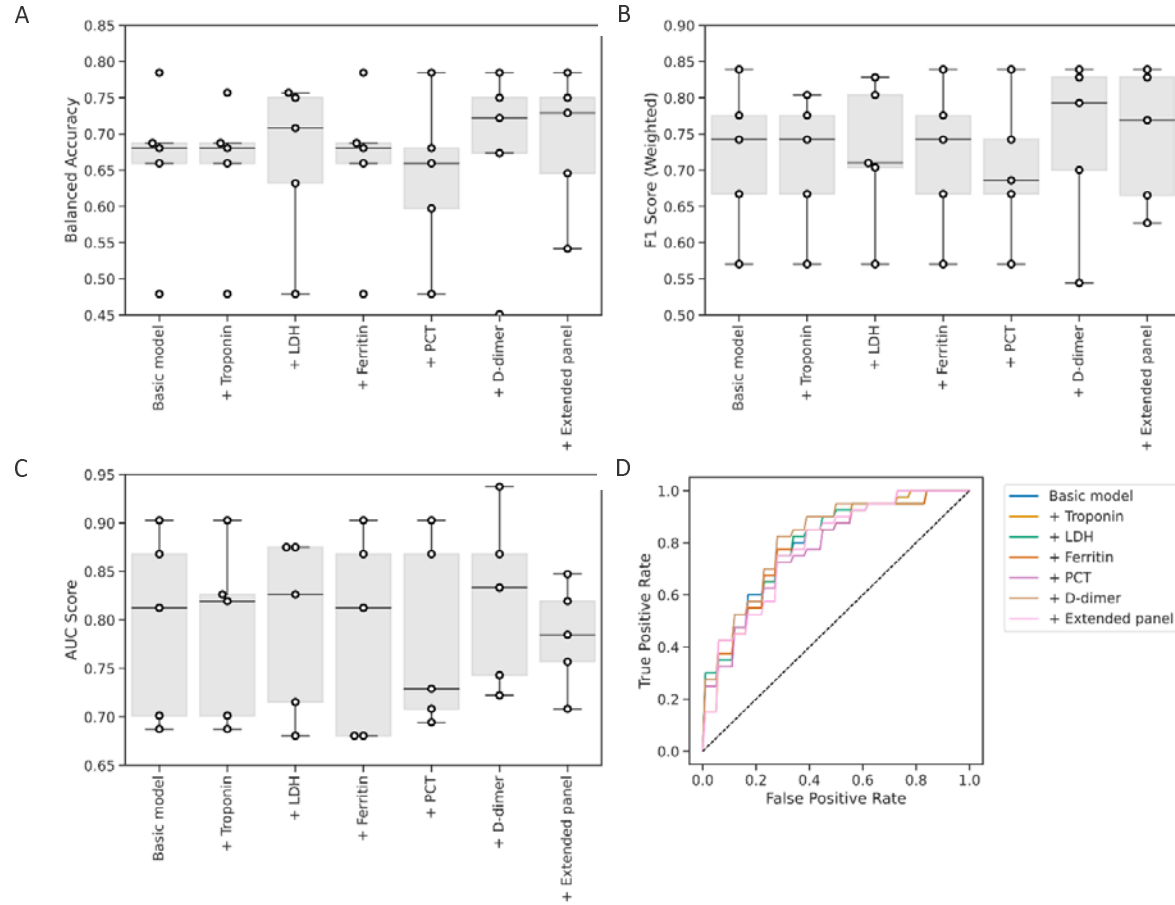


Figure 3: Balanced accuracy (A), weighted F1 score (B), AUC score (C) and ROC curves (D) for models with sequential inclusion of extended biomarkers for prediction



of 28 day mortality

Figure 4: Daily COVID-19 admission rates and test requesting patterns during the early admission period

Caption: Run-chart showing Emergency Unit (ED) admission rates for patients with confirmed laboratory-confirmed COVID-19 (right y-axis, black), and accompanying tests performed within 72 hours of ED attendance (left y-axis, blue) during the first wave of the COVID-19 pandemic. The dotted line indicates the roll-out of extended panel testing from 17th March 2020.

