Title: Can we predict mortality in COVID-19 patients?

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Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a viral infection identified in 2019, commonly known as COVID-19, is a global pandemic that has caused unprecedented medical and financial pressure, both within the UK and globally. Variation in the clinical presentation of patients infected with COVID-19 is significant, ranging from asymptomatic to those with multi-organ failure and subsequent death. The already limited resources within the NHS have been stretched to respond to high numbers of hospital admissions, and optimisation of diagnosis and treatment is required. If a panel of simple biomarkers can be used to identify the patients at highest risk of a severe disease course this could allow limited resources, such as intensive care beds, to be allocated using evidence-based medicine. Those patients stratified at lower risk using the biomarker evidence may be more safely provided with less intensive treatment and care.

Aim: The aim of this project is to advance current knowledge and establish if there is local evidence that commonly utilised biomarkers can be used to predict which patients with COVID-19 infection are at highest risk of severe disease (in whom there is the greatest mortality rate).

Method: A retrospective study was performed on all adult COVID-19 patients attending Bedford Hospital between 01.03.2020 and 31.11.2020. Age, gender, length of stay, mortality, and results of blood tests were retrieved from hospital records using the algorithms shown in figures 1 and 2.

Figure 1 Flow chart describing work process for identifying COVID-19 'survivor' study group.

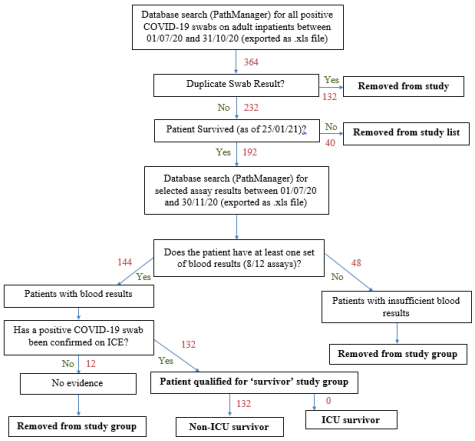
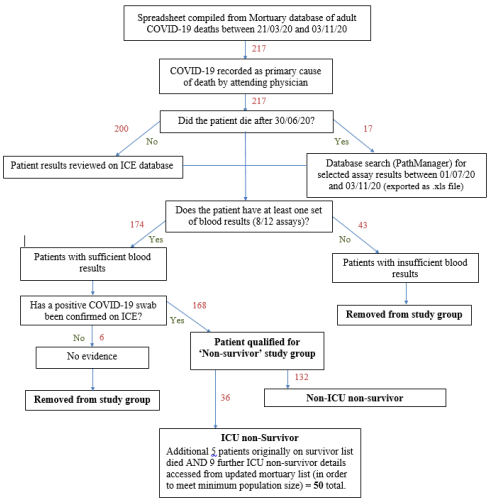


Figure 2 Flow chart describing work process for identifying COVID-19 'non-survivor' study group.



Results: Of 314 patients with COVID-19, 132 (42%) survived and 182 (58%) did not (50/182 intensive care unit (ICU); 132/182 non-ICU). Age and gender was similar to that seen internationally. Male patients in the top decile of life (80-89 years) had an increased mortality overall, whilst mortality was higher for ICU patients aged 50-59. Duration of hospital stay was similar to other NHS sites; this was longer for survivors than non-survivors ($p<0.05$).

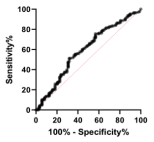
As shown in figure 3, there was a significant difference ($p<0.05$) between results for survivors and non-survivors for serum creatinine, lactate dehydrogenase (LDH), ferritin, high sensitive Troponin T (hs-TnT), and neutrophil count both on admission and peak results; APTT and D-dimer were also different for peak results ($p<0.05$). Albumin decrease during hospital stay was significantly different ($p<0.05$) between survivors and non-survivors. Receiver operating characteristic (ROC) curves for both initial and peak results were unable to demonstrate these markers as having sufficient accuracy or sensitivity for prognosis (figures 4-10).

Figure 3 Statistical analysis summary: are the initial and peak results statistically different between each study group, using a non-paired two-tail t-test, where $p<0.05$ is statistically significant (highlighted with '*')? *For assays marked with an [α], a Mann-Whitney U test was performed due to lower sample group sizes, indicating non-Guassian distribution.*

Assay	Initial			Peak		
	Survivors vs non-survivors study groups	Survivors vs ICU non-survivors study groups	ICU non-survivors vs non-ICU non-survivors study groups	Survivors vs non-survivors study groups	Survivors vs ICU non-survivors study groups	ICU non-survivors vs non-ICU non-survivors study groups
	P value	P value	P value	P value	P value	P value
Serum ALT	0.0775	0.0200*	0.2889	0.1814	0.0003*	<0.0001*
APTT	0.2147	0.8145	0.1956	0.0032*	<0.0001*	0.0004*
Serum creatinine	0.0001*	0.0485*	0.2743	<0.0001*	0.0006*	0.1891
Serum CRP	<0.0001*	<0.0001*	0.2011	<0.0001*	<0.0001*	0.0036*
D-Dimer	0.1420	0.2715	0.5859	0.0050*	0.0054*	0.8232
Serum ferritin	0.0059*	0.0021*	0.3737	0.0123*	0.0294*	0.7723
Serum LDH	0.0057*	0.0079*	0.0165*	0.0076*	0.0086*	0.8880
Lymphocyte count	0.2369	0.1727	0.6242	0.7529	0.8595	0.6363
Neutrophil count	0.0062*	0.0333*	0.6922	<0.0001*	<0.0001*	0.0019*
Serum procalcitonin	0.5100	0.6310	0.0002*	0.1570	0.5252	0.5640
Serum troponin T	0.0002*	0.0882	0.1530	<0.0001*	0.1570	0.0098*

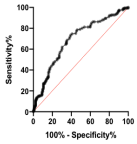
Figures 4 – 10 ROC curve and corresponding cut-off values between survivors and non-survivors of COVID-19 infection for specified tests, where significant difference between survivors and non-survivors was calculated.

4. Percentage albumin decrease



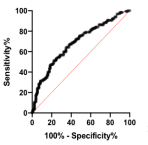
Area under the ROC curve	0.5910
Std. error	0.03801
95% confidence interval	0.5165 to 0.6655
P value	0.0168
Optimal % serum albumin decrease cut-point value according to Youden index (J)	29.4% (sensitivity: 52.2%, specificity: 68.2%, J: 19.37)

5. Initial serum creatinine (Jaffe)



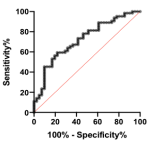
Area under the ROC curve	0.6885
Std. error	0.03051
95% confidence interval	0.6287 to 0.7483
P value	<0.0001
Optimal serum creatinine concentration cut-point value according to Youden index (J)	84.5 μmol/L (sensitivity: 73.5%, specificity: 60.6%, J: 34.1)

6. Initial serum CRP



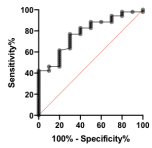
Area under the ROC curve	0.6846
Std. error	0.03014
95% confidence interval	0.6255 to 0.7437
P value	<0.0001
Optimal serum CRP concentration cut-point value according to Youden index (J)	45.5 mg/L (sensitivity: 63.7%, specificity: 65.4%, J: 29.1)

7. Initial serum ferritin



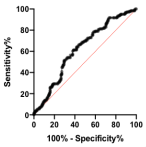
Area under the ROC curve	0.7203
Std. error	0.05055
95% confidence interval	0.6212 to 0.8193
P value	0.0001
Optimal serum ferritin concentration cut-point value according to Youden index (J)	803.6 μg/L (sensitivity: 59.4%, specificity: 78.1%, J: 37.4)

8. Initial serum lactate dehydrogenase (LDH)



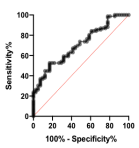
Area under the ROC curve	0.7779
Std. error	0.07243
95% confidence interval	0.6359 to 0.9198
P value	0.0057
Optimal serum LDH concentration cut-point value according to Youden index (J)	405.5 U/L (sensitivity: 76.9%, specificity: 70.0%, J: 46.9)

9. Initial neutrophil count



Area under the ROC curve	0.6215
Std. error	0.0326
95% confidence interval	0.5576 to 0.6854
P value	0.0002
Optimal neutrophil count cut-point value according to Youden index (J)	6.19 x10^9/L (sensitivity: 61.3%, specificity: 61.4%, J: 22.7)

10. Initial serum troponin T



Area under the ROC curve	0.7046
Std. error	0.04813
95% confidence interval	0.6102 to 0.7989
P value	0.0003
Optimal serum troponin T cut-point value according to Youden index (J)	39.85 pg/mL (sensitivity: 52.6%, specificity: 82.9%, J: 35.6)

Conclusion: This study indicates a number of standard biomarkers exhibit statistical differences between survivors and non-survivors in COVID-19 patients in an in-patient District General Hospital setting. Individually these markers do not have sufficient sensitivity or specificity for their use as prognostic tests, however further work may reveal the benefit of using combinations of these markers to enable patients to be stratified to different patient flow and care streams, improving patient care.