


Clinical Characteristics and Predictors of Mortality in Patients with COVID-19 Infection Outside Intensive Care

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Background/Introduction: The coronavirus disease 2019 (COVID-19) pandemic has affected all aspects of inpatient hospital medicine with patients admitted from level 1 (general medical wards) to level 3 (intensive care). Often, there are subtle physiological differences in these cohorts of patients. In particular, in intensive care, patients tend to be younger and have increased disease severity. Data, to date, has combined outcomes from medical and intensive care cohorts, or looked exclusively at intensive care. We looked solely at the level 1 (medical) cohort to identify their clinical characteristics and predictors of outcome.

Patients and Methods: This was a retrospective study of adult patients admitted to a central London teaching hospital with a diagnosis of COVID-19 from 23rd March to 7th April 2020 identified from the hospital electronic database. Any patients who required level 2 or 3 care were excluded.

Results: A total of 229 patients were included for analysis. Increased age and frailty scores were associated with increased 30-day mortality. Reduced renal function and elevated troponin blood levels are also associated with poor outcome. Baseline observations showed that increased oxygen requirement was predictive for mortality. A trend of increased mortality with lower diastolic blood pressure was noted. Lymphopenia was not shown to be related to mortality.

Conclusion: Urea and creatinine are the best predictors of mortality in the level 1 cohort. Unlike previous intensive care data, lymphopenia is not predictive of mortality. We suggest that these factors be considered when prognosticating and for resource allocation for the treatment and escalation of care for patients with COVID-19 infection.

Keywords: COVID-19, mortality, frailty, ICU, renal dysfunction, lymphopenia

Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome 2 (SARS-CoV-2) has had a devastating impact on a global scale with more than 5 million cases identified and 356,000 deaths in the space of less than 6 months.¹

To date, international data has been rapidly emerging showing that this disease adversely affects older age groups, males and more recent data has shown a clear trend towards poor outcomes in patients from Black and Minority Ethnic (BAME) groups.^{2,3} Comorbidities such as Hypertension, Chronic Kidney Disease and Diabetes Mellitus have been well documented in predicting which patients are more likely to have a poor outcome.⁴

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Much of the published literature on this disease combines all-cause mortality of the level 1 cohort (general medical wards without invasive ventilation or inotropic support) in addition to the most unwell patients deemed suitable for level 2 (high dependency – requirement of non-invasive ventilation and inotropic support) and level 3 (intensive care patients). In this study, we looked principally at predictors of outcomes for patients who were just treated on general medical wards (level 1 care).

Literature from COVID-19 patients in Milan, Italy has shown that in the Intensive Care setting lymphopenia, hyperinflation with raised C-reactive protein and elevated D-Dimer were predictors of early mortality.⁵ A recent meta-regression analysis has shown that certain aspects of the metabolic panel can predict which patients are most likely to require Intensive Care Unit (ICU) admission with raised; leukocyte count, alanine aminotransferase, aspartate transaminase, elevated lactated dehydrogenase (LDH) and raised procalcitonin as statistically significant predictors, whilst only raised leukocyte count and elevated LDH predicting mortality.⁶ To date, no study in the United Kingdom has analysed predictors of outcome for just the medical cohort of COVID-19 patients.

St Mary's Hospital in London is part of the Imperial College Health NHS Trust (ICHNT) which is a 443-bed hospital. This study aims to:

1. Describe the characteristics of the level 1 cohort in a large London tertiary centre.
2. Evaluate the baseline observations of patients deemed appropriate for level 1 care on admission to hospital and see if predictors of outcome can be based on these findings.
3. Evaluate the impact of the admission metabolic panel in level 1 care and determine which are predictors for mortality.

Patients and Methods

Patient Population

This was a retrospective study of adult patients admitted to St Mary's Hospital with a diagnosis of COVID-19 over a time period of two weeks from the 23rd March to 7th April 2020. They were identified from the hospital electronic database. Demographic and clinical data were obtained from hospital clinical databases and clinical records. Patients requiring above level 1 care were excluded. Baseline observations, ethnicity, previous

medical history, admission clinical frailty scores (defined by the National Institute for Health and Care Excellence) and blood on admission were recorded. Mortality data were retrieved from our medical databases as well as from the national database.

For the purpose of our analysis, the start date was defined as the first visit to the hospital with symptoms suggestive of COVID-19. Only patients with a polymerase chain reaction (PCR) swab result that was positive were included for analysis. The primary outcome of the study was the combined endpoint of 30-day all-cause mortality. Patients with incomplete data and those who were currently inpatients were not included in the study.

Clinical Data Collected

Beyond demographic data at the start of follow-up, information of the past medical history and medications was collected. Symptoms (cough, fever, shortness of breath, lethargy) and their duration were recorded. Ceilings of care, patients referred to ICU and those accepted were recorded. The baseline observations, venous blood gas and full standardized metabolic screen (as outlined in [Tables 3 and 4](#)) were then recorded from the included patients.

Ethics

The need for individual informed consent was waived for retrospective analysis of data collected for routine care, with no breach of privacy or confidentiality. The observational study qualified as a service evaluation as defined by the United Kingdom NHS Health Research Authority. This study adheres to the principles outlined by the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism version 8. Continuous variables are presented as mean \pm standard deviation or median [inter-quartile range]. Categorical variables are presented as number (percentage). Comparisons between groups were performed using the Wilcoxon rank sum tests for continuous variables and the chi-squared test for categorical variables. This was done as the data was non-parametric as tested by the Shapiro–Wilk test of normality. The relation between clinical parameters and outcome measures was assessed using univariable analysis, using the date of first presentation to the hospital. A 2-sided p-value of <0.05 was considered indicative of statistical significance. P-values

were corrected for multiple comparisons using Bonferroni correction. A multivariable logistic regression analysis was performed and adjusted for age, gender and ethnicity.

Results

Description of the Cohort

Two hundred and thirty-nine patients had a positive SARS-CoV-2 nasopharyngeal swab and were hospitalised at St Mary's Hospital between the 23rd March and 7th April 2020. All of the patients were identified from the medical take. Ten patients were excluded from analysis. Only patients whose index presentation on admission to hospital was suggestive of COVID-19 were retrieved from the medical database. Of the 13 patients excluded, 4 were jointly referred to ICU on admission and 6 were transferred to ICU during their admission. This left a total of 229 patients for inclusion. Amongst this cohort, all patients had a completed outcome. The median age was 73 (IQR 56–81), 144 were Male (63%). The breakdown of ethnic background was: White 85 (37.1%), Asian 50 (21.8%), Black 49 (21.3%), other ethnicities 42 (18.3%) and not stated 3 (1.5%). According to UK Census data from 2011, Westminster Borough, where the hospital is situated, has a demographic breakdown of: White 61.7%, Asian 14.5%, Black 7.5% and other 16.3%.

The mean time from symptom onset to admission to hospital was 7.74 days (SD 4.6). The most prevalent symptoms were as follows: cough 167 (72.3%), fever 170 (74.2%), shortness of breath 162 (70.7%), and lethargy 109 (47.6%), 206 (89.9%) of patients were admitted directly from home and 23 (10.1%) were admitted from institutional care. Of the patients admitted from home, 39 (18.9%) required help at home with a package of care. Thirty (13.1%) of patients had a history of Chronic Kidney Disease (CKD), 81 (35.4%) of patients with a diagnosis of Diabetes Mellitus, of which 18 (22.2%) were taking insulin and 52 (64.2%) were taking metformin on admission. One hundred and ten (48.0%) patients had been diagnosed with hypertension. Regarding admission medications, 77 (33.6%) of patients were taking an ACE inhibitor, 31 (13.5%) β -blocker, 27 (11.8%) Diuretic and 58 (25.3%) a calcium channel blocker.

Predictors of Mortality

In our cohort, the median age and clinical frailty score was significantly different between those who died or who were discharged home (Table 1). Correcting for multiple

Table 1 Baseline Demographics

	Home (N=154)					Death (N=75)					p value (Corrected)	p value (Uncorrected)
	Mean	Median	Standard Deviation	Minimum	Maximum	Mean	Median	Standard Deviation	Minimum	Maximum		
Age	65.76	68	16.19	28	96	76.61	78	11.6	51	96	<0.0001	<0.0001
Frailty Score	3.185	2	1.927	1	8	4.284	4	1.724	1	7	<0.0001	<0.0001
Duration of Symptoms	8.344	8	4.913	1	28	6.514	7	3.533	1	14	0.2212	0.0079

comparisons, age (78, 95% CI 75–80) was much greater in those who died within 30 days vs those who were successfully discharged home (68, 95% CI 61–73). Higher frailty scores were associated with increased mortality (4, 95% CI 4–5) vs (2, 95% CI 2–3).

On admission, increased FiO₂ requirement was linked to increased mortality (36, 95% CI 28–85) vs (21, 95% CI 21–28) in those successfully discharged. Furthermore, desaturation on admission (<94%) was also linked to increased mortality (95%, CI 92–96%) vs (96, CI 96–96%). A trend towards patients with lower diastolic blood pressure was noted (Table 2).

No hematological marker was statistically significant at predicting inpatient mortality (Table 3). Renal dysfunction, with raised urea (8.1, 95% CI 7–10.9) vs (5.5, 95% CI 4.9–6.1), increased creatinine (104, 95% CI 97–114) vs (82, 95% CI 77–90) and reduced eGFR (54, 96% CI 45–65) vs (77, 95% CI 67–84) were predictive of mortality. A raised Troponin T on admission (29, 95% CI 23–50) vs (10, 95% CI 7–12) predicted 30-day mortality (Table 4).

On multivariate regression analysis, decreased lymphocyte count (Odds Ratio (OR) 0.67 95% CI 0.35–1.27, p: 0.227) were not associated with increased mortality. Raised urea (OR: 1.045 95% CI 1.004–1.096, p: 0.031), Raised Creatinine (OR: 1.002, 95% CI 1.001–1.005, p: 0.04) and reduced eGFR (OR: 0.98 95% CI 0.97–0.99, p: 0.006) were associated with increased mortality. See Figure 1A–L for multiple comparisons.

Discussion

Predicting mortality from baseline observations and the metabolic panel of patients is advantageous. It allows patients to be stratified earlier and where appropriate – specific interventions and levels of care can be facilitated. This will help with framing prognosis for family members and patients on admission. Furthermore, in healthcare systems where resources are more limited, laboratory tests that predict outcomes can be applied to aid decisions regarding escalation of care.

From our results, it is clear that renal dysfunction indicated by raised creatinine, low eGFR or raised urea on admission to hospital is statistically significant in predicting 30-day inpatient mortality in the level 1 cohort.

An understanding of the pathophysiology of kidney damage in COVID-19 is rapidly emerging. It is likely multifactorial in nature – with cardiovascular comorbidities and other predisposing factors as precipitants. Autopsy data has shown virus particles present in renal

Table 2 Baseline Admission Observations

	Home (N=154)				Death (N=75)				p value (Corrected)	p value (Uncorrected)
	Mean	Median	Standard Deviation	Minimum	Maximum	Mean	Median	Standard Deviation	Minimum	Maximum
FiO ₂ (admission) %	35.49	21	24.41	21	100	56.83	36	34.47	8	100
SpO ₂ (%)	95.66	96	3.274	76	100	92.4	95	6.913	64	100
Heart Rate (bpm)	94.53	94	20.3	9	153	95.53	95	17.24	56	133
Systolic Blood pressure (mmHG)	132.6	130.5	26.37	12	214	126.6	126	24.84	74	212
Diastolic Blood pressure (mmHG)	75.12	75	14.23	36	122	69.47	69	15.22	30	111
Respiratory Rate	24.44	23	7.658	6	60	26.4	25	7.871	14	52
Temperature (°C)	37.79	37.85	0.9778	35.2	40.4	37.62	37.8	1.128	33.4	40.2

Abbreviations: FiO₂, fraction of inspired Oxygen; SpO₂, oxygen saturation level.

Table 3 Baseline Haematology Panel

	Home (N=154)				Death (N=75)				p value (Corrected)	p value (Uncorrected)
	Mean	Median	Standard Deviation	Minimum	Maximum	Mean	Median	Standard Deviation	Minimum	Maximum
Haemoglobin (g/L)	134.2	135.5	18.73	73	184	132.1	137	19.91	86	173
Platelets ($\times 10^9/L$)	236.2	214.5	101	62	693	200.8	193	104.1	8.5	683
WCC($\times 10^9/L$)	8.066	7.2	4.944	3	54.7	9.068	7.5	4.623	2.6	27.5
Neutrophils ($\times 10^9/L$)	6.416	5.6	4.643	2	49.1	7.543	6.3	4.207	1.6	18.8
Lymphocytes ($\times 10^9/L$)	1.04	0.9	0.5625	0.1	3	0.8747	0.8	0.4734	0.2	2.7
Monocytes ($\times 10^9/L$)	0.5831	0.5	0.4165	0.1	3.6	0.6453	0.5	0.8576	0	7.6

Table 4 Baseline Biochemistry Panel

	Home (N=154)				Death (N=75)				p value (Corrected)	p value (Uncorrected)
	Mean	Median	Standard Deviation	Minimum	Maximum	Mean	Median	Standard Deviation	Minimum	Maximum
Sodium (mmol/L)	137.7	137	6.29	121	168	137.2	139	15.64	17	163
Potassium (mmol/L)	4.158	4.1	0.4911	3	6	4.28	4.2	0.6483	2.8	6.2
Urea (mmol/L)	7.485	5.5	6.21	1.3	45.5	11.7	8.1	9.482	2.8	57.9
Creatinine ($\mu\text{mol/L}$)	110.1	82	97.94	40	764	169.5	104	192.9	7.2	1422
eGFR (mL/min/1.73 m^2)	68.29	77	23.76	6	90	52.33	54	26.99	2	90
ALT (U/L)	41.52	31.5	36.49	6	235	41.48	27	57.53	6	462
CRP (mg/L)	123.3	107.1	87.23	0.3	399.4	153.2	121.8	97.81	16.6	437.4
Ferritin (ng/mL)	1361	702	2035	81	17079	1433	838	1510	40	7281
Troponin ($\mu\text{g/L}$)	49.54	10	276.6	5	3105	154.7	29	483.2	5	3676
D-Dimer (ng/mL)	2570	1171	4127	280	20000	2798	1719	3742	151	20000
Lactate (mmol/L)	1.423	1.2	0.7586	0.5	5	7.42	7.43	1.462	6.8	7.57
Glucose (mmol/L)	9.176	7.45	6.979	2.4	70.2	9.944	7.9	6.039	4.9	40.8

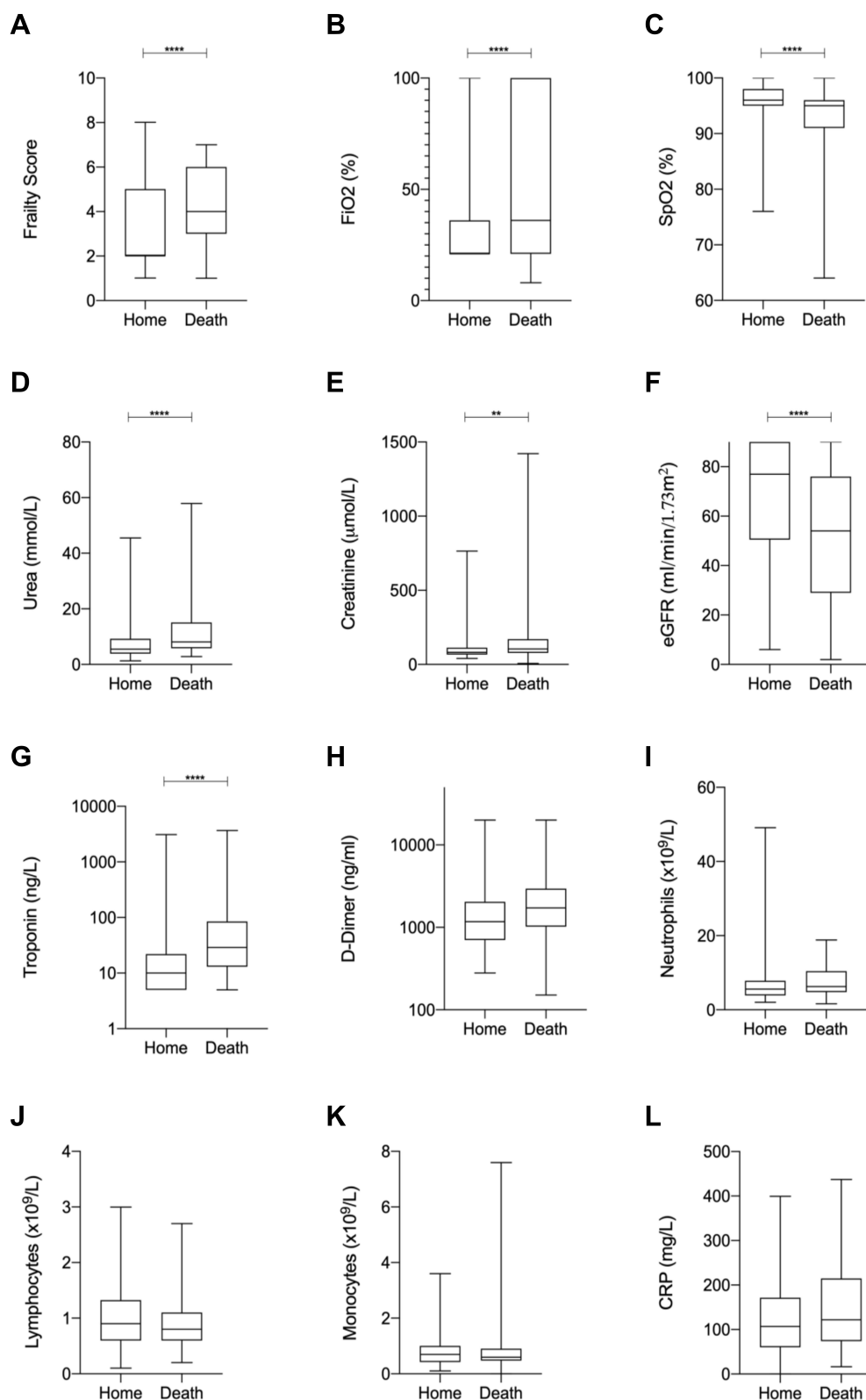


Figure 1 Patient Cohort Characteristics. (A–L) Patient cohort comparisons Home (n=154) compared with Death (n=75) for Frailty Score, Fraction of Inspired Oxygen (FiO₂), Oxygen Saturations (SpO₂), Urea, Creatinine, Estimated Glomerular Filtration Rate (eGFR), Troponin T, D-Dimer, Neutrophil count, Lymphocyte count, Monocyte count and C Reactive Protein (CRP). Displayed as Median, IQ range and maximum and minimum. Comparisons between groups were performed using the Wilcoxon rank sum tests for continuous variables and the chi-squared test for categorical variables. Corrected p values **p<0.01, ***p<0.0001.

endothelial cells with the suggestion that viremia may directly cause endothelial damage. The virus directly infects renal tubular epithelium and podocytes causing mitochondrial dysfunction and acute tubular necrosis. This is mediated through the angiotensin-converting-enzyme 2 (ACE2) dependent pathway.^{7,8}

Other postulated mechanisms involve cardio-renal syndrome. Left Ventricular Failure (LVF) will lead to renal hypoperfusion due to the low cardiac output state; whereas Right Ventricular Failure (RVF) caused by sepsis from a COVID-19 pneumonia will likely lead to renal dysfunction due to venous congestion of the kidneys.^{9,10}

In level 2 and 3 treatment, volume depletion is often treated more aggressively due to accurate fluid balance and the availability of invasive monitoring. In level 1 care, ensuring patients are adequately hydrated on admission may reduce incidence of renal dysfunction and lead to better outcomes in this cohort.

Raised Troponin T on admission was statistically significant in predicting mortality in a level 1 cohort of patients. Mechanisms for elevated Troponin T have been suggested secondary to a viral myocarditis. Given the significant mortality associated with patients with renal dysfunction and potential volume depletion on admission to hospital, the prevalence of Type 2 Myocardial Infarctions may be in part attributed to the high mortality associated with raised Troponin T on admission.¹¹

Lymphopenia is widely described as a poor prognostic marker for survival from COVID-19 infection.^{12–15} At present there is no clear pathological mechanism to explain this phenomenon, however several have been suggested. These include the raised levels of circulating pro-inflammatory cytokines including Interleukin-6 (IL-6), Monocyte Chemoattractant Protein-1 (MCP-1), granulocyte colony stimulating factor (G-CSF) and Tumour Necrosis Factor α (TNF α), causing lymphocyte apoptosis.¹⁶ The virus may have an affinity to ACE2 receptors found on lymphocytes causing immune dysfunction¹⁷ and even the direct effect of metabolic molecules produced as a response to severe systemic infection such as lactic acid causing reduced proliferation and cytotoxicity of T lymphocytes.¹⁸ It is worth noting that in our cohort increased lactic acidosis was not a significant predictor of mortality which may go some way to explain the lymphocyte data.

Much of the previous literature was taken from an ICU cohort who may have a different pathophysiological response to the virus leading to a differentiated bone marrow response. Our data does not demonstrate lymphopenia as a significant

predictor of mortality in the medical cohort of COVID-19 patients. Lymphopenia has a very poor specificity as it has such a multitude of causes. It is commonly found in severe sepsis as well as other causes of severe systemic injury such as major trauma where it acts as a handbrake on the inflammatory process.^{19,20} Apoptosis, particularly of immune cells, is an anti-inflammatory process designed to dampen the inflammatory response and induce resolution of inflammation.^{21,22} These potentially confounding factors may have been found in our discharged cohort resulting in a lack of significant difference between the groups.

It cannot be overlooked that lymphopenia as described in the previous COVID-19 literature is a marker not only of poor outcomes but a marker of severity of disease and that patients requiring intensive care management of COVID-19 infections are more likely to have been affected by any one of the other major potential drivers of lymphopenia as described above. We would therefore suggest that lymphopenia be treated with caution as a prognostic marker for patients suffering with mild to moderate COVID-19 infection requiring hospitalisation but not requiring an intensive care setting.

With National Institute of Clinical Excellence (NICE) guidance suggesting that patients with a Clinical Frailty Score (CFS) of greater than or equal to five and concurrent COVID-19 infection would not benefit from ICU admission,²³ it is imperative to further examine the link between frailty and outcomes to determine whether this advice is justified. Previous studies have shown frailty, independent of age, to correlate with poorer outcomes for respiratory diseases such as pneumonia.^{24,25} We demonstrated that increasing frailty score positively correlated with poorer outcomes in those with COVID-19. Further studies should aim to determine whether this link remains after accounting for age and other specific comorbidities.

Additionally, it is not clear that CFS is the optimal tool for predicting outcomes and determining suitability for ICU. For example, the CFS has not been validated in those aged under 65, nor those with chronically stable conditions such as cerebral palsy. Several new scoring systems have been proposed, aiming to incorporate known COVID-19 risk factors, such as male sex and smoking status. However, these tools have not yet been validated and, furthermore, have been assessed to be at high risk of bias.

Conclusion

Predictors of outcomes in patients diagnosed with COVID-19 should be stratified according to the level of

care they are receiving and by proxy their disease severity. In this level 1 cohort, admission blood with raised creatinine, urea and reduced eGFR and raised troponin had a significant association with predicting mortality. Further work investigating the effects of volume depletion and renal dysfunction on admission to hospital are required. In the Intensive Care setting, lymphopenia is a good predictor of disease severity. It is not as useful in determining which patients are likely to have poor outcomes in a level 1 cohort. These prognostic factors should be considered when making decisions about escalation of care. They may also be useful in an international setting where resources are more limited.

Ethics

The need for individual informed consent was waived for retrospective analysis of data collected for routine care, with no breach of privacy or confidentiality. The observational study qualified as a service evaluation as defined by the United Kingdom NHS Health Research Authority. This study adheres to the principles outlined by the Declaration of Helsinki.

Disclosure

Saadiq M Moledina and Alexander A Maini are co-first authors for this study. The authors report no conflicts of interest in this work.

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