

# BMJ Open Troponin and short-term mortality in hospitalised patients with COVID-19 infection: a retrospective study in an inner-city London hospital

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## ABSTRACT

**Objective** To investigate the association between troponin positivity in patients hospitalised with COVID-19 and increased mortality in the short term.

**Setting** Homerton University Hospital, an inner-city district general hospital in East London.

**Design** A single-centre retrospective observational study.

**Participants** All adults admitted with swab-proven RT-PCR COVID-19 to Homerton University Hospital from 4 February 2020 to 30 April 2020 (n=402).

**Outcome measures** We analysed demographic and biochemical data collected from the patient record according to the primary outcome of death at 28 days during hospital admission.

**Methods** Troponin positivity was defined above the upper limit of normal according to our local laboratory assay (>15.5 ng/L for females, >34 ng/L for males). Univariate and multivariate logistical regression analyses were performed to evaluate the link between troponin positivity and death.

**Results** Mean age was 65.3 years for men compared with 63.8 years for women. A  $\chi^2$  test showed survival of patients with COVID-19 was significantly higher in those with a negative troponin ( $p=3.23 \times 10^{-10}$ ) compared with those with a positive troponin. In the multivariate logistical regression, lung disease, age, troponin positivity and continuous positive airway pressure were all significantly associated with death, with an area under the curve of 0.889, sensitivity of 0.886 and specificity of 0.629 for the model. Within this model, troponin positivity was independently associated with short-term mortality (OR 2.97, 95% CI 1.34 to 6.61,  $p=0.008$ ).

**Conclusions** We demonstrated an independent association between troponin positivity and increased short-term mortality in COVID-19 in a London district general hospital.

## INTRODUCTION

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. The COVID-19 pandemic has so far resulted in over 515 million recorded infections and over 6 million deaths worldwide.<sup>1</sup> A significant proportion of patients develop acute respiratory distress syndrome and require hospitalisation and

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Use of real-world data for prognostication.
- ⇒ Troponin is a readily available, easy to measure biomarker.
- ⇒ Good ethnic minority representation in the data.
- ⇒ Relatively modest dataset.
- ⇒ Purely observational study.

ventilatory support with subsequent morbidity and mortality. Early data from Wuhan first outlined the association of COVID-19 and myocardial injury exhibited by elevated cardiac biomarkers.<sup>2,3</sup> This has subsequently been replicated in various studies and meta-analyses from around the world.<sup>4</sup>

The mechanisms for myocardial injury in COVID-19 are not fully understood. A combination of systemic hypoxia, cytokine storm, renal failure, coagulopathy and endothelial dysfunction appear to be implicated.<sup>5</sup> The SARS-CoV-2 virus gains entry to cells through binding to the ACE2 receptor, which can be found in a variety of organs including the heart, in theory having the propensity to have a direct effect on the myocardium.<sup>6</sup> Cardiac imaging studies of patients recovered from COVID-19 show evidence of a range of patterns and localisation of myocardial injury, with acute and subacute myocardial inflammation suggesting distinct pathways leading to myocardial damage.<sup>7</sup>

Elevated cardiac biomarkers have been found to be associated with poorer outcomes in COVID-19. Studies have shown that the presence of elevated cardiac biomarkers including cardiac troponin appear to be associated with both death and increased intensive care (ICU) admissions, as well as the requirement for ventilation.<sup>8</sup> As well as biochemical markers, multiple demographic factors have been identified as adverse

prognostic predictors in COVID-19 infection. These include increasing age, male sex, positive smoking status, comorbidities including diabetes and obesity, chronic major organ diseases and autoimmune diseases.<sup>9</sup>

COVID-19 infection will likely remain an ongoing public health issue with further surges and pandemics; continuing to characterise the clinical profile and prognostic features of patients with COVID-19 is important to identify those at higher risk of severe disease and hospitalisation. In this study, we primarily aimed to better delineate and clarify the relationship between elevated cardiac biomarkers and mortality in COVID-19 in a population of hospitalised COVID-19 patients at an inner-city London district general hospital during the first wave of the pandemic in early 2020. The study is evaluating the prognostic value of myocardial injury beyond the scope of type 1 myocardial infarction. We also investigated other factors that may be implicated in the prognostication of patients with COVID-19 including demographics such as age, ethnicity and smoking status, comorbidities including hypertension and diabetes mellitus and interventions such as continuous positive airway pressure (CPAP).

## METHODS

### Data collection

All adults admitted with swab-proven reverse-transcriptase polymerase chain reaction (RT-PCR) COVID-19 to Homerton University Hospital (HUH), London, from the date of the first positive swab from 2 March 2020 to 30 April 2020 were eligible for inclusion. Patients were identified using the hospital coding system applied to unselected adults admitted for acute medical care at HUH. Patients under the age of 18 years and those without a positive SARS-CoV-2 real-time RT-PCR were excluded.

We retrospectively analysed the patient records from the electronic patient record (EPR) with the primary outcome defined as mortality within 28 days of admission to HUH. Data including observations and laboratory tests (including serum high sensitivity troponin I (hs-TnI)) were automatically extracted from the EPR. Serum troponin was evaluated at different time points in patients and not performed systematically in all patients. Additional data including admission ECG, presenting symptoms and outcomes were then manually collected for these patients from EPR and patient case notes where required. Manual validation of a random sample of 10% of the dataset was completed.

### Patient and public involvement

Patients and the public were not involved in the design or analysis of the study.

### Laboratory methods

Serum hs-TnI levels were assessed by a high-sensitivity cardiac troponin I microparticle chemiluminescent immunoassay (ARCHITECT STAT, hs-TNI, Abbott) on

the fully automated Abbott ARCHITECT analyser (Abbott ARCHITECT STAT high sensitive troponin-I. Package insert. G1-0139/R02. 2013). The upper reference limit of hs-TNI defined as the 99th percentile of hs-TNI distribution in a reference population was 15.5 ng/L for females and 34 ng/L for males respectively. Limit of blank and limit of detection have been determined as 0.7–1.3 ng/L and 1.1–1.9 ng/L, respectively.

### Statistical analysis

Data were analysed according to the primary outcome of death during hospital admission. Patients with a type 1 myocardial infarction (MI), defined as having new ischaemic changes on ECG, a positive troponin and being started on therapeutic anticoagulation were excluded from regression analysis on the primary outcome but included in summary tables. A Mann-Whitney U test was performed to compare troponin values against the primary outcome, and a  $\chi^2$  test was performed to compare troponin positivity against the primary outcome. Further  $\chi^2$ , Fisher's exact and Mann-Whitney U tests were performed to compare troponin positivity to demographic, laboratory imaging and other outcomes including ICU admission, but these were not corrected for multiple testing and should be interpreted as exploratory. Confidence intervals (CIs) were computed for the above testing. A p-value <0.05 was considered as significant. Univariate and multivariate logistical regression analyses were performed to evaluate the link between troponin positivity and death in addition to a Cox proportional hazards model. Numerous different demographics, clinical and biochemical variables were tested for association with short-term mortality, and area under the curve (AUC) was computed for all regressions. Sensitivity and specificity were computed for the multivariate regression. A Kaplan-Meier survival analysis was completed. All data analysis was performed in the statistical computing software R (V.4.0.3). Statistical tests used were discussed with an independent statistician to ensure the appropriateness of the tests used.

## RESULTS

### Population characteristics

402 adult inpatients were found to have swab-proven RT-PCR COVID-19 between 2 March 2020 and 30 April 2020. 83 patients did not have a troponin measured and were therefore excluded. The in-hospital mortality of patients with (n=319) and without (n=83) troponin measurement was compared to check whether the included population was prognostically representative of the entire cohort of patients admitted due to COVID-19 during the study period. 103 patients died in those in whom troponin was measured compared with 20 deaths in those without a troponin measurement, with a p-value of 0.191 using the  $\chi^2$  test.

The baseline demographics and clinical characteristics for all patients included are shown in [table 1](#). There

**Table 1** Demographics and patient characteristics

Parameter	Troponin-positive group (n, %)	Troponin-negative group (n, %)	$\chi^2$ p-value	Missing troponin group (n, %)
	Troponin positive (n=124)	Troponin negative (n=195)		Troponin missing (n=83)
Gender				
Male	58 (46.8)	115 (59.0)	*p=0.0437	41 (49.4)
Female	66 (53.2)	80 (41.0)	*p=0.0437	42 (50.6)
Age (years)				
<18	0 (0)	0 (0)	***p<0.0001 (Mann-Whitney U)	0 (0)
18–35	0 (0)	20 (10.3)		14 (16.9)
36–49	4 (3.2)	25 (12.8)		9 (10.8)
50–64	30 (24.2)	83 (42.6)		16 (19.3)
≥65	90 (72.6)	67 (34.4)		44 (53.0)
Ethnicity				
White	38 (30.6)	52 (26.7)	p=0.709	33 (40.0)
Asian	7 (5.6)	12 (6.2)		6 (7.2)
Black	39 (31.5)	64 (32.8)		18 (22)
Mixed	3 (2.4)	2 (1.0)		1 (1.6)
Other	28 (22.6)	55 (28.2)		17 (20.0)
Not declared	9 (7.3)	10 (5.1)		8 (9.6)
Comorbidities				
Ischaemic heart disease	28 (22.6)	19 (9.7)	**p=0.00278	10 (12.0)
Heart failure	23 (18.5)	8 (4.1)	***p<0.0001	7 (8.4)
Chronic kidney disease	45 (36.3)	13 (6.7)	***p<0.0001	16 (19.3)
Hypertension	89 (71.8)	93 (47.7)	***p<0.0001	36 (43.4)
Diabetes mellitus	56 (45.2)	81 (41.5)	p=0.602	32 (38.6)
Dyslipidaemia	45 (36.3)	46 (23.6)	*p=0.0203	15 (18.1)
Lung disease	31 (25)	49 (25.1)	p=1.00	18 (21.7)
COPD	16 (12.9)	9 (4.6)	*p=0.013	6 (7.2)
Asthma	17 (13.7)	19 (9.7)	p=0.36	10 (12.0)
Other major organ disease	80 (64.5)	88 (45.1)	**p=0.00109	49 (59.0)
Presenting complaint				
Chest pain	7 (5.6)	15 (7.7)	p=0.634	0 (0)
Shortness of breath	68 (54.8)	113 (57.9)	p=0.667	25 (30.1)
Cough	60 (48.4)	104 (53.3)	p=0.455	22 (26.5)
Fever	55 (44.4)	99 (50.8)	p=0.316	30 (36.1)
Smoking status				
Current smoker	4 (3.2)	14 (7.2)	*p=0.00890	5 (6.0)
Ex-smoker	26 (21)	38 (19.5)	*p=0.00890	19 (22.9)
Never smoker	76 (61.3)	134 (68.7)	*p=0.00890	49 (59.0)
Not documented	18 (14.5)	9 (4.6)	*p=0.00890	10 (12.0)
Baseline medications				
Statin therapy	75 (60.4)	79 (40.5)	**p=0.000767	38 (45.8)
ACEi/ARB	85 (57.5)	53 (27.2)	***p<0.0001	24 (28.9)
Antiplatelets	41 (33.1)	25 (12.8)	***p<0.0001	15 (18.1)
Anticoagulation	16 (12.9)	12 (6.2)	p=0.06097	5 (6.0)

Continued

Table 1 Continued

Parameter	Troponin-positive group (n, %)	Troponin-negative group (n, %)	$\chi^2$ p-value	Missing troponin group (n, %)
	Troponin positive (n=124)	Troponin negative (n=195)		Troponin missing (n=83)
Beta blockers	45 (36.3)	33 (16.9)	**p=0.000151	17 (20.5)
MRA	8 (6.5)	0 (0)	**p=0.00126	1 (1.2)
Other diuretic	38 (30.6)	25 (12.8)	**p=0.0001741	11 (13.3)
Other antihypertensive	48 (38.7)	64 (32.8)	p=0.340	21 (25.3)

Note that where a multiclass comparator was made p-values (eg, for gender) are the same for all groups. Similarly, for some comparisons such as age, where the input data was continuous but has been converted to ordinal, the distributions of individual values within a group have been compared using a Mann-Whitney U test, and again the p-values are the same for all groups. The group where troponin was missing was not statistically compared with the troponin positive and negative groups.

ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist.

were more men than women in the troponin-negative group while the opposite was true for the troponin-positive group. Around one-third of patients had a black or Asian ethnicity. Hypertension was the most frequent recorded comorbidity, followed by diabetes mellitus in our study population. Hypertension, hyperlipidaemia, heart failure, ischaemic heart disease and chronic kidney disease were significantly more prevalent in the troponin-positive group. Higher use of medications in the troponin-positive group such as angiotensin-converting enzyme (ACE) inhibitors reflected the increased prevalence of these comorbidities. Chest pain was uncommon in both groups. However, there was no significant difference in presenting symptom between the two groups.

### Inpatient investigations

High D-dimer, low lymphocyte count and high CRP was evident in both the troponin positive and troponin negative result (see table 2). 73% of patients over 65 years old had a positive troponin. There were a low number of CT pulmonary angiograms performed in this cohort. In addition, only around one-third of troponin-positive cases had a transthoracic echocardiogram completed. Reported abnormalities on imaging included reduced left ventricular ejection fraction, regional wall motion abnormalities and pericardial effusion.

### Outcomes and inpatient management

Table 3 shows the cumulative outcomes in the troponin positive and negative groups. The average age of patients who died was 74.0 (95% CI 71.5 to 76.5) years, while the average age in those who survived was 60.4 (95% CI 58.3 to 62.5) years (see figure 1 panel A). Death rates were higher in the troponin-positive group.  $\chi^2$  test showed that survival of patients with COVID-19 was significantly higher in those with a negative troponin compared with those with a positive troponin ( $p=3.23 \times 10^{-10}$ ). Mean initial troponin in patients who survived was 70.0 ng/L (95% CI 5.6 ng/L to 134.4 ng/L), while in those who died it was 131.4 ng/L (95% CI 78.9 ng/L to 183.9 ng/L) (see figure 1 panel B). A

Mann-Whitney U test showed that initial troponin was significantly higher in those who died ( $p=2.24 \times 10^{-12}$ ) compared with those who were alive. COVID-19 was the primary cause of death in both patient populations on the medical certificate for cause of death. Only a minority of troponin-positive patients had cardiovascular disease mentioned on the death certificate (2.4% in part 1, and 15.5% in part 2). A higher proportion of the troponin-positive group received medical management for acute coronary syndrome (ACS); however, only one patient subsequently went on to have percutaneous coronary intervention.

### Predictors of outcome

Table 4 shows the results of the univariate and multivariate regression in our patient cohort. A histogram of the odds ratios (ORs) for the multivariate analysis can be seen in figure 2. Five patients were excluded from the final analysis due to having type I myocardial infarctions. In the multivariate logistical regression, lung disease, age, troponin positivity and CPAP were all significantly associated with death, with an AUC of 0.889, sensitivity of 0.886 and specificity of 0.629 for the model. Within this model, troponin positivity was independently associated with short term mortality (OR 2.97, 95% CI 1.34 to 6.61,  $p=0.008$ ). A Cox proportional-hazards model confirmed the same significant associations with mortality as the logistic regression but showed additionally a significant association between creatinine and mortality. The univariate logistical regression using only initial troponin positivity had an AUC of 0.683. When only patients aged under 65 years were included in the multivariate model only use of CPAP, smoking status and lung disease were significantly associated with mortality. A Kaplan-Meier survival analysis confirmed the significant increased mortality in the troponin-positive group (online supplemental materials).

### DISCUSSION

In this retrospective cross-sectional study, we have demonstrated that a positive initial troponin was independently



**Table 2** Inpatient investigations

Parameter	Troponin -positive group (n, %)	Troponin-negative group (n, %)	$\chi^2$ p-value
	Troponin positive (n=124)	Troponin negative (n=195)	
Biochemical findings on admission			
WCC low	8 (6.4)	19 (9.7)	**p=0.0003
WCC normal <sup>4-11</sup>	74 (60.0)	147 (75.4)	**p=0.0003
WCC high	42 (33.9)	29 (14.9)	**p=0.0003
Lymphocytes low	65 (52.4)	107 (54.9)	p=0.198
Lymphocytes normal <sup>1-4</sup>	57 (46.0)	88 (45.1)	p=0.198
Lymphocytes high	2 (1.6)	0 (0)	p=0.198
NLR<4	21	60	*p=0.008
NLR≥4	103	135	
Creatinine normal	48	143	***p<0.0001
Creatinine raised	76	52	
LDH positive	32 (34.5)	58 (29.7)	p=0.549 (Fisher's exact)
LDH not recorded	92 (64.9)	134 (68.7)	
D-dimer positive	61 (49.2)	84 (43.1)	**p=0.0028
No D-dimer on system	56 (45.2)	74 (37.9)	
CRP negative (<10)	6 (4.8)	7 (3.6)	p=0.795
CRP positive	118 (95.1)	188 (96.4)	p=0.7952
Imaging			
Transthoracic echo performed	21 (16.9)	33 (16.9)	p=1.0
LVEF below 50%	4 (19.0)	1 (3.0)	p=0.0689 (Fisher's Exact)
Regional wall motion abnormalities	8 (38.1)	1 (3.0)	**p=0.0013 (Fisher's Exact)
Pericardial effusion	2 (9.5)	7 (21.2)	p=0.456 (Fisher's Exact)
Severe aortic stenosis	0 (0)	0 (0)	p=1 (Fisher's Exact)
CTPA performed	14 (11.3)	38 (19.5)	p=0.0756
Pulmonary embolism detected	4 (3.2)	11 (5.6)	p=0.470

Note that where a multiclass comparator was made p-values (eg, for gender) are the same for all groups. Similarly, for some comparisons such as age, where the input data was continuous but has been converted to ordinal, the distributions of individual values within a group have been compared using a Mann-Whitney U test, and again the p-values are the same for all groups.

CRP, serum C reactive protein level; CTPA, CT pulmonary angiogram; LDH, serum lactate dehydrogenase level; LVEF, left ventricular ejection fraction; NLR, neutrophil to lymphocyte ratio; WCC, white cell count.

associated with short-term mortality in patients hospitalised with COVID-19. These findings line up with other studies and meta-analyses.<sup>2-4 10-12</sup> Papageorgeiou *et al*<sup>13</sup> similarly reported the association between a positive initial troponin and mortality across several London hospitals covering different geographical areas. Our data showed that 103 patients died, representing a third of the cohort, which may be higher than other published COVID-19 reports. Other studies have found correlation between elevated troponin and more severe disease, ICU admission and the requirement for non-invasive and mechanical ventilation.<sup>2 3 11 12 14</sup> We did not find any significant between group differences in CPAP use, ICU admission and intubation between troponin positive and negative groups. However, this observation was based on relatively

small numbers of patients and should be interpreted with caution. Troponin measurements appear to be helpful in identification of those at risk of death from COVID-19. Even in non-COVID-19 hospitalised populations in the UK, elevated troponin has been seen to be associated with mortality suggesting that myocardial injury forms part of the clinical picture in other non-cardiac severe illness.<sup>15</sup>

In addition to troponin, increasing age, the need for CPAP and underlying lung disease were also independently associated with increased mortality in our cohort. Increasing mortality with increasing age is clearly correlated.<sup>16</sup> Lung disease, in particular COPD and interstitial lung disease, has been shown to modestly increase the risk of severe COVID-19 in the UK, although asthma does not appear to confer increased risk.<sup>17</sup> The use of

**Table 3** Outcomes and inpatient management

Parameter	Troponin-positive group, n (%)	Troponin-negative group, n (%)	$\chi^2$ p-value
	Troponin positive (n=124)	Troponin negative (n=195)	
<b>Mortality</b>			
Alive on discharge	48 (38.7)	145 (74.4)	***p<0.0001
Inpatient death	66 (53.2)	37 (19.0)	***p<0.0001
Death following readmission	4 (3.2)	0 (0)	***p<0.0001
<b>Critical care management</b>			
CPAP	21 (16.9)	34 (17.4)	p=1.0
Intubation and ventilation	15 (12.1)	33 (16.9)	p=0.310
ITU admission	17 (13.7)	35 (17.9)	p=0.399
<b>In-hospital complications</b>			
New arrhythmia	11 (8.9)	2 (1.0)	**p=0.002
<b>Other in-hospital management</b>			
Dual antiplatelet	9 (7.3)	2 (1.0)	*p=0.0078
Anticoagulation	26 (21.0)	42 (21.5)	p=1.0
Antiarrhythmic	6 (4.8)	8 (4.1)	p=0.974
Angioplasty/PCI	1 (0.8)	0 (0)	p=0.819
ACS Medical protocol	7 (5.6)	2 (1.0)	*p=0.0373
Steroids started	15 (12.1)	14 (7.2)	p=0.197
Tocilizumab started	0 (0)	1 (0.5)	p=1

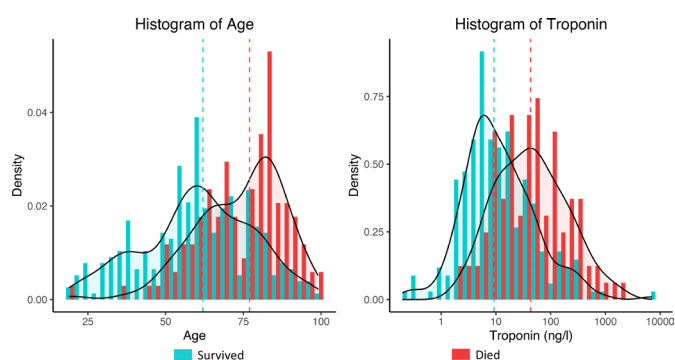
ACS, acute coronary syndrome; CPAP, continuous positive airway pressure ventilatory support; ITU, intensive treatment unit; PCI, primary coronary intervention.

CPAP was associated with an increased risk of mortality in our cohort suggesting another interesting clinical marker to identify patients at higher risk of mortality. The scope of this study was not to determine the effectiveness of CPAP; patients who require CPAP are clinically more unstable with severe disease and are more likely to deteriorate. The clear benefits of CPAP have been outlined in other studies designed as such.<sup>18</sup>

In our cohort, initial troponin was positive in 39% of patients in whom it was measured and 31% overall. Data from Wuhan initially outlined an incidence of 12%–27%.<sup>2 3</sup> Subsequent studies from western countries show a broad prevalence of myocardial injury. In general, there appears to be higher frequency of

troponin elevation in hospitalised patients in European and USA populations, when compared with China, with an incidence rising above 50% in some instances.<sup>8 13</sup> A large meta-analysis including 49 studies from a combination of the USA, Europe and China showed an incidence of troponin elevation in 20.8% when measured in the first 24 hours, rising to 34.2% when measured during the ongoing hospital stay.<sup>4</sup> Troponin values may change during the course of the disease. These variations in the frequency of troponin elevation may relate to differing disease durations prior to medical evaluation with early sampling resulting in under-estimation of the frequency of myocardial injury. Our finding appears to be broadly in line with the prevalence expected from the heterogeneous evidence base.

Hypertension, chronic kidney disease, ischaemic heart disease and heart failure were all more common in the troponin-positive group in our cohort, which is similarly seen in the large cohorts from the USA.<sup>12</sup> These comorbidities have been all found to be associated with increased risk of death COVID-19 in large studies, and similarly, we found a higher prevalence in those that died.<sup>19 20</sup> Dysfunction of the renin–angiotensin–aldosterone system (RAAS) may be implicated here. Binding of the virus to ACE2 with resultant loss of ACE2 may lead to increases in angiotensin II thereby contributing to endothelial dysfunction, vascular inflammation and thrombosis.<sup>21</sup> The dysfunctional RAAS seen in such



**Figure 1** Histograms of age and troponin coloured by mortality, with troponin logarithmically scaled.

**Table 4** Multivariate and univariate analysis of predictors for mortality

Variable	Univariate OR (95% CI)	Univariate p-value	Multivariate OR (95% CI)	Multivariate p-value
Heart failure	3.60 (1.82 to 7.24)	0.0002***	1.56 (0.54 to 4.54)	0.41
IHD	2.55 (1.44 to 4.53)	0.0013**	1.77 (0.68 to 4.55)	0.24
Lung disease	1.95 (1.20 to 3.15)	0.0063**	2.53 (1.16 to 5.66)	0.02*
Gender	1.00 (0.66 to 1.55)	0.972	0.79 (0.36 to 1.72)	0.55
Black/Asian ethnicity	0.95 (0.60 to 1.52)	0.823	1.01 (0.47 to 2.19)	0.99
Age	1.05 (1.04 to 1.07)	<0.0001***	1.07 (1.03 to 1.10)	<0.0001***
Smoking status	1.33 (0.91 to 1.91)	0.131	1.17 (0.61 to 2.23)	0.64
Hypertension	3.11 (1.97 to 4.97)	<0.0001***	1.74 (0.80 to 3.84)	0.16
Diabetes	1.38 (0.90 to 2.12)	0.161	1.10 (0.53 to 2.27)	0.80
Initial troponin positive	4.69 (2.85 to 7.83)	<0.0001***	2.94 (1.34 to 6.68)	0.008*
CPAP required	7.84 (4.19 to 15.4)	<0.0001***	27.78 (10.96 to 78.94)	<0.0001***
Initial creatinine	1.003 (1.001 to 1.005)	0.01*	1.00 (1.00 to 1.00)	0.26
Initial C reactive protein	1.004 (1.002 to 1.006)	0.0001**	1.00 (1.00 to 1.01)	0.09

ORs and p-values generated using a logistic regression.

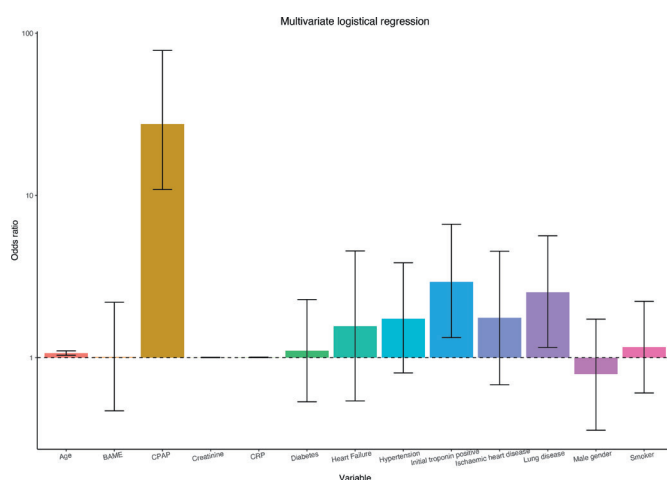
CPAP, continuous positive airway pressure ventilation; IHD, ischaemic heart disease.

comorbidities may lead to susceptibility to severe disease via further disruption through viral binding of ACE2. A significant percentage of the patients in those with positive troponins had chronic kidney disease. A correlation in declining estimated glomerular filtration rate (eGFR) and rising serum troponin is known and may account for some of the elevated troponin levels. However, there was a broad spread of patients across chronic kidney disease groups 1–5, so it is unlikely to explain troponin elevation in the entirety of this group.<sup>22</sup>

Severe COVID-19 is often characterised by a cytokine storm. The cytokine storm may be another factor implicated in myocardial injury as CRP levels have been seen to correlate with troponin levels.<sup>2</sup> In our univariate analysis of predictors of mortality, a positive CRP was associated with mortality in keeping with previous studies. High levels of circulating cytokines may have a direct effect on the

myocardium, as well as contributing to generalised endothelial dysfunction and coagulopathy.<sup>23</sup> This prothrombotic state found in COVID-19 can contribute to various sequelae that can lead to myocardial strain and injury including pulmonary emboli.<sup>24</sup> Pulmonary embolism has been reported in 13% of patients in a large systematic review; in our sample, the prevalence of pulmonary embolism was rather lower, and prevalence was higher in the troponin-negative group.<sup>25</sup> However, the number of CT pulmonary angiography scans performed in our sample was also low so our results should be interpreted with caution.

Case series of occlusive coronary disease in COVID-19 exist in the literature; however, it appears to be relatively uncommon.<sup>26</sup> This is reflected in our sample with only one patient proceeding to invasive coronary angiogram and only nine of the patients with positive troponin receiving medical ACS treatment during their admission. In ST elevation myocardial infarction associated with COVID-19 a higher thrombotic burden has been noted during angiography, suggesting that the prothrombotic state may be a contributing factor to coronary occlusion; however, clear causation is not yet proved.<sup>27</sup> There are case reports of myocarditis but the prevalence in autopsy studies appears to be relatively low with one compilation of autopsy studies estimating histopathological evidence myocarditis at 7.2%, being functionally significant in <2%.<sup>28</sup> In our cohort, we did not identify any cases of myocarditis. However, we acknowledge that myocarditis is recognised to rarely occur following COVID-19 infection and vaccination, but this association needs to be further investigated.<sup>29</sup> Acute COVID-19 myocarditis has been detected on cardiac MRI, but we were unable to correlate this in our study.<sup>7</sup>



**Figure 2** ORs and associated p-values for input variables to multivariate logistic regression investigating associations with mortality.

Only around a third of those with a positive troponin underwent echocardiography in our cohort. The prevalence of regional wall motion abnormalities, impaired left ventricular systolic function and pericardial effusion were proportionally higher in the troponin-positive group. These findings have previously been characterised as part of the clinical picture of myocardial injury in COVID-19.<sup>30</sup> However, our results on echocardiographic findings should be approached with caution as the number of patients in the troponin-positive group undergoing echocardiography was three times higher than that in the negative group.

There are some limitations to our findings. First, our sample was a small retrospective analysis of patients with COVID-19 requiring hospitalisation. Second, within this cohort of patients, a significant proportion (approximately 20%) did not have blood troponin levels measured and were excluded from the analysis. These results reflect outcomes in patients prior to the availability of vaccination and before other evidence based interventions were available to hospitalised patients. Furthermore, there were differences in timing of sampling of blood troponin between patients during their hospital stay. Also, potentially important data such as body mass index was not available in this dataset.

## CONCLUSIONS

Troponin positivity was independently associated with increased short-term mortality in hospitalised patients with COVID-19 during the first wave of the pandemic. The mechanisms implicated in myocardial injury in COVID-19 are not fully understood and require further investigation.

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## REFERENCES

- World Health Organization. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data [Internet], 2022. Available: <https://covid19.who.int/> [Accessed 11 May 2022].
- Guo T, Fan Y, Chen M, *et al*. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:811.
- Shi S, Qin M, Shen B, *et al*. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiology* 2020;5:802.
- Zhao B-C, Liu W-F, Lei S-H, *et al*. Prevalence and prognostic value of elevated troponins in patients hospitalised for coronavirus disease 2019: a systematic review and meta-analysis. *J Intensive Care* 2020;8:88.
- Imazio M, Klingel K, Kindermann I, *et al*. COVID-19 pandemic and troponin: indirect myocardial injury, myocardial inflammation or myocarditis? *Heart* 2020;106:1127–31.
- Chen L, Li X, Chen M, *et al*. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res* 2020;116:1097–100.
- Kotecha T, Knight DS, Razi Y, *et al*. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. *Eur Heart J* 2021;42:1866–78.
- Majure DT, Gruberg L, Saba SG, *et al*. Usefulness of elevated troponin to predict death in patients with COVID-19 and myocardial injury. *American Journal of Cardiology* 2020.
- Izcovich A, Ragusa MA, Tortosa F, *et al*. Prognostic factors for severity and mortality in patients infected with COVID-19: a systematic review. *PLoS One* 2020;15:e0241955.
- Parohan M, Yaghoubi S, Seraji A. Cardiac injury is associated with severe outcome and death in patients with coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. *Eur Heart J Acute Cardiovasc Care* 2020;9:665–77.
- Li J-W, Han T-W, Woodward M, *et al*. The impact of 2019 novel coronavirus on heart injury: a systematic review and meta-analysis. *Prog Cardiovasc Dis* 2020;63:518–24.
- Majure DT, Gruberg L, Saba SG, *et al*. Usefulness of elevated troponin to predict death in patients with COVID-19 and myocardial injury. *Am J Cardiol* 2021;138:100–106.
- Papageorgiou N, Sohrabi C, Prieto Merino D, *et al*. High sensitivity troponin and COVID-19 outcomes. *Acta Cardiol* 2022;77:81–8.
- Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis. *Prog Cardiovasc Dis* 2020;63:390–1.
- Kaura A, Panoulas V, Glampson B, *et al*. Association of troponin level and age with mortality in 250 000 patients: cohort study across five UK acute care centres. *BMJ* 2019;367:l6055.
- Levin AT, Hanage WP, Owusu-Boaitey N, *et al*. Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. *Eur J Epidemiol* 2020;35:1123–38.



- 17 Aveyard P, Gao M, Lindson N, *et al*. Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study. *Lancet Respir Med* 2021;9:909–23.
- 18 Perkins GD, Ji C, Connolly BA. An adaptive randomized controlled trial of non-invasive respiratory strategies in acute respiratory failure patients with COVID-19. *medRxiv* 2021:2021.08.02.21261379.
- 19 Deng G, Yin M, Chen X, *et al*. Clinical determinants for fatality of 44,672 patients with COVID-19. *Crit Care* 2020;24:179.
- 20 Docherty AB, Harrison EM, Green CA, *et al*. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020;369:m1985.
- 21 South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. *Am J Physiol Heart Circ Physiol* 2020;318:H1084–90.
- 22 Chung JZY, Dallas Jones GR, Jones GRD. Effect of renal function on serum cardiac troponin T--Population and individual effects. *Clin Biochem* 2015;48:807–10.
- 23 Tersalvi G, Vicenzi M, Calabretta D, *et al*. Elevated troponin in patients with coronavirus disease 2019: possible mechanisms. *J Card Fail* 2020;26:470–5.
- 24 Abou-Ismaïl MY, Diamond A, Kapoor S, *et al*. The hypercoagulable state in COVID-19: incidence, pathophysiology, and management. *Thromb Res* 2020;194:101–15.
- 25 Malas MB, Naazie IN, Elsayed N, *et al*. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: a systematic review and meta-analysis. *EClinicalMedicine* 2020;29:100639.
- 26 Stefanini GG, Montorfano M, Trabattoni D, *et al*. ST-Elevation myocardial infarction in patients with COVID-19: clinical and angiographic outcomes. *Circulation* 2020;141:2113–6.
- 27 Choudry FA, Hamshere SM, Rathod KS, *et al*. High Thrombus Burden in Patients With COVID-19 Presenting With ST-Segment Elevation Myocardial Infarction. *J Am Coll Cardiol* 2020;76:1168–76.
- 28 Halushka MK, Vander Heide RS. Myocarditis is rare in COVID-19 autopsies: cardiovascular findings across 277 postmortem examinations. *Cardiovasc Pathol* 2021;50:107300.
- 29 Kim HW, Jenista ER, Wendell DC, *et al*. Patients with acute myocarditis following mRNA COVID-19 vaccination. *JAMA Cardiol* 2021;6:1196.
- 30 Sud K, Vogel B, Bohra C, *et al*. Echocardiographic findings in patients with COVID-19 with significant myocardial injury. *J Am Soc Echocardiogr* 2020;33:1054–5.