TROPONIN IS INDEPENDENTLY ASSOCIATED WITH DEATH IN PATIENTS WITH COVID: A RETROSPECTIVE STUDY

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Competing Interest Statement:

VSS is an NIHR Clinical Fellow. There are no other competing interests.

Abstract

Objective We performed a single-centre retrospective observational study investigating the association between troponin positivity in patients hospitalised with COVID-19 and increased mortality in the short term.

Methods All adults admitted with swab-proven RT-PCR COVID-19 to Homerton University Hospital (HUH) from 04.02.20 to 30.04.20 were eligible for inclusion.

We retrospectively analysed demographic and biochemical data collected from the physical and electronic patient records according to the primary outcome of death at 28 days during hospital admission.

Troponin positivity was defined above the upper limit of normal according to our local laboratory assay (>15.5ng/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 length of stay for all 402 hospitalised COVID-19 patients at HUH was 9.1 days (SD 12.0). Mean age was 65.3 years for men compared to 63.8 years for women. A chi-squared test showed that survival of COVID-19 patients was significantly higher in those with a negative troponin ($p = 3.23 \times 10^{-10}$) compared to those with a positive troponin. In the multivariate logistical regression, lung disease, age, troponin positivity and CPAP were all significantly associated with death, with an AUC of 0.8872, sensitivity of 0.9004 and specificity of 0.6292 for the model. Within this model, troponin positivity was independently associated with short term mortality (OR 3.23, 95% CI 1.53-7.16, p=0.00278).

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

Key Questions

What is already known about this subject? An elevated Troponin is associated with increased mortality. Troponin is known to be elevated in some patients who test positive for COVID-19 infection.

What does this study add? This study shows an association between an elevated troponin in hospitalised COVID-19 patients and increased short-term mortality.

How might this impact on clinical practice? Troponin is a readily available, easy to measure biomarker which can be used to predict the severity of COVID-19 illness and could aid prognostication in hospital.

Introduction

The COVID-19 pandemic has so far resulted in over 200 million recorded infections and over 4 million deaths worldwide (1) . A significant proportion of patients develop acute respiratory distress syndrome (ARDS), require hospitalisation and 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 (2–4). This has subsequently been replicated in various studies and meta-analyses from around the world (5).

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 (6). 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 (7–9). Cardiac imaging studies of patients recovered from COVID-19 show evidence of a range of patterns and localisation of myocardial injury, with acute and sub-acute myocardial inflammation suggesting distinct pathways leading to myocardial damage (10).

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 troponins appears to be associated with both death and increased intensive care admissions, as well as the requirement for ventilation (11). 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 (12).

With the widespread administration and uptake of vaccinations in western nations the risk of severe COVID-19 has been significantly mitigated but not eliminated(13). This relates to the emergence of vaccine resistant variants, and endemicity of infection in the population in vulnerable and non-

vaccinated individuals. 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. We also investigated other factors that may be implicated in the prognostication of COVID-19 patients.

Methods

Data collection

All adults admitted with swab-proven RT-PCR COVID-19 to Homerton University Hospital (HUH), London, from the date of the first positive swab from 02/03/2020 to 30/04/2020 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 were excluded and those who did not have a positive SARS-CoV-2 real time reverse-transcriptase polymerase chain reaction test (RT-qPCR) 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. 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. The study was submitted to the HRA (Health Research Authority) and was approved by the HUH trust board.

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 (URL) 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. A Mann Whitney U Test was performed to compare troponin values against the primary outcome, and a Chi-squared test was performed to compare troponin positivity against the primary outcome. Further Chi-square, 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 (tables 1-3). Confidence intervals were computed for the above testing. A p value < to 0.05 was considered as significant. Univariate and multivariate logistical regression analyses were performed to evaluate the link between troponin positivity and death. 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. All data analysis was performed in the statistical computing software R (version 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 02/03/2020 30/04/2020. 83 patients did not have a troponin measured and were therefore excluded. The baseline demographics and clinical characteristics for all patients are shown in table 1. There was a male preponderance to the troponin negative group with the inverse the case in the troponin positive group. Around one third of patients had a Black or Asian ethnicity. Hypertension was the most frequent recorded co-morbidity, 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 ACE-I reflected the increased prevalence of these co-morbidities. Chest pain was uncommon in both groups. However, there was no significant difference in presenting symptom between the two groups.

Table 1: Demographics and patient characteristics. Note that where a multiclass comparator was made p-values (for example for gender) p-values 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.

Parameter	Troponin positive group (n, %)	Troponin negative group (n, %)	Chi-square P-value
	Troponin positive (N=124)	Troponin negative (N=195)	
Gender			
Male	58 (46.8)	115 (59.0)	*P = 0.0437
Female	66 (53.2)	80 (41.0)	*P = 0.0437
Age			
<18	0 (0)	0 (0)	***P<0.0001 (Mann-Whitney U)
18-35	0 (0)	20 (10.3)	
36-49	4 (3.2)	25 (12.8)	
50-64	30 (24.2)	83 (42.6)	
≥65	90 (72.6)	67 (34.4)	
Ethnicity			
White	38 (30.6)	52 (26.7)	P = 0.709
Asian	7 (5.6)	12 (6.2)	
Black	39 (31.5)	64 (32.8)	
Mixed	3 (2.4)	2 (1.0)	
Other	28 (22.6)	55 (28.2)	
Not declared	9 (7.3)	10 (5.1)	
Comorbidities			
Ischaemic heart disease	28 (22.6)	19 (9.7)	**P = 0.00278
Heart Failure	23 (18.5)	8 (4.1)	***P<0.0001
Chronic Kidney Disease	45 (36.3)	13 (6.7)	***P<0.0001
Hypertension	89 (71.8)	93 (47.7)	***P<0.0001
Diabetes Mellitus	56 (45.2)	81 (41.5)	P = 0.602

Dyslipidaemia	45 (36.3)	46 (23.6)	*P = 0.0203
Lung disease	31 (25)	49 (25.1)	P = 1.00
Other major organ disease	80 (64.5)	88 (45.1)	**P = 0.00109
Presenting complaint			
Chest pain	7 (5.6)	15 (7.7)	P = 0.634
Shortness of Breath	68 (54.8)	113 (57.9)	P = 0.667
Cough	60 (48.4)	104 (53.3)	P = 0.455
Fever	55 (44.4)	99 (50.8)	P = 0.316
Smoking status			
Current smoker	4 (3.2)	14 (7.2)	*P = 0.00890
Ex smoker	26 (21)	38 (19.5)	*P = 0.00890
Never smoker	76 (61.3)	134 (68.7)	*P = 0.00890
Not documented	18 (14.5)	9 (4.6)	*P = 0.00890
Baseline medications			
Statin therapy	75 (60.4)	79 (40.5)	**P = 0.000767
ACEi/ARB	85 (57.5)	53 (27.2)	***P<0.0001
Antiplatelets	41 (33.1)	25 (12.8)	***P<0.0001
Anticoagulation	16 (12.9)	12 (6.2)	P = 0.06097
Beta blockers	45 (36.3)	33 (16.9)	**P = 0.000151
MRA	8 (6.5)	0 (0)	**P = 0.00126
Other diuretic	38 (30.6)	25 (12.8)	**P = 0.0001741
Other antihypertensive	48 (38.7)	64 (32.8)	P = 0.340

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 computed tomography pulmonary angiograms (CTPAs) 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.

Table 2: Inpatient investigations. Note that where a multiclass comparator was made p-values (for example for gender) p-values 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.

Parameter	**Troponin positive group (n, %)**	**Troponin negative group (n, %)**	**Chi-square p-value**
	Troponin positive (N=124)	Troponin negative (N=195)	
Biochemical findings on admission			
WBC low	8 (6.4)	19 (9.7)	**P = 0.0003
WBC normal (4-11)	74 (60.0)	147 (75.4)	**P = 0.0003
WBC high	42 (33.9)	29 (14.9)	**P = 0.0003

Lymphocytes low	65 (52.4)	107 (54.9)	P = 0.198
Lymphocytes normal (1-4)	57 (46.0)	88 (45.1)	P = 0.198
Lymphocytes high	2 (1.6)	0 (0)	P = 0.198
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

Outcomes and inpatient management

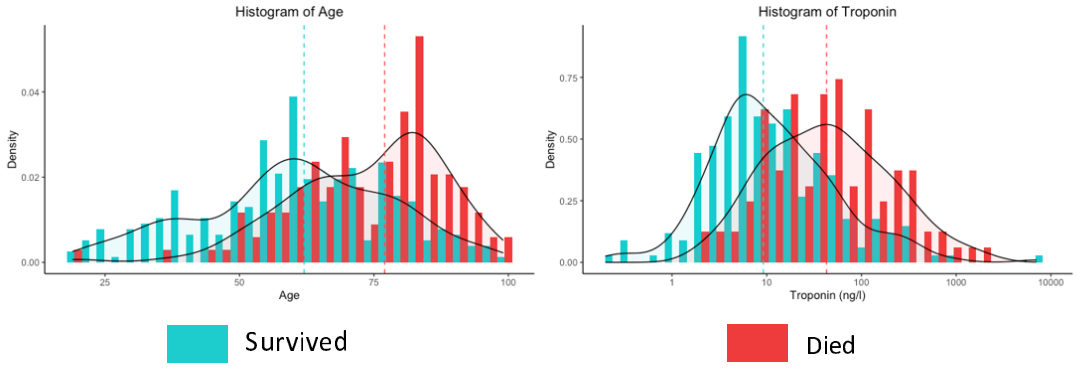
Table 3 shows the cumulative outcomes in the troponin positive and negative groups. The average age of patients who died was 74.0 (95 CI 71.5 – 76.5) years whilst the average age in those who survived was 60.4 (95 CI 58.3 – 62.5) years (see figure 1 panel C). Death rates were higher in the troponin positive group. Chi-squared test showed that survival of COVID-19 patients was significantly higher in those with a negative troponin compared to those with a positive troponin ($p = 3.23 \times 10^{-10}$). Mean initial troponin in patients who survived was 70.0ng/l (95 CI 5.6ng/l – 134.4ng/l), whilst in those who died it was 131.4ng/l (95 CI 78.9ng/l - 183.9ng/l) (see figure 1 panel D). A Mann Whitney U test showed that initial troponin was significantly higher in those who died ($p = 2.24 \times 10^{-12}$) compared to those who were alive. COVID-19 was the primary cause of death in both patient populations on the medical certificate for cause of death (MCCD). 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 ACS, however only one patient subsequently went on to have percutaneous coronary intervention

Table 3: Outcomes and inpatient management

Parameter	**Troponin positive group, n,(%)**	**Troponin negative group, n(%)**	**Chi-square P-value**
	Troponin positive (N=124)	Troponin negative (N=195)	
Mortality			
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
Critical care management			
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
Other in-hospital management			
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
Immunosuppression	8 (6.5)	21 (10.8)	P = 0.268

Figure 1. Histograms of age and troponin coloured by mortality. It is worth noting here that troponin is logarithmically scaled.



Predictors of outcome

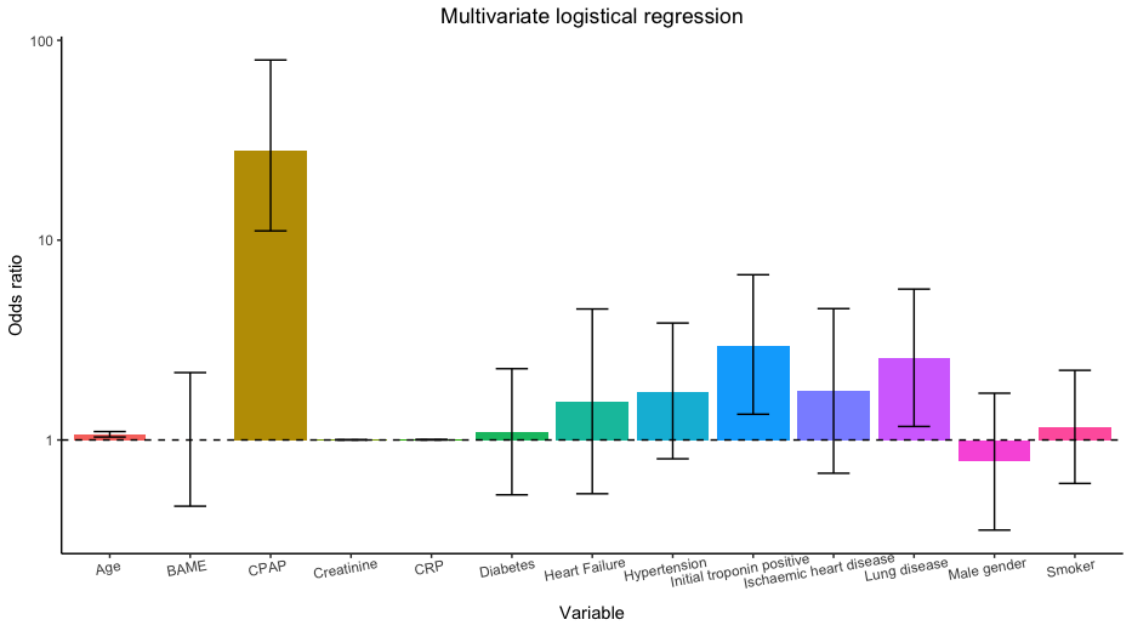
Table 4 shows the results of the univariate and multivariate regression in our patient cohort. A histogram of the odds ratio for the multivariate analysis can be seen in figure 2. In the multivariate logistical regression, lung disease, age, troponin positivity, and CPAP were all significantly associated with death, with an AUC of 0.893, sensitivity of 0.896 and specificity of 0.662 for the model. The receiver-operator (ROC) curve is shown in figure 3. Within this model, troponin positivity was independently associated with short term mortality (OR 2.96, 95% CI 1.34-6.71, p=0.0077).

Table 4: Multivariate and univariate analysis of predictors for mortality. Odds ratios and p-values generated using a logistic regression.

Variable	Univariate OR (95 CI)	Univariate p-value	Multivariate OR (95 CI)	Multivariate p-value
Heart Failure	3.56 (1.81-7.16)	0.0003 ***	1.56 (0.54-4.52)	0.41
IHD	2.53 (1.42-4.48)	0.0015 **	1.76 (0.68-4.54)	0.24
Lung disease	2.00 (1.24-3.22)	0.0044 **	2.55 (1.17-5.69)	0.020 *

Gender	0.99 (0.65-1.52)	0.964	0.78 (0.35 - 1.71)	0.544
Black/Asian ethnicity	1.00 (0.63-1.60)	0.998	1.00 (0.466-2.17)	0.99
Age	1.05 (1.04-1.07)	<0.0001 ***	1.07 (1.03-1.11)	<0.0001 ***
Smoking status	1.31 (0.90-1.89)	0.215	1.16 (0.606-2.23)	0.64
Hypertension	3.14 (2.00-5.03)	<0.0001 ***	1.74 (0.81-3.85)	0.16
Diabetes	1.36 (0.88-2.09)	0.161	1.09 (0.53-2.27)	0.69
Initial troponin positive	4.77 (2.90-7.95)	<0.0001 ***	2.96 (1.34-6.71)	0.0077 *
CPAP required	8.05 (4.31-15.8)	<0.0001 ***	28.1 (11.12-79.70)	<0.0001 ***
Initial creatinine	1.003 (1.001-1.005)	0.011*	1.00 (1.00-1.00)	0.26
Initial c-reactive protein	1.004 (1.002-1.006)	0.0002 **	1.00 (1.00-1.01)	0.094

Figure 2: Odds ratios and associated p-values for input variables to logistic regression.



Discussion

In this retrospective cross-sectional study, we have demonstrated that a positive initial troponin was independently associated with short-term mortality in patients hospitalized with COVID-19 These findings line up with other studies and meta-analyses (3–5,14–18,20,22,41–44). Papargeorgeiou et al. similarly reported the association between a positive initial troponin and mortality across several London hospitals covering different geographical areas (20). Other studies have found correlation between elevated troponin and more severe disease, ICU admission and the requirement for non-invasive and mechanical ventilation (3,4,14,22,42,43,45,46). We did not find any significant between group differences in CPAP use, ITU admission and intubation between troponin positive and negative groups. However, this observation 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 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 (47).

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 (48). 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 doesn't appear to confer increased risk (49). The use of 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 (50).

In our cohort initial troponin was positive in 31% of patients. Data from Wuhan initially outlined an incidence of 12-27% (2–4). Subsequent studies from western countries show a broad prevalence of myocardial injury. In general, there appears to be higher frequency of troponin elevation in hospitalized patients in European and USA populations, when compared to China, with an incidence rising above 50% in some instances (11,14–21). 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 (5). Our finding appears to be broadly in line with the prevalence expected from the heterogenous 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 (18,22). These co-morbidities have been all been 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 (23,24). 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 (25). The dysfunctional RAAS seen in such co-morbidities 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 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 (26).

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 (3). High levels of circulating cytokines may have a direct effect on the myocardium, as well as

contributing to generalised endothelial dysfunction and coagulopathy (27). This prothrombotic state found in COVID-19 can contribute to various sequalae that can lead to myocardial strain and injury including pulmonary emboli (28). 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 (29). 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 (30,31). This is reflected in our sample with only 1 patient proceeding to invasive coronary angiogram and only 9 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 (32,33). Case reports of clinical myocarditis do exist in the literature, however the prevalence in autopsy studies appears to be relatively low with one compilation of autopsy studies estimating histopathological evidence myocarditis at 7.2%, being only functionally significant in <2% (34–36). 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 (37). Acute COVID-19 myocarditis has been detected on cardiac MRI but we were unable to correlate this in our study (10).

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 (38–40). 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 hospitalization. Second, within this cohort of patients, a significant proportion (approximately 20%)did not have blood troponin levelsmeasured and were excluded from the analysis. Furthermore, there were differences in timing of sampling of blood troponin between patients during their hospital stay.

Conclusions

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

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