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RESEARCH ARTICLE

Elevated Troponin and Mortality in Patients with COVID-19: A Multicenter Retrospective Cohort Study

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Abstract:

Introduction:

Myocardial injury, causing elevated troponin levels, have been associated with worse outcomes in coronavirus disease 2019 (COVID-19) disease patients. However, our anecdotal experience did not consistently reflect this pattern. Therefore, we evaluated the outcomes of COVID-19 patients with elevated troponin.

Methods:

This is a retrospective study of 1,024 COVID-19 patients admitted to two hospitals in Southern California in the United States. We categorized the troponin levels as normal (≤1× upper reference limit (URL)), mildly elevated (>1 to ≤3× URL), and severely elevated (>3× URL). We compared the characteristics of the three troponin groups using chi-square for categorical variables and one-way Anova for the continuous variables. Finally, backward selection Cox regression analysis was carried out using mortality as a dependent variable.

Results:

Of the COVID-19 1,024 patients included in the study, 944 (92%) had normal troponin, 45 (4.4%) had mild elevation, and 35 (3.4%) had a severe elevation in troponin levels. In the multivariate Cox regression analysis, troponin elevation in patients without ST-elevation on ECG was not independently associated with mortality (hazard ratio 0.92, 95% CI 0.64-1.3). Increased risk of death was independently associated with age as well as serum C-reactive protein and serum creatinine levels.

Conclusion:

Elevated troponins without ST-elevation on ECG on hospital admission were not independently associated with increased mortality in hospitalized COVID-19 patients. However, further research is needed to fully understand the absence of a relationship between troponin elevation and mortality in our study population.

Keywords: COVID-19, SARS-CoV-2, Troponin, Myocarditis, Mortality, ICU admission, Mechanical ventilation, Length of stay.

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1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus (SARS-CoV-2) and was first identified in 2019 in Wuhan, China, before quickly spreading around the world [1]. The World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020 [1]. The virus is well-known for causing a range of mild to severe pulmonary illnesses. The disease can also progress from pneumonia to more severe complications such as acute respiratory distress syndrome and possibly, sepsis [2]. In addition, many individuals with comorbidities such as diabetes, cancer, and chronic obstructive pulmonary disease (COPD) are at a higher risk of becoming seriously ill and possibly dying [2]. This rapidly evolving virus persists worldwide [3].

The disease comes with various symptoms varying from person to person and affecting multiple organ systems [4]. Typical symptoms include fever, cough, shortness of breath, fatigue, chills, and sore throat. In addition, patients have

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reported myalgia, gastrointestinal symptoms (*e.g.*, nausea, vomiting, diarrhea) and anosmia [4]. The virus is also responsible for causing cardiovascular pathology by directly injuring cardiomyocytes, causing them to release troponins, which then increases the probability of mortality [5, 6]. The elevation in troponins can also assist in evaluating the severity of the disease in hospitalized patients [5, 6]. However, our anecdotal experience did not consistently show worse outcomes in COVID-19 patients with elevated troponin. Therefore, we evaluated the difference in in-hospital mortality, length of hospital stay, intensive care unit (ICU) admission and need for invasive mechanical ventilation in patients with different levels of troponin elevation.

2. MATERIALS AND METHODS

This is a retrospective study of 1,024 COVID-19 patients admitted to two hospitals in Southern California in the United States between March 2020 and March 2021. The study includes all patients with a COVID-19 infection confirmed by a positive polymerase chain reaction (PCR) nasopharyngeal swab and assessed serum troponin within 48 h of admission. We excluded 92 patients who did not have serum troponin assessment within 48 h of hospital admission. Cardiac troponin I was used in the two hospitals with a 0-0.4 ng/ml reference range. Similar to a prior study, we categorized the troponin levels as normal (≤1× upper reference limit (URL)), mildly elevated (>1 to ≤3× URL), and severely elevated (>3× URL) [6]. We also reviewed the electrocardiograms (ECG) of the patients; none of them had ST elevation on admission.

For COVID-19 patients admitted to the hospital more than once during the study period for COVID-19-related symptoms, their last hospital admission data was used for the study. We used the last hospital admission for COVID-19-related symptoms because some patients died from COVID-19 complications during subsequent hospital admission. Therefore, we used their last hospital admission to avoid a misclassification bias. Otherwise, we may have misclassified some patients who died as survivors if we only used their initial hospitalization for COVID-19. Relevant de-identified data were extracted from the electronic medical record, including age, sex, race, ethnicity, marital status, comorbidities, laboratory results on admission, date of admission, date of discharge, medications received during admission, and disposition at discharge. The primary outcome was in-hospital mortality. Secondary outcomes were: length of hospital stay, the proportion of patients admitted to ICU, and the proportion of patients requiring invasive mechanical ventilation.

Univariate analysis of variables was carried out using means and percentages. We compared the characteristics of the three troponin groups using chi-square for categorical variables and one-way Anova for the continuous variables, with a 2-sided $p<0.05$ considered significant. Finally, backward selection Cox regression analysis used mortality as a dependent variable. We included variables with statistical significance in the bivariate analysis, such as age, sex, comorbidities, and inflammatory markers, including CRP, ferritin, and lactate dehydrogenase (LDH), as independent variables in the multivariate model. The effect was expressed in terms of hazards ratio (HR) with a 95% confidence interval (CI). Statistical analysis was carried out using International Business machines Statistical Package for the Social Sciences (IBM SPSS) version 27 (Armonk, NY, USA). The study was approved by the Western Institutional Review Board (WIRB)-Copernicus Group (WCG) institutional review board (IRB) (approval number 13410516).

3. RESULTS

We had a total of 1,116 patients admitted with COVID-19 during the study period. After excluding 92 patients (8%) who did not receive troponin assessment within 48 h of admission, 1,024 patients were included in the study. Of those included in the study, 944 (92%) had normal troponin, 45 (4.4%) had mild elevation, and 35 (3.4%) had a severe elevation in troponin levels. Patients with elevated troponin were older than those with normal troponin (p=0.001). Inflammatory markers, including CRP (p=0.007), LDH (p<0.001), d-dimer (p<0.001), and ferritin (p<0.001), were significantly higher in the patients with elevated troponin compared with those with normal troponin. In addition, creatinine was significantly higher in those with mild troponin than those with normal troponin levels (p<0.001) (Table **1**).

Table 1. Characteristics of patients in the three troponin groups.

-	-	Troponin Level (URL)			
Variable	**All patients (n = 1024)**	**Normal (n = 944)**	**>1 to ≤3× (n = 45)**	**>3× (n = 35)**	**p**
Age (years) (mean (range))	66.5 (20-101)	66.0 (20-101)	71.8 (23-95)	74.5 (48-93)	0.001
BMI (Kg/m^2) (mean (range))	30.8 (14.7-83.1)	31.0 (14.7-83.1)	29.8 (17.6-64.4)	27.8 (17.0-57.1)	0.089
CRP (mg/dl)	9.07 (0.05-31.22)	8.87 (0.05-31.02)	11.53 (0.34-31.22)	11.42 (0.27-20.81)	0.007
LDH (iU/L)	408.6 (87-10543)	372.0 (87-4752)	753.4 (155-7201)	971.1 (204-10543)	<0.001
D-dimer (ng/ml)	1334.07 (135-5250)	1245.94 (135-5250)	2240.10 (277-5250)	2731.79 (287-5250)	<0.001
Ferritin (ng/ml)	811.12 (5.1-51813)	712.77 (5.1-40280)	1219.88 (19.6-7562)	2855.89 (49.2-51813)	<0.001
Creatinine (mg/dl)	1.62 (0.24-21.3)	1.55 (0.24-21.3)	2.81 (0.64-10.28)	2.03 (0.48-5.65)	<0.001
Sex, n (%)					
Female	485 (47.4%)	452 (47.9%)	19 (42.2%)	14 (40.0%)	0.512
Male	539 (52.6%)	492 (52.1%)	26 (57.8%)	21 (60.0%)	
Race, n (%)					
White	834 (81.4%)	772 (81.8%)	35 (77.8%)	27 (77.1%)	0.818

(Table 1) contd.....

-	-	Troponin Level (URL)			
Variable	**All patients (n = 1024)**	**Normal (n = 944)**	**>1 to ≤3× (n = 45)**	**>3× (n = 35)**	**p**
Black	74 (7.2%)	66 (7.0%)	5 (11.1%)	3 (8.6%)	
Others	116 (11.3%)	106 (11.2%)	5 (11.1%)	5 (14.3%)	
Coronary artery disease, n (%)	200 (19.5%)	162 (17.2%)	20 (44.4%)	9 (51.4%)	<0.001
Chronic obstructive pulmonary disease, n (%)	147 (14.4%)	131 (13.9%)	9 (20.0%)	7 (20.0%)	0.325
Heart failure, n (%)	185 (18.1%)	158 (16.7%)	15 (33.3%)	12 (34.3%)	0.001
Chronic kidney disease, n (%)	217 (21.2%)	188 (19.9%)	15 (33.3%)	14 (40%)	0.002
Hypertension, n (%)	639 (62.4%)	577 (61.1%)	35 (77.8%)	27 (77.1%)	0.015
Diabetes mellitus, n (%)	471 (46.0%)	433 (45.9%)	20 (44.4%)	18 (51.4%)	0.792

BMI: Body Mass Index, CRP: C-Reactive Protein, LDH: Lactate Dehydrogenase

No difference in troponin elevation by sex (p=0.51) or race (p=0.82) existed. However, there were higher troponin levels reported in those with coronary artery disease (p<0.001), heart failure (p=0.001), chronic kidney disease (p=0.002), and hypertension (p=0.015). Patients with mildly and severely elevated troponin had a more significant coronary artery disease and heart failure burden than patients with normal troponin. While 17% of patients with normal troponin had coronary artery disease, 44% of those with mildly elevated troponin, and 51% of those with severely elevated troponin had coronary artery disease (p<0.001). Similarly, 17% of patients with normal troponin had heart failure, compared to 33% of those with mildly elevated troponin and 34% with severely elevated troponin (p=0.001) (Table **1**).

Patients with mild and severely elevated troponin were more significantly likely to require ICU admission (p<0.001) and mechanical ventilation (p<0.001) than those with normal troponin levels. For example, while 21% of patients with normal troponin were admitted to the ICU, it was 40% for those with mild troponin elevation and 46% for those with severe troponin elevation (p<0.001). Similarly, 18% of patients with normal troponin required mechanical ventilation compared with 40% in those with mild troponin elevation and 46% in patients with severe troponin elevation (p<0.001) (Table **2**). Furthermore, the hospital length of stay was lower in patients with normal troponin than those with mild or severe elevated troponin (p=0.009). The mean length of stay was nine days for the normal troponin group, 11.7 days for those with mild troponin elevation, and 12.5 days for patients with severe troponin elevation (p=0.009) (Table **2**).

In the bivariate analysis, those with mild and severe troponin elevation were significantly more likely to die than those with normal troponin (p<0.001). While 25% of patients with normal troponin died, it was 47% for those with mild troponin elevation and 60% for those with severe troponin elevation (Table **2**). However, in the multivariate Cox regression analysis, including covariates of age, sex, hypertension, coronary artery disease, heart failure, CKD, CRP, LDH, d-dimer, ferritin, creatinine, ICU admission, and mechanical ventilation, troponin elevation was not independently associated with mortality (HR 0.92, 95% CI 0.64-1.3). Increased risk of death was independently associated with age, serum CRP and serum creatinine levels, while ICU admission was protective against mortality (Table **3**).

Table 2. Outcomes by troponin groups.

-	Troponin Level (URL)				
Variable	**All patients (n = 1,024)**	**Normal (n = 944)**	**>1 to ≤3× URL (n = 45)**	**>3× URL (n = 35)**	**p**
Primary Outcome					
Died, n (%)	277 (27.1%)	235 (24.9%)	21 (46.7%)	21 (60.0%)	<0.001
Secondary Outcomes					
ICU admission, n (%)	231 (22.6%)	197 (20.9%)	18 (40.0%)	16 (45.7%)	<0.001
Mechanical ventilation, n (%)	199 (19.4%)	169 (17.9%)	17 (37.8%)	13 (37.1%)	<0.001
Length of stay (days) (mean (range))	9.3 (0-64)	9.1 (0-64)	11.7 (0-46)	12.5 (1-58)	0.009

ICU: Intensive Care Unit.

Table 3. Cox regression showing factors that predict mortality in COVID-19 patients.

	B	SE	Wald	df	p	Hazard ratio	95.0% CI for the hazard ratio	
							Lower	Upper
Age	.038	.006	46.416	1	.000	1.039	1.028	1.050
ICU admission	-1.058	.149	50.478	1	.000	.347	.259	.465
Troponin	-.086	.183	.220	1	.639	.918	.641	1.313
CRP	.037	.010	12.429	1	.000	1.038	1.017	1.059
Creatinine	.113	.026	18.448	1	.000	1.119	1.063	1.178

ICU: Intensive Care Unit, CRP: C-Reactive Protein

4. DISCUSSION

As our primary outcome of interest, we studied troponin elevation in COVID-19 patients with in-hospital mortality. Additionally, our secondary outcomes of interest were the length of hospital stay, the proportion of patients admitted to ICU, and the proportion of patients requiring invasive mechanical ventilation. Our study did not find any significant independent relationship between troponin elevation and mortality in COVID-19 patients. In addition, our sensitivity analysis comparing mortality in patients with normal troponin and a sub-set of patients with severe troponin elevation (>3× upper reference limit) did not show increased mortality with troponin elevation. This finding contradicts other studies showing elevated troponin is independently associated with increased mortality [6 - 9]. Our study findings are unclear, but one likely cause is that our study population differs from the other studies. In our study, 8% of the patients had elevated troponin levels on admission, much lower than other studies that saw increased mortality with troponin elevation [7]. Thus, the lack of effect seen in our study may be due to the small proportion of patients with elevated troponin.

Our study also found that patients with elevated troponin were more likely to be older, stay longer in the hospital, and have increased inflammatory markers, including CRP, LDH, ferritin, and d-dimer, which were consistent with prior studies [6, 10]. However, there was no relationship between gender and race with troponin elevation, as reported in an earlier study that reported more elevated troponin in males [6]. Furthermore, elevated CRP and creatinine were independent predictors of mortality in our patients, consistent with prior studies [6, 11].

The etiology of elevated troponin I in COVID-19 patients is likely multifactorial. In general, elevation in troponin I could be due to reversible or irreversible myocardial ischemia. In COVID-19 patients, elevation in troponin could be from direct viral-mediated myocardial injury, direct and indirect myocardial injury from inflammation and cytokine storm, microangiopathic disease from hypercoagulability, hypoxic respiratory failure, tachyarrhythmias, and myocardial infarction [12 - 14]. None of the patients had an ST elevation on ECG in our study. However, some patients were diagnosed with possible non-ST elevated myocardial infarction, but none had an angiogram due to their active COVID-19 infection. Moreover, troponin elevation was associated with increased inflammatory markers, making it likely that the troponin elevation was related to COVID-19 inflammation. Our findings are similar to another study that showed that <1% of COVID-19 patients with elevated troponin had clinical evidence of acute coronary syndrome [10].

Since most troponin elevation in COVID-19 patients is attributable to non-ischemic causes of myocardial injury, dual antiplatelet therapy, anticoagulants, or early coronary angiography is usually not indicated [14]. However, these patients may have underlying coronary artery disease and may benefit from a non-acute ischemic workup later on. Some have suggested that COVID-19 patients with myocardial injury from inflammation may benefit from a combination of immunoglobin and steroid therapy [14]. Conversely, with appropriate personal protective equipment, COVID-19 patients with regional ST-segment elevation on ECG and myocardial ischemia symptoms still require emergent coronary angiography [14]. In our study, none of the patients with elevated troponin on admission had acute ST-segment elevation on ECG, and none had a coronary angiogram during admission.

5. CLINICAL IMPLICATIONS

Our study showed that mild or severe troponin elevation without ST-elevation on ECG could predict an increased risk of in-hospital mortality, ICU admission, and length of hospital stay in COVID-19 patients, as shown in our bivariate analysis. However, after adjusting for comorbidities and pre-existing cardiovascular disease, mild or elevated troponin levels were not independently associated with in-hospital mortality, but older age, high CRP and elevated creatinine levels were. The clinical implication is that in COVID-19 patients without ST elevation on ECG, increased patient age, CRP level, and worsening renal function may predict worse outcomes than mild or severe troponin elevation when triaging patients.

6. LIMITATIONS

Our study has several limitations. First, it is a retrospective study, and we might not have adjusted for all confounders. Secondly, the limited number of patients with elevated troponin may have affected the association between troponin and mortality. Thirdly, all participants in our study were inpatients, and the result may not be generalizable to COVID-19 patients that do not require hospitalization. Finally, follow-up mortality data were unavailable; survival data were limited to the hospital admission period.

CONCLUSION

The proportion of COVID-19 patients with elevated troponin in our study was 8%, which is lower than in many prior studies. In addition, contrary to many previous studies, we observed that elevated troponin without ST-elevation on ECG was not independently associated with increased mortality in hospitalized COVID-19 patients. However, older age, high CRP, and elevated creatinine levels were independently associated with increased in-hospital mortality. Further research is needed to fully understand the low incidence of troponin elevation and the absence of a relationship between troponin elevation and mortality in our study population.

LIST OF ABBREVIATIONS

COVID-19	=	Coronavirus disease 2019
WHO	=	World Health Organization
COPD	=	Chronic Obstructive Pulmonary Disease
PCR	=	Polymerase Chain Reaction
LDH	=	Lactate Dehydrogenase
CI	=	Confidence Interval
HR	=	Hazards Ratio
IRB	=	Institutional Review Board
WIRB	=	Western Institutional Review Board

IBM SPSS = International Business machines Statistical Package for the Social Sciences

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Western Institutional Review Board (WIRB)-Copernicus Group (WCG) institutional review board (IRB), and the study IRB approval number is 13410516.

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. The principles of the Declaration of Helsinki were followed in our study. Deidentified retrospective patients' data was used for analysis with IRB approval.

CONSENT FOR PUBLICATION

Informed consent was obtained.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest, financial or otherwise.

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REFERENCES

[1] Shoaib MH, Ahmed FR, Sikandar M, Yousuf RI, Saleem MT. A journey from SARS-CoV-2 to COVID-19 and beyond: a comprehensive insight of epidemiology, diagnosis, pathogenesis, and overview of the progress into its therapeutic management. Front Pharmacol 2021; 12: 576448. [http://dx.doi.org/10.3389/fphar.2021.576448] [PMID: 33732150]

[2] Galiatsatos P. COVID-19 lung damage Available from: https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus/what-coronavirus-does-to-the-lungs

[3] World Health Organization. Tracking SARS-CoV-2 variants Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/

[4] Center for Disease Control. Symptoms of COVID-19 Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

[5] Jain U. Effect of COVID-19 on the Organs. Cureus 2020; 12(8): e9540. [PMID: 32905500]

[6] Majure DT, Gruberg L, Saba SG, Kvasnovsky C, Hirsch JS, Jauhar R. Usefulness of elevated troponin to predict death in patients with COVID-19 and myocardial injury. Am J Cardiol 2021; 138: 100-6. [http://dx.doi.org/10.1016/j.amjcard.2020.09.060] [PMID: 33058800]

[7] Zhao BC, Liu WF, Lei SH, *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(1): 88. [http://dx.doi.org/10.1186/s40560-020-00508-6] [PMID: 33292649]

[8] Lala A, Johnson KW, Januzzi JL, *et al.* Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. J Am Coll Cardiol 2020; 76(5): 533-46. [http://dx.doi.org/10.1016/j.jacc.2020.06.007] [PMID: 32517963]

[9] Lombardi CM, Carubelli V, Iorio A, *et al.* Association of troponin levels with mortality in Italian patients hospitalized with coronavirus disease 2019: results of a multicenter study. JAMA Cardiol 2020; 5(11): 1274-80. [http://dx.doi.org/10.1001/jamacardio.2020.3538] [PMID: 32845276]

[10] Singh N, Anchan RK, Besser SA, *et al.* High sensitivity Troponin-T for prediction of adverse events in patients with COVID-19. Biomarkers 2020; 25(8): 626-33. [http://dx.doi.org/10.1080/1354750X.2020.1829056] [PMID: 32981387]

[11] Qin JJ, Cheng X, Zhou F, *et al.* Redefining cardiac biomarkers in predicting mortality of inpatients with COVID-19. Hypertension 2020; 76(4): 1104-12. [http://dx.doi.org/10.1161/HYPERTENSIONAHA.120.15528] [PMID: 32673499]

[12] Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D. Elevated troponin in patients with coronavirus disease 2019: possible mechanisms. J Card Fail 2020; 26(6): 470-5. [http://dx.doi.org/10.1016/j.cardfail.2020.04.009] [PMID: 32315733]

[13] Imazio M, Klingel K, Kindermann I, *et al.* COVID-19 pandemic and troponin: indirect myocardial injury, myocardial inflammation or myocarditis? Heart 2020; 106(15): 1127-31. [http://dx.doi.org/10.1136/heartjnl-2020-317186] [PMID: 32499236]

[14] Chapman AR, Bularga A, Mills NL. High-sensitivity cardiac troponin can be an ally in the fight against COVID-19. Circulation 2020; 141(22): 1733-5. [http://dx.doi.org/10.1161/CIRCULATIONAHA.120.047008] [PMID: 32251612]