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Assessment of relationship between cardiac troponin-I and mortality in patients with severe COVID-19 infection

Mariam Aijaz Ahmad[1], Prakash Rao[2]

[1] Junior Resident, Department of General Medicine, KVG Medical College and Hospital, Sullia, DK, Karnataka, India

[2] Professor, Department of General Medicine, KVG Medical College and Hospital, Sullia, DK, Karnataka, India

Abstract

Background and Objectives: the on-going COVID-19 pandemic is responsible for over 5 million deaths worldwide. The SARS-COV2 virus is now well known to affect respiratory, cardiovascular and neurological systems. Troponin I, traditionally used as a cardiac biomarker usually for the diagnosis of acute coronary syndrome (ACS). Troponin I levels were found to be raised in COVID patients requiring admission to the ICU. This study is aimed to evaluate the relationship between Troponin I and mortality in such patients and whether Troponin I levels can be used as a prognostic tool to determine severity in COVID patients.

Materials and Methods: This study included patients diagnosed with COVID-19 via RTPCR from nasopharyngeal and pharyngeal samples, who were admitted to the ICU between May 2021 and August 2021. The Troponin I levels were measured for each patient at the time of admission and the patients were stratified into two groups (elevated vs. normal). Data was retrospectively reviewed and analysed.

Results: The study included 257 COVID patients requiring admission to the ICU. Patients with elevated Troponin I levels were found to be older (77±13 vs. 58±16 years, $p<0.0001$). They were also more likely to be suffering from diabetes ($p=0.0019$), hypertension ($p<0.0001$), coronary artery disease ($p<0.0001$) and heart failure ($p=0.0011$). Patients with raised Troponin I levels at admission were more likely to have higher all-cause mortality (52% vs. 10%, $p<0.0001$).

Conclusion: Elevation of Troponin I is commonly seen in patients with severe SARS-COV2 infection and is significantly associated with increased mortality.

Keywords: COVID-19, SARS-COV2, troponin I, mortality

Introduction

Coronavirus disease 2019 (COVID-19) is a newly recognized infectious disease that spread rapidly responsible for more than 5 million deaths worldwide. Furthermore, the number of fatalities due to COVID-19 continues escalating with around 500,000 deaths in India [1]. The COVID-19 infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS COV-2) has spread from the Wuhan province of China since December 2019 and is responsible for a pandemic, causing morbidity and mortality [2].

SARS COV-2 virus infects humans, causing respiratory, enteric, cardiovascular, and neurological diseases. Mortality increases with comorbidities such as diabetes, hypertension, cardiovascular disease, chronic lung disease, malignancy and advancing age [3]. Although COVID-19 infection is classically known to affect the respiratory system, Recent studies have highlighted that cardiac damage occurs with COVID-19-associated high troponin levels [2, 3, 4]. Cardiac troponin-I elevation has been historically known to predict worse mortality in both cardiovascular and non-cardiovascular diseases [5, 6, 7]. The presence of myocardial injury has been significantly associated with a higher rate of morbidity and mortality in COVID-19 patients [8].

This study attempts to study the association between troponin-I level at the time of admission and all-cause in-hospital mortality in patients with COVID-19.

Materials and Methods

Study design and participants

This retrospective, single centre, observational study was performed at KVG Medical College & Hospital, Sullia, Karnataka. We retrospectively analysed patients diagnosed with COVID-19 via reverse transcription-polymerase chain reaction (RTPCR) from nasopharyngeal and pharyngeal samples, who were admitted to the ICU between May 2021 and August 2021.

Clinical information was collected on admission and during hospitalization by the study team. The files of the patients were analysed retrospectively, and all data were recorded. Informed consent forms were obtained from patients and their relatives. Approval to conduct the study was obtained from the ethics committee of the hospital

and affiliated university. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.
Patients age 18 years and older were initially stratified into two groups based on their cardiac troponin-I level at the time of admission (elevated vs. normal). A normal cardiac troponin-I level was defined as ≤0.3 ng/mL, which falls below the 99th percentile in the blood test based on our facility's laboratory data. An elevated troponin-I value was defined as >0.3 ng/mL. Furthermore, patients were grouped according to whether they survived (survivors group) or died (survivors group) during period of their hospitalization.

Inclusion criteria
Patients age 18 years and older who were admitted to the ICU with a confirmed diagnosis of COVID-19, and had a troponin-I level drawn at the time of admission.

Exclusion criteria
We did not include patients with troponin I elevation due to an ischemic etiology. We excluded the patients with symptoms of myocardial ischemia, ischemic electrocardiographic (ECG) changes, pathological Q waves on their ECGs or those with regional wall motion abnormality on echocardiography consistent with an ischemic etiology. Patients who did not require ICU care or those below 18 years of age, were also excluded from this study.

Data collection
The medical records of the patients were reviewed. Patient data including demographics, medical history, laboratory examinations, comorbidities, complications, treatment measures, and outcomes were collected and analysed.

Statistical analyses
Statistical evaluation of the data was performed using SPSS for Windows Version 20. Continuous variables were expressed as means with standard deviation (± SD). A comparison of means (baseline characteristics and predictors) was done using analysis of variance (ANOVA). A comparison of categorical variables (expressed as percentage) was done using a Chi-square test. Results were considered significant if P values < 0.05.

Results
A total of 257 hospitalized patients with COVID-19 were included in the final analysis. This cohort of 257 patients included 122/257 (47%) women.
Comparison of clinical characteristics between elevated troponin and normal troponin groups
As demonstrated in Table1and Figure 1, patients with an elevated troponin-I level were older (77±13 vs. 58 ± 16 years, P < 0.0001), have a history of hypertension (P < 0.0001), diabetes mellitus (P = 0.0019), atrial fibrillation or flutter (P = 0.0009), coronary artery disease (P < 0.0001), and heart failure (P = 0.0011) when compared to the normal troponin group.
Furthermore, as shown in Table 2 and Figure 2, patients with an elevated troponin-I level on admission were more likely to have additional biochemical abnormalities at the time of admission, such as elevated blood urea nitrogen (P < 0.0001), creatinine (P < 0.0001), lactic acid (P = 0.0046), serum sodium (P = 0.0235), random blood sugar (P = 0.0091), total bilirubin (P = 0.0055), but a lower albumin level (P < 0.0001) compared to the normal troponin group.

Table 1: Baseline Characteristics and Mortality of Patients with COVID-19 Based on the Cardiac Troponin-I level (N = 257)

Baseline Characteristics	Elevated Troponin[a] (n = 71)	Normal Troponin[b] (n = 186)	P Value
Age, years (Mean ± SD)	77 ± 13	58 ± 16	< 0.0001*
Sex, female	35(49%)	87(46%)	0.7174
Body mass index, kg/m^2 (Mean ± SD)	26 ± 6.6	30 ± 7.9	0.0002*
Asthma	4(5%)	17(9%)	0.3509
Chronic obstructive lung disease	2(2%)	5(2%)	0.9621
Diabetes mellitus	30(42%)	42(22%)	0.0019*
Hypertension	56(79%)	85(45%)	< 0.0001*
Chronic heart failure	11(15%)	7(3%)	0.0011*
Coronary artery disease	21(30%)	10(5%)	< 0.0001*
Atrial fibrillation/flutter	14(20%)	11(6%)	0.0009*
Chronic kidney disease	7(10%)	3(1%)	0.0024*
Stroke	4(5%)	6(3%)	0.3786

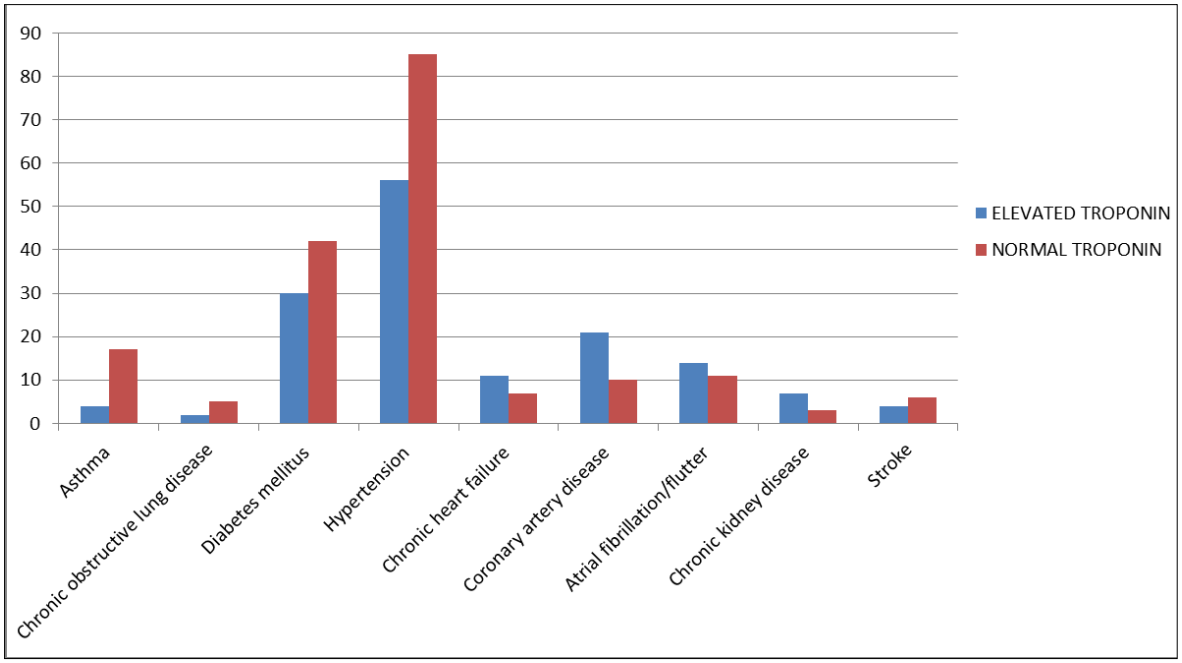

Fig 1: Baseline Characteristics Based On Troponin Levels

Table 2: Baseline Characteristics and Mortality of Patients with COVID-19 Based on the Cardiac Troponin-I level (N = 257)

Laboratory Data at the Time of Admission	Elevated Troponin[a] (n = 71)	Normal Troponin[b] (n = 186)	P Value
Blood urea nitrogen, mg/dL (Mean ± SD)	40 ± 31	17 ± 12	< 0.0001*
Creatinine, mg/dL (Mean ± SD)	1.7 ± 1.3	0.9 ± 0.7	< 0.0001*
Random blood glucose level, mg/dL (Mean ± SD)	181 ± 131	138 ± 68	0.0091*
Absolute neutrophil count/mm^3 (Median (min–max))	8000 (2000–8300)	3560 (1400–1970)	<0.001*
Absolute lymphocyte count/mm^3 (Median (min–max))	810 (100–690)	1280 (360–3330)	0.007*
NLR (Median (min–max))	11.1 (2.21–30)	2.5 (0.89–31)	<0.001*
Lactic acid, mmol/L (Mean ± SD)	3 ± 4	1.2 ± 0.5	0.0046*
Albumin, mg/dL (Mean ± SD)	3.5 ± 0.5	3.9 ± 0.4	< 0.0001*
CRP, mg/dl (Median (min–max))	148 (5.1–273)	13.2 (0.01–319)	<0.001*
D Dimer, ng/ml (Median (min–max))	2271 (271–8802)	422 (0–8902)	<0.001*

[a] Elevated Troponin >0.3 ng/ml, [b]Normal Troponin ≤0.3 ng/ml SD Standard Deviation, NLR Neutrophil-lymphocyte Ratio, CRP C-Reactive Protein.

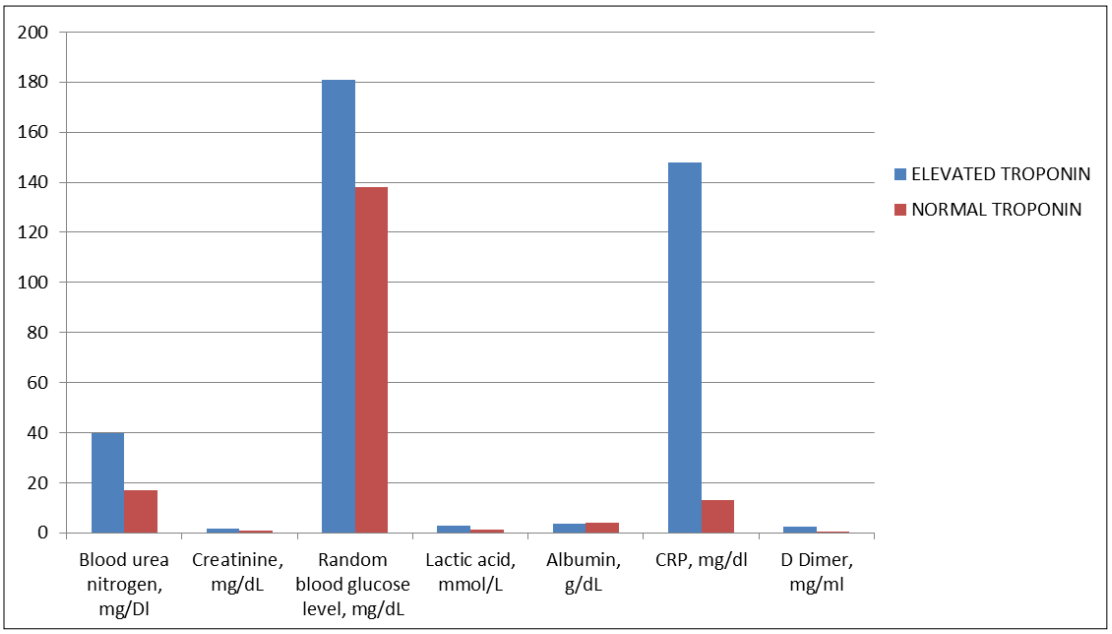

Fig 2: Baseline Laboratory Values Based On Troponin Levels

Table 3: Baseline Characteristics and Mortality of Patients with COVID-19 Based on the Cardiac Troponin-I level (N = 257)

Outcome	Elevated Troponin[a] (n = 71)	Normal Troponin[b] (n = 186)	P Value
In-hospital mortality	37(52)	19(10)	**< 0.0001***

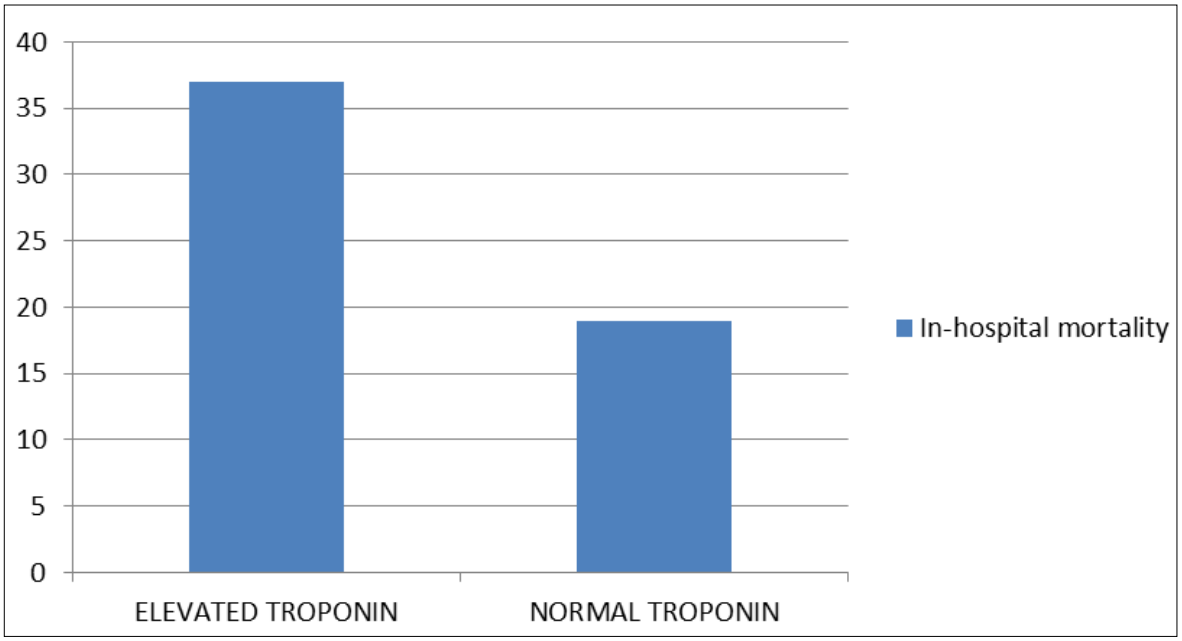

Fig 3: In-Hospital Mortality Based On Troponin Levels

Outcome

In-hospital mortality or discharge to hospice occurred in 56/257 (21.7%) patients diagnosed with COVID-19. Patients with an elevated troponin-I at admission were more likely to have higher in-hospital mortality (52% vs. 10%, P < 0.0001) (Table 3 and Figure 3).

Discussion

As of today, there is substantial evidence connecting COVID-19 as a cause of myocardial injury indicated by elevated cardiac troponin-I levels [9-11]. This study demonstrates that patients with an elevated cardiac troponin-I level at the time of admission have a significantly higher all-cause mortality when compared to patients with a normal troponin-I level. The elevation of troponin in COVID-19 patients can be explained by several possible mechanisms. These include viral myocarditis, microangiopathy, myocardial infarction, and cytokine storm [12].

In COVID-19, the role of angiotensin-converting enzyme 2 (ACE2), the binding receptor for SARS-CoV-2 cellular entry, has been suggested strongly [13]. ACE2 is highly expressed in the pericytes of the heart, which suggests susceptibility of the heart to SARS-CoV-2 infection [14]. Myocarditis is an inflammatory disease of the myocardium diagnosed by histological, immunological, imaging and immunohistochemical criteria [15], making its confirmation very difficult. Only a very few known case reports of COVID-19 myocarditis in adults have been published [16-21] where myocarditis was confirmed by either myocardial biopsy or cardiac magnetic resonance scanning. This suggests that myocarditis is possible but less commonly the reason for myocardial injury.

Microangiopathy results in the capillary walls become thickened and weak causing bleeding, leakage of proteins, and disruption of blood flow. Endothelial dysfunction, oxidative stress, and angiotensin-II upregulation may explain the coagulopathy and microangiopathy frequently seen in severe coronavirus disease [12, 24]. Microangiopathy can often also precipitate thrombotic coagulopathy resulting in myocardial injury. Several studies have described an association between disease severity and D-dimer elevation, suggesting a thromboembolic tendency in patients with COVID-19 [23]. Guo *et al.* [24] and several other studies [25, 26, 27] have shown that D-dimer levels were significantly higher in the group with high troponin levels than in the group with normal troponin levels. Hence, some medical centres around the globe are using therapeutic anticoagulation in patients with COVID-19 and elevated D-Dimer levels to prevent or treat these thromboembolic complications.

Cytokine storm has been extensively studied in patients with heart failure due to its role in infection, inflammatory modulation, myocyte stress, myocyte injury, fibroblast activation, and extracellular matrix remodeling [28]. Huang *et al.* emphasized that the imbalance of T helper 1 and T helper 2 responses in patients with COVID-19 results in a cytokine storm and contributes to myocardial injury [29]. Cytokines, caused by circulating systemic inflammation, lead to thrombus formation, atherosclerotic plaque instability and rupture causing ischemic myocardial injury [30]. C-reactive protein is one of the markers of cytokine storm and has been reportedly elevated in patients with COVID-19 and associated with higher mortality. In several studies [2, 24, 31], a

positive correlation was observed between elevated troponin and CRP levels, suggesting that myocardial damage may be related to inflammatory pathogenesis.

Myocardial infarction is one of the suggested hypotheses resulting in elevated troponin-I. Patients with pre-existing coronary artery disease and those with risk factors for atherosclerotic cardiovascular disease are at an increased risk of developing acute coronary syndrome (ACS) during acute infections [32]. Several cases suggesting the occurrence of ACS in COVID-19 patients were also reported.

Troponin elevation might be due several systemic complications such as acute respiratory distress syndrome, arrhythmias, acute coagulopathy, and acute kidney injury. Therefore, the first troponin I value received on admission to the hospital would be more objective. If the values in the later days of hospitalization were used for this study, we might have misjudged the cardiac involvement due to COVID 19. A normal troponin level at admission may have a negative correlation with all-cause mortality in such a situation which might be more relevant and important when compared to those having raised troponin values. This can aid in risk stratifying patients at the time of admission and may allow physicians to identify those at lower risk to preserve limited resources while initiation of advanced therapies for those at higher risk for developing complications.

This study suggests that troponin-I level obtained at the time of admission in patients with COVID-19, may help in assessing risk and estimating mortality, especially in those with severe disease.

Limitations

Similar to other observational studies of this nature several biases can be introduced. All other risk factors enumerated above could have contributed to the mortality of the non-survivors. Secondly, the patient population consists of hospitalized patients with severe disease requiring ICU care and does not represent mild or moderate disease. Also, the mean age for this study population was 63 ± 17 years, which may underrepresent the younger patient population in whom mortality is less likely.

Conclusions

In summation, troponin-I elevation is commonly seen in patients with COVID-19 and is significantly associated with fatal outcomes. Several mechanisms may explain this phenomenon: viral myocarditis, cytokine-driven myocardial damage, microangiopathy, ACS, and type II myocardial infarction. However, a normal troponin-I level on admission may suggest less risk for development of complications and is of value to risk-stratify patients with COVID-19.

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