

## RESEARCH ARTICLE

### STUDY OF TROPONIN-I LEVELS IN COVID-19 PATIENTS

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**ABSTRACT: BACKGROUND AND OBJECTIVES:** Elevated Troponin-I levels either due to direct or indirect cardiac injury can present as asymptomatic to fulminant myocarditis and circulatory shock in COVID-19 patients. Our objective is to evaluate the Troponin-I levels in covid patients. **AIM:** To evaluate the possible myocardial involvement in covid-19 patients with the help of Troponin-I levels as an indicator of cardiac injury and its prognostic implication and significance as it is associated with increased mortality in patients with COVID-19. **METHODS:** This was a both a prospective and retrospective cohort study done from 1<sup>st</sup> January 2021 to 1<sup>st</sup> July 2021. A total of 240 admitted patients were included and whose Troponin-I levels were evaluated and in a comparative analysis was performed for the demography, clinical features, biochemical markers and their outcome with their Troponin-I levels. **RESULTS:** Out of 250 covid-19 positive hospitalized patients, 15 patients have elevated Troponin-I levels. Among these 15 patients 60% had preexisting co morbidities like hypertension, diabetes and history of cardiac disease. Patients with elevated troponin level had mean age of 61.1 years, length of stay was >14 days in 60% patients. In 46% patients Troponin-I levels were more than 200ng/L. These patients had a higher need for intensive care with mortality of 73%. **CONCLUSION:** Etiology of myocardial involvement is multifactorial. Our study also concluded that elevated troponin levels in patients with covid19 have high mortality. Therefore, the measurement of cardiac biomarkers, including Troponin-I and brain natriuretic peptide (BNP), should be performed on admission.

**KEYWORD:** Myocarditis, Troponin-I, co morbidities, Covid-19.

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## **INTRODUCTION:**

The global pandemic of corona virus disease 2019 (COVID-19) continues to be the cause of considerable morbidity and mortality worldwide.<sup>[1]</sup> First case of Corona virus disease 2019 (COVID-19) was reported in late December 2019 followed by several isolated cases of cryptogenic pneumonia in Wuhan, China.<sup>[2]</sup> Most patients had respiratory symptoms comprising of fever, cough, cold, shortness of breath.<sup>[9]</sup> However there was a wide spectrum of clinical manifestations ranging from asymptomatic cases to mild and non-specific symptoms or severe complications as acute respiratory distress and death.<sup>[3,9]</sup> As described by various studies approximately 15% of patients who are infected by this COVID-19 virus will develop severe disease, patient can present with pneumonia initially and that may subsequently progress to acute respiratory distress syndrome (ARDS) and multi-organ failure (MOF), with high mortality.<sup>[4]</sup>

It has been evaluated those multiple organs can be involved in Covid-19. A subset of population was detected with elevated Troponin-I levels either due to direct or indirect cardiac injury. Acute myocardial injury can range from asymptomatic elevation of cardiac Troponins to fulminant myocarditis and subsequently resulting in circulatory shock in COVID-19 patients.<sup>[10]</sup> Fulminant myocarditis was reported in 7% of patients with lethal outcomes.<sup>[5]</sup> The virus infects lung epithelial cells causing mainly respiratory signs and symptoms. There has also been a rise in cases that presented with COVID-19 induced cardiac damage. Several mechanisms have been proposed to that explain the underlying path physiology of COVID-19-related myocardial damage.<sup>[6-7]</sup>

Myocarditis, an inflammatory disease of the myocardium, has been proposed to account for a proportion of cardiac injury, in addition to systemic inflammation. It has been suggested that direct viral contact through angiotensin-converting enzyme 2 (ACE-2) signaling pathways might have a role in the myocardial injury. In addition, cytokine release

syndrome has been proposed to be the main path physiology of COVID-19-induced acute fulminant myocarditis.<sup>[8]</sup> Several cardiovascular complications were reported in literature like arrhythmias, myocarditis, pericarditis, heart failure, myocardial ischemia, myocardial infarction. Several mechanisms may explain this phenomenon: viral myocarditis, cytokine-driven myocardial damage, microangiopathy, and unmasked CAD.<sup>[11]</sup>

In this case-based review, we aimed to describe the clinical characteristics, co-morbidities, in-hospital disease course, biochemical markers and outcome of Covid-19 patients showing elevated Troponin-I. In addition, we have tried to identify the possible underlying mechanisms of COVID-19-related rise in Troponin-I levels, whether it is caused by direct viral damage or an inadequate host immune response. It is recommended to evaluate Covid-19 patients for possible cardiac injury, inflammatory response, endothelial dysfunction and micro vascular damage in hospitalized patients or high-risk patients with other co-morbidities because an early diagnosis has shown a significant positive role in changing management and overall prognosis.

## **METHODS:**

The study was done at Aakash Healthcare Super Specialty Hospital, which is NABH accredited with an NABL accredited laboratory located at Dwarka New Delhi, India. It is a prospective as well as retrospective cohort study. We evaluated the consecutive patients admitted in our Internal medicine wards for symptomatic SARS-CoV-2 infection confirmed by TrueNAT Real Time Polymerase chain reaction testing of nasopharyngeal specimens. Of the 250 screened cases, we specifically evaluated Covid-19 positive patients who were admitted in emergency or wards with elevated Troponin-I levels >19ng/L. The data was obtained from the electronic health records available with hospital. The method used for estimation of Quantitative Troponin-I in human serum/ plasma (lithium heparin) is by ELFA technique (Enzyme

Linked Fluorescent Assay). The physician notes and all the tests done during the stay of patient were obtained and analyzed. The demographic data, age, sign and symptoms of presentation, underlying co morbidities, and coexisted infection, CT Score of patients, duration of stay at hospital, outcome and treatment received were populated. Routine laboratory evaluation included total leukocyte count, differential leukocyte count (Neutrophilia or leucopenia), d-dimer, C- reactive protein, Interleukin -6, Ferritin, Procalcitonin, Troponin-I, Creatine kinase. The disease outcome in Troponin-I patients were calculated by evaluating following parameters e.g. duration of stay at hospital, requirement of ventilator support and mortality rate. Cardiac injury was suspected if the serum concentration of Troponin-I was above the upper limit of the reference range (>19 ng/L). Reference ranges for other biochemical markers are as follows:

D-dimer - 0-232ng/ml, CRP- 0-0.5 mg/dl, IL-6 – 0-7pg/ml, NT Pro BNP- 0-125pg/ml.

The ethical approval for this study and the need for written informed consent was not required.

### Statistical analysis

Appropriate statistical methods have been applied wherever necessary and results have been expressed as percentage, charts, tables and diagrams.

### RESULTS:

During the study 250 covid-19 positive IPD patients were admitted in hospital who were detected positive for SARS CoV-19. Out of 250 Covid-19 patients, 15 (6%) patients had showed elevated Troponin-I values. The patients who showed elevated Troponin-I levels had mean age of 61.1 years and among them 80% of patients were male. The youngest patient was less then 1 year old. Common clinical presentation were fever and shortness of breath (67%), cough(40%), dyspnea(27%) and chest pain and

fatigue (13%). Total leucocyte count was elevated in 53% patients, 33% of the patients showed marked neutrophilia and 66.7% showed marked lymphocytopenia. [Refer Table 1]

**Table 1. Demographic data and clinical presentation n- frequency, %- percentage**

| VARIABLES                       | n         | %    |
|---------------------------------|-----------|------|
| <b>Gender</b>                   |           |      |
| Male                            | 12        | 80   |
| Female                          | 3         | 20   |
| Mean age                        | 61.1years |      |
| <b>Symptoms</b>                 |           |      |
| Fever and Shortness of breath   | 10        | 67   |
| cough                           | 6         | 40   |
| Dyspnea and palpitation         | 3         | 27   |
| Chest pain and fatigue          | 2         | 13   |
| <b>CTscore–Day1(CT scan)</b>    |           |      |
| <14                             | 3         | 21.4 |
| ≥ 14                            | 11        | 78.6 |
| <b>Average stay in hospital</b> |           |      |
| <14Days                         | 6         | 40   |
| ≥ 14Days                        | 9         | 60   |

Troponin-I was found to be increased in all the patients with suspected cardiac injury. Creatine kinase was increased in 20% of the patients (only 4 patients were evaluated for CK). In all the patients, Troponin-I was done at the time of admission as elevations in Troponin-I level is taken as a biomarker of myocardial injury. It has also been observed that patients with acute myocardial injury were older and male with a higher prevalence of co-morbidities including preexisting CVD and were more likely to require ICU admission. (Table 2)

**Table 2. Biochemical markers .IL-6- Interleukin 6, Pro BNP- brain natriuretic peptide, CRP- C- reactive protein**

| VARIABLES   | CASE S (n) | PERCENTAG E (%) |
|---|------------|-----------------|
| <b>D-Dimer Normal Reference range &lt; 500 ng/ml</b>          |            |                 |
| <500  | 8          | 53.3            |
| 500-1000  | 3          | 20              |
| >1000   | 4          | 27.7            |
| 5 <sup>TH</sup> day D dimer >500                              | 4          | 27              |
| 10 <sup>th</sup> day D-dimer >500                             | 7          | 47              |
| <b>C- reactive protein Normal Reference range 0-0.5 mg/dl</b> |            |                 |
| <5  | 6          | 40              |
| 5-10  | 4          | 27              |
| >10   | 3          | 13              |
| <b>CRP on first day of admission</b>                          |            |                 |
| ELEVATED  | 14         | 93              |
| NORMAL  | 1          | 7               |
| <b>IL-6(pg/ml) Normal Reference range 0-7pg/ml</b>            |            |                 |
| 0-10  | 6          | 40              |
| >10   | 3          | 27              |
| >100  | 4          | 33              |
| Elevated IL-6 on day one of admission                         | 15         | 100             |
| <b>Pro BNP (pg/ml)(Reference range 0-125pg/ml)</b>            |            |                 |
| >200  | 3          | 20              |
| >1000   | 8          | 53              |

Covid-19 infection with elevated Troponin-I levels and associated co-morbidities was seen in 60% patients. Out of these patients, 3 (20%) patients had a history of coronary artery disease, 7 (46.7%) had systemic hypertension, 5 (33%) had diabetes mellitus, 5 (33%) had other co morbidities like chronic kidney disease, chronic liver disease, anemia, 1 had history of congenital heart disease and rest 6

(40%) had no history of any no cardiac disease or associated co morbidity. [Refer Table 3]

**Table 3. Co-Morbidities and Clinical Diagnosis**

| Co-Morbidities            | CASES (n) | PERCENTAGE (%) |
|---------------------------|-----------|----------------|
| Systemic Hypertension     | 7         | 46.7           |
| Diabetes mellitus         | 5         | 33             |
| Chronic kidney disease    | 3         | 20             |
| Chronic artery disease    | 3         | 20             |
| Anemia                    | 1         | 7              |
| Liver disease             | 1         | 7              |
| Congenital heart disease  | 1         | 7              |
| No co-morbidities         | 6         | 40             |
| <b>Diagnosis</b>          |           |                |
| Respiratory failure       | 11        | 73             |
| ARDS                      | 9         | 60             |
| Kidney disease            | 5         | 33             |
| Septic shock              | 3         | 20             |
| MODS                      | 2         | 13             |
| Coronary artery disease   | 4         | 27             |
| Pulmonary Thromboembolism | 3         | 20             |
| Viral myocarditis         | 4         | 27             |
| Severe pneumonia          | 3         | 20             |
| MIS-C                     | 1         | 7              |

ARDS- Acute respiratory distress syndrome, MODS- multi organ dysfunction syndrome, MIS-C- multisystem inflammatory syndrome in children During hospitalization, 11 (73%) patients died, 11 (73%) developed respiratory failure, 9 (60%) developed acute respiratory distress syndrome, 5 patients (33%) developed acute chronic kidney/acute kidney disease, 3 (20%) developed pulmonary thrombo-embolism, 3 (20%) septic shock, 2 (13%) patients developed MODS, 3 (20%) patients has severe pneumonia, 1 (7%) Child which was included

in study developed MIS-C. (Table 3). Patients were also evaluated for the overall outcome as per following parameters: Average stay at hospital, need for ventilator support, morbidity and mortality. The average length of stay was 14 days. (Table 4 & Figure 1 &2)

Table 4. Outcome

| VARIABLES                 | CASES(n) | PERCENTAGE (%) |
|---------------------------|----------|----------------|
| <b>Ventilator support</b> |          |                |
| Needed                    | 11       | 73             |
| Not needed                | 4        | 27             |
| <b>Outcome</b>            |          |                |
| Expired                   | 11       | 73             |
| Stable                    | 4        | 27             |

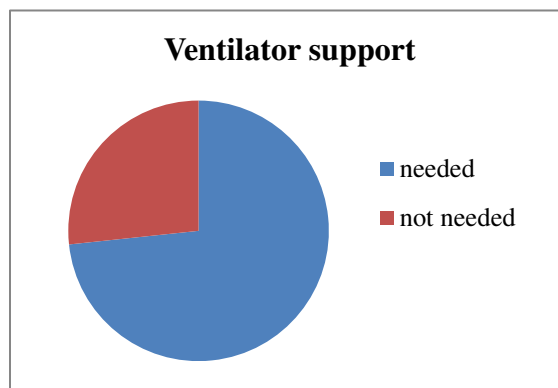


Figure 1. Ventilator support

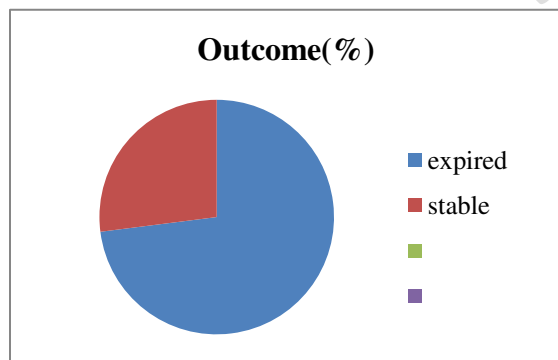


Figure 2. Outcome

Troponin levels observed in patients with early rise of troponin was much higher then in patients with

which troponin level rised late and showed higher mortality. Patients who showed early rise were mostly in which cardiac injury was direct. (Table 5)

Table 5. Troponin-I levels and mortality

| Troponin I(ng/l)<br>(Reference range<br><19 ng/L),           | No. | %  | Mean<br>Troponin I<br>level(ng/L) | Mortality<br>(%) |
|--|-----|----|-----------------------------------|------------------|
| Early rise of<br>Troponin I<br>(<7days<br>of<br>admission)   | 8   | 53 | 1386ng/L                          | 87.5             |
| Late rise of<br>Troponin I<br>(After 7 days of<br>admission) | 7   | 47 | 38ng/L                            | 42.9             |

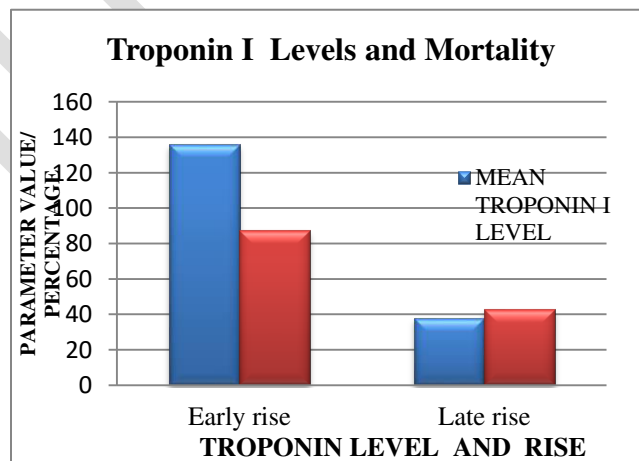
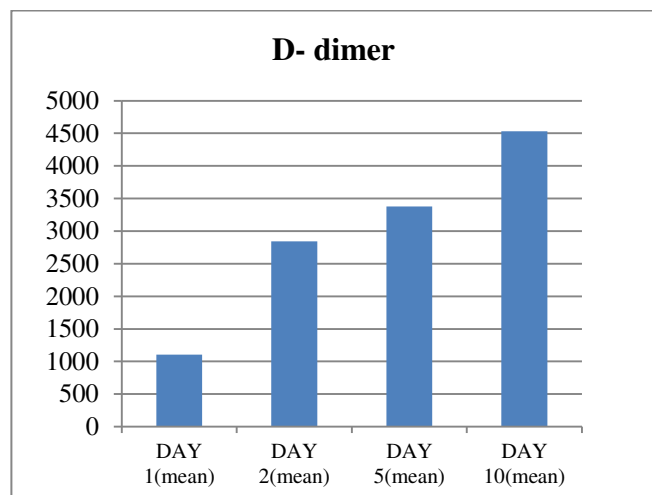


Figure 3. Troponin-I levels and mortality

5 patients showed direct cardiac involvement, out of which 4 (27%) developed a clinically suspected viral myocarditis and 1(7%) developed dilated cardiomyopathy. (Table 1) Mean age was for elderly was 60.18 years and one patient was less than one year old. All had a history of CAD with 100% mortality. Mean stay at hospital was 10 days. Mean Troponin I was 3897 and pro BNP was 6947 in these patients which is significantly higher than the rest of the patients.



Increased D-dimer has also proven to predict the disease severity and increased mortality. The D-dimer of admitted patients was evaluated on daily basis and presented as mean. An increasing trend was noticed in patients who were critically ill and deteriorating. [Refer Fig-4]. In our hospital, overall mortality in Covid-19 patients was 17.3%, however mortality in our study of Covid-19 patients with elevated Troponin-I levels was significantly higher at 73%. [Refer Table-6]



**Figure 4. D-dimer levels (mean) showing increasing trend with disease progression.**

**Table 6. Comparison of mortality in Covid-19 Patients (overall) with ones having elevated Troponin-I levels**

| Mortality  | Covid-19 positive patients (Overall) | Covid-19 positive patients with elevated Troponin-I levels |
|------------|--------------------------------------|--|
| Percentage | 17.3%                                | 73%  |

**DISCUSSION:**

In this study of biomarkers and mortality in a cluster of patients hospitalized with COVID-19 were evaluated who presented with elevated Troponin-I levels, and subsequently we identified several other important findings, which are: Abnormal levels of NT Pro BNP, CRP, IL-6, and D-dimer and are shown to correlate with severe COVID-19. The study also showed impact of co-morbidities and high mortality in these patients. Myocardial injury can be caused by multiple mechanisms and there is a need of clinical, radiological and biochemical study to evaluate. Troponin-I level elevation in covid patients has been reported in range of 7.2% to 36% of patients hospitalized with COVID-19<sup>[3]</sup> and thus demonstrating significant association between cardiac injury and mortality in patients with COVID-19. We aimed to investigate the prognostic implications of an early cardiac involvement in hospitalized patients with COVID-19 which was 6% in our study. Some studies showed higher incidence of 20% and 27.8%.<sup>[23,24]</sup> In our study the covid patients admitted in IPD were majorly older and men, 73% required mechanical ventilation with mortality of 73%. The mortality in these patients was much higher as compared to patients without cardiac injury, 15% was reported by a study group.<sup>[23]</sup> However, total mortality in covid-19 patients in our hospital was 17.3%.

Cardiac injury identified from an increase in cardiac biomarkers such as cardiac troponins have shown to be associated with more severe disease in COVID-19 and was predictive of ICU admission and mortality.<sup>[11]</sup> Several mechanisms have been proposed which indicates SARS-CoV-2 targets myocardial ACE2 receptors.<sup>[12]</sup> ACE2 can be found on the ciliated columnar epithelial cells of the respiratory tract, type II pneumocytes, and cardiomyocytes.<sup>[13-14]</sup> ACE2 was mainly expressed in arterial vascular cells in fibrotic lungs, which might cause blood transmission of SARS-CoV-2.<sup>[15]</sup> Patients with COPD bear a high mortality rate after

being infected with SARS-CoV-2.<sup>[16]</sup> Cell entry of corona virus depends on binding of the viral spike (S) proteins to cellular receptors and on S protein priming by host cell proteases.<sup>[12]</sup> This expression pattern provides a possible explanation for the direct cardiac injury and related manifestations and severity. Direct viral entrance may cause cytopathological changes in the myometrium leading to elevation of cardiac markers along with clinical manifestations and associated radiological changes.

In our study clinical diagnosis of viral myocarditis was made in 4 (27%) patients who showed markedly elevated cardiac markers and significant radiological changes with mortality of 100%. It has been reported that myocardial injury can occur with COVID-19 infection due to a 'cytokine storm' that is stimulated via an imbalanced response involving Th1 and Th2 cells and can cause respiratory dysfunction, hypoxemia, shock, or hypotension.<sup>[17]</sup> IL-6 may play a pro-inflammatory role in myocardial inflammation.<sup>[18]</sup> Additionally in our study, critically ill patients showed cytokine storm indicated by markedly elevated levels of IL6 with later rise of Troponin-I levels indicating indirect injury to myocardium. A study showed that patients with COVID-19 who were admitted to the intensive care unit had higher plasma levels of cytokines.<sup>[22]</sup> Endothelial dysfunction, cytokine storm, oxidative stress, and Ang-II up regulation may explain the coagulopathy frequently seen in severe coronavirus disease.<sup>[19]</sup> The dysfunction of endothelial cells which is induced by virus results in excess thrombin formation indicating hypercoagulable state.<sup>[20]</sup> D-dimer is used as a marker to predict the thrombotic complications in covid 19 patients which was significantly high at the day of admission and increased exponentially by 5<sup>th</sup> and 10<sup>th</sup> day. (Fig4)

In our study patients presented most commonly with symptoms of fever (67%), shortness of breath (67%) and cough (40%) and palpitation (27%). Another study reported Fever (80%), cough (34.6%) and shortness of breath (28%).<sup>[23]</sup>

In this cohort of patients, 60% had at least 1 co morbidity, another study also reported 72.2% with associated comorbidities and hypertension as most common co morbidity, followed by cardiovascular disorders and diabetes.<sup>[21,25]</sup>

### **CONCLUSION:**

In Covid infected patients with cardiac injury, there is more chances of severe acute illness, manifested by elevated troponin-I levels and abnormal laboratory and radiographic findings, such as higher levels of C-reactive protein, NT-proBNP, and; higher CT score and a greater proportion requiring noninvasive or invasive ventilation. Therefore, the measurement of cardiac biomarkers, including Troponin-I and brain natriuretic peptide (BNP), should be performed on admission along with D-dimer to evaluate thromboembolic episode and inflammatory markers like IL-6 and C reactive protein to predict hyper immune response. We noted that most cases had elevated troponin, BNP levels, D-dimer, IL, CRP levels on admission.

Cardiac injury could be caused by the combined effects of direct effect of virus, inflammation, cardiovascular comorbidities, and other risk factors (eg, older age). There is also the possibility of non-coronary myocardial injury and stress cardiomyopathy.

Elevation of Troponin I can be caused by multiple factors like direct cardiac injury, inflammatory response, endothelial dysfunction and microvascular damage. Early screening with Troponin I levels and others biochemical markers can predict the prognosis and early management of possible complications.

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