ORIGINAL\RESEARCH ARTICLE

Cardiac Biomarkers in Patients with COVID-19

Barnali Das[1], Seema Y Bhatia[2], Rashmi Patil[3]

Abstract

Objectives: The primary aim of the study is to evaluate the role of cardiac biomarkers like high-sensitive troponin I (hs troponin I), N terminal-pro B-type natriuretic peptide (NT-proBNP) in coronavirus disease 2019 (COVID-19) patients who were admitted to the intensive care unit (ICU) with positive test results of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) in Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai, India.

This study comprises two main objectives:

- To evaluate the significance of cardiac markers in COVID-19 patients by *t* test and receiver operating characteristic (ROC) analysis in 85 patients presented with complaints of chest pain and tested positive for SARS-CoV-2 by rRT-PCR. To represent the data considered in case and control groups for hs troponin I and NT-proBNP graphically in a box plot. Box plots may also have lines extending from the boxes (whiskers) indicating variability outside the upper and lower quartiles.
- To determine the percentage positivity and mortality rate of COVID-19 patients with cardiac injury in 1 month period (August 1, 2020 to August 31, 2020) data of 261 individuals.

Materials and methods: In the first part of the study, a total of 125 individuals (13–95 years) were considered for this study. Among the total number of patients considered, 85 individuals considered in the case group in the age group of 13–95 years (median age 65 years) had complaints of chest pain. The case group consisted of 22 females and 63 males. Forty healthy adults without any history and clinical evidence suggestive of COVID-19 and without any comorbidities, like diabetes, hypertension, chronic lung disease, cardiac disease, cancer, and immunocompromised status, were considered as a control group for the study. The control group comprises 8 females and 32 males in the age group of 13–86 years (median age 57 years). Cardiac biomarkers (hs troponin I and NT-proBNP) of these 85 patients were used to evaluate the cardiac injury found in COVID-19 patients. Statistical analysis was carried out on the data after determining whether the data had a normal/log-normal distribution and their significance was determined by calculating the *p* value. The accuracy of the biomarkers (NT-proBNP and hs troponin I) was checked using ROC analysis. The percentage of patients showing abnormal cardiac markers was also calculated.

In the second part of the study, we have analyzed 1-month data (August 1, 2020 to August 31, 2020) of 261 individuals to evaluate the percentage positivity and mortality rate of COVID-19 patients with a cardiac injury.

Results: The data were found to have normal/log-normal distribution. We found a significant increase in mean values of both hs troponin I and NT-proBNP in COVID-19 patients with chest pain than the control group. We applied the ROC curve to discriminate case population more precisely than the control population. Receiver operating characteristic analysis for NT-proBNP and hs troponin I showed that the area under the curve (AUC) of NT-proBNP is 1.0 and the AUC of hs troponin I is 0.91. The percentage of patients tested positive for SARS-CoV-2 with cardiac injury within 1 month time period (August 1, 2020 to August 31, 2020) was found to be 10%. The percentage recovery and death among the number of patients tested positive for SARS-CoV-2 with cardiac injury was found to be 88 and 12%, respectively.

Conclusion: Both the cardiac markers (NT-proBNP and hs troponin I) have an excellent accuracy in patients with COVID-19 with chest pain, suggestive of cardiac injury.

Clinical significance: Understanding the cardiac biomarkers in COVID-19 patients with chest pain appears to be beneficial to triage, risk-stratify, and prognosticate patients with COVID-19 based on the evidence of cardiac injury and the presence of underlying cardiovascular disease.

Keywords: Cardiac injury, Cardiovascular disease, Coronavirus disease 2019, High-sensitive troponin I, N terminal-pro B-type natriuretic peptide, Severe acute respiratory syndrome coronavirus 2.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into the cells via human angiotensin-converting enzyme 2 (ACE 2) receptor, which is expressed mainly in the lungs and also in the cardiovascular system.[1] Some patients infected with this novel coronavirus disease develop an acute respiratory distress syndrome (ARDS) along with other complications following a multiorgan failure.[2] Although the primary organ for damage is the lungs, COVID-19 is reported as a systemic disease as it involves other vital organs like the liver, heart, and kidney. The prevalence of cardiovascular dysfunction in patients with COVID-19 disease is reported to be high.[3] In one of the

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reports, China has reported cardiac injury to be a prominent feature of the COVID-19 disease.[4] Among the hospitalized patients, China has reported cardiac injuries in 20 to 30% of patients which has contributed to 40% of the deaths.[4] Also, there have been multiple reports that have confirmed increased mortality and morbidity due to COVID-19 infection in individuals with preexisting cardiovascular disease (CVD). Cardiovascular disease includes hypertension, coronary artery disease, and heart failure.[5–7] It is also known that the clinical outcomes of COVID-19 disease in patients with existing cardiac disease are more adverse when compared with that in patients without CVD.[8]

This zoonotic coronavirus outbreak is a global health burden and pandemic affecting countries worldwide.[2] The main route of transmission of the virus is through respiratory droplets and by direct human-to-human contact.[9] The individuals infected with this novel COVID-19 either have asymptomatic infection, a mild upper respiratory tract infection or an upper respiratory tract failure or severe viral pneumonia.[10] According to the Centre for Disease Control (CDC), COVID-19 patients have reported a wide range of symptoms ranging from mild to severe illness. Its incubation period ranges from 2 to 14 days post-exposure to the virus.[2]

A significant rise in cardiac biomarkers like natriuretic peptides and troponins is observed in COVID-19. This significant increase is seen to be associated with COVID-19 complications and increases mortality. The possible mechanisms of cardiac injury in COVID-19 patients include inflammation, cytokine storm, micro/macro thrombosis, direct viral invasion, and supply or demand imbalance.[11] The cardiac biomarkers are believed to aid triaging, clinical decision-making, risk-stratification, and prognostication of patients with COVID-19.[12]

Based on the association of the CVD with COVID-19 infection and the importance of understanding the influence of COVID-19 on the cardiovascular system, we have studied the cardiac makers, N terminal-pro B-type natriuretic peptide (NT-proBNP) and high-sensitive troponin I (hs troponin I) in COVID-19 patients. Based on the fact that NT-proBNP and hs troponin I are important indicators of cardiac dysfunction,[13] we aim to study these biomarkers in COVID-19 patients presented with chest pain aiding a better patient care and a better understanding of the cardiac markers in such patients. We have divided the study based on two main objectives:

- Evaluation of the significance of cardiac markers in COVID-19 by *t* test and receiver operating characteristic (ROC) analysis in 85 patients tested positive for SARS-CoV-2 by real-time reverse transcriptase-polymerase chain reaction (rRT-PCR). The data considered in case and control groups for hs troponin I and NT-proBNP were plotted in the form of a box plot with whiskers.
- Determination of the percentage positivity and mortality rate of COVID-19 patients with cardiac injury in 1 month (August 1, 2020 to August 31, 2020) data of 261 individuals.

Materials and Methods

This study was conducted at Kokilaben Dhirubhai Ambani Hospital and Medical Research Centre, Mumbai, India. The study comprises 85 individuals admitted in an intensive care unit (ICU) with complaints of chest pain, tested positive for SARS-CoV-2 by rRT-PCR, belonging to the age group of 13–95 years (median age 65 years) comprising of 21 females (39–81 years, median age 60 years) and 64 males (13–95 years, median age 60 years). The control group consists of 40 healthy individuals belonging to the age group of 13–86 years (median age 57 years), comprising of 8 females (39–81 years, median age 55 years) and 32 males (13–86, median age 58 years). The data considered for the study were checked for normal and log-normal distribution using a histogram with a fit curve and probability plot. The significance of the data was confirmed by calculating the *p* value by *t* test analysis.

N terminal-pro B-type natriuretic peptide was measured by electrochemiluminescence immunoassay (ECLIA) using Roche COBAS e411 (Roche Diagnostics, Basel, Switzerland), whereas hs troponin I was analyzed by Chemiluminescent Microparticle Immunoassay (CMIA) on either ARCHITECT i1000sr or ARCHITECT i2000sr (Abbott Diagnostics, Abbott Park, IL, USA).

To check the sensitivity and specificity of the cardiac markers (NT-proBNP and hs troponin I), ROC curve analysis was carried out. The ROC curve is an assessment for identifying the test accuracy.

Additionally, 1-month data (August 1, 2020 to August 31, 2020) consisting of 261 individuals were considered to calculate the percentage of COVID-19 patients with cardiac injury and mortality rate.

The statistical analysis for this study was done using Prism (Graph pad Software, San Diego, CA, USA) and Minitab (Minitab Inc., PA, USA) statistical software packages.

Results

In the first part of the study, the data considered in case and control groups for hs troponin I and NT-proBNP were plotted in the form of a box plot with whiskers. Box plots have lines extending from the boxes (whiskers) indicating variability outside the upper and lower quartiles.

High-sensitive Troponin I

In the control group, the first quartile (Q1/25th percentile) of hs troponin I was found to be 1.93 pg/mL, the third quartile (Q3/75th percentile) was found to be 7.35 pg/mL, interquartile range (IQ range) was found to be 5.43 pg/mL with a median of 3.45 pg/mL and whiskers to 1.1 and 15.4 pg/mL.

In the case group, the first quartile (Q1) of hs troponin I was found to be 37.18 pg/mL, the third quartile (Q3) was found to be 1,410.78 pg/mL, the IQ range was found to be 1,373.6 pg/mL with a median of 101.2 pg/mL and whiskers to 1.6 and 2,984.1 pg/mL.

N Terminal-pro B-type Natriuretic Peptide

In the control group, the first quartile (Q1) of NT-proBNP was found to be 20.99 pg/mL, the third quartile (Q3) was found to be 107.9 pg/mL, IQ range was found to be 86.91 pg/mL with a median of 49.29 pg/mL and whiskers to 5 and 124.1 pg/mL.

In the case group, the first quartile (Q1) of NT-proBNP was found to be 625.23 pg/mL, the third quartile (Q3) was found to be 11,441.5 pg/mL, IQ range was found to be 10,816.3 pg/mL with a median of 3,638.5 pg/mL and whiskers to 126.4 and 23,924 pg/mL.

The box plots of the case and control group for hs troponin I and NT-proBNP are shown in Figures 1 and 2, respectively.

The normal distribution of the data was determined by plotting a histogram with a fit curve for NT-proBNP and hs troponin I. The normal distribution analysis of the data is shown in Figures 3 and 4, respectively. A probability plot was used to confirm the log-normal distribution of the data. A log-normal distribution analysis (probability plot) indicates that the data considered for the analysis lies within a 95% confidence interval (CI) of log-normal fit.

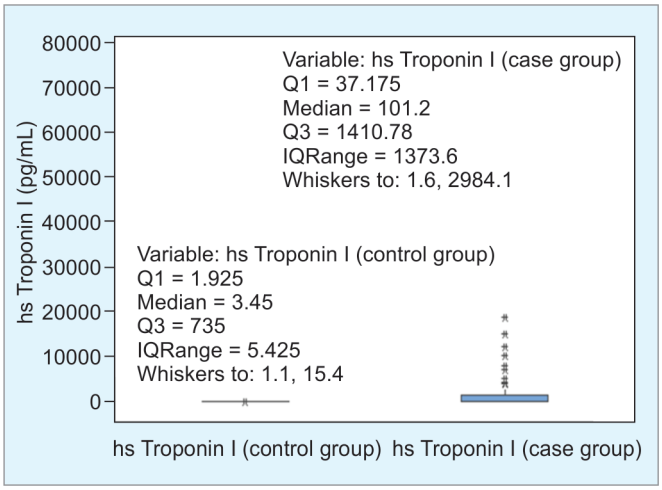

Fig. 1: Box plot—data representation of hs troponin I (control and case group)

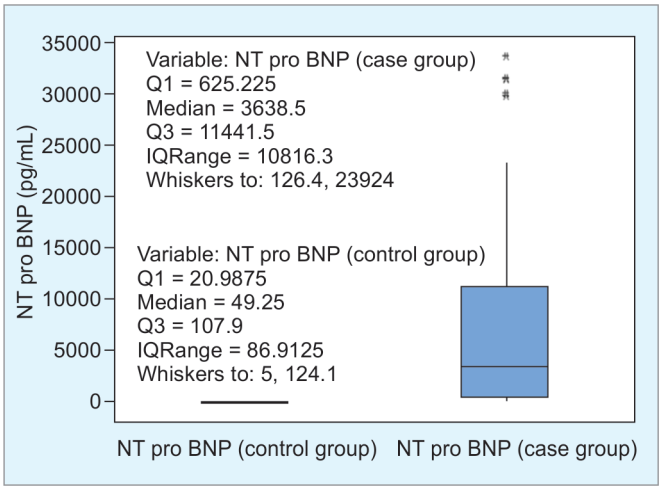

Fig. 2: Box plot—data representation of NT-proBNP (control and case group)

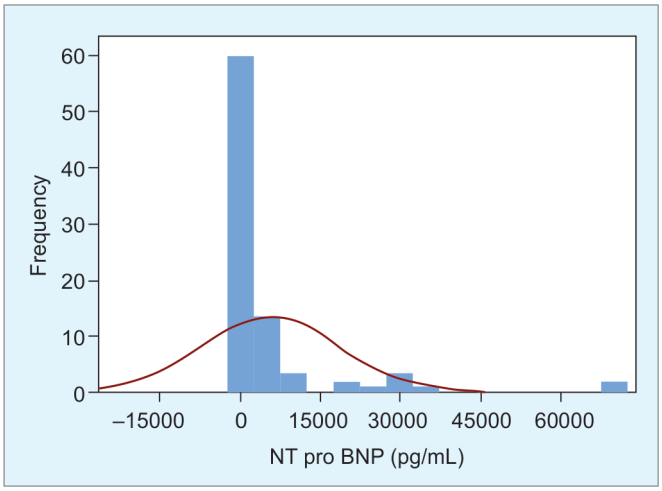

Fig. 3: Normal distribution curve of NT-proBNP

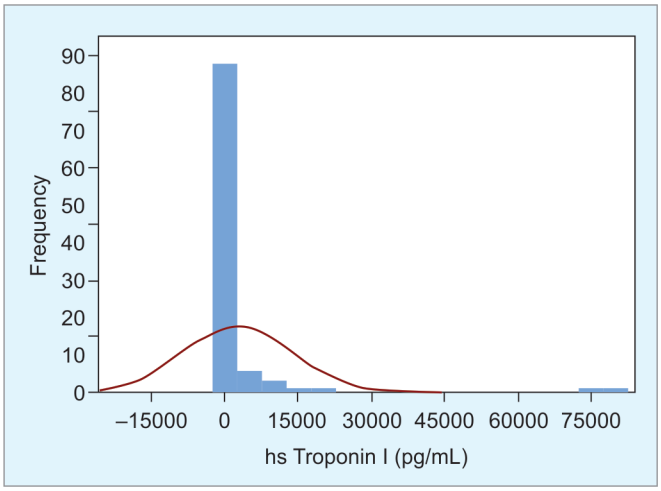

Fig. 4: Normal distribution curve of hs troponin I

After confirming the normal, log-normal distribution of the data, the *p* value was calculated for the data by carrying out a *t* test. The *p* value of the data considered was found to be <0.005 indicating that the data are significant to be distributed as a case and control group.

The data were subjected to ROC curve analysis to check the sensitivity and specificity of the biomarkers considered. The area under the curve (AUC) determined from the ROC analysis is equivalent to the probability that the particular biomarker is higher for the infected patients (case group) than that for the healthy population (control group). Figures 5 and 6 show the ROC analysis for NT-proBNP and hs troponin I, respectively. On the one hand, the AUC for NT-proBNP was found to be 1.0 with 95% CI and a *p* value of <0.0001. The AUC of 1.0 means that a random individual selected from the case group will have a greater value of NT-proBNP than that of the individual randomly selected from the control group for 100% of the time. On the other hand, the hs troponin I had an AUC of 0.91 with 95% CI and a *p* value of <0.0001. The AUC of 0.91

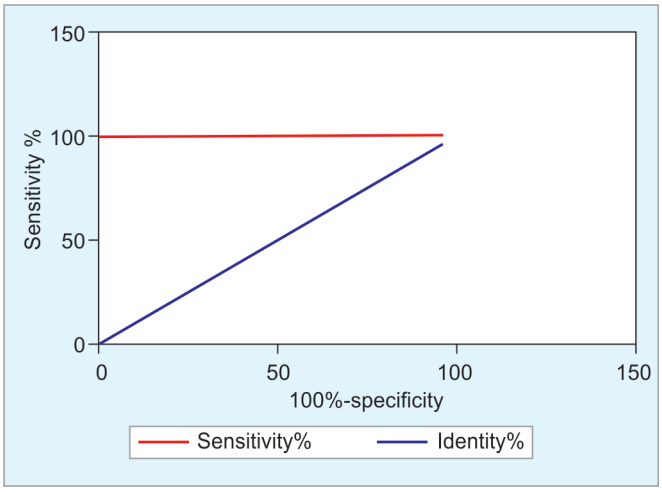

Fig. 5: ROC analysis of NT-proBNP

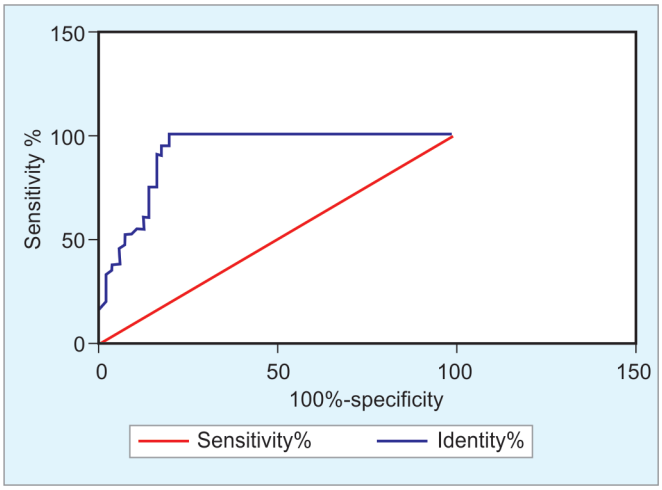

Fig. 6: ROC analysis of hs troponin I

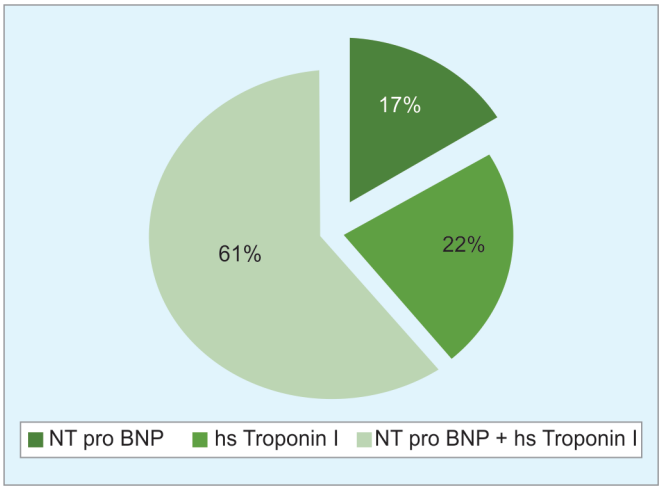

Fig. 7: Percentage of patients who have undergone estimation of cardiac markers (NT-proBNP and hs troponin I)

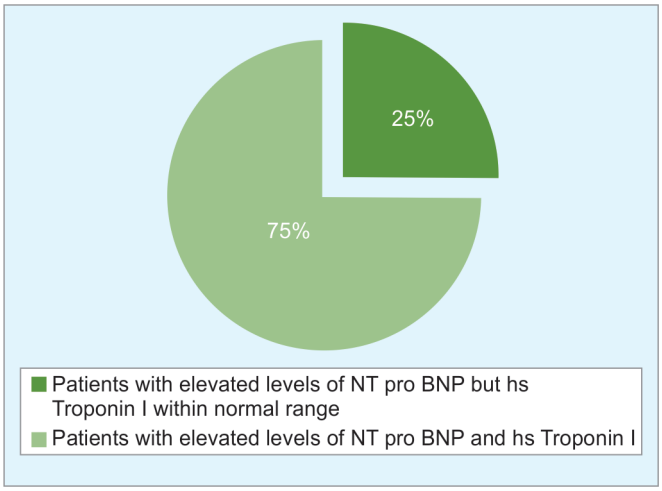

Fig. 8: Percentage of patients with abnormal levels of cardiac markers (NT-proBNP and hs troponin I)

Table 1: Patients with cardiac injury undergoing estimation of cardiac biomarkers (NT-proBNP and hs troponin I)

Total no. of patients with cardiac injury	*Patients undergoing estimation of hs troponin I*	*Patients undergoing estimation of NT-proBNP*	*Patients undergoing estimation of NT-proBNP + hs troponin I*
85	19	14	52

means that a random individual selected from the case group will have a greater value of hs troponin I than that of the individual randomly selected from the control group for 91% of the time. The interpretation of AUC in ROC analysis is as follows:

Area under the curve 0.90 to 1: excellent accuracy, 0.80 to 0.90: good accuracy, 0.70 to 0.80: fairly accurate, 0.60 to 0.70: poor accuracy, and 0.50 to 0.60: failure. Both NT-proBNP and hs troponin I showed excellent accuracy (AUC 0.90–1).

Among the total number of patients (85 individuals) who were tested positive for a COVID-19 infection admitted in ICU with complaints of chest pain, 61% of the patients had undergone estimation of both the cardiac markers (NT-proBNP and hs troponin I), 17% of the patients had undergone estimation of only NT-proBNP, and 22% of the patients had undergone estimation of only hs troponin I. Table 1 represents the data for patients with cardiac injury undergoing estimation of both cardiac biomarkers (NT-proBNP and hs troponin I) and Figure 7 shows the diagrammatic representation of the percentage of patients who have undergone an estimation of cardiac markers (NT-proBNP and hs troponin I).

Additionally, the percentage of patients with elevated levels of NT-proBNP but normal levels of hs troponin I was also estimated. It was found that 25% of the patients who had undergone estimation of both the cardiac markers (NT-proBNP and hs troponin I) had elevated levels of NT-proBNP but the hs troponin I levels were found to be within the normal range. The rest 75% of patients showed elevated levels of NT-proBNP as well as hs troponin I. There was no such case where hs troponin I levels were elevated but NT-proBNP was found to be within the normal range. Table 2 represents the data for patients showing elevated/normal levels of cardiac marker (NT-proBNP and hs troponin I) and Figure 8 shows the diagrammatic representation of the percentage of patients with abnormal levels of cardiac markers (NT-proBNP and hs troponin I).

In the second part of the study, the total number of patients (261 individuals) tested positive for SARS-CoV-2 within the time period of August 1, 2020, to August 31, 2020, was analyzed to

Table 2: Patients showing elevated/normal levels of cardiac markers

Total no. of patients with cardiac injury	*Patients undergoing estimation of NT-proBNP + hs troponin I*	*Patients with elevated levels of NT-proBNP but hs troponin I within the normal range*	*Patients with elevated levels of NT-proBNP and hs troponin I*
85	52	13	39

Table 3: Patients tested positive for SARS-CoV-2 by rRT-PCR and COVID-19 patients with a cardiac injury

No. of patients tested positive for SARS-CoV-2 (August 1–August 31, 2020)	*No. of patients with cardiac injury tested positive for SARS-CoV-2 (August 1–August 31, 2020)*
261	25

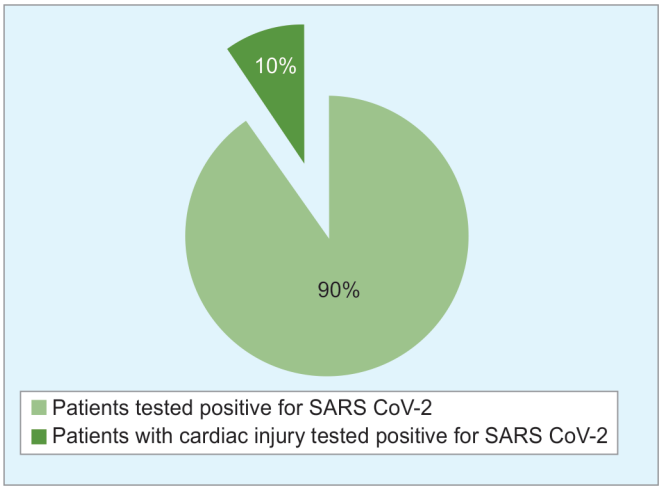

Fig. 9: Percentage of patients tested positive for SARS-CoV-2 along with cardiac injury

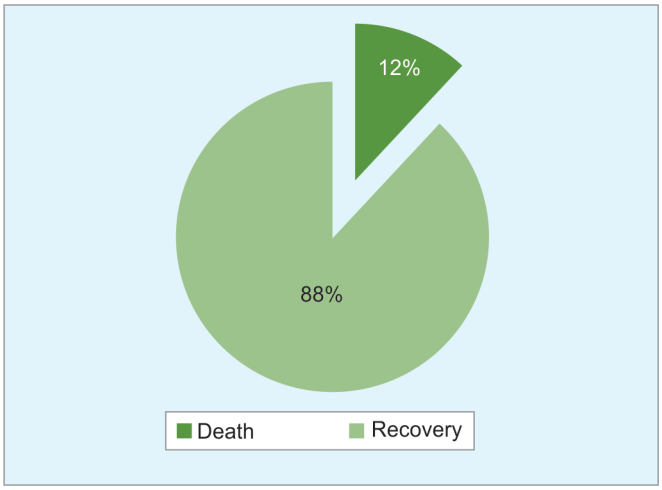

Fig. 10: Percentage of recovery and death in patients tested positive for SARS-CoV-2 along with cardiac injury

Table 4: Death and recovery count reported in patients tested positive for COVID-19 by rRT-PCR with a cardiac injury

No. of patients with cardiac injury tested positive for SARS-CoV-2 (August 1–August 31, 2020)	*No. of death recorded in patients with cardiac injury tested positive for SARS-CoV-2 (August 1–August 31, 2020)*	*No. of patient recovered among the patients with cardiac injury tested positive for SARS-CoV-2 (August 1–August 31, 2020)*
25	3	22

calculate the percentage of positive patients with a cardiac injury. It was found that 10% of the total numbers of patients who were tested positive for SARS-CoV-2 by rRT-PCR had cardiac injury. Table 3 represents the data for patients tested positive for COVID-19 by rRT-PCR and COVID-19 patients with cardiac injury. Figure 9 shows the diagrammatic representation of the percentage of patients tested positive for SARS-CoV-2 along with cardiac injury.

The death and recovery percentage was calculated among the total no. of patients with cardiac injury tested positive for SARS-CoV-2 in a span of a month (August 1, 2020 to August 31, 2020). The percentage of patients who were recorded dead within the above-mentioned period was found to be 12% whereas the percentage of recovery was found to be 88%. Table 4 represents the data for death and recovery count reported in patients tested positive for COVID-19 by rRT-PCR with cardiac injury and Figure 10 shows the diagrammatic representation of the percentage of recovery and death in patients tested positive for SARS-CoV-2 along with cardiac injury.

Discussions

Severe acute respiratory syndrome coronavirus 2, the pathogen causing COVID-19 disease, causes a pro-inflammatory state by cytokine storm activation. This pro-inflammatory state may give rise to multiple conditions like pulmonary vascular endothelialitis, microangiopathy, diffuse thrombosis, myocarditis, heart failure, cardiac arrhythmias, and acute coronary syndromes.[14] As per the World Health Organization (WHO) COVID-19 report on September 16, 2020, around 29,444,198 individuals have been infected with COVID-19 disease with 931,321 confirmed deaths.[15] The coronavirus accounts for 10–30% of respiratory tract infections. The main route of transmission of this virus is through respiratory droplets, direct human-to-human contact, and contaminated fomites contact followed by self-contamination (eyes, nose, or mouth). The virus can be transmitted through symptomatic as well as asymptomatic individuals.[9,14,16] It is known that the virus is most contagious in symptomatic patients although human-to-human transmission of this virus can occur in the asymptomatic incubation phase (2–10 days) of COVID-19.[17] The case-fatality rate of SARS-CoV-2 appears to be lower than that of SARS outbreak 2002 to 2003.[4]

A combination of lung injury (pneumonia/ARDS) and heart failure due to myocardial injury or acute coronary syndrome (ACS) may be the reason for respiratory distress in patients with severe COVID-19. Effective management of such patients may be the identification of the cardiac origin of respiratory distress, circulatory failure, and hypoxemia.

The ever-evolving interplay between the cardiovascular system and COVID-19, studies suggest that there have been 7–28% of patients with severe COVID-19 infection tend to develop acute cardiac injury (measured by elevated troponin levels) during the course of illness. This in turn increases the COVID-19 complications and mortality rate.[2,10,18] Acute cardiac injury has been described by multiple mechanisms. These acute cardiac injuries include myocardial infarction (type I MI), myocardial demand-supply mismatch (type II MI), viral myocarditis, and inflammation and oxidative stress-induced myocardial damage.[18] There is a significant role of troponin and natriuretic peptide [B-type natriuretic peptide (BNP) or NT-proBNP] estimation for cardiac risk stratification and prognostication of patients with severe COVID-19.[12]

As cardiac biomarkers reflect myocardial injury or any kind of myocardial stretch or remodeling, these biomarkers aid in the diagnosis, risk assessment, prognosis, and management of heart failure.[19] The two important biomarkers known to reflect cardiac injury/cardiac dysfunction include NT-proBNP and hs troponin I.[13] B-type natriuretic peptide, a 32 amino acid polypeptide, contains a 17 amino acid ring structure with two cysteine residue connected by a disulfide bond.

The gene located on chromosome 1 encodes for BNP.[1] When myocardial wall stretch takes place, it leads to the synthesis of

pre-proBNP which is then processed to proBNP. This is further processed to biologically inactive NT-proBNP and biologically active BNP fragments.[20] B-type natriuretic peptide as well as NT-proBNP is considered to be reliable and valuable biomarkers for the diagnosis of heart failure and in determining patient prognosis. These biomarkers also aid the determination of severity, prognosis, and guidance to relevant treatment strategies in case of heart disease.[1]

On the contrary, the regulation of the contraction of striated muscles is carried out by troponin. It has three subunits, troponin C, troponin I, and troponin T. Troponin C binds to calcium ions, troponin T binds to tropomyosin, and troponin I binds to actin. The binding of troponin I to actin decreases the troponin C affinity for calcium leading to actin–myosin interaction.[21] The presence of troponin T and troponin I is seen in cardiac and skeletal muscles.[22] Cardiac troponin I is one of the preferred markers for the differential diagnosis of ACS.[23] Sex differences in 99th percentile value have been reported for hs troponin I assay in multiple studies.[24]

There have been international guidelines that recommend clinical relevance in the increase in cardiac troponin I and cardiac troponin T levels over the 99th percentile upper reference limit. The measure of this cut-off value should be with an imprecision ≤10 CV%.[24–27]

One of the earlier studies shows that the sensitivity and specificity of troponin can be used for the diagnosis of myocardial damage, whereas that of NT-proBNP can be used for diagnosis and to judge the effectiveness of cardiovascular therapy.[13] The release of NT-proBNP and troponin takes place by the cardiac myocytes in case of increased wall stress due to heart failure and myocardial dysfunction along with other natriuretic peptides.[13,28] Research has shown evidence of CVD to be common comorbidity in COVID-19 patients.[7] In our study, we have highlighted the cardiac marker levels in COVID-19 patients. The study is to aid a better understanding of cardiac biomarkers in COVID-19 patients with chest pain.

Conclusion

On analyzing the data, it was observed that both NT-proBNP and hs troponin I levels are significantly higher in the case group (COVID-19 patients with chest pain) compared with the control group (healthy individuals). N terminal-pro B-type natriuretic peptide and hs troponin I have excellent accuracy with an AUC of 1.0 and 0.91, respectively. Both NT-proBNP and hs troponin I are excellent biomarkers for cardiac injury.

The box plot of hs troponin I (control group) showed Q1 of 1.93 pg/mL, the third quartile Q3 of 7.35 pg/mL, the IQ range of 5.43 pg/mL with a median of 3.45 pg/mL and whiskers to 1.1 and 15.4 pg/mL. The box plot of hs troponin I (case group) showed Q1 of 37.18 pg/mL, Q3 of 1,410.78 pg/mL, the IQ range of 1,373.6 pg/mL with a median of 101.2 pg/mL and whiskers to 1.6 and 2,984.1 pg/mL.

The box plot of NT-proBNP (control group) showed Q1 of 20.99 pg/mL, Q3 of 107.9 pg/mL, the IQ range of 86.91 pg/mL with a median of 49.29 pg/mL and whiskers to 5 and 124.1 pg/mL. The box plot of NT-proBNP (case group) showed Q1 of 625.23 pg/mL, Q3 of 11,441.5 pg/mL, the IQ range of 10,816.3 pg/mL with a median of 3,638.5 pg/mL and whiskers to 126.4 and 23,924 pg/mL.

While analyzing the 1-month data (August 1, 2020 to August 31, 2020) of 261 COVID-19 patients, 10% of the COVID-19 patients showed cardiac injury and the mortality rate among the cardiac injury patients is 12%.

Both the cardiac markers (NT-proBNP and hs troponin I) have an excellent accuracy in patients with COVID-19 with chest pain, suggestive of cardiac injury.

Understanding the cardiac biomarkers in COVID-19 patients with chest pain appears to be beneficial to triage, risk-stratify, and prognosticate patients with COVID-19 based on the evidence of cardiac injury.

Ethical Approval

Institutional Ethics Committee Approval was taken.

Acknowledgments

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