ORIGINAL ARTICLE

FREQUENCY OF RAISED CARDIAC BIOMARKERS IN PATIENTS WITH COVID-19 INFECTION AND ITS ASSOCIATION WITH MORTALITY

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ABSTRACT

Background: Myocardial injury with raised Troponin levels and other cardiac biomarkers has been reported in COVID-19 and is associated with increased mortality. Data regarding clinical presentation and associated risk factors in patients with raised cardiac biomarkers in COVID-19 are limited. This study aimed to assess the frequency of myocardial injury as evidenced by raised cardiac markers in COVID-19 patients along with its association with mortality.

Material and Methods: This retrospective cohort study was conducted at Sindh Infectious Diseases Hospital and Research Centre. Data for different clinical variables were collected on a structured pro forma from the medical records and clinical outcomes were seen for hospital discharge or in-hospital mortality. SPSS software (version 25.0) was used for data analysis. Categorical variables were analyzed using frequencies and percentages and compared using the x^2 test or Fisher's exact test. Continuous variables were analyzed using the mean, and median. A *p*-value less than 0.05 was considered statistically significant. The multivariate logistic regression model was used to see the association of mortality with independent risk factors.

Results: A total of 384 patients were studied; 243 (63.3%) were males. The mean age was 64.46 years. There were 373 (97.1%) individuals with raised pro-BNP levels, and 167(43.5%) had raised troponin-I values. Also, 156(40.62%) patients had increased both troponin-I and pro-BNP levels. The most common clinical presentation was shortness of breath seen in 321 (83.6%) patients. Cytokine Release Syndrome (CRS) was seen in 169 (44%). A low ejection fraction was present in 31 (8.1%). The average mean hospital stay was 8.97 days. Two hundred and thirteen (55.46%) patients were in ICU. Mortality was seen in 159 (41.4%). Survival was significantly associated with normal troponin-I (OR: 4.8, 95%CI: 3.0-7.5, P=0.00), normal ejection fraction EF>45% (OR: 2.3, 95%CI: 1.0-5.33, P=0.034) and age more than 60 years (OR: 0.6, 95%CI: 0.38-0.94 P=0.027) while raised pro-BNP has no association with mortality (P-value <0.129).

Conclusion: COVID-19 infection associated with myocardial injury as evidenced by raised cardiac enzymes and decreased ejection fraction is associated with high mortality in patients less than 60 years of age.

Keywords: COVID-19, Cardiac biomarkers, Troponin I, Pro-BNP, Myocardial injury

BACKGROUND

Severe acute respiratory syndrome secondary to COVID-19 infection has affected millions of individuals with increased deaths.[1] Many of these patients also suffer myocardial injuries.[2,3] Studies have shown that certain viral infections like influenza can lead to adverse myocardial outcomes.[4] Now studies show newly developed cardiovascular diseases in COVID-19 patients as well.[5,6]

The underlying pathology may be related to high oxygen demand, hyper-coagulability, and direct injury to myocardial cells.[7,8] There are mixed results associating myocardial disease severity in COVID-19 patients as measured by cardiac enzymes.[9-12] However, in a few studies, there is a report of increased mortality in patients with increased troponin levels and underlying myocardial damage.[13-16]

Data regarding clinical presentation and associated risk factors in patients with raised cardiac biomarkers in COVID-19 are unknown. So, we aimed to study our patient population who developed myocardial damage as evidenced by increased cardiac enzymes, admitted to a tertiary care unit specifically designed to manage COVID-19-infected individuals.

MATERIAL AND METHODS

We conducted a retrospective cohort study on 384 patients admitted with COVID-19 infection at Sindh Infectious Diseases Hospital and Research Centre from 04th July 2020 till 31st March 2021, with raised cardiac enzymes (troponin-I, troponin-I; B-type natriuretic peptide, pro-BNP). Patients included were adults (more

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than 18 years of age) with COVID-19 infection, proven by PCR done in nasopharyngeal or oropharyngeal swabs. Patients with recurrent COVID-19 infection and those with known structural heart disease with a baseline ejection fraction of less than 45% were excluded, while patients with stable ischemic heart disease were included.

We used national guidelines to define COVID-19 infection, Cytokine Release Syndrome (CRS), and COVID-19 disease severity as mild, moderate, severe, or critical.[17] Cardiac enzymes were defined as raised and normal, according to values above the upper limit of normal levels of high-sensitivity troponin-I (> 53 pg/ml in male, >34pg/ml female) and pro-BNP (> 220 pg/ml) as per institutional laboratory normal ranges. Acute respiratory distress syndrome (ARDS) was defined as a week onset of acute hypoxic respiratory failure with bilateral lung infiltrates not fully explained by cardiac or volume overload (PaO2/FiO2 </= 300mmHg).

The study was conducted after approval from the Institutional Review Board of Dow University of Health Sciences (IRB-2111/DUHS/Approval/2021/578). SIDH&RC is a 170-bedded tertiary care facility currently designed to manage COVID-19-infected patients. Data for different variables like, COVID-19 status, age, sex, co-morbidities, raised troponin, raised pro-BNP, ejection fraction on echocardiography, clinical disease severity, treatment, ICU stay, hospital stay, hospital discharge, or death was collected on a structured pro forma from the medical records. No personal identifiers like name or medical record number were obtained to maintain confidentiality. Clinical outcome was measured for the hospital stay, ICU stay, hospital discharges, and in-hospital mortality.

SPSS software (version 25.0) was used for data analysis. Categorical variables were analyzed using frequencies and percentages. Association of mortality with different variables x2 test, or Fisher's exact test was used as needed, and a p-value less than 0.05 was considered statistically significant. Those with significant values were further analyzed by a multivariate logistic regression model, and results were written as odds ratio: 95% confidence intervals (OR: 95% CI). Continuous variables were analyzed using mean, median, and Inter-quartile Range (IQR).

RESULTS

A total of 384 patients were studied, n=243 (63.3%) were males, and n=141(36.7%). The mean age was 64.46 years (Standard deviation ± 11.76), and the median age was 64 years (IQR, 55-72, Table-1). There were n=373 (97.1%) individuals who had raised pro-BNP levels, and n=167 (43.5%) had raised troponin-I values. Also, n=156 (40.62%) patients had both raised troponin-I and pro-BNP levels ARDS, acute respiratory distress syndrome; CRS, Cytokine release syndrome. Low ejection fraction was more common in males n=21 (67.74%) than in females n=10(32.25%). The distribution of disease severity is shown in Figure-1.

The average mean hospital stay was 8.97 days (standard deviation SD, 6.185 days). Approximately n=213 (55.46%) were in the intensive care unit (ICU), with a mean stay of 7 days (SD 5.71). Mortality was seen in n=159 (41.4%) with more males n=105 (66%) than females n=54 (34%). Around n=197 (51.30%) were discharged, n=20 (5.2%) were referred to other hospitals, and n=8 (2%) were left against medical advice. Compared to no survivors, survivors had normal troponin levels (OR:4.8, 95% CI: 3.0-7.5, *p*-value <0.01,), normal ejection fraction EF > 45% (OR:2.3, 95%CI: 1.0-5.33, P=0.034) and age more than 60 years (OR:0.6, 95%CI: 0.38-0.94, P=0.027), while Pro-BNP levels were the same in both the groups (98%/95%, P- value < 0.129).

Table-1: Demographic details and clinical characteristics.

Age in years	64.46 (Mean)	11.76 (SD)
Gender:	243 Males 141 Females	(M=63.3%), (F=36.7%)
Co-morbid conditions:		
Hypertension	229	(59.6%)
Diabetes mellitus	179	(53.4%)
Ischemic heart disease	98	(25.5%)
Chronic kidney disease	19	(4.9%)
Autoimmune disorders	17	(4.4%)
Stroke	9	(2.3%)
Chronic lung disease	7	(1.8%)
Clinical presentation:		
Shortness of breath	321	(83.6%)
Tachycardia	310	(80.7%)
ARDS	203	(52.9%)
CRS	169	(44%)
Low ejection fraction	31	(8.1%)
Altered mental status	11	(2.9%)
Chest pain	3	(0.8%)

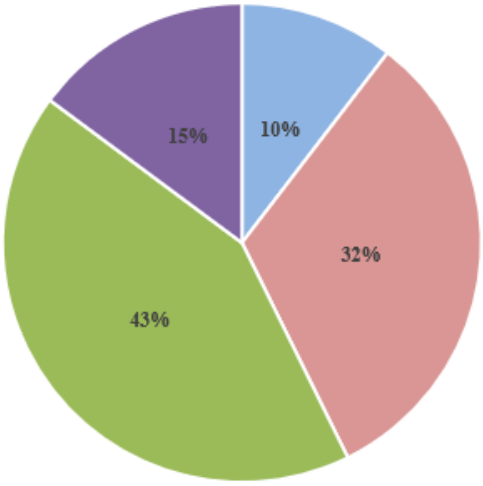

Figure-1: The distribution of disease severity.
Purple: Critical, Green: Severe, Red: Moderate, Blue: Mild

DISCUSSION

In this study, we observed that most patients with raised cardiac biomarkers namely Troponin-I and pro-BNP in COVID-19 infection presented with shortness of breath, tachycardia, ARDS, and CRS. Low ejection fraction (EF≤ 45%) was present in a minority of cases. Most of them were in the severe disease category and were admitted to ICU care. Mortality was significantly associated with raised Troponin-I levels, low ejection fraction, and a relatively younger patient population. But not with raised pro-BNP.

Currently, available literature suggests an association between SARS-COV 2 infection and myocardial injury as evidenced by raised Troponin-I and pro-BNP levels.[2,3,17] A large multicenter observational study from the US reported a 36% prevalence of Myocardial injury in their cohort indicated by raised levels of cardiac enzymes.[13] Earlier reports from China showed the prevalence between 7-28% in various single-center studies.[15] We observed a greater number of patients with raised cardiac biomarkers as compared to those reported in studies by Lala *et al* (Raised Trop-I in 19.4% of patients) and Shi *et al* (19.7%).[14,15] However, the clinical characteristics of patients in our study were similar to the patients reported in previous studies.

Though patients with pre-existing cardiac diseases are known to be at increased risk of severe illness with COVID-19, evidence has shown an increased prevalence of cardiovascular complications in patients with no prior cardiac conditions.[15] There are multiple proposed mechanisms of myocardial injury in COVID-19, including direct myocardial involvement by SARS-COV 2, cytokine storm, increased thrombogenicity, severe hypoxemia, endothelial dysfunction due to vascular involvement, sympathetic stimulation, and right heart overload as a consequence of the pulmonary disease.[15] Troponin-I is a marker of direct myocardial injury, while a raised pro-BNP is a marker of cardiac stress and can be seen elevated in other conditions as well.[18]

Patients with severe COVID-19 usually present with pulmonary complications including pneumonia, ARDS, respiratory failure, and pulmonary thrombo-embolism, all associated with increased mortality. [1, 2, 15] It has been observed that such patients can also have an increased frequency of raised cardiac biomarkers and cardiac complications like myocardial infarctions, arrhythmias, heart failure, and acute myocarditis irrespective of the presence of pre-existing cardiovascular disease.[15] Similar to these findings, in our study patients with severe pulmonary complications like ARDS and cytokine release syndrome (CRS), were also seen as having raised cardiac biomarkers, especially pro-BNP levels. However, we could not find its association of mortality with CRS, ARDS, or disease severity. Most of the patients in our study were elderly males with multiple co-morbidities, most commonly hypertension, and the majority were admitted to the ICUs, similar to findings observed by Shai *et al.* and other large observational studies.[13,14] Our observations add to the current evidence in establishing an association between COVID-19 infection and increased risk of cardiac complications, indicated by raised Troponin I and pro-BNP levels, especially in patients less than 60 years of age and heart failure. Early detection can help stratify patients at risk of severe illness and institute timely management including cardiology consultation and follow-up.

We observed an association of mortality with raised Troponin I levels but not with pro-BNP, which could be due to the fact that pro-BNP levels can be elevated in multiple other non-cardiac conditions co-existing in COVID-19 infections like acute kidney injury, ARDS, and excessive cortisol use, rendering it difficult to establish a direct association between mortality and raised pro-BNP levels as a cardiac biomarker[18]. This finding was also reported in a meta-analysis of five observational studies by Dawson *et al* as well. Although raised Troponin I level is a marker of cardiac injury, it can also be found elevated in other non-

cardiac conditions like renal failure, pulmonary embolism, and septic shock, and this can be difficult to rule out in COVID -19infections because of multisystem involvement. Correlating with clinical findings, ECG and echocardiography can make the differentiation possible.[19, 18] Unfortunately for our study, we were unable to gather such data on all of our patients but in patients with significantly raised levels of Troponin I or those with serial elevation, we can safely establish an association of mortality with raised Troponin I as an indicator of myocardial injury. Another finding in our study was having no association between pre-existing cardiovascular disease and mortality. This finding is corroborated by existing literature showing patients with pre-existing CVD and no myocardial injury having favorable outcomes in terms of mortality as compared to those with evidence of severe myocardial injury and no prior CVD.[13,14,15] Patients with severe myocardial injury have three times increased risk of mortality.[15] Early detection of elevated Troponin I and serial echocardiography in high-risk group patients can help predict mortality and help in time management to prevent the progression of the disease. [20]

LIMITATIONS

This is a single-center observational study; data for echocardiographic and electrocardiographic findings were absent in several patients. Also, none of the patients with evidence of myocardial injury had a tissue diagnosis for myocarditis.

CONCLUSION

COVID-19 infection associated with myocardial injury as evidenced by raised cardiac enzymes and decreased ejection fraction is associated with high mortality in patients less than 60 years of age. More large-scale studies are required to establish a definitive diagnosis and treatment optimization at an early stage to decrease mortality in COVID-19 patients.

AUTHOR CONTRIBUTION

Ishfaque Ahmed: Conception, the acquisition, analysis, interpretation of data and manuscript writing
Beenish Syed: Conception, Analysis and interpretation of data, manuscript writing
Muneeba Ahsan Sayeed: Conception, Analysis and interpretation of data, manuscript writing
Fizza Jameel Farooqui: Interpretation of data, manuscript writing
Laiba Fazal: Data collection and analysis
Shaiza Farman: Data collection and analysis

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