Original Article

Evaluation of cardiac biomarkers among dead and alive COVID-19 patients in Southwest Iran

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Abstract

Introduction: The need to understand the global burden of heart failure following the pandemic has arisen as a result of an increase in papers that support cardiac involvement in coronavirus disease 2019 (COVID-19). Therefore, the current study aims to provide a more thorough explanation of the function and use of cardiac biomarkers in dead and alive COVID-19 patients. **Methods:** All patients who were referred and admitted to Razi Hospital, Ahvaz, Iran, from March 2020 to March 2021 with a diagnosis of COVID-19 were included in this study. **Results:** During the study period, 753 patients were hospitalized with a diagnosis of COVID-19. In total, 157 cases died from the disease (case fatality rate: 20.84%). Pre-existing cerebrovascular accidents (CVAs) were more frequent in dead cases (14% vs. 6.4%). It was observed that atrial fibrillation was normal in most of the alive cases in comparison to dead patients (*P* value = 0.014). Moreover, it was seen that CRP, IL-6, and procalcitonin were increased in dead patients. Also, an association was found between ejection fraction (EF) value and death rate (*P* value = 0.035). The higher frequency of positive troponin occurring in the dead group suggested a possible adverse effect on the mortality rate (22.3% vs. 16.4%). **Conclusion:** Adults with COVID-19 commonly have cardiac manifestations, including symptoms of myocardial damage. In light of the recognized utility of troponin, ejection fraction, procalcitonin, IL-6, and CRP in COVID-19 patients with suspected myocardial damage, we should develop a safe and precise diagnostic algorithm that may contain patients' clinical histories and additional variables that may facilitate the prediction of myopericarditis.

Keywords: Biomarker, COVID-19, ejection fraction, heart failure

Introduction

The coronavirus disease 2019 (COVID-19) created an unprecedented public health event. Therefore, the World Health Organization deemed the novel coronavirus as a pandemic in March 2020. COVID-19, an illness with a broad spectrum of clinical manifestations, may be brought on by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 infection).[1] This disease may range from a minor illness with flu-like symptoms to a serious respiratory ailment requiring specialist care in intensive care units (ICUs) and may have poor long-term prognoses and lingering chronic impairment. Although the clinical manifestations of COVID-19 are dominated by respiratory symptoms, some patients have severe cardiovascular damage and involvement.[2] Acute coronary syndrome (ACS) patients with SARS-CoV-2 infection frequently have a bad prognosis. Due to myocardial ischemia or necrosis, a cardiac

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functional reserve may be diminished in ACS patients. Heart failure is more likely to develop in SARS-CoV-2-infected individuals, which might increase their mortality rate. Severe symptoms of SARS-CoV-2 infection may exacerbate the illness and create complications involving acute myocardial injury.[3,4]

There is a hypothesis that angiotensin-converting enzyme 2 (ACE2) receptors may be connected to the mechanism of acute myocardial damage brought on by SARS-CoV-2 infection. Intense cytokine and chemokine release caused by SARS-CoV-2 may contribute to cardiac inflammation in addition to vascular inflammation and atherosclerotic plaque instability. Therefore, demand ischemia, stress cardiomyopathy, microvascular thrombosis, and systemic inflammation side effects are potential reasons for the higher cardiovascular biomarker levels in these patients.

Another potential cause of myocardial injury is the direct viral infection of the myocardium.[5] The prospect of direct viral infection of the vascular endothelium and myocardium is raised by SARS-special CoV-2's affinity for the host ACE2; hence, in some cases, COVID-19-associated myocardial damage could be viral myocarditis. The diagnosis, treatment, and prognosis of COVID-19 can be greatly aided by cardiac biomarkers.[6,7] However, there is inconsistent data connecting myocardial injury as determined by cardiac biomarkers to the severity of the disease. A lower threshold of cardiac biomarkers would be appropriate for diagnosis and prognosis, although it was observed that cardiac biomarkers increase in the majority of COVID-19 patients and have a more robust predictive potential for worse outcomes as the disease progresses.[8] Given that the septic shock of SARS-CoV-2 is typically coupled with multiorgan damage, combining the study of cardiac biomarkers with the markers of damage to other organs is expected to provide a better picture of future outcomes. Accordingly, the current study aims to provide a thorough explanation of the function and use of cardiac biomarkers in dead and alive COVID-19 patients.

Methods

Patients

All patients who were referred and admitted to Razi Hospital, Ahvaz, Iran, from March 2020 to March 2021 with a diagnosis of COVID-19 were included in this study. All of the patients had either a confirmed diagnosis of COVID-19 (as determined by a positive outcome on real-time polymerase chain reaction testing of nasopharyngeal and oropharyngeal samples) or a probable diagnosis of COVID-19 (as determined by a positive chest computerized scan/X-ray characteristic for COVID-19, according to the World Health Organization criteria).

The clinical signs of SARS-CoV-2 infection in patients might range from no symptoms to serious illness. Based on the CDC definition, adults with SARS-CoV-2 infection can be grouped into the following severity of illness categories. A person is considered to be suffering from a mild illness if they exhibit any of COVID-19's various signs and symptoms (such as a fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, or a loss of taste and smell) but not abnormal chest imaging, dyspnea, or shortness of breath. Patients with moderate sickness are those who exhibit signs of lower respiratory disease in a clinical examination or imaging and who have an oxygen saturation level (SpO2) of less than 93%. Patients with a SpO2 below 93%, a PaO_2/FiO_2 ratio below 300 mm Hg, a respiratory rate above 30 breaths per minute, or lung infiltrates above 50% are considered to have severe sickness.

The following information was extracted based on the review of patients' files. The echocardiographic data of all patients were measured by a Samsung portable echocardiographic machine (UGEO HM70A and GE VIVD 3 Echocardiographic Machine). Details related to ejection fraction (EF), PAP, and valve dysfunction were reviewed. Based on the results extracted from the patients' files, it was determined that all patients had an EKG taken upon their arrival at the hospital.

Data collection

The admitting physician gathered the following information in the emergency room from patients who were hospitalized with a diagnosis of COVID-19: age, sex, and presence of fever. After the patients' medical records were analyzed, further information was gathered. Additionally, data on underlying chronic health issues (self-declared) related to diabetic mellitus (DM), hypertension (HTN), the heart, and the nervous system were evaluated.

Statistical analysis

In this descriptive study, continuous variables were provided as means and standard deviations, and the values of categorical variables were presented as the number (percentage) of participants. Pearson's Chi-square and *t*-test were used for univariate comparisons. Multivariate logistic regression analyses were performed to assess the adjusted odds ratio (OR) of dead versus alive COVID-19 patients. Covariates that were significant in univariate analysis (P value < 0.2) and had clear clinical significance (HTN) were included. All data were analyzed using SPSS version 21 (SPSS Inc., Chicago, IL). The statistical significance level in all the analyses was set to 0.05.

Results

During the study period, 753 patients were hospitalized with a diagnosis of COVID-19. In total, 157 cases died from the disease (case fatality rate: 20.84%). A comparison of the ages of the dead and alive patients revealed that the deceased patients were significantly older (66.72 ± 12.61 vs. 72.74 ± 12.45) than the alive patients. Sex distribution was not homogenous, and most of the patients were male in both groups (P value $= 0.017$). It turned out that the prevalence of mild, moderate, and severe COVID-19 cases was significantly different between dead and alive patients (P value < 0.001). Pre-existing cerebrovascular

accidents (CVAs) were more frequent in dead cases than alive cases (14% vs. 6.4%). It was observed that atrial fibrillation was normal in most of the living cases in comparison with the dead patients (*P* value = 0.014). New atrial fibrillation was more frequent in dead cases than in alive cases (*P* value = 0.001), while old atrial fibrillation was not significantly different in the two groups. Moreover, it was seen that CRP, IL-6, and procalcitonin were increased in dead patients. Also, an association was found between EF and death rate (*P* value = 0.035). The higher frequency of positive troponin occurring in the dead group suggested a possible adverse effect on the mortality rate (22.3% vs. 16.4%). Regarding smoking, DM, HLP, ESR, and HF, it was found that both groups were similar. More details are provided in Table 1. An evaluation of the relation between IHD and new AF showed a significant association (*P* value = 0.001). In addition, regarding the association between new AF and old AF with CVA, patients with pre-existing AF were more likely to experience CVA (*P* value = 0.013), while no association was found for AF during hospitalization and CVA (*P* value = 0.12). Figures 1 and 2 show more details about these results.

The results of the binary logistic regression analysis show that older patients are more susceptible than younger patients to dying from COVID-19 (*P* value < 0.001). Males are more likely to die than females, and the odds are estimated at 1.60 (0.98–2.62). Patients with positive troponin were also more likely to die of COVID-19 during their hospital admission (OR = 1.95, 95% CI: 1.05–3.62). The level of EF was significantly associated with increased mortality odds in comparison with the normal range of EF. The multivariable logistic regression analysis identified smoking, CVA, HTN, length of stay, hospitalization department, IL-6, procalcitonin, and CRP as independent contributors to death from COVID-19 (not shown in the table). More details are provided in Table 2.

Discussion

According to the results of the current study, male sex, old age, positive troponin, and a lower level of EF are all important factors that raise the risk of death following hospitalization for COVID-19. The pathogenic cause of COVID-19, a continuing

Table 1: Univariate analysis for comparisons between alive and dead COVID-19 patients

Variable	Alive (*n*=596)	Death (*n*=157)	*P*
Age	66.72±12.61	72.74±12.45	<0.001
Sex (Male: Female)	301:295 (50.5%:49.5%)	96:61 (61.1%: 38.9%)	0.017
Disease status			
Mild	210 (35.2%)	28 (17.8%)	<0.001
Moderate	205 (34.4%)	46 (29.3%)	
Severe	128 (21.5%)	60 (38.2%)	
No cardiovascular symptoms	53 (8.9%)	23 (14.6%)	
Diabetic Mellitus	316 (53.0%)	71 (45.2%)	0.082
CVA	38 (6.4%)	22 (14.0%)	0.002
HLP	75 (12.6%)	12 (7.6%)	0.085
HTN	371 (62.2%)	90 (57.3%)	0.15
Smoker	29 (4.9%)	12 (7.6%)	0.17
IHD	431 (72.3%)	112 (71.3%)	0.84
Atrial fibrillation			
Old	96 (16.1%)	31 (19.7%)	0.27
New	25 (4.2%)	17 (10.8%)	0.001
Normal sinus rhythm	128 (21.5%)	20 (12.7%)	0.014
STEMI	59 (9.9%)	17 (10.9%)	0.71
Hospitalization department			
ICU	53 (9.9%)	107 (68.2%)	<0.001
CCU	200 (33.6%)	23 (14.6%)	
General	343 (57.6%)	27 (17.2%)	
EF value			
<30	172 (28.9%)	60 (38.2%)	0.063
30–35	83 (13.9%)	18 (11.5%)	
40–50	243 (40.8%)	63 (40.1%)	
50 –75 (Normal)	98 (16.4%)	16 (10.2%)	
Positive Troponin	98 (16.4%)	35 (22.3%)	0.027
CRP	43.80±61.16	51.80±38.03	0.045
ESR	45.85±42.28	46.19±37.49	0.92
Procalcitonin	0.52±6.21	3.44±23.35	0.007
IL-6	9.96±112.71	55.46±378.54	0.01
HF	0.30±1.80	0.21±0.409	0.53
Length of Stay	6.15±4.47	7.73±5.38	<0.001

Note: Bold *P* values are statistically significant at 0.05%. Abbreviation: CVA, cerebrovascular accident; HLP, Hyperkeratosis lenticularis perstans; HTN, Hypertension; IHD, ischemic heart disease; HF, Heart Failure

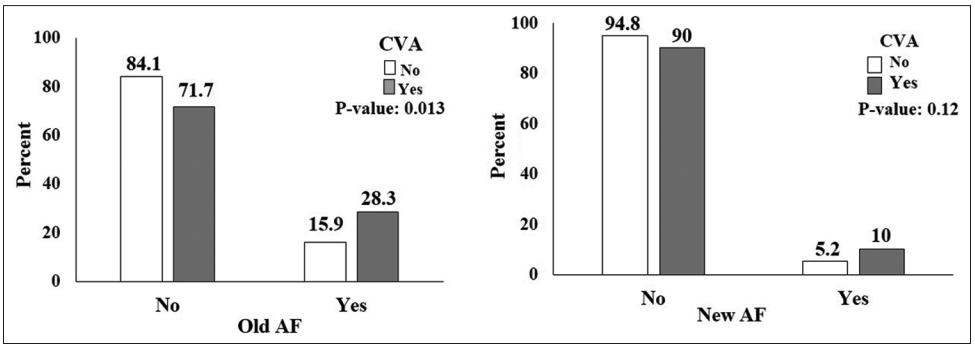

Figure 1: CVA and new/old AF association among COVID-19 patients

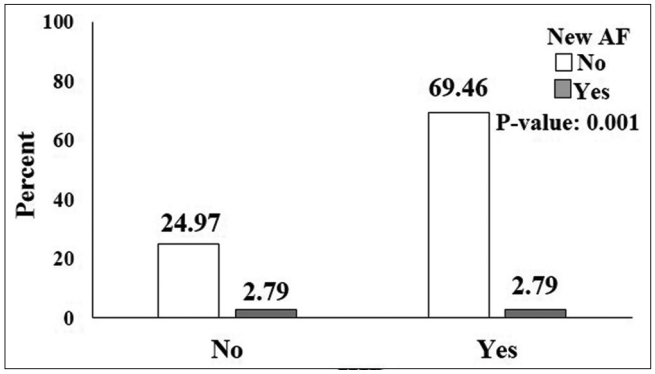

Figure 2: IHD and new AF Association among COVID-19 patients

worldwide pandemic, is SARS-CoV-2. Cardiovascular morbidity and mortality in this cohort are becoming increasingly recognized, along with expected respiratory mortality. The existence of cardiac injury has been attributed to in-hospital mortality in hospitalized COVID-19 patients. However, heart disease symptoms in COVID-19 patients frequently include indicators of myocardial injury. Similar associations have been noted regarding other coronavirus outbreaks, such as SARS and the Middle East respiratory illness, but there is still a crucial knowledge deficit regarding the possible effects of CVD and damage in COVID-19.

Patients with acute COVID-19 may exhibit a variety of cardiac clinical manifestations, including symptomatic heart disease, no clinical evidence of heart disease, and no symptoms but abnormal cardiac test results (e.g., elevated serum cardiac troponin or no symptoms but cardiac arrhythmias). Myocardial injury, heart failure, cardiac shock, and cardiac arrhythmias, including abrupt cardiac arrest, are all examples of cardiac problems. The general incidence of HF in COVID-19 patients may be linked to acute illnesses in people with known or undiscovered heart disease (such as coronary artery disease or hypertension), acute hemodynamic stress (such as acute pulmonary blindness), or acutely accelerated aging. Autopsy results obtained from examined cardiac tissues of 39 COVID-19 fatality patients revealed that SARS-CoV-2 was present in 62% of the specimens, indicating a high rate of viral presence in the myocardium. The direct viral damage and the systemic immune response brought on by infection remain the two fundamental questions regarding the cardiac injury and inflammation that have been observed so far.[9]

Table 2: Significant associations between COVID-19 clinical characteristics and death

Variable	OR (95% CI)	*P*
Age	1.53 (1.03–1.76)	<0.001
Male sex (vs. female)	1.60 (0.98–2.62)	0.046
Troponin (vs. negative)	1.95 (1.05–3.62)	0.032
EF levels (vs. normal range: 50–75)		
<30	2.13 (1.16–3.91)	0.014
30–35	1.32 (0.63–2.76)	0.44
40–50	1.58 (0.87–2.88)	0.12

P values are statistically significant at 0.05%

A lower EF value was identified as an influential factor that increased the death rate in hospitalized COVID-19 patients. In line with another study, it was found that heart failure with reduced ejection fraction was significantly associated with in-hospital mortality.[10] Moreover, in another study, it was observed that myocarditis-induced heart failure with low ejection fraction and viral-induced cardiac inflammatory changes might occur.[11] The effects of right ventricular anomalies and left ventricular diastolic dysfunction were the two main findings of the echocardiographic assessments performed on hospitalized COVID-19 patients. Ninety percent of COVID-19 patients observed in Israel (mean age: 66 years) had normal left ventricular ejection fraction, and the most frequent anomalies were right ventricular enlargement (39%) and left ventricular diastolic dysfunction (16%).[12]

A comparison in the current study found an increasing level of IL-6 in dead patients. Freaney *et al.*[13] revealed that proinflammatory cytokines, including IL-1 and IL-6, are released as a result of SARS-CoV-2 infection, having an impact not only on the respiratory system but also on the myocardium, both directly and indirectly. The role of inflammatory cells and pathways during an acute initial injury to the myocardium, such as an ischemic insult or a viral injury (e.g., influenza) contributing to heart failure with preserved ejection fraction (HFpEF), has been confirmed. Although case reports have described severe COVID-19 myocarditis that resulted in HFpEF, it is possible that the more typical manifestation in the COVID-19 era was HFpEF, which was caused primarily by the discovery of subclinical HFpEF and secondarily by the emergence of new HFpEF after SARS-CoV-2 infection. The identification of COVID-19

as a possible risk factor for HFpEF should induce screening and treatment to stop the progression of the condition and its unfavorable outcomes on an individual basis, thereby mitigating the rising morbidity, mortality, and inequalities of the condition.

The current research shows that positive troponin plays a significant role in COVID-19 deaths and increases the odds of mortality by 1.95 times. Consequently, high troponin levels are linked to high mortality in COVID-19 patients. During the current outbreak, troponin has served as a helpful indicator of the course and prognosis of the illness. As was seen in Guo *et al*.'s study,[14] 16% of the patients who had underlying CVD but normal troponin levels had fairly good results. Myocardial biomarkers should be assessed in patients with CVD who acquire COVID-19 to risk-stratify patients and perhaps guide earlier and more aggressive therapies. Similar results were found in another study showing that patients with troponin levels of 0.34 ng/mL had significantly higher atrial tachyarrhythmias, ventricular tachyarrhythmias, and 30-day in-hospital mortality than those with less severe troponin elevation.[15,16]

High-sensitivity troponin plays a critical role in SARS-CoV-2. This suggests that the cardiovascular system is acutely involved in the most severe presentations. Additionally, it can prompt the consideration of an infectious cause of acute myocardial injury, which might help us make the best treatment decision and run follow-up diagnostic tests. Since patients who are suspected of having myocardial involvement should get a cardiac MRI and a myocardial biopsy to confirm the diagnosis, it is currently challenging to evaluate the correlation between COVID-19 and myocarditis by troponin dose alone.

A review of the potential effects of coronaviruses on the cardiovascular system was undertaken by Madjid *et al*.[17] Viral pneumonia caused by COVID-19 with additional extra-pulmonary symptoms and consequences was confirmed in this research. In particular, immediate cardiac injury has been frequently observed in the most severe instances and has been linked to a greater mortality rate (indirectly demonstrated by high levels of high-sensitivity troponin). Additionally, as recently confirmed by Varga *et al*.,[18] a rise in troponin may be linked to clinical diseases that are not restricted to the heart, such as pulmonary embolism, renal failure, or the broad involvement of endothelial cells.

As was indicated, CRP and procalcitonin are two biomarkers with an increased level in dead patients. However, based on logistic regression results, no further information was found about the odds of death. According to another study, measurements of procalcitonin and CRP may help identify patients with subsequent bacterial infections and enable the targeted use of antibiotics, thus encouraging antibiotic stewardship. Therefore, it seems that critically ill COVID-19 patients develop secondary bacterial infections, which cause death.[19]

Overall, it is suggested that further research should be conducted involving histological examinations of cardiac tissues in COVID-19 patients to determine the relationship between COVID-19 and myocardial injury. Since biopsy-proven myocarditis may occur in the absence of troponin release, autopsy studies of COVID-19 victims, regardless of troponin levels, will help clarify whether SARS-CoV-2 is a novel cause of viral myocarditis.

There are some limitations in the current study. The study's main limitation is its non-randomized observational design, which means that all the registered cases involving the patients who were admitted to the hospital were included without taking the inclusion and exclusion criteria into account. The effects of several elements on the results were neglected due to a lack of information regarding some crucial data, such as body mass index, which could have a negative impact on the generalizability of the results. In addition, the studied patients had visited the hospital at different stages of their illness, and their case information and histories were related to the time of the visit, which caused differences in the results, the comparisons of the people, and the impacts of risk factors.

Conclusion

Despite this study's limitations, the findings show that in the studied population, adults with COVID-19 usually have manifestations of heart disease, including symptoms of myocardial damage. The presence and level of increased troponin are associated with more severe diseases and worse outcomes. There was no significant relationship between IHD and the mortality rate caused by COVID-19, while the mortality rate was higher in these people. Older age in COVID-19 patients increases the risk of mortality and length of hospitalization. In light of the recognized utility of troponin, ejection fraction, procalcitonin, IL-6, and CRP in COVID-19 patients with suspected myocardial damage, a safe and precise diagnostic algorithm should be developed that may contain patients' clinical histories and additional variables that may facilitate the prediction of myopericarditis. Furthermore, assessing biomarkers of cardiac injury may improve the identification of patients with the highest risk and may lead to improved treatments.

Ethics approval and consent to participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of The Ahvaz University of Medical Sciences Review Board Research Committee and the Helsinki Declaration as a minimal-risk investigation using the data gathered for standard clinical practice. Ethical approval was obtained from the Research Ethics Committee of Ahvaz University of Medical Sciences: (Ethical code: IR.AJUMS.REC.1400.298).

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are not publicly available. We used the electronic database of HIS (Hospital Information System) of referral tertiary Razi Hospital (during the COVID-19 pandemic). All data of this study are available from the corresponding author upon reasonable request.

Authors' contributions

S.M.H. Adel and E.H. Sardabi conceived and designed the analysis, M. Sayadian and S. Saki Pour collected the data, N. Akiash and M. Mohammadi contributes data or analysis tools, P. Amini performed the analysis and S.M.H. Adel wrote the paper. All authors reviewed the manuscript.

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Informed consent

Informed consent was obtained from all individual participants included in the study.

Limitation of this study

The main limitation of our study is its non-randomized observational design. First, all recorded cases are included in this study related to patients visiting the hospital between the years 2020 and 2021 without an inclusion/exclusion criterion.

Second, we relied on patient questionnaires to obtain clinical parameters such as blood pressure, and body mass index as this information was not otherwise available. Third, since this study included hospitalized patients with COVID-19, there is a higher likelihood that elderly individuals or those with comorbidities and at the severe end of the disease spectrum may be overrepresented in our analysis. Fourth we attempted to account for this by including a large portion of COVID-19 patients who visited the emergency department with mild symptoms and did not require admission. While biomarkers such as troponin were still measured in individuals with the most severe disease where indications were present, other blood tests were not conducted in patients who were not admitted.

Research recommendations

1. Conduct studies on a larger sample of patients with positive COVID-19 PCR and investigate other biomarkers such as Presepsin.
2. Investigate inflammatory biomarkers and coagulation factors and their clinical outcomes in COVID-19 patients.
3. Explore the predictive value of cardiac biomarkers on mortality in hospitalized patients and long-term mortality after discharge in patients with COVID-19 pneumonia.
4. Examine the impact of ischemic heart disease and acute cardiac injury on COVID-19 mortality.

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Conflicts of interest

There are no conflicts of interest.

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