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Original Research

The Association of Elevated Levels of LDH and CK-MB with Cardiac Injury and Mortality in COVID-19 Patients

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Abstract

Background: A new type of beta-coronavirus, named acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused coronavirus disease 2019 (COVID-19). Although COVID-19 is primarily associated with respiratory symptoms, cardiovascular complications can also occur. Herein, we aimed to evaluate whether the serum levels of enzymes related to cardiac injury, lactate dehydrogenase (LDH) and creatine kinase-MB (CK-MB), may associate with the mortality of COVID-19 patients to provide new insights to enhance clinical care.

Methods: Based on hospital information systems (HIS) and patient records, we have retrospectively extracted laboratory findings of 159 patients with confirmed COVID-19 disease. The data of LDH and CK-MB of patients were defined as the day onset when the patients were admitted to the hospital.

Results: The average age of all patients was almost 62 years old; the mean age in dead patients and recovered patients were 70 and 55 years old, respectively. The average aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatine phosphokinase (CPK) values were 91.74, 66.20 U/L, and 268.24 U/L, respectively in all patients. The average LDH was 758.69 U/L, and CK-MB was 39.87 U/L in all of the COVID-19 patients. Among all 140 patients, laboratory results revealed that 121 (86.4%) patients had an elevated LDH level. In total, for 159 patients, the results indicated that 114 (71.69%) patients had an elevated CK-MB value. The average LDH value in dead patients was 1012.22 U/L, while in recovered patients was 545.20 U/L ($P<0.0001$). Also, the average CK-MB level in dead patients was 60.84 U/L, while in recovered patients was 35.17 U/L ($P=00.0026$).

Conclusion: Elevated levels of LDH and CK-MB following COVID-19 disease increase the risk of death in these patients.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread throughout the world and caused the coronavirus disease 2019 (COVID-19) pandemic.[1,2] Respiratory symptoms are the most significant complication of COVID-19, which can range from mild to acute respiratory distress syndrome (ARDS).[3] However, despite the fact that the central manifestation of the virus being respiratory symptoms, cardiovascular involvement can also occur in these patients.[4] Acute cardiac injury is the most reported cardiovascular disorder among patients with COVID-19, which occurs in 8% to 12% of patients.[5] In another investigation by Wang et al it has been indicated that arrhythmias occurred in 16.7% of the 138 COVID-19 patients.[6] Besides, cardiac arrhythmias, acute coronary syndrome (ACS), and venous thromboembolism are some of the other cardiac complications associated with COVID-19.[7-9] Several pathogenic mechanisms underlying cardiovascular complications have been reported in COVID-19. In this regard, binding of the spike protein at the virus surface to the angiotensin-converting enzyme (ACE2), which acts as a receptor for the virus and is highly expressed in heart cells, can lead to direct injury to the myocardium.[10] Afterward, triggering of immune responses and subsequent uncontrolled production of inflammatory mediators, i.e., interleukin (IL)-6, known as the cytokine storm, can cause cardiovascular complications of SARS-

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CoV-2.[11] For instance, COVID-19-associated myocarditis and acute cardiac injury following SARS-CoV-2 infection have been reported to be directly caused by SARS-CoV-2 through this mechanism.[12,13] Moreover, it has been shown that COVID-19-related ACS is caused by the virus-induced hypercoagulable condition that leads to coronary artery thrombosis.[14] The hypoxemia due to respiratory dysfunction is other suggested mechanisms of cardiac complications of the SARS-CoV-2.[15] Various studies have demonstrated that the severity of COVID-19 is significantly increased by cardiac injuries.[16-18] For instance, patients with cardiac injury more frequently developed ARDS, were more likely to have ventricular tachycardia or ventricular fibrillation, and had increased mortality rates compared with patients without ventricular tachycardia or ventricular fibrillation.[17,19] Additionally, cardiac injury was shown to be an independent mortality risk factor of COVID-19.[16-18] Moreover, some investigations demonstrated that COVID-19 patients had an elevated values of myocardial damage related biomarkers, e.g., lactate dehydrogenase (LDH) and creatine kinase-MB (CK-MB).[20, 21] In line with this, it has been found that increased CK-MB and LDH levels have been associated with the emergence of severe disease and the requirement for intensive care unit (ICU) admission.[22] As a result, for risk stratification and COVID-19 patients' management, comprehension of cardiac involvement and its monitoring in the clinical setting are crucial. In light of this, it is required to carefully monitor the patient's serum levels of LDH and CK-MB, which can potentially address and diminish the patient's clinical issues and enhance clinical treatment. Accordingly, we aimed to evaluate whether the serum levels of LDH and CK-MB, may associate with the mortality of COVID-19 patients. Our findings showed that elevated levels of LDH and CK-MB following COVID-19 increase the risk of death in these patients.

Patients and Methods

We collected data on 159 patients with confirmed COVID-19 from 1 March to 20 April 2020 at Imam Reza hospital in Tabriz, Iran, for this retrospective, single-center investigation. All recruited patients in this study were hospitalized as confirmed COVID-19 patients with positive RT-PCR and chest CT-scan. Laboratory findings, clinical features, and epidemiological data about these individuals were evaluated. According to the guidelines of the infectious disease society of the America/American thoracic society (IDSA/ATS), pneumonia was diagnosed.[23] In patients with pneumonia, fever, cough, pleuritic chest pain, and dyspnea are the most prominent clinical symptoms. All suspected COVID-19 cases were swabbed at admission, and RT-PCR tests were conducted. Neither of these patients had a history of cardiac complication, and their cardiovascular involvement was caused by COVID-19.

Data collection

Based on hospital information systems (HIS) and patient records, we have retrospectively extracted laboratory findings. The data of LDH, CK-MB, complete blood count (CBC), and serum biochemical tests, were defined as the day of onset when the patients were admitted to the hospital.

Statistical analysis

All the raw data were analyzed with Excel 2016 software. The results have been shown as mean ± standard deviation (SD) with the significance cut-off of P value < 0.05.

Results

A total of 159 patients with COVID-19 were involved in this study. 53 (33.3%) patients were recruited from the ICU, and 106 (66.7%) patients were recruited from infectious units. Of these 159 patients, 70 (44.02%) patients included the deceased, and 89 (55.97%) of them had the recovered. Among patients recruited from ICU, 44 had the dead, and 9 had the recovered. Among patients recruited from infectious wards, 26 patients included the deceased, and 80 included the recovered (Table 1).

The average age of the patients was 62 years old, and among them, 97 patients were male, and 62 patients were female. The average aspartate aminotransferase (AST) was 91.74 U/L, alanine aminotransferase (ALT) was 66.20 U/L. The average blood urea nitrogen (BUN) was 58.61 U/L, and creatinine was 1.43 U/L. The average LDH level was 758.69 U/L, and creatine phosphokinase (CPK) was 268.24 U/L. The average CK-MB level was 39.87 U/L. In dead patients, the average of patients was 70 years old, while in recovered patients was 55 years old. The average AST in dead patients was 162.75 U/L, while in recovered patients was 38.08 U/L (P=0.0025), and the average ALT in dead patients was 114.95 U/L, while in recovered patients, was 29.36 U/L (P=0.0025). The average BUN value in dead patients was 83.87 mg/dL, while in recovered patients was 38.81 mg/dL (P<0.0001), as well as the average creatinine in dead patients was 1.78 mg/dL, while in recovered patients was 1.17 mg/dL (P=0.0001). Significantly, the average LDH value in dead patients was 1012.22 U/L, while in recovered patients was 545.20 U/L (P<0.0001), as well as the average CPK in dead patients, was 353.47 U/L, while in recovered patients was 206.46 U/L (P=0.0067). Also, the average CK-MB value in dead patients was 60.84 U/L, while in recovered patients was 35.17 U/L (P=0.0026) (Table 2).

In total, for 159 patients, the results indicated that 114

Table 1. Frequency of dead and recovered patients based on hospital units

Demographic information		Total, No. (%)	Deaths, No. (%)	Recovered, No. (%)
Hospital units	Infectious units	106 (66.7)	26 (37.1)	80 (89.9)
	ICU	53 (33.3)	44 (62.9)	9 (10.1)
Total		159 (100)	70 (100)	89 (100)

ICU, Intensive care unit.
Note: The ICU at Imam Reza Hospital had the highest percentage of deaths, at 62.9%, according to the data in this table.

Table 2. Characteristics and laboratory results of the patients hospitalized with COVID-19 in Imam Reza hospital in Tabriz, Iran

Demographic information		Reference ranges	Deaths	Recovered	*P* value
Total number	159		70 (44)	89 (56)	
Age (y), No. (%)	62		70	55	<0.0001
15-49	41 (25.8)				
50-64	41 (25.8)				
>65	77 (48.4)				
Gender, No. (%)					
Male	97 (61)				
Female	62 (39)				
Laboratory measures, mean (SD)					
Lymphocyte (%)	16.50 (±12.50)	16-45	11.02 (±8.95)	20.85 (±13.24)	<0.0001
INR	1.27 (±0.81)	0.8-1.2	1.31 (±0.46)	1.24 (±1.02)	0.5796
PT (s)	15.81 (±5.62)	11.5-13	17.16 (±6.04)	14.76 (±5.06)	0.0091
PT activity	83.66 (±17.08)		77.44 (±18.18)	88.51 (±14.53)	<0.0001
PTT (s)	38.08 (±13.79)	30-45	37.93 (±8.42)	38.20 (±16.61)	0.9098
BUN (mg/dL)	58.61 (±44.88)	3.5-23	83.87 (±49.85)	38.81 (±27.70)	<0.0001
Creatinine (mg/dL)	1.43 (±0.98)	0.5-1.5	1.78 (±1.02)	1.17 (±0.88)	0.0001
AST (U/L)	91.74 (±253.85)	5.0-31.0	162.75 (±376.12)	38.08 (±20.80)	0.0025
ALT (U/L)	66.20 (±171.62)	5.0-47.0	114.95 (±253.61)	29.36 (±18.91)	0.0025
LDH (U/L)	758.69 (±590.14)	140-280	1012.22 (±781.81)	545.20 (±176.03)	<0.0001
CPK (U/L)	268.24 (±317.17)	24-195	353.47 (±313.20)	206.46 (±307.39)	0.0067
CK-MB (U/L)	39.87 (±76.64)	<24	60.84 (±25.86)	35.17 (±66.14)	0.0026

(71.69%) patients had an elevated CK-MB value. In dead patients (n = 70), 62 (88.57%) patients had an elevated CK-MB, while in recovered patients (n = 89), 52 (58.42%) patients had an elevated CK-MB. Based on LDH, for total patients (n = 140), the results revealed that 121 (86.42%) patients had increased values. In dead patients (n = 64), 61 (95.31%) had an elevated LDH, while in recovered patients (n = 76), 60 (78.94 %) patients had elevated LDH (Table 3).

Discussion

The recently discovered SARS-CoV-2 has caused a new infectious disease named COVID-19 that has spread rapidly around the world.[24,25] In addition to causing respiratory damage, SARS-CoV-2 infection can affect other body parts, i.e., the liver, kidneys, and cardiovascular system.[26-28] The higher death rate among COVID-19 patients is primarily associated with SARS-CoV-2-related cardiac injury.[29] Direct damage to the myocardium by viral function, indirect inflammatory damage, and an imbalance of supply and demand for O2 can lead to cardiac complications following COVID-19.[7,30] Various cardiac complications can occur as a result of COVID-19.[31] Acute cardiac injury, cardiac arrhythmias, ACS, and venous thromboembolism are among the cardiac complications that have been reported among COVID-19 patients.[7-9] The most frequent cardiac complication associated with COVID-19 disease is acute cardiac injury.[32] Zhou et al have shown that 44 out of 191 patients with COVID-19, equivalent to 23% of patients, had acute cardiac injury.[33] The development of acute cardiac injury can result in an increased risk of death.[34] Also, it has been reported that this complication was associated with a poor prognosis for COVID-19 disease.[4,33,35] Besides, a study by Du et al on 85 patients with COVID-19 indicated that arrhythmias were present in 60% of patients, with cardiac arrest or malignant arrhythmias causing death in more than 10% of cases.[36] Hence, evaluating the possibility of cardiac complications in SARS-CoV-2 patients is essential for determining the patient's prognosis and for the timely administration of preventative and protective interventions. In this regard, cardiac injury-related enzymes including LDH and CK-MB are useful biomarkers for the diagnosis of cardiac dysfunction in patients.[37] In the context of COVID-19, Guan et al have found that 13.7% of COVID-19 patients had elevated levels of CK, and 37.2% had high levels of LDH.[38] Furthermore, patients with elevated CK-MB and LDH were at higher risk of developing or needing ICU admission for serious illness.[39] As a result, it is important to carefully monitor the patient's serum levels of LDH and CK-MB, which may support addressing and managing their clinical problems and improving their clinical care. Herein, the impacts of SARS-CoV-2 infection on cardiac function were investigated by analyzing laboratory data from 159 hospitalized COVID-19-confirmed patients. Our results showed that the LDH and CK-MB values were increased in COVID-19 patients. Moreover, we found that higher levels of LDH and CK-MB following COVID-19 were associated with an increased risk of death in these patients. These results are consistent with other studies.

Table 3. Frequency of patients based on normal and elevated CK-MB and LDH values.

Demographic information		Deaths, No. (%)	Recovered, No. (%)
CK-MB	Normal value (Range: < 24 U/L)	8 (11.4)	37 (41.6)
	Elevated value	62 (88.6)	52 (58.4)
Total		70 (100)	89 (100)
LDH	Normal value (Range:140-400 U/L)	3 (4.7)	16 (21.0)
	Elevated value	61 (95.3)	60 (79.0)
Total		64 (100)	76 (100)

In accordance with our study, an elevation of LDH and CK-MB among COVID-19 patients has been reported by Zhang and colleagues.[40] They have stated that patients with COVID-19 who had elevated LDH levels were at increased risk of COVID-19-related death.[40] Also, Shi et al have indicated that the risk of in-hospital mortality among severe COVID-19 patients was associated with elevated levels of CK-MB.[8] It has also been reported that higher values of CK-MB were associated with the severity of COVID-19.[18] In another study, it was reported that ICU patients had elevated levels of CK-MB than non-ICU patients, and non-survivors had considerably higher levels of CK-MB than survivors.[6] Despite the large number of patients investigated in this study, several limitations were encountered, such as the death of some COVID-19 patients and the inability to gather information on patients who were discharged from the hospital, making it impossible to assess the long-term impact of the SARS-CoV-2 infection. Overall, our findings show that SARS-CoV-2 affects the proper function of the heart and causes abnormality in its role. However, to accurately assess this problem and its prevalence in COVID-19 individuals, more studies are needed.

Conclusion

These findings show that there was a significant cardiovascular complications prevalence among hospitalized COVID-9 patients in Tabriz, Iran. A non-specific acute inflammation following COVID-19 injures the heart and leads to an abnormal elevation of cardiac biomarkers. Another explanation for elevated cardiac-associated biomarkers might be the activation of general immunity and the cytokine storm that followed the COVID-19 infection. Taken together, the mortality rate of COVID-19 patients may be reduced with early diagnosis of cardiac complications and effective monitoring of LDH and CK-MB values.

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Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethical Issues

All procedures were conducted in compliance with the ethical principles of Tabriz University of Medical Science, Tabriz, Iran and approved by the regional ethical committee for medical research (Ethical code: IR.TBZMED.REC.1399.008).

Conflict of Interest

The authors certify that there is no potential conflict of interest in relation to this article.

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