The Value of Cardiac Biomarkers in Predicting in-Hospital Death in COVID-19 Patients

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Received: 04 Apr. 2022; Accepted: 11 Nov. 2022

Abstract- Given the strong evidence of direct invasion of coronavirus to myocardial tissue, as well as increasing the patient's susceptibility to inflammatory and thrombotic phenomena, it has been hypothesized that elevated levels of cardiac enzymes can predict disease severity and its poor prognosis. We aimed to determine the value of cardiac prognostic biomarkers along with other laboratory parameters in predicting in-hospital mortality of COVID-19 patients. This prospective study was performed on 30 consecutive patients with the definitive diagnosis of severe COVID-19. On admission, along with recording demographic characteristics, intravenous blood samples were extracted from the patients after at least 8 hours of fasting to evaluate other laboratory parameters. Comparing laboratory parameters across the survived and non-survived groups showed significantly higher mean CK-MB level in non-survived group than alive group (70.90±29.79 versus 43.56±22.02, *P*=0.020). Also, positive troponin I was reported in 38.1% of non-survived group, while in none of the patients in survived group (*P*=0.031). Using the logistic regression model, raised CK-MB could effectively predict in-hospital death among COVID-19 patients (OR=1.047, *P*=0.043). Area under the ROC curve analysis showed high value of raised CK-MB for predicting in-hospital death among COVID-19 patients. Raised CK-MB level on admission can predict in-hospital death in patients with severe COVID-19.

Acta Med Iran 2023;61(1):21-25.

Keywords: Coronavirus disease 2019 (COVID-19); Cardiology; Mortality; Biomarker

Introduction

Pneumonia with an unknown cause was initially diagnosed in December 2019 in Wuhan, China and subsequent studies identified the new coronavirus as its related etiology (1-3). This new virus called the coronavirus type 2 which causes severe acute respiratory syndrome or SARS-CoV-2 and thus, the resulting disease was named COVID-19 by the World Health Organization (4). The virus is the seventh member of the Corona family of RNA viruses with envelope, along with other family viruses such as SARS and MERS. The first cluster of patients affected by the virus was identified among aquatic sellers in the city of Wuhan, and eventually the transfer from person to person was confirmed at the same time (5-7). With the global spread of the virus, its count was reported as a pandemic in China and then in all countries (8). Therefore, many articles on clinical and epidemiological evidence were immediately published (9-11). Severe respiratory distress syndrome and progressive pneumonia are prominent sequels of SARS-CoV-2 in affected patients, however due to triggering cytokine storm manifested by overproduction of pro-inflammatory cytokines such as interleukin-6, interleukin-1-beta, and tumor necrosis factor-α, the occurrence of other inflammation-related processes such as thromboembolic and atherosclerotic events are highly expected (12,13). In this regard, higher likelihood of cardiovascular disorders is expected in COVID-19 patients. The clinical studies could show also a strong association between cardiovascular events and the outcome of COVID-19 (14). Also, it seems that the COVID-19 patients are significantly prone to cardiac ischemic events due to myocardial injury mediated by both activating inflammation cascade and also direct invasion of virus to cardiac tissue. According to the

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reports, SARS-CoV-2 can promote acute coronary syndrome, cardiac arrhythmias, acute heart failure, and even sudden cardiac death. Pathophysiological assessments could demonstrate a critical role for cardiac angiotensin-converting enzyme 2 (ACE2) receptors as the main target for entering SARS-CoV-2 virus and therefore its-related adverse cardiac events. Given the risk of ischemic heart damage due to virus invasion into myocardial tissue, an increase in ischemic heart markers would also be conceivable. Such changes have been reported in some studies. In this regard, raised troponin level in COVID-19 patients and its probable association with disease prognosis has been revealed (15). In another study, the association between raised CK-MB and increased the likelihood of cardiac death in COVID-19 patients has been suggested (16). It seems that the main mechanisms for increasing this marker include viral myocarditis, microangiopathy, and cytokine-driven myocardial damage. But an important question remains unanswered in that what is the weight and strength of cardiac markers compared to other laboratory markers in predicting disease prognosis? In the present study, the value of cardiac prognostic biomarkers along with other laboratory parameters in predicting in-hospital mortality of patients was evaluated.

Materials and Methods

This prospective study was performed on 240 consecutive patients with the definitive diagnosis of COVID-19 according to initial clinical manifestations, chest CT scanning, and detection of virus RNA using the molecular technique. Only those who suffer from severe COVID-19 that were clinically judged to be necessary for hospitalization (due to disease progression) were included into the study and thus those patients were managed as outpatient were not entered. The patients with previous history of cardiovascular disorders or receiving any cardiac diagnostic or therapeutic interventions, patients with history of chronic inflammatory, rheumatologic, or metabolic disturbances were not included into the study. On admission, along with recording demographic characteristics, intravenous blood samples were extracted from the patients after at least 8 hours of fasting to evaluate other laboratory parameters. The cardiac biomarkers targeted in the present study included troponin I (assessed by the ARCHITECT STAT High Sensitive Troponin-I immunoassay) technique, Creatine kinase-MB (CK-MB) (assessed by the standard photometric immunological UV-test), Creatine phosphokinase (CPK) (measured by the photo-colorimetric method), and lactate dehydrogenase (LDH) (assessed by enzymatic spectrophotometric assay). Besides, the serum levels of other biomarkers including the inflammatory markers, liver enzymes, and complete blood cells counts were also determined. Our main goal was to first determine the value of cardiac biomarkers to predict in-hospital death and then to weight these markers compared to other laboratory parameters.

For statistical analysis, results were presented as mean±standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. For statistical analysis, the t test or Mann-Whitney U test was used to compare quantitative variables with normal and abnormal distribution respectively. The Chi-Square test or Fisher's exact test was also employed to compare categorical variables. The roc curve analysis was employed to determine the value of laboratory indices to predict in-hospital death. The weight of cardiac markers along with other laboratory indices for predicting patients' in-hospital death was assessed using the multivariable logistic regression modeling. P of ≤ 0.05 were considered statistically significant. For the statistical analysis, the statistical software SPSS version 23.0 for windows (IBM, Armonk, New York) was used.

Results

Thirty patients suffering COVID-19 with the mean age of 65.53±14.89 years (120 men and 120 women) were included into our cohort study. The details of laboratory parameters are summarized in Table 1. Regarding cardiac biomarkers, the mean level of CPK was 407.60±536.88, the mean level of LDH was 624.06±279.99 and the mean CK-MB was 45.08±26.61. Also, raised troponin I was found in only 16 patients (6.7%). Following-up the patients led to record 168 non-survived patients with the death rate of 70.0%. Comparing laboratory parameters across the survived and non-survived groups (Table 2) showed significantly higher mean CK-MB level in non-survived group than alive group (70.90±29.79 versus 43.56±22.02, P=0.020). Also, positive troponin I was reported in 38.1% of non-survived group, while in none of the patients in survived group (P=0.031). We found no difference in other laboratory parameter across the two groups. By adjusting sex and age variables and using the logistic regression model, raised CK-MB could effectively predict in-hospital death among COVID-19 patients (OR=1.047,95%CI: 1.001-1.097, P=0.043), however

such role was not found for positive troponin I. Area under the ROC curve analysis showed high value of raised CK-MB for predicting in-hospital death among COVID-19 patients (AUC=0.733, 95%CI:0.533-0.933, *P*=0.046). In this regard, the best cutoff value for CK-MB to predict in-hospital death was 41.0 yielding a sensitivity of 81.0% and a specificity of 66.7% (Figure 1).

Table 1. Laboratory indices in patients with COVID-19

Parameter	Mean (SD)	Minimum	Maximum
White blood cell count	11.06±4.35	2.1	23.8
Hemoglobin (g/dl)	12.89±4.14	2.4	26.3
Lymphocyte count	13.28±9.09	3.0	45.7
Iron	26.80±9.39	17.0	38.0
Albumin	3.20±0.55	1.4	4.0
ESR	44.18±27.35	6.0	102.0
Direct bilirubin	1.26±1.41	0.4	6.6
ALT	60.07±36.79	12	200.0
AST	83.30±63.59	16	288.0
ALKP	257.57±204.00	15.1	890.0
CPK	407.60±536.88	47.0	2776.0
LDH	624.06±279.99	117.6	1349.0
CK-MB	45.08±26.61	13	124

Table 2. Laboratory indices in survived and non-survived patients with COVID-19

Parameter	Non-survived (n=168)	Survived (n=72)	*P*
White blood cell count	11.48±4.55	9.97±3.86	0.416
Hemoglobin (g/dl)	12.84±4.56	13.01±3.02	0.926
Lymphocyte count	13.23±9.89	13.42±7.16	0.962
Iron	30.00±11.35	22.00±4.24	0.428
Albumin	3.12±0.60	3.37±0.43	0.337
ESR	44.00±26.05	44.56±31.58	0.961
Direct bilirubin	1.04±0.72	1.92±2.62	0.236
ALT	57.90±38.55	65.11±33.94	0.631
AST	85.28±72.72	78.66±37.44	0.799
ALKP	268.04±222.84	226.15±142.13	0.647
CRP			0.833
Negative	80 (47.6)	24 (33.3)	
1+	40 (23.8)	16 (22.2)	
2+	32 (19.0)	24 (33.3)	
3+	16 (9.5)	8 (11.1)	
CPK	430.88±627.31	361.02±311.28	0.757
LDH	611.60±266.18	661.42±338.28	0.691
CK-MB	70.90±29.79	43.56±22.02	0.020
Troponin (+)	64 (38.1)	0 (0.0)	0.032

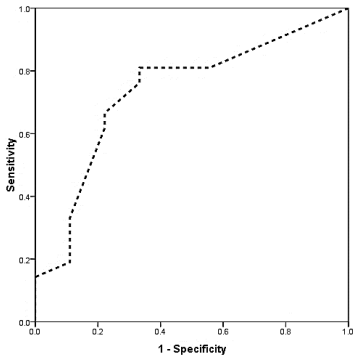

Figure 1. ROC curve analysis for determining the value of CK-MB in predicting in-hospital death

Discussion

Early detection of COVID-19, especially its threatening complications such as cardiovascular defects lead to properly saving the patient's survival. This is especially much more vital for patients with high disease severity who are admitted to a hospital, especially to intensive care units. Unfortunately, there are two major problems in this regard. First, many patients are asymptomatic in the early stages of the disease or present with nonspecific and mild manifestations of the disease. Second, no specific paraclinical tools have been introduced for early detection of the disease that even according to existing guidelines, attention to clinical manifestations is far more important than imaging techniques or molecular techniques. Therefore, researchers have always sought to use available, fast, inexpensive, yet accurate and less invasive methods to diagnose the disease and to predict the consequences of the disease, especially in the first week after the disease. Given the strong evidence of direct invasion of coronavirus to myocardial tissue, as well as increasing the patient's susceptibility to inflammatory and thrombotic phenomena, it has been hypothesized that elevated levels of cardiac enzymes, especially with advanced disease, can predict disease severity subsequent mortality. In this regard, efforts have been made to prove the value of these enzymes in predicting disease outcome. In the present study, in addition to confirming the high value of the CK-MB in predicting early mortality, its high sensitivity in such a role was also confirmed. In this regard, CK-MB levels higher than 41 could effectively predict in-hospital death with high sensitivity and acceptable specificity. However, the role of other cardiac biomarkers such as troponin I, CPK, or LDH could not be demonstrated that might be due to our low sample size employed, no considering high-sensitive troponin I, or limited cardiac damages in our samples. Obviously, in case of extensive myocardial involvement, it is quite conceivable to predict the increase of this enzyme and therefore the worse prognosis of patients. However, in some similar studies, the association of both cardiac markers with poor prognosis has been well established. In a study by Henry *et al*., (17) and similarly, higher concentration in serum CK-MB level along with raised ultra-TnI, and NT-proBNP were associated with the severity and death rate in COVID-19 patients. In a meta-analysis by Danwang *et al*., (18), both CK-MB and Troponin I biomarkers were linked to the severity of COVID-19. Li *et al*., (19,20) could demonstrate that patients with elevated CK-MB levels were at a 3.2 times higher risk of developing severe disease or even requiring ICU admission. In another study by Qin *et al*., (21,22), 4.8 times higher risk for 30-day death was predicted in COVID-19 patients. We finally believed that concurrently considering cardiac biomarkers especially CK-MB and troponin I can be used to predict poor disease prognosis. In this regard, applying and detecting such biomarkers can also help to escalate treatment in a timely fashion in such patients.

In line with previous studies, our study could show high value of raising serum CK-MB to predict in-hospital death in patients suffering severe COVID-19 patients. In this regard, the CK-MB values of higher than 41 with high sensitivity and acceptable specificity could discriminate survived from non-survived groups. Thus, these biomarkers along with other cardiac and non-cardiac markers may allow risk stratification for COID-19 prognosis and also can be used to design new scoring systems for predicting poor prognosis for the disease.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020:382:727-33.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. China. Lancet 2020:395:497-506.
3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020:395:507-13.
4. The International Committee on Taxonomy of Viruses (ICTV) Coronaviridae Study Group. Naming the 2019 Coronavirus. (Accessed at Ahttps://talk.ictvonline.org./)
5. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020:395:514-23.
6. Phan LT, Nguyen TV, Luong QC, Nguyen TV, Nguyen HT, Le HQ. Importation and Human-to-Human Transmission of a Novel Coronavirus in Vietnam. N Engl J Med 2020:382:872-4.
7. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China.

JAMA 2020;323:1061-9.

8. National Health Commission of China. "Report of the latest situation of novel coronavirus pneumonia in China as of February 18, 2020" (Accessed at February 18, 2020, http://www.nhc.gov.cn/xcs/yqtb/202002/8f2cfd17f4c040d89c69a4b29e99748c.shtml.)
9. Yang Y, Lu Q, Liu M, Wang Y, Zhang A, Jalali N. Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China. medRxiv 2020.
10. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med 2020;382:1199-207.
11. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX. Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv 2020.
12. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC stateof-the-art review. J Am Coll Cardiol 2020:75:2950-73.
13. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. J Thromb Haemost 2020:18:1559-61
14. Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D. Elevated Troponin in Patients With Coronavirus Disease 2019: Possible Mechanisms. J Card Fail 2020:26:470-5.
15. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA Cardiol 2020;5:831-40.
16. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JA, Masoumi A, et al. COVID-19 and cardiovascular disease. Circulation 2020:141:1648-55.
17. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. J Am Coll Cardiol 2020:5:2352-71.
18. Danwang C, Endomba FT, Nkeck JR, Wouna DLA, Robert A, Noubiap JJ. A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). Biomark Res 2020;8:37.
19. Li X, Pan X, Li Y, An N, Xing Y, Yang F, et al. Cardiac injury associated with severe disease or ICU admission and death in hospitalized patients with COVID-19: a meta-analysis and systematic review. Crit Care 2020:28;24:468.
20. Shi L, Wang Y, Wang Y, Duan G, Yang H. Meta-Analysis of Relation of Creatine kinase-MB to Risk of Mortality in Coronavirus Disease 2019 Patients. Am J Cardiol 2020:130:163-5.
21. Shi S, Qin M, Cai Y, Liu T, Shen B, Yang F, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. Eur Heart J 2020;41:2070-79.
22. Han H, Xie L, Liu R, Yang J, Liu F, Wu K, et al. Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. J Med Virol 2020:92:819-823.