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A Potent Predictor of Poor COVID-19 Outcomes: Troponin/ Creatine Kinase-MB Ratio

Kötü COVID-19 Sonuçlarının Güçlü Bir Öngörücüsü: Troponin/Kreatin Kinaz-MB Oranı

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ÖZ

Amaç: Bu çalışmada daha önce yapılan çalışmalarda çalışılmayan troponin/CK-MB oranının öngörüsünü değerlendirerek belirleyici çıkarımlar elde etmeyi amaçladık.
Araçlar ve Yöntem: Nisan 2020 ile Eylül 2022 tarihleri arasında yoğun bakım ünitesine (YBÜ) kabul edilen tüm COVID-19 hastalarını taradık. Tüm tıbbi kayıtlar, laboratuvar sonuçları ve hastane içi ölüm kaydedildi.
Bulgular: Bu çalışmaya 182 hastayı dahil ettik. Amaçlanan modelin genel doğru sınıflandırma oranı %83.0'dır. Nagelkerke R2 değeri incelendiğinde mortalitedeki varyansın %55.8'ini açıklamaktadır. En belirleyici değişken troponin/CK-MB oranıydı. Troponin/CK-MB oranındaki 1 birimlik artış ölüm riskini 108.90 kat artırdı. Troponin/CK-MB oranı için en belirleyici laboratuvar parametresi olan kesme değeri 0.00745 olarak belirlendi.
Sonuç: Troponin/CK-MB oranının hastane içi COVID-19 mortalitesini öngörmede potansiyel bir etkisi vardır. Yoğun bakımda COVİD-19 yönetiminde kötü sonuçları tahmin etmek için Troponin/CK-MB oranı kullanılmalıdır. Dolayısıyla hekimlerin COVID-19'un optimal takibini yönetmelerine yardımcı olabilir.

Anahtar Kelimeler: doğuştan gelen inflamatuar yanıt; kardiyovasküler anormallikler; ölüm oranı; SARS-CoV-2

ABSTRACT

Purpose: In this study, we aimed to derive significant implications by evaluating the predictive value of the troponin/CK-MB ratio, which has not been studied in previous research.
Materials and Methods: We screened all COVID-19 patients admitted to the intensive care unit(ICU) between April 2020 and September 2022. All medical records, laboratory results, and in-hospital mortality were recorded.
Results: We included 182 patients in this study. The overall correct classification rate of the proposed model was 83.0%. The Nagelkerke R^2 value explained 55.8% of the variance in mortality. The most predictive variable was the troponin/CK-MB ratio. An increase of 1 unit in the troponin/CK-MB ratio elevated the mortality risk by 108.90 times. A cut-off value for the troponin/CK-MB ratio, identified as the most predictive laboratory parameter, was determined to be 0.00745.
Conclusion: The Troponin/CK-MB ratio has the potential to predict in-hospital mortality in COVID-19 patients. In the management of COVID-19 in the ICU, this ratio should be used to predict poor outcomes, assisting physicians in determining the optimal follow-up care for these patients

Keywords: cardiovascular abnormalities; innate inflammatory response; mortality rate; SARS-CoV-2

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INTRODUCTION

A betacoronavirus causes the coronavirus illness 2019 (COVID-19). The World Health Organization (WHO) reported that the COVID-19 death rate was 3.4% worldwide.[1,2]

The rapidly progressing pathway leading to mortality is triggered by coagulation and inflammation.[3,4] This dysfunction and the dysregulation of the immunologic and thrombotic processes present as a respiratory failure, a multiorgan failure, and cardiac diseases.[5-8] Cardiac diseases cause mortality mostly with myocardial injury, myocardial infarctions, myocarditis, and pericarditis.[6]

It has been reported that the initial stage in the early mechanism of the COVID-19 infection is the angiotensin-converting enzyme 2 (ACE2) receptor on the cell membrane.[7,8] On the cell surface of the pericytes in human hearts, ACE2 is highly expressed.[8] This elevated expression is linked in the literature to the cardiac problems of COVID-19.[6,8] Numerous studies have demonstrated that cardiac biomarkers like troponin and creatine kinase-MB (CK-MB) can predict the unfavorable outcomes of COVID-19.[9,10]

Troponin, a calcium-regulatory protein, controls the calcium-dependent contraction of skeletal and cardiac muscles. Since 1995, cardiac troponins have been quantified for use in clinical settings. With the introduction of high-sensitivity cardiac troponin assays, there has been a notable increase in cardiac selectivity and, particularly, improved sensitivity, which have been clearly demonstrated in the clinical follow-up of cardiovascular conditions.[11]

The catalysis of the reversible phosphorylation of creatine by adenosine triphosphate (ATP) occurs by creatine kinase (CK), a dimeric enzyme. The myocardium contains 15% CK-MB and 85% CK-MM while skeletal muscles 1% to 3% CK-MB. So the specific use of CK-MB is executed in clinical practice. These cardiac biomarkers are elevated with indirect myocardial injury with non-ischemic or ischemic processes.[8] Ischemic heart disease is indicated by ischemic myocardial processes and 1st death cause in the world according to the WHO.[12]

Some studies have evaluated the high mortality associated with ischemic cardiac diseases and chronic ischemic processes as an important factor, raising doubts about the reliability of elevated cardiac biomarker levels in predicting outcomes in COVID-19. The findings in previous studies showed the predictivity of cardiac biomarkers.[13] Increased troponin and CK-MB levels are used to diagnose non-ischemic myocardial processes and myocardial injury.[13] According to reports in the setting of COVID-19, systemic inflammation, thromboembolic illnesses, myocarditis, and adrenergic hyperstimulation during cytokine storm syndrome are the main causes of the non-ischemic cardiac processes.[8] In this study, we aimed to obtain determinative implications by researching the predictivity of the troponin/CK-MB ratio in COVID-19 that was not evaluated in previous studies and includes the cardiac biomarkers found as predictors.

MATERIALS and METHODS

Patients

This study was approved by Kırşehir Ahi Evran University Clinical Research Ethics Committee (Date: 09.08.2022, Number: 2022-15/138). We screened all the patients hospitalized with COVID-19 infection in the intensive care unit (ICU) between April 2020 and September 2022.

The inclusion criteria for this study were being over 18 years of age and being hospitalized in the ICU with a COVID-19 infection. The exclusion criteria were being under 18 years of age, acute coronary syndrome during the ICU hospitalization, having pregnancy, and life-threatening conditions such as severe heart failure, renal failure, and malignancy that can increase the mortality risk. The primary endpoint of this study was the rate of in-hospital mortality and patients were divided into survivors and non-survivors. The existence or non-existence of acute coronary syndrome was clarified by consulting cardiologists in suspicious cases. The demographic data of the patients, comor-

bidities, Acute Physiology, and Chronic Health Evaluation (APACHE) II, the sequential organ failure assessment (SOFA) score, Glasgow Coma Scale (GCS) scores, and in-hospital mortality were recorded. Medical information and laboratory test results were recorded from the hospital system. The diagnosis of COVID-19 infection was confirmed by a positive polymerase chain reaction (PCR) test. This study was performed according to the rules in the Helsinki Declaration.

Statistical Analysis

Statistical analyses of this study were carried out using Statistical Package for Social Sciences version 25.0 software for Windows (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp., USA). Since the assumptions of normality and homogeneity were not met, the parameters were compared using the Mann-Whitney U test, a nonparametric analysis method. Risk factors for mortality were analyzed using the 2x2 crosstab-based chi-square method. The logistic regression analysis was performed to study the predictivity of neutrophil to lymphocyte ratio (NLR), troponin to CK-MB ratio, serum albumin levels, SOFA scores, and invasive mechanical ventilation.

RESULTS

We included 182 patients in this study. The study sample included 59.9% male (n: 109) and 40.1% female (n:73) patients. The comparison of the clinical and demographic parameters of the two groups is shown in Table 1. There was a significant difference between age, APACHE II, and SOFA scores ($p<0.05$). On the other hand, there was no discernible difference between the two groups' GCS and BMI. The need for invasive mechanical ventilation occurred significantly higher in the exitus group($p<0.05$).

Table 1. The comparison of the clinical and demographic parameters of the two groups.

Parameter	Exitus	N	Mean	Std. Deviation	P
Age	No	83	58.33	15.18	.000*
	Yes	99	70.89	13.55	
BMI	No	83	28.44	4.14	.361*
	Yes	99	27.81	4.98	
APACHEII	No	83	15.80	4.49	.000*
	Yes	99	20.20	5.50	
SOFA	No	83	3.63	1.22	.000*
	Yes	99	4.91	1.99	
GCS	No	83	14.48	1.63	.087
	Yes	99	13.98	2.20	
Duration of hospitalization before admission to the ICU	No	83	2.35	3.65	.222
	Yes	99	3.12	4.66	

*p<0.05, BMI: Body mass index, GCS: Glasgow Coma Scale

The comparison of the laboratory results is shown in Table 2. The neutrophil count, procalcitonin, C-reactive protein (CRP), D-dimer, ferritin, uric acid, lactate dehydrogenase (LDH), troponin, CK-MB, creatine kinase (CK), lactate levels were significantly higher in exitus group($p<0.05$). Serum albumin and hemoglobin levels were lower($p<0.05$) (Table 2). Other laboratory measurements did not differ significantly ($p>0.05$) between the two groups.

The logistic regression analysis of the independent parameters is shown in Table 3. The most predictive variable was the troponin/CK-MB ratio. An increase of 1 unit in the troponin/CK-MB ratio increased mortality risk 108.90 times. Contrary to other dependent parameters, the decreased serum albumin levels were a risk factor for mortality (Table 3). A cut-off value for the troponin/CK-MB ratio, the most predictive laboratory parameter was determined as 0.00745(Figure 1)

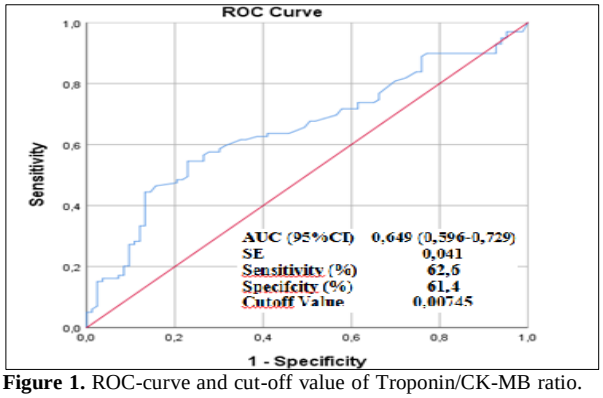

Figure 1. ROC-curve and cut-off value of Troponin/CK-MB ratio.

Table 2. The comparison of the laboratory results.

Parameter	Exitus	N	Mean	Std. Deviation	p
White blood cell count	No	83	10038.31	6075.65	0.229
	Yes	99	11089.9	5668	
Lymphocyte count	No	83	1440.95	3975.41	0.121
	Yes	99	805.66	727.13	
Neutrophil count	No	83	7961.33	3848.62	.012*
	Yes	99	9791.72	5499.05	
Hemoglobin	No	83	12.95	1.86	.043*
	Yes	99	12.35	2.09	
Platelet count	No	83	241240.96	104886.65	0.555
	Yes	99	232292.93	98748.21	
Procalcitonin	No	82	0.33	0.57	.009*
	Yes	99	1.37	3.51	
C-reactive protein	No	83	117.19	84.1	.032*
	Yes	99	144.2	83.46	
Serum albumin	No	83	3.23	0.44	.000*
	Yes	99	2.92	0.43	
D-dimer	No	83	1.57	2.11	.002*
	Yes	99	3.2	4.32	
Fibrinogen	No	83	552.67	148.03	1
	Yes	99	552.69	172.75	
Ferritin	No	83	474.42	367.81	.034*
	Yes	99	660.89	719.76	
Uric acid	No	83	5.31	1.99	.000*
	Yes	99	6.74	2.86	
LDH	No	83	414.84	164.75	.016*
	Yes	99	537.89	436.1	
Troponin	No	83	27.95	58.16	.007*
	Yes	99	174.73	487.64	
CK-MB	No	83	2.42	1.93	.001*
	Yes	99	6.56	13.79	
AST	No	83	44.23	45.46	0.614
	Yes	99	82.94	296.66	
ALT	No	83	40.07	59.17	0.222
	Yes	99	48.14	134.83	
CK	No	83	124.96	207.21	.000*
	Yes	99	362.45	1755.3	
Lactate	No	83	1.51	0.57	.001*
	Yes	99	2.24	1.71	
Creatine	No	83	0.85	0.37	0.925
	Yes	99	1.32	1.18	

*p<0.05, LDH: Lactate dehydrogenase, CK-MB: Creatin kinase-MB, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CK: Creatine kinase

Table 3. The logistic regression analysis of the independent parameters.

Redictor	Estimate (B)	S.E.	Z	Sig.	Odds Ratio
Intercept	3.4001	1.7268	1.97	0.049	29.966
NLR	0.0421	0.0168	2.51	0.012*	1.043
Troponin/CK-MB	22.6132	10.7983	2.09	0.036*	108.904
Serum albumin	-2.1351	0.5665	-3.77	< .001*	0.118
IMV	3.0954	0.5698	5.43	< .001*	22.096
SOFA	0.3690	0.1682	2.19	0.028*	1.446

Note: Estimates represent the log odds of "Exitus=yes" vs. " Exitus= no"
NLR: Neutrophil to lymphocyte ratio
IMV: Invasive mechanical ventilation

Table 4. The overall correct classification rate of the intended model.

Observed		Predicted Mortality		Percentage Correct
		No	Yes	
Mortality	No	69	14	83.1
	Yes	17	82	82.8
Overall Percentage				83.0

Nagelkerke R Square (R^2)=0.558

The overall correct classification rate of the intended model is 83.0%(Table 4). When the Nagelkerke R2 value is examined, it explains 55.8% of the variance in mortality(Table 4).

DISCUSSION

We showed that the Troponin/CK-MB ratio was a predictor for poor prognosis of COVID-19 in the ICU.

The troponin/CK-MB ratio has not been investigated as a prognostic biomarker in COVID-19 in previous studies. As a result, this study could contribute to guidelines aimed at improving the optimal follow-up and management of COVID-19 infection. Due to the lack of prior research, we can discuss the components of this biomarker and the underlying mechanisms behind its predictive value.

In the mini-review of Gaze, the key role of non-ischemic cardiac complications was emphasized in follow-up and treatment of COVID-19.[14] The pathophysiological processes were associated with a cardio-inflammatory immune system response, which was primarily accompanied by elevated CRP and other acute-phase reactants. Accordingly, the elevated troponin levels were linked to severe COVID-19 infection.

The initial mechanism of COVID-19 infection has a critical role in evaluating the inflammatory response at cellular level. Viral binding to cells occurs through ACE2 receptors and after binding inflammation and edema are mediated by chemokines leading to respiratory failure.[7] Elevated cardiac troponin was associated with poor prognosis and infection severity. The importance of the measurement of cardiac biomarkers is implicated in cardioprotective intervention.

Myocardial damage, which is defined as increased troponin levels over the 99th percentile, ranged from 7.2% to 36% in COVID-19, according to the editorial commentary by Maloberti et al.[15]

There were three queries. The first query concerned the predictive role of myocardial damage for both short- and long-term COVID-19 outcomes. The correlation between higher cardiac biomarkers and poor prognosis in some studies, particularly when associated with male sex, advanced age, and cardiovascular comorbidities, made it simple to respond to this issue.[7,13] Potential causes of cardiac injury included direct viral damage to cardiomyocytes, a dysregulated inflammatory response driven by a cytokine storm, endothelial dysfunction, microvascular damage, a hypercoagulable state, hypoxia, and elevated oxidative stress.

The second question addressed the etiology of myocardial injury: Was it caused by direct viral damage to myocytes, or was it a result of severe impairment during viral sepsis?

Myocarditis occurs as a main ischemic myocardial disease due to COVID-19 infection. Even though COVID-19 was supposed to affect the cardiovascular system at the beginning of the pandemic, only 14% of cases in research on tissue biopsies from individuals who died with COVID-19. The minority of myocarditis cases and the majority of inflammatory infiltration of myocytes without direct damage suggest that myocardial injury occurs primarily through indirect damage to myocytes, mediated by a dysregulated inflammatory response.

The long-term effects of COVID-19 infection on the cardiovascular system was the third query. Only a small number of papers have documented findings of long-term vascular (endothelial dysfunction and arterial rigidity) and cardiac (diastolic dysfunction as seen on echocardiography and chronic inflammation on magnetic resonance).[16,17]

The Tersalvi et al. review also highlighted the first COVID-19 infection mechanism with the significant presence of ACE2 receptors in adult human heart pericytes.[18] It was explained how ACE2 functions in the renin-angiotensin-aldosterone system as a vasoconstrictor, proinflammatory, prooxidant, pro-proliferative, and profibrotic factor. Myocardial injury were linked to microvascular injury, vessel hyperpermeability, and vasospasm.[18] Myocardial injury was reported to predict mortality of COVID-19 in pregnant women, similar to SOFA score, need for invasive mechani-

cal ventilation.[19] Furthermore this hyperinflammation, epithelial damage, and hypercoagulation at the microvascular level cause disruption of oxygen homeostasis and mortality. The proinflammatory and thrombotic processes cause also premature birth, fetal distress, and low birth weight.[19] There are limited studies on the treatment of this fatal condition. Iloprost is a long-acting prostaglandin I2 (PGI2) analog and it was evaluated as a treatment option for COVID-19 infection. Anyway, iloprost was reported to improve the oxygenation. On the other hand, it did not affect the mortality in the study of Sarı Küçük et al.[20] This fatal condition still occurs in patients with respiratory failure hospitalized in the ICU. Even in the second year of the Pandemic, clinicians face many difficulties in managing the treatment and follow-up of COVID-19. Respiratory support with non-invasive and invasive mechanical ventilation is required in the ICU due to hypoxia.[21] This point leads to the implication that the treatment and follow-up of COVID-19 is still an important process to highlight.

According to reports, cytokine storm impairs pulmonary gas exchange and causes significant lung inflammation.[22] As a result, prioritized and more aggressive treatments were recommended for individuals with underlying cardiovascular diseases to reduce mortality.

Several studies are researching the association between COVID-19 mortality and troponin and CK-MB both. Guadiana-Romualdo et al conducted a multicenter, retrospective observational study enrolling 179 hospitalized COVID-19 patients.[23] Cardiac troponin was measured on admission and the primary outcome was 30-day mortality. Regardless of the cardiac troponin assay and cut-offs used to detect myocardial damage, elevated troponin was a reliable predictor of 30-day death.

Papageorgiou et al. conducted an observational multi-ethnic multi-center study with 434 COVID-19 patients across six hospitals.[24] The primary outcome was all-cause mortality. The rate of myocardial injury was 66.4% (n:288). Patients with elevated troponin levels were significantly older and had a higher prevalence of comorbidities such as hypertension, hyperlipidemia, asthma, and COPD, all of which were associated with a poorer COVID-19 prognosis. Troponin-positive patients were remarkable with the longer duration of hospitalization. Evaluating disease presentation, the symptoms seemed more aggravated in troponin-positive patients.

In a retrospective multi-center study of Majure et al, 6247 COVID-19 patients were included.[25] An elevated risk of mortality was independently associated with older age, male sex, a history of diabetes mellitus, serum creatinine, and a marked elevation in inflammatory markers. The mortality risk was significantly increased by elevated troponin. Cardiovascular disease, increased acute phase, and inflammatory markers did not affect mortality risk.

In a systematic review and meta-analysis conducted by Wibowo et al, increased mortality was linked to higher troponin levels [odds ratio (OR) 4.75, 95% confidence interval (CI) 4.07-5.53].[26]

The correlation did not differ after adjusting for age, male sex, or comorbidities, according to meta-regression. Positive likelihood ratios were 2.7 (2.2-3.3), negative likelihood ratios were 0.56 (0.49-0.65), diagnosis odds ratios were 5 (4-5), and the area under the curve was 0.73 (0.69-0.77) for the connection between increased troponin and mortality. individuals with raised troponin had a 45% chance of dying, compared to 14% of patients with non-elevated troponin.

Higher levels of CK-MB, other proinflammatory cytokines, and biomarkers were reported as a predictor of poor COVID-19 prognosis in the review of Battaglini et al.[13]

A meta-analysis of 70 trials and 15,354 patients was conducted by Hu et al.[10] Although this meta-analysis focused on acute cardiac injury and cardiovascular diseases, it has significant implications, particularly in highlighting the predictive value of laboratory markers, especially cardiac markers.

Based on corrected data, Hu et al. conducted a meta-analysis and found that high CK-MB was a standalone risk

factor for COVID-19 mortality.[27] Nevertheless, they emphasized the heterogeneity of the previous studies.

Shi et al conducted a quantitative meta-analysis to obtain a determinative conclusion about the association between elevated CK-MB and increased COVID-19 mortality due to inconsistent results of previous studies.[9]

We aimed to show the association between inflammation and non-ischemic myocardial injury by excluding the patients with ischemic myocardial processes to obtain more determinative results. As a result of excluding patients with ischemic myocardial processes, we could draw clearer conclusions.

This study was performed to clarify the risk factors of in-hospital mortality in the ICU. We excluded the ischemic myocardial injury to obtain definitive results. The low number of previous studies about the predictive role of the troponin/CK-MB ratio is the most important point. We conducted a study to contribute to the current literature to optimize COVID-19 management. More studies in the future would improve and clarify our implications.

Recently, this study with an optimal design has a potential to contribute to the current literature considering the low number of previous studies. The troponin/CK-MB ratio has a potential role in the anticipation of in-hospital mortality in COVID-19. The Troponin/CK-MB ratio can be useful in predicting poor prognosis. It may help clinicians to manage the optimal follow-up of COVID-19.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

This study was approved by Kırşehir Ahi Evran University Clinical Research Ethics Committee (Date: 09.08.2022, Number: 2022-15/138).

Authors' Contributions

Concept/Design: AZ, CA. Data Collection and/or Processing: AZ, NZ. Data analysis and interpretation: AZ, CA. Literature Search: NZ, CA. Drafting manuscript: NZ, CA. Critical revision of manuscript: AZ.

REFERENCES

1. Ho JPTF, Donders HCM, Zhou N, Schipper K, Su N, de Lange J. Association between the degree of obstructive sleep apnea and the severity of COVID-19: an explorative retrospective cross-sectional study. PLoS One. 2021;16(9):e0257483.
2. WHO Director-General's opening remarks at the media briefing on COVID-19 – 3 March 2020. Geneva: World Health Organization; 2020. Available at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarksat-the-media-briefing-on-covid-19---3-march-2020 Accessed September 10, 2023.
3. Ciceri F, Beretta L, Scandroglio AM, et al. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. Crit Care Resusc. 2020;22(2):95-97.
4. Henry BM, Vikse J, Benoit S, Favaloro EJ, Lippi G. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: A novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. Clin Chim Acta. 2020;507:167-173.
5. Menga LS, Berardi C, Ruggiero E, Grieco DL, Antonelli M. Noninvasive respiratory support for acute respiratory failure due to COVID-19. Curr Opin Crit Care. 2022;28(1):25-50.
6. Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A. Myocardial injury and COVID-19: Possible mechanisms. Life Sci. 2020;253: 117723.
7. Devaux CA, Rolain JM, Raoult D. ACE2 receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. J Microbiol Immunol Infect. 2020;53(3):425-435.
8. Imazio M, Klingel K, Kindermann I, et al. COVID-19 pandemic and troponin: indirect myocardial injury, myocardial inflammation or myocarditis? Heart. 2020;106 (15):1127-1131.
9. 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;130:163-165.
10. Zhu Z, Wang M, Lin W, et al. Cardiac biomarkers, cardiac injury, and comorbidities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. Immun Inflamm Dis. 2021;9(4):1071-1100.
11. Stark M, Kerndt CC, Sharma S. Troponin. [Updated 2023 Apr 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available at: https://www.ncbi.nlm.nih.gov/books/NBK507805/ Accessed September 10, 2023.
12. WHO Global Health Estimates. Available at: https://www.who. int/news-room/fact-sheets/detail/the-top-10-causes-of-death Accessed September 10, 2023.

13. Battaglini D, Lopes-Pacheco M, Castro-Faria-Neto HC, Pelosi P, Rocco PRM. Laboratory Biomarkers for Diagnosis and Prognosis in COVID-19. Front Immunol. 2022;13:857573.
14. Gaze DC. Clinical utility of cardiac troponin measurement in COVID-19 infection. Ann Clin Biochem. 2020;57(3):202-205.
15. Maloberti A, Biolcati M, Giannattasio C. Troponin elevation in COVID-19 patients: An important stratification biomarker with still some open questions. Int J Cardiol. 2021;341:107-109.
16. Schnaubelt S, Oppenauer J, Tihanyi D, et al. Arterial stiffness in acute COVID-19 and potential associations with clinical outcome. J Intern Med. 2021;290(2):437-443.
17. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020;5(11):1265-1273.
18. 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(6):470-475.
19. Baykara N; PREGCOVID-ICU study group. Clinical Characteristics, Outcomes, and Risk Factors for Mortality in Pregnant/Puerperal Women with COVID-19 Admitted to ICU in Turkey: A Multicenter, Retrospective Study from a Middle-Income Country. J Intensive Care Med. 2024;39(6):577-594.
20. Sarı Küçük R, Uluç K, Merve Çolakoğlu Ş, Kılınç Berktaş C, Mutlu S, Turgut N. The effect of using iloprost on prognosis in COVID-19 patients with ARDS: a retrospective clinical study. Eur Rev Med Pharmacol Sci. 2023;27(9):4269-4279.
21. Güngör S, Ediboğlu Ö, Yazıcıoğlu Moçin Ö, et al. Evaluation of Patients with COVID-19 Followed Up in Intensive Care Units in the Second Year of the Pandemic: A Multicenter Point Prevalence Study. Thorac Res Pract. 2023;25(1):11-16.
22. Xiong TY, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. Eur Heart J. 2020;41(19):1798-1800.
23. García de Guadiana-Romualdo L, Morell-García D, Rodríguez-Fraga O, et al. Cardiac troponin and COVID-19 severity: Results from BIOCOVID study. Eur J Clin Invest. 2021;51(6):e13532.
24. Papageorgiou N, Sohrabi C, Prieto Merino D, et al. High sensitivity troponin and COVID-19 outcomes. Acta Cardiol. 2022;77(1):81-88.
25. Majure DT, Gruberg L, Saba SG, Kvasnovsky C, Hirsch JS, Jauhar R. Northwell Health COVID-19 Research Consortium. Usefulness of Elevated Troponin to Predict Death in Patients With COVID-19 and Myocardial Injury. Am J Cardiol. 2021;138:100-106.
26. Wibowo A, Pranata R, Akbar MR, Purnomowati A, Martha JW. Prognostic performance of troponin in COVID-19: A diagnostic meta-analysis and meta-regression. Int J Infect Dis. 2021;105:312-318.
27. Hu Q, Cheng C, Li Y, Duan G, Chen S. Elevated Creatine Kinase-MB Is an Independent Risk Factor for Mortality of COVID-19: Based on Adjusted Data. Arch Iran Med. 2022;25(2):124-125.