THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Evaluation of Ischemic Modified Albumin Levels in Coronavirus Disease 2019-Positive and -Negative Patients with Acute Cardiac Injury

ORIGINAL INVESTIGATION

ABSTRACT

Background: The severe acute respiratory syndrome coronavirus 2 is the source of the global pandemic known as coronavirus disease 2019, and the disease prognosis is also linked to the prevalence of cardiac problems. In our study, we aimed to contribute to the early diagnosis and treatment of cardiac complications by evaluating ischemic modified albumin levels in adults with coronavirus disease 2019 disease.

Methods: Our study was conducted with a total of 176 cases: group 1 (n = 70) with cardiac injury and coronavirus disease 2019 (+), group 2 (n = 57) with cardiac injury and coronavirus disease (−), and group 3 (n = 49) with healthy volunteers. The Mann–Whitney *U* test, the average, SD, minimum and maximum values, intergroup comparison of the results, and statistical significance were evaluated with the Pearson correlation coefficient.

Results: As a result of the bilateral comparisons, ischemic modified albumin measurements of the coronavirus disease 2019 (+) and coronavirus disease 2019 (−) groups were higher than the control group ($P = .006$ and $P = .006$, respectively). There was no statistically significant difference between ischemic modified albumin measurements of coronavirus disease 2019 (+) and coronavirus disease 2019 (−) groups.

Conclusion: Ischemic modified albumin measurement accelerates the diagnosis and treatment process in the evaluation of cardiac injuries in coronavirus disease 2019 patients.

Keywords: Ischemic modified albumin, COVID-19, acute cardiac injury, cardiac biomarkers

INTRODUCTION

Various complications occur in the majority of patients with severe coronavirus disease 2019 (COVID-19). Among these complications, the most common are arrhythmias (16.7%), acute cardiac damage (7.2%), and shock (8.7%).[1,2] Acute cardiac injury is defined as a high-sensitivity troponin-I value higher than the upper limit of the reference range (>28 pg/mL) within approximately 34 hours following the injury and occurs in approximately 20% of cases. Acute myocardial injury is thought to be due to infection-related myocarditis and/or ischemia, which is of important prognostic importance in COVID-19.[2,3] Ischemic modified albumin (IMA), a modified form of albumin under oxidative stress, is an important marker that can be used in the diagnosis of acute myocardial ischemia.

The N-terminal region of human serum albumin undergoes structural alterations as a result of endothelial and extracellular hypoxia, acidosis, and free radical damage during ischemia. As a result, albumin's capacity to bind transition metal ions like cobalt, nickel, and copper is decreased. Because of this mechanism, changes in the level of IMA in clinical pictures of ischemia have been a frequently researched subject in recent years.[4]

METHODS

Our study was planned between September and December 2020 with 176 patients who were admitted to the emergency department of our center with a complaint of chest pain in the last 6 hours and whose corona tests were polymerase chain

Seyhan Ördekçi[1]
Şebnem Tekin Neijmann[2]
Arda Güler[3]

[1]*Department of Clinical Microbiology, İstanbul University of Health Sciences, Mehmet Akif Ersoy Thoracic Cardiovascular Surgery Training and Research Hospital, İstanbul, Türkiye*
[2]*Department of Rare Diseases, İstanbul University, Institute of Health Sciences, İstanbul, Türkiye*
[3]*Department of Cardiology, İstanbul University of Health Sciences, Mehmet Akif Ersoy Thoracic Cardiovascular Surgery Training and Research Hospital, İstanbul, Türkiye*

Corresponding author: Arda Güler
✉ drardaguler@gmail.com

Received: May 8, 2023
Accepted: August 7, 2023
Available Online Date: September 20, 2023

Cite this article as: Ördekçi S, Tekin Neijmann Ş, Güler A. Evaluation of ischemic modified albumin levels in coronavirus disease 2019-positive and negative patients with acute cardiac injury. *Anatol J Cardiol.* 2023;27(12):706-711.

DOI:10.14744/AnatolJCardiol.2023.3431

reaction positive and 60 healthy volunteers without a history of chronic disease and no history of corona infection in the last 6 months. The subjects included in the study were as follows: group 1 (n=70) with cardiac injury and COVID-19 (+), group 2 (n=57) with cardiac injury and COVID-19 (-), and group 3 (n=49) with healthy volunteers (control group). The control was selected from volunteers of similar age who did not have a history of chronic illness. The groups (1 and 2) had no history of chronic diseases such as autoimmune disease, cancer, or infection in the last 6 months. We took blood samples from patients, shortly after they were admitted to the hospital with acute coronary syndrome (ACS) signs and symptoms (within 10-15 minutes), because the release of markers is dependent on the time necrosis begins. The routine cardiac markers troponin-T (cTnT) and CK-MB were evaluated using an electrochemiluminescence immune assay based on the sandwich principle of electrochemiluminescence technology (Roche, Mannheim, Germany, Cobas e411). For cTnT and CK-MB, the reference intervals were 0-14 ng/L and 0-6.22 ng/mL, respectively. For IMA measurement, enzyme-linked immunosorbent assay (ELISA) was used according to the manufacturer's instructions; the assay is based on the method of quantitative sandwich enzyme immunoassay. Intra-assay and inter-assay coefficients of variation were 8% and 10%, respectively (Bioassay Technology Laboratory, Zhejiang, China, Catalog No: E1172Hu). For ELISA analysis, an ELx50 Microplate Strip Washer and an ELx800 Absorbance Microplate Reader (BioTek® Instruments, Inc., Winooski, Vt, USA) were used. We did not measure any hemolytic or lipemic samples for the assays. An electrogram is recorded to allow differentiation of patients without or with ST-segment changes.

Statistical Anaylsis

While evaluating the findings obtained in the study, IBM performed statistical analyses. Statistical Package for the Social Sciences (SPSS) Statistics 23 (IBM, Chicago, Illinois, USA) was used. Descriptive statistical methods (mean, SD, median, frequency, ratio, minimum, maximum, and quartiles) were used to evaluate the study data.

Compliance of quantitative data with a normal distribution was analyzed by Kolmogorov–Smirnov, Shapiro–Wilk, skewness, and kurtosis tests, and graphical evaluations were used. The one-way analysis of variance was used for the comparisons of 3 or more groups with a normal distribution, and one-way ANOVA test was used for pairwise comparisons. The Bonferroni test and Kruskal–Wallis test were used for comparisons of 3 or more groups that did not show a normal distribution, and the Bonferroni–Dunn test was used for pairwise comparisons. The Pearson chi-square test was used to compare qualitative data. The McNemar test and Cohen's kappa test were used to harmonize qualitative data. The receiver operating characteristic (ROC) curve analysis was used to determine cutoffs for diagnostic screening tests [sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)] and for parameters. The generalized linear model (GLM) analysis was used to analyze the relationship between groups and variables after adjusting for the effect of age. Significance was evaluated at least at $P < .05$ level.

HIGHLIGHTS

- The prompt increase in levels of a biomarker like ischemic modified albumin (IMA) can expedite the assessment, diagnosis, and treatment of cardiac injury in coronavirus disease 2019 (COVID-19) patients.
- The IMA values can provide useful information regarding the COVID-19 prognostic process.
- The threshold value of ≥55 for measuring IMA was established based on the COVID (+) and control groups.

RESULTS

The study was conducted between November 2020 and February 2021 with 127 patients who were admitted to the emergency department of our center with a complaint of chest pain in the last 6 hours and 49 healthy volunteers, of whom 40.3% (n=71) were female and 59.7% (n=105) were male. The ages of the patients ranged from 28 to 87 years, and the mean age was 56.09 ± 13.86 years. While 39.8% (n=70) of the cases included in the study were COVID-19 (+), 32.4% (n=57) were COVID-19 (–), and 27.8% (n=49) were in the control group. A statistically significant difference was observed in the mean ages of the subjects across the groups ($P=.015$). Post hoc pairwise comparisons revealed that the COVID (+) group had a lower mean age than the COVID (–) group ($P=.025$). However, no significant difference in age was found between the other groups. Additionally, a statistically significant difference was found in the age groups of the subjects based on the groups ($P=.040$). The COVID (+) group had a higher proportion of subjects under the age of 40 compared to the COVID (–) group ($P=.002$). On the other hand, the COVID (–) group had a higher proportion of subjects aged 70 or older compared to the control group ($P=.021$). No significant differences in age distributions were found between the other groups. Furthermore, the gender distribution of the patients across the groups did not show a statistically significant difference (Table 1).

Due to the significant effect of the age variable, separate weighted analyses were performed for CK-MB, troponin, and IMA variables using GLMs (Table 2). According to the groups, statistically significant differences were detected in CK-MB measurements among the cases ($P < .001$). Post hoc pairwise comparisons revealed that CK-MB measurements of the COVID (–) group were significantly higher than those of the COVID (+) and control groups ($P < .001$). However, there was no statistically significant difference in CK-MB measurements between the COVID (+) group and the control group. Similarly, statistically significant differences were observed in cTnT measurements among the groups ($P < .001$). Post hoc pairwise comparisons showed that cTnT measurements of the COVID (–) group were significantly higher than both the COVID (+) and control groups ($P < .001$). Nevertheless, there was no statistically significant difference in cTnT measurements between the COVID (+) group and the control group ($P=.658$). Furthermore, there were statistically significant

Table 1. Evaluation of Demographic Characteristics According to the Presence of COVID-19

	Total (n = 176)	COVID-19 (+) (n = 70)	COVID-19 (–) (n = 57)	Control Group (n = 49)	*P*
Age (years)					
Mean ± SD	55.5 (28-87)	53 (30-83)	61 (28-87)	51 (32-81)	[a]**.015***
Minimum–maximum	56.09 ± 13.86	53.6 ± 14.59	60.44 ± 13.7	54.08 ± 11.94	
Age (years), n (%)					
<40	24 (13.6)	16 (22.9)	2 (3.5)	6 (12.2)	[b]**.040***
40-49	39 (22.2)	13 (18.6)	12 (21.1)	14 (28.6)	
50-59	38 (21.6)	6 (22.9)	12 (21.1)	10 (20.4)	
60-69	43 (24.4)	14 (20.0)	15 (26.3)	14 (28.6)	
≥70	32 (18.2)	11 (15.7)	16 (28.1)	5 (10.2)	
Gender, n (%)					
Female	71 (40.3)	30 (42.9)	27 (47.4)	14 (28.6)	[b].124
Male	105 (59.7)	40 (57.1)	30 (52.6)	35 (71.4)	

ANOVA, analysis of variance; COVID-19, coronavirus disease 2019.
[a]One-way ANOVA test.
[b]Pearson chi-square test.
**P* < .05 and bold expressions indicate statistical significance.

Table 2. Evaluation of Laboratory Findings According to the Presence of COVID-19

	[1]COVID-19 (+) (n = 70)	[2]COVID-19 (–) (n = 57)	[3]Control Group (n = 49)		
	Mean ± SD	Mean ± SD	Mean ± SD	[a]*P*	[b]*P*
CK-MB	3.05 ± 31.63	23.86 ± 29.88	1.04 ± 31.59	**< .001****	2 > 1, 3
Troponin-T	21.51 ± 66.89	61.82 ± 63.20	6.22 ± 66.81	**< .001****	2 > 1, 3
IMA	174.70 ± 161.21	124.10 ± 152.32	57.42 ± 161.03	**< .001****	1 > 3

[a]Generalized linear models (GLMs).
[b]Bonferroni test. In [b]*P column 1=COVID-19 (+), 2=COVID-19 (-), 3=Control group.*
***P* < .05 and bold expressions indicate statistical significance.
CK-MB, creatine kinase-MB; COVID-19, coronavirus disease 2019; IMA, ischemic modified albumin.

differences in IMA measurements among the groups (*P* < .001). Post hoc pairwise comparisons revealed that the COVID (+) group had significantly higher IMA measurements compared to the control group (*P* < .001). However, there were no statistically significant differences in IMA measurements between the COVID (–) group and the control group (*P* = .088) or between the COVID (+) and COVID (–) groups (*P* = .209).

Based on this significance, the cutoff point was calculated for IMA measurement. According to the COVID (+) and control groups, the cutoff point for IMA measurement was determined as ≥55. For the 55.5 cutoff value of the IMA measurement, sensitivity was 64.29%, specificity was 61.22%, PPV was 70.31%, NPV was 54.55%, and 95% confidence interval was between 0.555 and 0.749 (*P* = .005). In the resulting ROC curve, the underlying area was 65.2% and the standard error was 5.0% (Table 3).

The ROC curve of IMA levels according to COVID-19 (+) and control groups is shown in Figure 1A.

According to the COVID-19 (–) and control groups, the cutoff point for IMA measurement was determined to be ≥55. For the cutoff value (i.e., 55) of IMA measurement, the sensitivity is 70.18%, the specificity is 61.22%, the PPV is 67.80%, the NPV is 63.83%, and the accuracy is 66.04%. The standard error of the area under the ROC curve obtained was 69.2% and 5.2% (Table 4).

The ROC curve of IMA levels according to COVID-19 (–) and control groups is shown in Figure 1B.

Table 3. Diagnostic Screening Tests and ROC Curve Results for Ischemic Modified Albumin Measurement by COVID-19 (+) and Control Groups

	Diagnostic Scan					ROC Curve		
	Cutoff	Sensitivity	Specificity	PPV	NPV	Area	95% Confidence Interval	*P*
IMA	**≥ 55.5**	64.29	61.22	70.31	54.55	**0.652**	0.555-0.749	**.005***

**P* < .05 and bold expressions indicate statistical signifance.
COVID-19, coronavirus disease 2019; IMA, ischemic modified albumin; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.

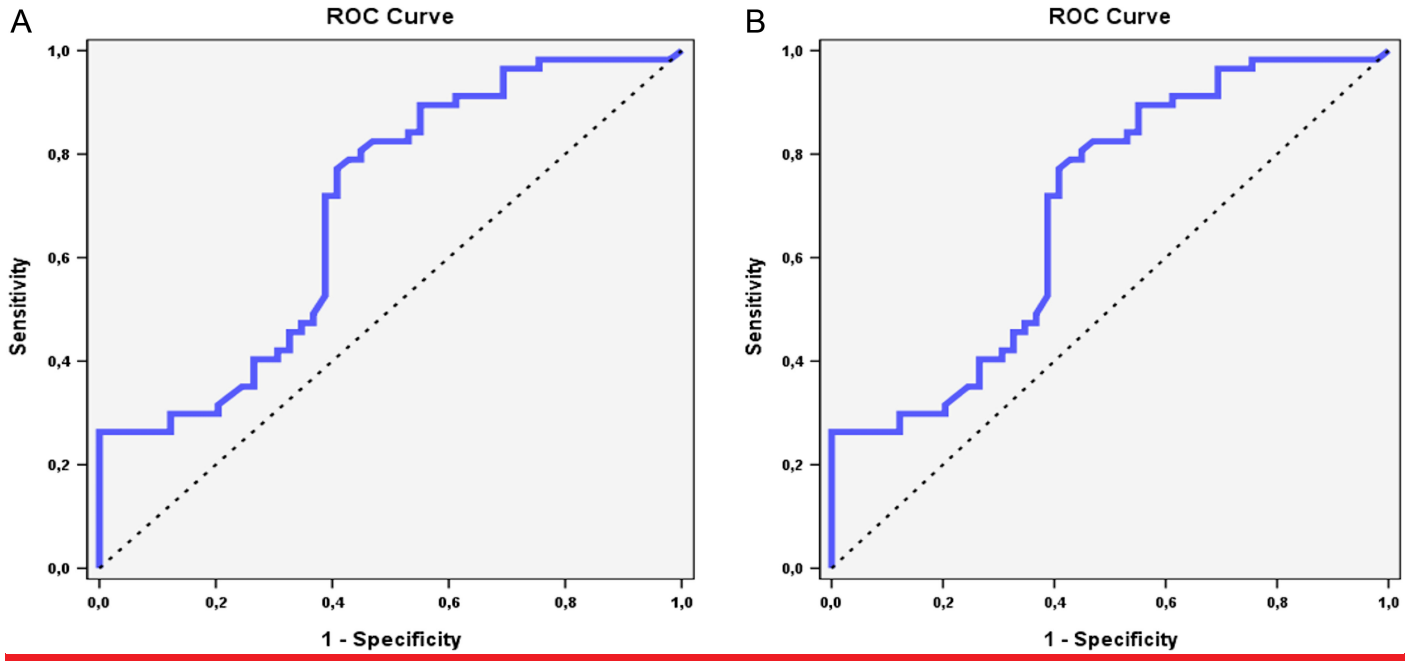

Figure 1. (A) ROC curve for ischemic modified albumin levels by COVID-19 (+) and control groups. (B) ROC curve for ischemic modified albumin levels by COVID-19 (–) and control groups. COVID-19: coronavirus disease 2019; ROC: receiver operating characteristic. Dotter line: random classifier, Purple line: ROC curve of ischemic modified albumin level.

Table 4. Diagnostic Screening Tests and ROC Curve Results for Ischemic Modified Albumin Measurement by COVID-19 (–) and Control Groups

	Diagnostic Scan					ROC Curve		
	Cutoff	Sensitivity	Specificity	PPV	NPV	Area	95% Confidence Interval	*P*
IMA	≥ **55**	70.18	61.22	67.80	63.83	**0.692**	0.590-0.794	**.001***

**P* < .05 and bold expressions indicate statistical signifance.
COVID-19, coronavirus disease 2019; IMA, ischemic modified albumin; NPV, negative predictive value; PPV, positive predictive value.

DISCUSSION

The ACS is a pathophysiological spectrum of heart conditions caused by atherosclerotic coronary plaque erosion. Atherosclerosis develops and progresses as a result of oxidative stress and inflammation, which damages circulation proteins such as IMA.[4] In COVID-19, Acute respiratory distress syndrome (ARDS) and acute cardiac injury are statistically significant and independently associated with mortality. A recent study discovered that patients with high cTnT levels died at a significantly higher rate than those with normal levels. Patients with pre-existing cardiovascular disease who developed cTnT elevation during infection died at the highest rate. Patients who do not have cTnT elevation during infection have a lower risk of death, even if they have underlying cardiovascular disease.[5,6] The incidence of acute cardiac injury is higher in men. Although acute cardiac injury appears to occur in older and more severely hospitalized patients, acute cardiac injury remains an important mortality indicator even after adjusting for all possible variables.[1] Acute cardiac injury and ventricular arrhythmias may be the first signs of severe acute respiratory syndrome coronavirus 2 infection. A patient with COVID (+) cardiac damage who was admitted to the emergency department with chest pain was found to have no evidence of lung disease.[6,7] Again, cases of sudden cardiac death while being treated at home with mild findings have been reported. Therefore, it is useful to look at myocardial markers for risk classification in all COVID-19 patients. It can occur in ACSs in COVID-19 patients, and this has been attributed to thrombotic factors.[8] Since angiography, which is the gold standard method for diagnosing COVID-19 patients with ACS, will increase the risk of transmission, supporting the diagnosis with laboratory methods and treating and following up on the patients with thrombolytic therapy have gained importance.[9] Our knowledge of the pathophysiology of cardiac complications in COVID-19 is very limited. The increase in cardiac markers during infection may be a condition that reflects only systemic illness in critical patients, as well as in individuals with underlying chronic cardiovascular disease, it may be due to the limited cardiac reserve's inability to meet the increased metabolic demands associated with it.[1] It is also a well-known fact that viral infections can trigger ACSs, arrhythmias, and heart failure. This condition is thought to be due to vascular inflammation localized at the level of arterial plaque in addition to the severe systemic inflammatory response. Increased need

and myocardial damage due to the inflammatory response are thought to be the causes of cardiac complications that occur during COVID-19.[10-12] Our results, as we have shown in Table 1 and Figure 1, support the relationship between COVID-19 positivity and cardiac injury described in the literature.

Albumin is synthesized in the liver, and half its life span is 19–20 days.[13,14] It binds drugs, bilirubin, hormones, fatty acids, cations (Ca^{+2}, Na^{+2}, and K^{+}), and other ligands in the blood reversibly or covalently.[15] It is also a carrier agent for toxic substances of endogenous and exogenous origin in circulation. The amino end of the albumin molecule (N-terminal) is the primary binding site of transitional metal ions such as aspartyl-alanyl-histidyl-lysine, cobalt (Co^{+2}), nickel (Ni^{+2}), and copper (Cu^{+2}). In cases such as free radical damage, energy-induced membrane destruction, exposure to free iron and copper, acidosis, and hypoxia, the N-terminal end of albumin is modified, and its capacity to bind transitional metals such as Co^{+2}, Ni^{+2}, and Cu^{+2} decreases.[16-19] This modified form of albumin is called IMA. The IMA is caused by muscle damage in the hypoxic heart tissue, mechanisms caused by decreased coronary blood flow, and albumin modification by reactive oxygen species, which is exacerbated by ischemic damage.[20] Biochemical markers currently used [CK, CK-MB, lactate dehydrogenase (LDH), troponins (cTnI and cTnT), and myoglobin] are secreted from myocytes when cell necrosis develops.[13,14-17] Although classical cardiac biochemical markers have high sensitivity and specificity, the rise of these markers occurs hours after the attack.

Recently studied markers for the early diagnosis of ACS are choline, IMA, heart-type fatty acid-binding protein, and N-terminal B-type natriuretic peptide.[14,21] The IMA rises within minutes immediately after the onset of ischemia, remains elevated for 6-12 hours, and returns to normal within 24 hours. In a study, IMA sensitivity, specificity, and NPV were 92% in the diagnosis of ischemia. In the same patient group, the sensitivity of the myoglobin-CK-MB-cTnI trio was 57%, while the co-sensitivity of IMA-myoglobin-CK-MB-TnI was 97%, and the NPV was 92%.[20] Recent studies have shown that the rise of IMA has severe cardiac outcomes, such as death, myocardial infarction, and refractory ischemia. It has been emphasized that it can be an independent determinant.[22] In our study, as we stated in Tables 3 and 4, IMA sensitivity and specificity were lower than those reported in the patient information, and the time of admission to the hospital within 3-4 hours could not be evaluated. Due to higher-than-ant icipated levels of cTnT and, notably CK-MB, both of which were expected to show an increase after IMA, these markers were also found to be elevated in some patients. In assessing myocardial injury, IMA is a molecule with higher specificity in the early period than biomarkers such as cTn and CK-MB, which are routinely used in most centers. A high IMA level is found not only in myocardial hypoxia but also in other types of tissue hypoxia. A high IMA level is used as a diagnostic biomarker, especially in cases of pulmonary thromboembolism, mesenteric ischemia, peripheral arterial occlusion, deep vein thrombosis, and acute cardiac arrest manifested by tissue hypoxia.[23]

CONCLUSION

In conclusion, given the data we have obtained so far and the heavy inflammatory burden of COVID-19, it seems inevitable that serious cardiovascular complications associated with COVID-19 will occur. The cTn T-I measurement is the most commonly used method to evaluate myocardial ischemia. The time elapsed between myocardial damage and the fact that these proteins reach measurable values after being released into the blood, on the other hand, delays the detection of the degree of myocardial damage. A biomarker such as IMA, whose levels rise within minutes, will accelerate the diagnosis and treatment process of assessing the cardiac injury of COVID-19 patients and provide information about the prognosis of the disease. As a result, in patients with chest pain and suspected cardiac injury, IMA levels should be evaluated alongside cardiac troponins.

Ethics Committee Approval: Our study was approved by the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Ethics Committee on 09/06/2020 with the decision number 2020/50.

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.Ö.; Design – S.Ö.; Supervision – Ş.T.N.; Resources – A.G.; Materials – S.Ö.; Data Collection and/or Processing – S.Ö., A.G.; Analysis and/or Interpretation – Ş.T.N.; Literature Search – A.G.; Writing – S.Ö., Ş.T.N.; Critical Review – Ş.T.N.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069. [CrossRef]
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. [CrossRef]
3. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5(7):802-810. [CrossRef]
4. Binti NN, Ferdausi N, Anik MEK, Islam LN. Association of albumin, fibrinogen, and modified proteins with acute coronary syndrome. *PLOS ONE*. 2022;17(7):e0271882. [CrossRef]
5. Guo T, Fan Y, Chen M, et al. Association of cardiovascular disease and myocardial injury with outcomes of patients hospitalized with coronavirus disease (COVID-19). *JAMA Cardiol*. 2020;5(7):811-818. [CrossRef]
6. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *Eur Heart J*. 2021;42(2):206. [CrossRef]
7. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(7):819-824. [CrossRef]

8. Libby P, Simon DI. Inflammation and thrombosis: the clot thickens. *Circulation*. 2001;103(13):1718-1720. [CrossRef]
9. Welt FGP, Shah PB, Aronow HD. Catheterization laboratory considerations during the coronavirus (COVID-19) pandemic: from ACC's Interventional Council and SCAI. *J Am Coll Cardiol*. 2020;75(18):2372-2375.
10. Madjid M, Miller CC, Zarubaev VV, et al. Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34,892 subjects. *Eur Heart J*. 2007;28(10): 1205-1210. [CrossRef]
11. Kwong JC, Schwartz KL, Campitelli MA, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med*. 2018;378(4):345-353. [CrossRef]
12. Vardeny O, Solomon SD. Influenza vaccination: a one-shot deal to reduce cardiovascular events. *Eur Heart J*. 2017;38(5):334-337. [CrossRef]
13. Chawla R, Goyal N, Calton R, Goyal S. Ischemia modified albumin: A novel marker for acute coronary syndrome. *Indian J Clin Biochem*. 2006;21(1):77-82. [CrossRef]
14. Gaze DC. Ischemia modified albumin: a novel biomarker for the detection of cardiac ischemia. *Drug Metab Pharmacokinet*. 2009;24(4):333-341. [CrossRef]
15. Lee E, Eom JE, Jeon KH, et al. Evaluation of albumin structural modifications through cobalt-albumin binding (CAB) assay. *J Pharm Biomed Anal*. 2014;91:17-23. [CrossRef]
16. Sbarouni E, Georgiadou P, Voudris V. Ischemia modified albumin changes- review and clinical implications. *Clin Chem Lab Med*. 2011;49(2):177-184. [CrossRef]
17. Worster A, Devereaux PJ, Heels-Ansdell D, et al. Capability of ischemia-modified albumin to predict serious cardiac outcomes in the short term among patients with potential acute coronary syndrome. *CMAJ*. 2005;172(13):1685-1690. [CrossRef]
18. Erdem SS, Yerlikaya FH, Çiçekler H, Gül M. Association between ischemia-modified albumin, homocysteine, vitamin B(12) and folic acid in patients with severe sepsis. *Clin Chem Lab Med*. 2012;50(8):1417-1421. [CrossRef]
19. Zurawska-Płaksej E, Grzebyk E, Marciniak D, Szymańska-Chabowska A, Piwowar A. Oxidatively modified forms of albumin in patients with risk factors of metabolic syndrome. *J Endocrinol Invest*. 2014;37(9):819-827. [CrossRef]
20. Anwaruddin S, Januzzi JL Jr, Baggish AL, Lewandrowski EL, Lewandrowski KB. Ischemia-modified albumin improves the usefulness of standard cardiac biomarkers for the diagnosis of myocardial ischemia in the emergency department setting. *Am J Clin Pathol*. 2005;123(1):140-145. [CrossRef]
21. Ertekin B, Kocak S, Defne Dundar ZD, et al. Diagnostic value of ischemia-modified albumin in acute coronary syndrome and acute ischemic stroke. *Pak J Med Sci*. 2013;29(4):1003-1007. [CrossRef]
22. Consuegra-Sanchez L, Bouzas-Mosquera A, Sinha MK, Collinson PO, Gaze DC, Kaski JC. Ischemia-modified albumin predicts shortterm outcome and 1-year mortality in patients attending the emergency department for acute ischemic chest pain. *Heart Vessels*. 2008;23(3):174-180. [CrossRef]
23. Turedi S, Cinar O, Kaldirim U, et al. Ischemia-modified albumin levels in carbon monoxide poisoning. *Am J Emerg Med*. 2011; 29(6):675-681. [CrossRef]