INTERNATIONAL JOURNAL OF
MEDICAL BIOCHEMISTRY

DOI: 10.14744/ijmb.2023.74436
Int J Med Biochem 2023;6(3):143-149

Research Article

The relationship between ischemia-modified albumin/albumin ratio levels and disease severity in COVID-19 patients

Murat Aksit[1], Merve Zeytinli Aksit[2], Musab Kazar[1], Taner Caliskan[3], Suheyla Serin Senger[4], Harun Akar[5], Gursel Ersan[4], Nisel Yilmaz[6], Banu Isbilen Basok[1], Ayfer Colak[1]

[1]Department of Medical Biochemistry, Izmir Tepecik Training and Research Hospital, Izmir, Turkiye
[2]Department of Medical Biochemistry, Bakircay University Cigli Training and Research Hospital, Izmir, Turkiye
[3]Department of Anesthesiology and Reanimation Intensive Care, Izmir Tepecik Training and Research Hospital, Izmir, Turkiye
[4]Department of Infectious Diseases and Clinical Microbiology, Izmir Tepecik Training and Research Hospital, Izmir, Turkiye
[5]Department of Internal Medicine, Izmir Tepecik Training and Research Hospital, Izmir, Turkiye
[6]Department of Medical Microbiology, Izmir Tepecik Training and Research Hospital, Izmir, Turkiye

Abstract

Objectives: In COVID-19 infection, oxidative stress occurs with the abnormal release of proinflammatory cytokines and the disruption of the balance between oxidants and antioxidants. In our study, we aimed to investigate the relationship between ischemia-modified albumin (IMA), a biomarker of oxidative stress, and the severity of the disease in hospitalized COVID-19 patients.
Methods: One hundred and twenty-four hospitalized patients with a diagnosis of COVID-19 were included in the study. These patients were divided into critical and non-critical groups. Serum IMA levels were measured by the colorimetric albumin cobalt-binding method. The IMA-albumin ratio (IMAR) was calculated by dividing IMA values by albumin values.
Results: The IMA and IMAR values of the critical COVID-19 group were statistically significantly higher than the non-critical group. In the multivariate analysis, the two variables IMAR and glucose were found to have the most important role in the severity of COVID-19 disease. For IMAR, the area under the ROC curve had a value of 0.725 (95% confidence interval 0.636–0.803).
Conclusion: IMA and IMAR levels of the critical group were found to be higher than the non-critical group in COVID patients. We have observed that IMAR levels are associated with the severity of the disease and that IMAR is an independent prognostic risk factor for the disease.
Keywords: Albumin, COVID-19, IMAR, ischemia-modified albumin, oxidative stress

How to cite this article: Aksit M, Zeytinli Aksit M, Kazar M, Caliskan T, Serin Senger S, Akar H, et al. The relationship between ischemia-modified albumin/albumin ratio levels and disease severity in COVID-19 patients. Int J Med Biochem 2023; 6(3):143-149.

In December 2019, the Coronavirus disease (COVID-19), caused by a virus called SARS-CoV-2, was detected in Wuhan, China. COVID-19 quickly spread throughout China and the whole world [1]. The World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020 due to its uncontrollable spread [2]. The COVID-19 pandemic has been responsible for more than 649,000,000 cases and 6,600,000 deaths as of December 2022 [3]. COVID-19 can be asymptomatic or symptomatic. The symptomatic form may have a disease spectrum ranging from mild upper respiratory tract disease to severe interstitial pneumonia, resulting in respiratory failure and even death [4, 5]. Therefore, identifying potentially critically ill patients is extremely important. With the early detection of these patients and appropriate treatment options, both hospitalization and mortality rates can be reduced.

In many studies, a relationship between the inflammatory state called cytokine storm and the deterioration of the clinical condition of COVID-19 patients has been reported [4, 6, 7]. It is

Address for correspondence: Murat Aksit, MD. Department of Medical Biochemistry, Izmir Tepecik Training and Research Hospital, Izmir, Turkiye
Phone: +90 537 542 59 92 **E-mail:** murataksit3545@gmail.com **ORCID:** 0000-0003-2106-9130
Submitted: May 23, 2023 **Revised:** July 17, 2023 **Accepted:** July 18, 2023 **Available Online:** August 18, 2023

accepted that cytokine storm has an important effect on the formation of acute respiratory distress syndrome and multiple organ dysfunction [6]. With the abnormal release of proinflammatory cytokines, and as a result of an uncontrolled inflammatory response, the balance between oxidants and antioxidants is disrupted, resulting in oxidative stress, which stimulates inflammatory cells to produce a greater number of cytokines. Therefore, it is stated that oxidative stress plays a very important role in the development and maintenance of inflammation [8].

Human serum albumin is a polypeptide consisting of 585 amino acids and three homologous helices. The region of the first 3 amino acids at the N-terminal has a specific binding site for transition metals (cobalt, copper, and nickel). This part of the albumin is most prone to degradation. In albumin ischemia/reperfusion states, the binding capacity of transition metals decreases. This newly formed chemically modified albumin is called ischemia-modified albumin (IMA) [9].

Many studies have demonstrated the excellent potential of IMA as a biomarker of oxidative stress and increase in its levels in conditions such as pneumonia, acute coronary syndrome, and ischemia [10–13]. It has been reported that there is an increase in IMA levels in the first moments of infection in COVID-19 patients and that IMA is an efficient biomarker with relatively high sensitivity and specificity for the early stage of COVID-19 [14]. In a study evaluating the relationship between the prognosis of patients with COVID-19 infection and IMA levels, it was stated that IMA levels predicted the severity of the disease [15], while another study suggested that there was no significant relationship between the severity of the disease and IMA levels [16]. Therefore, in our study, we aimed to investigate the relationship between IMA levels and the severity of the disease in hospitalized COVID-19 patients.

Materials and Methods

Study population

This prospectively designed study included 124 patients who were diagnosed with COVID-19 at the University of Health Sciences Turkey, Izmir Faculty of Medicine, Izmir Tepecik Training and Research Hospital between March 3 and April 15, 2022. Our hospital is a tertiary care hospital that plays a leading role in the management of COVID-19 throughout the pandemic. Informed consent for participation was obtained from all patients included in the study. Approval was obtained from the ethics committee of our institution within the Declaration of Helsinki, with the decision dated February 15, 2022, and numbered 2022/02-42.

Patients were diagnosed as mild, moderate, severe, and critically ill based on the WHO's survival guidelines for the clinical management of COVID-19 [17]. Patients diagnosed with COVID were divided into two groups critical and non-critical (moderate and severe). The non-critical group included symptomatic patients that had no indication of hypoxia or pneumonia as well as patients that had symptoms of moderate pneumonia such as dyspnea, cough, and fever and oxygen saturation (SpO_2) ≥90% on room air. The critical group included patients that had at least one of the following: respiratory rate >30/min, severe respiratory distress, SpO2<90% on room air, and arterial partial pressure of oxygen/fraction inspiratory O_2≤300 mmHg in addition to symptoms of pneumonia such as dyspnea, cough, and fever as well as patients that required mechanical ventilation due to respiratory failure [17].

Analysis of parameters and data collection

Blood samples, in addition to those taken for routine analyses, taken from all patients were collected in clot activator tubes with gel (BD Vacutainer SST II Advance, lot 2068015; Becton, Dickinson and Company, Franklin Lakes, NJ, USA), and then centrifuged for 10 min at 1800g after a 30-min clotting time. The serum samples obtained were immediately frozen in Eppendorf tubes and stored at −80°C until IMA levels were analyzed. Data on demographic characteristics, symptoms, and comorbidities were retrieved from the hospital information management system.

Glucose, creatinine, total bilirubin (T.Bil), direct bilirubin (D.Bil), alanine aminotransferase (ALT), aspartate aminotransferase, albumin, and C-reactive protein (CRP) were analyzed using AU 5800 (Beckman Coulter Inc., CA), USA autoanalyzer, and complete blood counts were determined using a UniCel D×H 800 haematology analyzer (Beckman Coulter, Miami, FL, USA). Prothrombin time and activated partial thromboplastin time (aPTT) levels were studied in the Sysmex CS2500 (Sysmex Inc., Kobe, Japan) coagulation device. ADVIA Centaur XP immunoassay analyzer (Siemens Healthineers, Erlangen, Germany) was used for the analysis of high-sensitivity troponin I (hs-TNI) and procalcitonin. Prealbumin level was analyzed on the BN II device (Siemens Healthineers, Marburg, Germany). Serum IMA levels were measured spectrophotometrically at 470 nm by the colorimetric albumin cobalt binding method described by Bar-Or and expressed in absorbance units [18].

The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count (NEU) by the absolute lymphocyte count (LYM) and the lymphocyte-to-monocyte ratio (LMR) by dividing the absolute LYMby the absolute monocyte count (MON). Furthermore, the CRP-albumin ratio (CAR) was calculated by dividing CRP values by albumin values, and the IMA-albumin ratio (IMAR) was calculated by dividing IMA values by albumin values.

Statistical analysis

Continuous variables were expressed as mean±standard deviation when the data were normally distributed, and as the median (interquartile range) when they were not normally distributed. Numbers (n) and percentages (%) were used to express categorical variables. The conformity of the variables to the normal distribution was examined using the Shapiro–Wilk test. In the comparison of continuous variables, the Student's t-test

Table 1. Demographic and clinical characteristics of COVID-19 patients

Variables	Non-critical ill (n=62)		Critical ill (n=62)		Total (124)		p
	n	%	n	%	n	%	
Age (years)	70 (59–83)		71 (58–82)		71 (59–82)		0.988
Gender							
Female	32		17		49		**0.006**
Male	30		45		75		
Clinical symptoms							
Fever	19	30.6	13	20.9	32	25.8	0.218
Cough	16	25.8	10	16.1	26	20.9	0.186
Fatigue	13	20.9	10	16.1	23	18.5	0.488
Headache	5	8.1	3	4.8	8	6.4	0.465
Dyspnea	22	35.5	23	37.1	45	36.3	0.852
Death	6	9.7	23	37.1	29	23.3	**<0.001**
Comorbidities							
Diabetes mellitus	29	46.8	24	38.7	53	42.7	0.364
Hypertension	31	50.0	31	50.0	62	50.0	1.000
Coronary artery disease	18	29.0	13	20.9	31	25.0	0.300
Chronic renal failure	12	19.4	14	22.6	26	20.9	0.659
Chronic obstructive pulmonary disease	8	12.9	6	9.7	14	11.3	0.570
Asthma	3	4.8	1	1.6	4	3.2	0.309
Hepatitis B	2	3.2	0	0	2	1.6	0.154
Cerebrovascular disease	5	8.1	6	9.7	11	8.8	0.752
Malignancy	13	20.9	8	12.9	21	16.9	0.231

was used for variables with normal, and the Mann–Whitney U test with non-normal distribution. The Chi-square test was used to compare categorical variables. Pearson or Spearman correlation test was used to evaluate the relationship between variables. Univariate and multivariate binary logistic regression analyses were employed to evaluate the potential risk factors for severe COVID-19 and to estimate odds ratios (OR)and 95% confidence intervals (CI). When distinguishing the severity of COVID-19, the area under the curve (AUC) and threshold values were determined using receiver operating characteristic (ROC) curve analysis. MedCalc 15.0 (MedCalc, Ostend, Belgium) and SPSS 25.0 (IBM Corp., NY, USA) programs were used for statistical analysis. P<0.05 was considered statistically significant.

Results

Sixty-two critical and 62 non-critical COVID-19 patients were included in the study. Although the ages of the groups were comparable, there was a significant difference between the groups in terms of gender distribution (p:0.006). Although the most common clinical symptoms in all patients were fever (25.8%) and shortness of breath (36.3%), the comorbidities with the highest incidence were diabetes mellitus (42.7%) and hypertension (50%), without any significant intergroup differences in terms of these comorbidities. The mortality rates of the critical COVID-19 group were significantly higher (p<0.001) (Table 1). The IMA and IMAR values of the critical COVID-19 group were significantly higher (p=0.022 and p<0.001), and the albumin, prealbumin, LYM, LMR, and PLT values were statistically significantly lower (p=<0.001, p<0.005, p<0.001, p<0.001, and p<0.04 respectively than the non -critical ill Covid 19 patients). There was no significant difference between the groups in ALT, MON, and aPTT levels. Other parameters were found to be significantly higher in the critical ill group (Table 2). In the correlation analysis, there was a significant positive correlation between IMAR and CRP, procalcitonin, NLR, and CAR in all cases (r=0.503, p<0.001; r=0.502, p<0.001; r=0.277, p=0.002; and r=0.593, p<0.001, respectively), and a significant negative correlation between IMAR and prealbumin, PLT, LYM, and LMR (r=–0.434, p<0.001; r=–0.210, p=0.023; r=–0.297, p=0.001; and r=–0.208, p=0.024, respectively).

Although the gender of the patients, IMAR, CRP, CAR, glucose, WBC, NEU, and NLR parameters were found to be associated with critical COVID-19 in univariate analysis, IMAR (OR: 3.020, 95% CI: 1.365–6.680) and glucose (OR: 1.011, 95% CI: 1.003–1.019) were the two variables that had the most important role in the severity of COVID-19 disease in multivariate analysis (Table 3). Based on the ROC curve analysis, the optimal cut-off point for the IMAR variable was determined as 2.2 (sensitivity and specificity of the cut-off points were 62.3% and 71.9%, respectively) and AUC was determined as 0.725. The optimal cut-off point for the glucose variable was determined as 131 (sensitivity and specificity of the cut-off points were 63.9% and 70.2%, respectively) and AUC was de-

Table 2. Laboratory results of the COVID-19 patients

Test	Non-critical (n=62)	Critical (n=62)	p
Albumin (g/L)	31.8±4.9	26.9±6.2	**<0.001**
IMA (ABSU)	0.603±0.131	0.660±0.144	**0.022**
IMAR	0.019 (0.015–0.023)	0.025 (0.020–0.032)	**<0.001**
CRP (mg/L)	63.6 (14.5–103.3)	105.5 (38.5–186.2)	**0.002**
CAR	1.76 (0.38–3.45)	4.34 (1.28–9.15)	**<0.001**
Prealbumin (g/L)	0.13 (0.09–0.19)	0.11 (0.07–0.16)	**0.005**
Glucose (mmol/L)	6.5 (5.4–8.4)	8.7 (6.4–12.4)	**<0.001**
Creatinine (µmol/L)	92.82 (63.64–133.48)	114.92 (79.56–213.93)	**0.017**
AST (U/L)	20.0 (15.7–30.5)	26.0 (19.0–42.2)	**0.010**
ALT (U/L)	15.5 (12.0–27.2)	19.5 (12.7–42.0)	0.061
Total bilirubin (µmol/L)	8.21 (6.33–10.60)	11.80 (8.04–17.27)	**0.002**
Direct bilirubin (µmol/L)	1.88 (1.20–2.39)	2.91 (1.88–4.96)	**<0.001**
hs-TNI (ng/L)	7.7 (3.0–31.4)	52.9 (9.6–238.7)	**<0.001**
Procalcitonin (ng/ml)	0.08 (0.05–0.26)	0.45 (0.16–4.43)	**<0.001**
WBC ($\times10^9$/L)	7.35 (5.37–9.67)	10.60 (7.35–14.80)	**<0.001**
NEU ($\times10^9$/L)	5.25 (3.65–7.77)	9.35 (5.20–13.75)	**<0.001**
LYM ($\times10^9$/L)	0.95 (0.60–1.50)	0.50 (0.30–0.93)	**<0.001**
NLR	5.38 (2.87–10.73)	19.23 (9.01–37.06)	**<0.001**
MON ($\times10^9$/L)	0.60 (0.40–0.80)	0.60 (0.30–0.90)	0.990
LMR	1.67 (1.00–3.06)	0.94 (0.59–2.07)	**0.001**
PLT ($\times10^9$/L)	217.5 (173.5–266.3)	188.0 (138.5–263.7)	**0.040**
PT (sec)	12.9 (12.1–14.7)	14.0 (12.7–15.4)	**0.038**
aPTT (sec)	26.1 (23.4–29.2)	27.3 (23.9–30.4)	0.317

IMA: Ischemia-modified albumin; IMAR: IMA/albumin ratio; CRP: C-reactive protein; CAR: CRP/albumin ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; hs-TNI: High-sensitive troponin I; WBC: White blood cell; NEU: Neutrophil; LYM: Lymphocyte; NLR: Neutrophil-to-lymphocyte ratio; MON: Monocyte; LMR: Lymphocyte-to-monocyte ratio; PLT: Platelet; PT: Prothrombin time; aPTT: Activated partial thromboplastin time.

Table 3. Regression analysis of risk factors for critical COVID-19

	Univariate analysis		Multivariate analysis	
Variables	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**
Gender	0.030	0.429 (0.200–0.922)		
IMAR	<0.001	3.017 (1.706–5.334)	0.006	3.020 (1.365–6.680)
CRP	0.001	1.008 (1.003–1.012)		
CAR	0.001	1.233 (1.095–1.387)		
Glucose	0.002	1.011 (1.004–1.017)	0.008	1.011 (1.003–1.019)
WBC	0.001	1.157 (1.060–1.263)		
NEU	<0.001	1.225 (1.105–1.358)		
NLR	<0.001	1.077 (1.038–1.117)		

OR: Odds ratio; CI: Confidence interval; IMAR: IMA/albumin ratio; CRP: C-reactive protein; CAR: CRP/albumin ratio; WBC: White blood cell; NEU: Neutrophil; NLR: Neutrophil-to-lymphocyte ratio.

termined as 0.691 (Table 4 and Fig. 1).

Discussion

The effects of albumin on the prognosis and mortality of COVID-19 have been focused and it has been stated that decreased albumin concentration may be a risk factor for mortality [15]. However, it has been suggested that albumin, besides acting as an important anti-inflammatory agent in our body, also has antioxidative and antithrombotic activities and may

Table 4. Prediction analysis of parameters

Biomarker	AUC (95% CI)	Cut-off	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Positive predictive value (%) (95% CI)	Negative predictive value (%) (95% CI)
IMAR	0.725 (0.636–0.803)	2.2	62.3 (49.0–74.4)	71.9 (58.5–83.0)	70.4 (56.4–82.0)	64.1 (51.1–75.7)
Glucose	0.691 (0.600–0.773)	131	63.9 (50.6–75.8)	70.2 (56.6–81.6)	69.6 (55.9–81.2)	64.5 (51.3–76.3)

AUC: Area under the ROC curve; CI: Confidence interval; IMAR: IMA-albumin ratio.

exhibit antiviral properties by specifically binding to the SARS-CoV-2 spike protein S1 subunit [15].

In COVID-19 infection, modifications occur in the structure of albumin due to oxidative stress induced by neutrophils and hypoxia [15]. IMA, a form of human serum albumin in which N-terminal amino acids cannot bind transition metals, is a biomarker whose levels are increased as a result of hypoxia and acidosis [14].

In our study, among COVID patients, IMA and IMAR levels of the critical group were found to be statistically significantly higher than the non-critical group. IMAR levels have been associated with the severity of the disease, and IMAR was observed to be an independent risk factor for the prognosis of the disease.

In the study of Ducastel et al., [16] in which oxidative stress biomarkers were evaluated, COVID-19 severity classification was made according to the NIH classification (mild, moderate, severe, and critical), and patients without CT findings were included in the mild class. It was determined that there was a significant difference between the IMA levels of the mild class and the other classes, and they stated that the level of IMA predicts disease severity and the need for intensive care in patients with COVID-19.

In the study of Sanchez et al., [14] patients were divided into three groups according to RT-qPCR and anti-Spike S1 IgG antibodies: no infection (PCR negative and IgG negative), early infection (PCR positive and IgG negative), and acute/active infection (PCR positive and IgG positive). It was stated that a remarkable increase in IMA levels was observed in early infected patients compared to the control group. In acute infection, IMA levels were higher than in the control group, although not as high as in the early infection group. It has been suggested that IMA in the early stage of COVID-19 has excellent diagnostic value. In our study, the IMAR value was found to be moderately predictive, and patients with an IMAR value above 2.2 are likely to have a more severe course of COVID-19 disease. IMAR can be used as a potential parameter to distinguish critically ill COVID-19 patients in need of intensive care.

Altıntaş et al. [19] could not find a statistically significant difference between the patients with COVID-19 pneumonia and the control group in terms of blood IMA levels. When blood IMA levels were compared according to the severity of pneumonia, any statistically significant difference could not be found between mild-moderate and severe pneumonia groups. However, patients with lung involvement were included in both groups, and it was reported that no difference was found between mild-moderate and severe groups due to the classification difference between studies [19].

Yıldız et al. [20] compared IMA levels of COVID-19 patients with and without lung involvement. They observed that higher levels of IMA, a marker of oxidative damage, were associated with the severity of pulmonary involvement, and suggested that IMA may be a predictive factor of pulmonary involvement.

Yucel et al. [21] determined that IMA levels in COVID-19 patients in the intensive care unit were relatively higher compared to healthy controls. They also observed that IMA levels in COVID-19 patients with chronic disease were significantly higher compared to those without and stated that the presence of chronic disease may lead to an increase in IMA levels by aggravating oxidative stress.

In the study of Erol et al., [22] IMA levels of healthy pregnant women and pregnant patients with COVID-19 infection were similar, and no significant difference was found between the two groups. It was stated that a few minutes after the onset of ischemia, the levels of IMA in the blood began to rise, reached a peak within 6 h, and remained high up to 12 h, and indicated that lack of any intergroup difference in terms of IMA levels suggested the presence of non-acute ischemic processes.

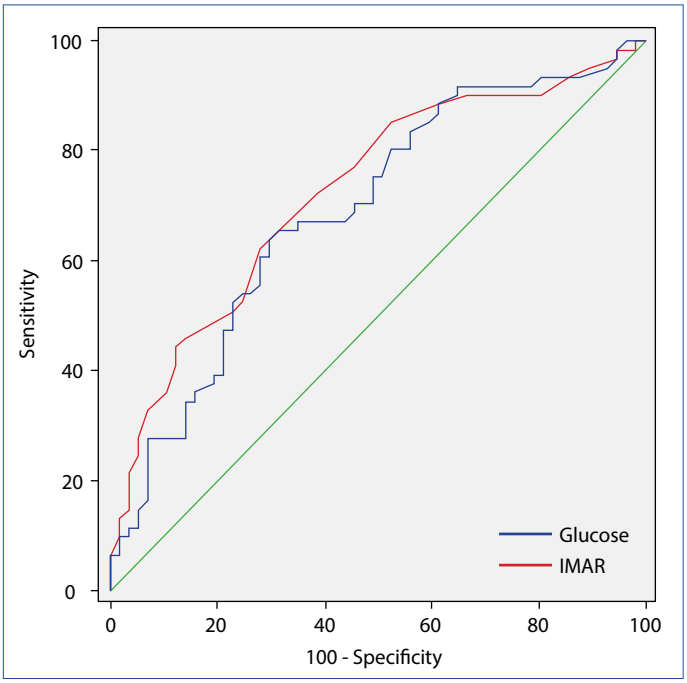

Figure 1. ROC analysis for IMAR and glucose.
ROC: Receiver operating characteristic; IMAR: IMA-albumin ratio.

Wang et al. and Karakoyun et al. [23, 24] reported that CRP, CAR, and NLR parameters were significantly higher in severe COVID-19 patients compared to the non-severe group. It has been reported that the CAR parameter may be a prognostic marker to predict the severity of COVID-19 at the time of first admission to the hospital, as CAR has a higher AUC than CRP in the ROC analysis. In the study of Uzum et al., [25] the CRP and CAR values of patients with severe COVID-19 disease were statistically higher than those with mild-to-moderate severity, and the CAR value was found to be moderately predictive. It has been reported that the risk of developing severe disease may be higher when the CAR value is above 21.47. Similarly, in the study of Torun et al., [26] CRP, CAR, and NLR parameters were higher in the severe group. In the ROC curve analysis, the AUC of CAR was found to be greater than NLR and it was suggested that CAR was more effective than NLR in predicting the severity of COVID-19. In our study, similar to the literature, the CRP, CAR, and NLR values of the critical group were higher than that of the non-critical group.

The strengths of our study are that it had a prospective design and evaluated many parameters. Remarkably, it was the first study that assessed IMAR in COVID patients.

The limitations of our study are that it was a single-centred study performed on relatively few patients, in which other oxidative stress markers could not be evaluated.

Conclusion

IMAR can be a new biomarker for the early phase of COVID-19, and it may shed light on the development of preventive and therapeutic solutions and the mechanisms underlying the pathophysiology of COVID-19, as well. Therefore, we think that increases in IMAR levels should be taken into account in the early stages of infection, as serum IMAR levels may be associated with the severity of the disease, the need for intensive care unit, and mortality in COVID-19 infection.

Acknowledgements: The authors thank all participants who voluntarily participated in this study.

Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: The study was approved by The University of Health Sciences Izmir Tepecik Training and Research Hospital Non-interventional Research Ethics Committee (No: 2022/02-42, Date: 15/02/2022).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – M.A., A.C., S.S.S., B.I.B.; Design – M.A., H.A., S.S.S., T.C.; Supervision – M.A., M.Z.A., S.S.S., G.E., B.I.B., A.C.; Funding – B.I.B., A.C.; Materials – B.I.B., A.C., S.S.S., T.C.; Data collection &/or processing – M.A., M.K., T.C., S.S.S., G.E., N.Y., H.A.; Analysis and/or interpretation – M.A., M.Z.A., B.I.B., A.C., N.Y.; Literature search – M.A., H.A., M.Z.A., M.K., N.Y.; Writing – M.A., M.Z.A.; Critical review – M.A., M.Z.A., B.I.B., A.C.

References

1. Kumar A, Singh R, Kaur J, Pandey S, Sharma V, Thakur L, et al. Wuhanto World: The COVID-19 pandemic. Front Cell Infect Microbiol 2021;11:596201. [CrossRef]
2. WHO. Virtual press conference on COVID-19 - March 11, 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/transcripts/who-audio-emergencies-coronavirus-press-conference-full-and-final-11mar2020.pdf. Accessed Aug 14 ,2023.
3. WHO. Coronavirus disease (COVID-19) pandemic. Numbers at a glance. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed Dec 20, 2022.
4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel corona virus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507–13. [CrossRef]
5. Baj J, Karakuła-Juchnowicz H, Teresiński G, Buszewicz G, Ciesielka M, Sitarz R, et al. COVID-19: Specific and non-specific clinical manifestations and symptoms: the current state of knowledge. J Clin Med 2020;9(6):1753. [CrossRef]
6. Sun X, Wang T, Cai D, Hu Z, Chen J, Liao H, et al. Cytokine storm intervention in the early stages of COVID-19 pneumonia. Cytokine Growth Factor Rev 2020;53:38–42. [CrossRef]
7. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel corona virus in Wuhan, China. Lancet 2020;395(10223):497–506. [CrossRef]
8. Wieczfinska J, Kleniewska P, Pawliczak R. Oxidative stress-related mechanisms in sars-cov-2 infections. Oxid Med Cell Longev 2022;2022:5589089. [CrossRef]
9. Bahinipati J, Mohapatra PC. Ischemia modified albumin as a marker of oxidative stress in normal pregnancy. J Clin Diagn Res 2016;10(9):15–7. [CrossRef]
10. Shevtsova A, Gordiienko I, Tkachenko V, Ushakova G. Ischemia-modified albumin: origins and clinical implications. Dis Markers 2021;2021:9945424. [CrossRef]
11. Sinha MK, Roy D, Gaze DC, Collinson PO, Kaski JC. Role of "Ischemia modified albumin", a new biochemical marker of myocardial ischaemia, in the early diagnosis of acute coronary syndromes. Emerg Med J 2004;21(1):29–34.
12. Bolatkale M, Duger M, Ülfer G, Can Ç, Acara AC, Yiğitbaşı T, et al. A novel biochemical marker for community-acquired pneumonia: Ischemia-modified albumin. Am J Emerg Med 2017;35(8):1121–5.
13. Roy D, Quiles J, Gaze DC, Collinson P, Kaski JC, Baxter GF. Role of reactive oxygen species on the formation of the novel diagnostic marker ischaemia modified albumin. Heart 2006;92(1):113–4. [CrossRef]
14. Sanchez BG, Gasalla JM, Sánchez-Chapado M, Bort A, Diaz-Laviada I. Increase in ischemia-modified albumin and pregnancy-associated plasma protein-A in COVID-19 patients. J ClinMed 2021;10(23):5474.
15. Wybranowski T, Napiórkowska M, Bosek M, Pyskir J, Ziomkowska B, Cyrankiewicz M, et al. Study of albumin oxidation in COVID-19 pneumonia patients: possible mechanisms and consequences. Int J Mol Sci 2022;23(17):10103. [CrossRef]

16. Ducastel M, Chenevier-Gobeaux C, Ballaa Y, Meritet JF, Brack M, Chapuis N, et al. Oxidative stress and inflammatory biomarkers for the prediction of severity and ICU admission in unselected patients hospitalized with COVID-19. Int J Mol Sci 2021;22(14):7462. [CrossRef]
17. WHO. Living guidance for clinical management of COVID-19. November 23, 2021. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2. Accessed Aug 15, 2023.
18. Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia-a preliminary report. J Emerg Med 2000;19(4):311–5.
19. Altintas E, Sabirli R, Yuksekkaya E, Kurt O, Koseler A. Evaluation of serum ischemia modified albumin in patients with covid-19 pneumonia: a case-control study. Cureus 2022;14(8):e28334.
20. Yildiz H, Alp HH, Ekin S, Arisoy A, Gunbatar H, Asker S, et al. Analysis of endogenous oxidative damage markers and association with pulmonary involvement severity in patients with SARS-CoV-2 pneumonia. Infect Dis Now 2021;51(5):429–34.
21. Yucel K, Fuat Gurbuz A. Hypoxia-inducible factor-1α and ischemia-modified albumin levels in intensive care COVID-19 Patients. Horm Mol Biol Clin Investig 2022;43(4):415–20.
22. Erol SA, Anuk AT, Tanaçan A, Semiz H, Keskin HL, Neşelioğlu S, et al. An evaluation of maternal serum dynamicthiol-disulfide homeostasis and ischemia modified albumin changes in pregnant women with COVID-19. Turk J Obstet Gynecol 2022;19(1):21–7.
23. Wang X, Xu Y, Huang H, Jiang D, Zhou C, Liao H, et al. An increased pretreatment C-reactive protein-to-albumin ratio predicts severe novel coronavirus-infected pneumonia. Research Square. 2020 Jun 5. Doi: 10.21203/rs.3.rs-31723/v1. [Epub ahead of print].
24. Karakoyun I, Colak A, Turken M, Altin Z, Arslan FD, Iyilikci V, Yilmaz N, Kose S. Diagnostic utility of C-reactive protein to albumin ratio as an early warning sign in hospitalized severe COVID-19 patients. Int Immunopharmacol. 2021 Feb;91:107285. [CrossRef]
25. Uzum Y, Turkkan E. Predictivity of CRP, albumin, and CRP to albumin ratio on the development of intensive care requirement, mortality, and disease severity in covid-19. Cureus 2023;15(1):e33600. [CrossRef]
26. Torun A, Çakırca TD, Çakırca G, Portakal RD. The value of C-reactive protein/albumin, fibrinogen/albumin, and neutrophil/lymphocyte ratios in predicting the severity of COVID-19. Revista da Associação Médica Brasileira 2021;67(3):431–6.