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Original Article

Evaluation of ischemia-modified albumin in the diagnosis and the clinical severity of COVID-19 in children

Eda Karadağ Öncel[1], Ayşegül Elvan Tüz[1], Yıldız Ekemen Keleş[1], Aslıhan Şahin[1], Gülnihan Üstündağ[1], Selin Taşar[1], Tuba Kansu Altan[2], İnanç Karakoyun[2], Banu İşbilen Başok[2], Salim Neşelioğlu[3], Ahu Kara Aksay[1], Dilek Yılmaz[1,4], Özcan Erel[3]

[1]*Department of Pediatric Infectious Diseases, University of Health Sciences, Tepecik Training and Research Hospital, İzmir;* [2]*Department of Medical Biochemistry Clinic, University of Health Sciences, Tepecik Training and Research Hospital, İzmir;* [3]*Department of Medical Biochemistry Clinic, Yıldırım Beyazıt University, Ankara City Hospital, Ankara;* [4]*Department of Pediatric Infectious Diseases, İzmir Katip Çelebi University, İzmir, Türkiye.*

ABSTRACT

Background. There is no specific biomarker used in the diagnosis of COVID-19 and predicting its clinical severity. This study aimed to investigate the utility of ischemia-modified albumin (IMA) in diagnosing and predicting clinical severity in children with COVID-19.

Methods. Between October 2020 and March 2021, 41 cases constituted the COVID-19 group and 41 cases constituted the healthy control group. IMA levels were measured at admission (IMA-1) and 48-72 hours (IMA-2) in the COVID-19 group. In the control group, it was measured at admission. COVID-19 clinical severity was classified as asymptomatic infection, mild, moderate, severe, or critical disease. Patients were divided into two groups (asymptomatic/mild and moderate/severe) to evaluate IMA levels in terms of clinical severity.

Results. In the COVID-19 group, the mean IMA-1 level was 0.901±0.099, and the mean IMA-2 level was 0.866±0.090. The mean level of IMA-1 in the control group was 0.787±0.051. When IMA-1 levels of COVID-19 and control cases were compared, the difference was statistically significant ($p<0.001$). When clinical severity and laboratory data are compared, C-reactive protein, ferritin and ischemia-modified albumin ratio (IMAR) were statistically significantly higher in moderate-severe clinical cases ($p=0.034$, $p=0.034$, $p=0.037$ respectively). However, IMA-1 and IMA-2 levels were similar between the groups ($p=0.134$, $p=0.922$, respectively).

Conclusions. To date, no study has been conducted on IMA levels in children with COVID-19. The IMA level may be a new marker for the diagnosis of COVID-19 in children. Studies with a larger number of cases are needed to predict clinical severity.

Key words: ischemia-modified albumin, COVID-19, child, diagnosis, clinical severity.

The COVID-19 pandemic caused by SARS-CoV-2 is a major public health crisis threatening humanity all over the world. Although the disease seems to be milder in children, severe cases can be seen. The disease is associated with the laboratory and clinical features of a cytokine storm that triggers the pro-inflammatory state associated with severe tissue damage.[1] The SARS-CoV-2 infection leads to many abnormal laboratory indicators. Associated biomarkers include hematological, biochemical, coagulation-fibrinolysis system, and inflammatory markers.[1] There is no specific biomarker used in the diagnosis of COVID-19 or for predicting its clinical severity.

Ischemia-modified albumin (IMA), a new marker of oxidative stress, measured by

✉ Eda Karadağ Öncel
dredakaradag@gmail.com

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the albumin cobalt binding test is a marker whose level increases secondary to ischemia of myocardial and skeletal muscle.[2] In the literature, IMA levels have been investigated in inflammatory diseases such as obesity, asthma, appendicitis, irritable bowel syndrome, and nephrotic syndrome. IMA has additionally been evaluated in infectious diseases such as bacteremia, neonatal sepsis, and pneumonia.[3-5] Many biomarkers were evaluated in the diagnosis and for evaluating the clinical severity in children with COVID-19, predictors of a more severe course of the disease would help clinicians identify high-risk patients. The aim of the study was to establish the utility of IMA in the diagnosis and evaluation of clinical severity in children with COVID-19. To the best of our knowleadge, there was only one study published in the English literature including children with COVID-19.[3] However, our study is the first to examine the following IMA levels in children with COVID-19._

Material and Methods

Study Design and Definitions

This case-controlled study was conducted by the pediatric infectious diseases clinic of İzmir Tepecik Training and Research Hospital between October 2020 and March 2021. In the patient group, there were 41 cases of SARS-CoV-2 detected in the respiratory sample by reverse transcriptase-polymerase chain reaction method (Bio-speedy SARS CoV-2 double gene RT-qPCR kit, Bioeksen-Türkiye). The control group included 41 healthy children without any known chronic diseases.

Demographic characteristics, clinical findings, hemogram, biochemistry, coagulation, and cardiac enzyme levels of COVID-19 cases were recorded. IMA levels were measured at admission (IMA-1) and 48-72 hours (IMA-2) in the COVID-19 group, while in the control group they were measured at the time of admission. In accordance with the report of the WHO-China Joint Mission on COVID-19, patients with COVID-19 were divided into mild, moderate, severe, and critical disease.[6] Mild illness may have any of the various signs and symptoms of COVID-19, such as shortness of breath or abnormal chest imaging. The moderate disease was defined as pneumonia. Severe disease was defined by dyspnea, a respiratory rate greater than 30 per min, blood oxygen saturation (SpO2) of 93% or less, a PaO2/FiO2 ratio below 300, and/or lung infiltration in more than 50% of the lung field. Patients with critical diseases (respiratory failure requiring mechanical ventilation, septic shock, and/or organ failure requiring intensive care) were not included.[7] Patients were divided into two groups (asymptomatic/mild and moderate/severe) to evaluate IMA levels in terms of clinical severity.

The study protocol was approved by the Ethics Committee of Health Sciences University, İzmir Tepecik Training and Research Hospital (Decision number: 2021/01-36). Informed consent was obtained from the families of the participants for the study.

Laboratory analyses

Participants blood samples were collected into the clot-activating tubes containing gel separator (Ref No: 367955; BD Vacutainer® SST II Advance tube, 5 mL, 13x100 mm, NJ, USA). Serum samples were separated by centrifugation for 10 minutes at 1,500×g following blood sampling. Then, serum specimens were aliquoted and stored at −80°C until further analyses.

IMA levels were determined by the albumin cobalt binding test, a rapid colorimetric method developed by Bar-Or et al.[2] The method is based on the binding ability of reduced cobalt ions (Co^{2+}) in human serum albumin due to ischemia. Briefly, a known amount of exogenous Co ($CoCl_2$) was added to serum samples. Albumin, which is altered as a result of ischemic processes, binds to the Co (II) to a far lesser extent, and the excess (unbound) amount of Co^{2+} forms a colored complex with dithiothreitol which is measured spectrophotometrically at 480 nm.

Serum albumin levels were measured using the AU5800 autoanalyzer using the bromocresol green method (AU5800, Beckman Coulter Inc., USA). In an attempt to correct the IMA values for serum albumin levels, the following formula was applied: (individual serum albumin/mean albumin in the population) × IMA value.[8] This formula showed the albumin-adjusted IMA (adj-IMA). The ischemia-modified albumin ratio (IMAR) value was obtained by proportioning the IMA value to individual serum albumin.

Statistical Analysis

Statistical data were analyzed with IBM SPSS for Windows version 25.0 (Chicago, IL). Values for numerical variables were given as median (interquartile range) (IQR) or mean ± standard deviation, depending on the normality distribution. Categorical variables were presented as numbers and percentages. Continuous variables following normal distribution were compared using a one-way analysis of variance or t-tests. When distribution was not expected, the Kruskal-Wallis test was used. Categorical variables were compared using the chi-square test. Receiver operating characteristic (ROC) curve analyses were performed to determine diagnostic cut-off values and their sensitivity, specificity, and area under curve (AUC) values. In evaluating the accuracy of a diagnostic test, sensitivity and specificity were calculated at 95% confidence interval (CI). A p-value of <0.05 was considered statistically significant for all predictions.

Results

A total of 82 children were evaluated, 41 of them had COVID-19 and 41 were healthy subjects. There was no statistically significant difference in terms of ages and gender (p>0.05).

Twenty-two (53.7%) of the cases in the COVID-19 group were male and their median age was 123 (2-214) months. The most common symptoms were fever in 22 (53.7%) cases, cough in 15 (36.6%) cases, headache in 14 (34.1%) cases, nausea-vomiting in 9 (22%) cases, and diarrhea in 8 (19.5%) cases. When evaluated in terms of clinical severity; 35 (85.4%) showed asymptomatic or mild clinical severity; 6 (14.6%) presented with a moderate-severe clinic. The clinical and laboratory findings of the patients with COVID-19 are shown in Table I. In the COVID-19 group, the mean IMA-1 level was 0.901±0.099, and the mean IMA-2 level was 0.866±0.090. The mean level of IMA-1 in the control group was 0.787±0.051. When IMA-1 levels of COVID-19 and control cases were compared, the difference was statistically significant (p<0.001) (Fig. 1). In addition, IMA-1, IMA-2, albumin, IMAR, and adj-IMA values in the COVID-19 group are shown in Figure 2. However, there was no significant difference between IMA-1 and IMA-2 values in COVID-19 cases (p=0.241).

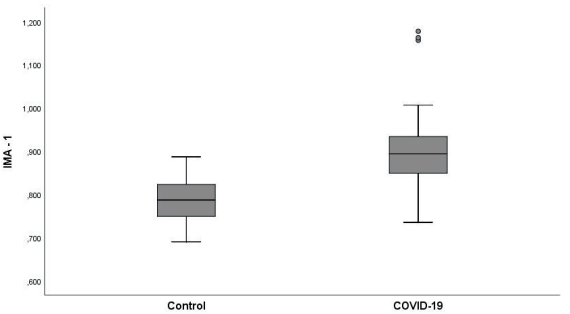

Fig. 1. Comparison of IMA-1 levels between COVID-19 group and control group (p<0.001).
IMA-1: Ischemia-modified albumin at admission

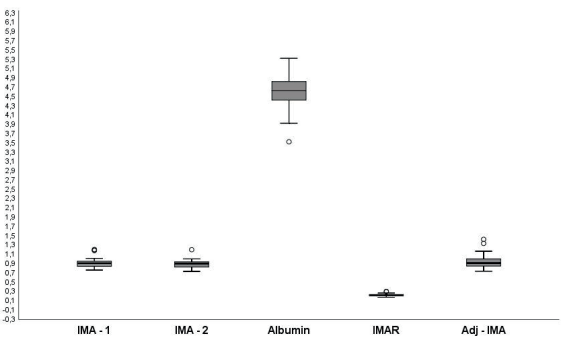

Fig. 2. IMA-1, IMA-2, albumin, IMAR and adj-IMA values in the COVID-19 group.
adj-IMA: Albumin-adjusted ischemia-modified albumin, IMA-1 and -2: IMA at admission and at 48-72 hours, IMAR: IMA ratio

Table I. Clinical and laboratory findings of patients.

	COVID-19 Group (n=41)	Control Group (n=41)	*P* Value
Age (months) , median (Q1-Q3)	131 (2-214)	138 (12-210)	>0.05
Gender (male), n (%)	22 (53.7)	26 (63.4)	>0.05
Clinical findings, n (%)			
Fever	22 (53.7)		
Cough	15 (36.6)		
Throat ache	7 (17.1)		
Rhinorrhea	4 (9.8)		
Nasal congestion	1 (2.4)		
Dyspnoea	4 (9.8)		
Nausea-vomiting	9 (22)		
Diarrhea	8 (19.5)		
Abdominal pain	5 (12.2)		
Headache	14 (34.1)		
Myalgia	2 (4.9)		
Anosmia-ageusia	5 (12.2)		
Clinical Severity, n (%)			
Asymptomatic/Mild	35 (85.4)		
Moderate/Severe	6 (14.6)		
Laboratory findings			
Total WBC (10^3/μL), median (Q1-Q3)	5700 (3200-15900)		
Platelet counts (10^3/μL), mean±SD	249317±84310		
Mean platelet volume (fL), mean±SD	8.2±1.01		
C-reactive protein (mg/L), median (Q1-Q3)	4.3 (0.1-157.4)		
Procalcitonin (μg/L), median (Q1-Q3)	0.05 (0.01-0.94)		
Ferritin (ng/mL), median (Q1-Q3)	59 (8-354)		
D-dimer (μg/L), median (Q1-Q3)	430 (190-4140)		
Fibrinogen (mg/dL), mean±SD	324±108		
IMA-1 (ABSU), mean±SD	0.901±0.099	0.787±0.051	***<0.001***
IMA-2 (ABSU), mean±SD	0.866±0.090		
Albumin (g/dL), mean±SD	4.41±0.43		
IMAR (ABSU), mean±SD	0.21±0.03		
Adj-IMA, median (Q1-Q3)	0.864 (0.709-1.398)		

ABSU: absorbance units, Adj-IMA: albumin-adjusted ischemia-modified albumin, IMA: ischemia-modified albumin, IMAR: ischemia-modified albumin ratio, SD: standart deviation, WBC: white blood cell.

When clinical severity and laboratory data were compared, C-reactive protein, ferritin and IMAR were statistically significantly higher in moderate-severe clinical cases (p=0.034, p=0.034, p=0.037 respectively). However, IMA-1 and IMA-2 levels were similar between the groups (p=0.134, p=0.922, respectively). There was also no difference between other inflammatory markers in terms of clinical severity. The laboratory data comparisons in both groups are summarized in Table II.

The optimal cut-off value for IMA-1 was identified by plotting ROC curves to predict the diagnosis of COVID-19. The cut-off value of IMA-1 to predict a diagnosis of a child with COVID-19 was 0.848 with a sensitivity

Table II. Comparison of laboratory data according to the clinical severity of COVID-19.

	Asymptomatic/Mild COVID-19 (n=35)	Moderate/Severe COVID-19 (n=6)	*P* Value
Age (months), median (Q1-Q3)	123 (2-214)	197 (60-214)	0.060
Gender, n (%)			0.280
Male	20 (57.1)	2 (33.3)	
Female	15 (42.9)	4 (66.7)	
Total WBC (10^3/μL), median (Q1-Q3)	5700 (3200-15900)	4800 (3300-10500)	0.293
Platelet counts (10^3/μL), mean±SD	254543±82793	218833±94588	0.344
Mean platelet volume (fL), mean±SD	8.2±1.06	8.38±0.7	0.691
C-reactive protein (mg/L), median (Q1-Q3)	3.4 (0.1-157.4)	35.35 (4.3-54.7)	***0.034***
Procalcitonin (μg/L), median (Q1-Q3)	0.05 (0.01-0.94)	0.05 (0.01-0.09)	0.852
Ferritin (ng/mL), median (Q1-Q3)	50 (8-354)	217 (54-256)	***0.034***
D-dimer (μg/L), median (Q1-Q3)	420 (190-4140)	685 (310-1740)	0.166
Fibrinogen (mg/dL), mean±SD	314±109	378±86	0.180
Troponin I (ng/L), median (Q1-Q3)	2.5 (2.5-1044)	2.5 (2.5-3.16)	0.284
IMA-1 (ABSU), mean±SD	0.891±0.096	0.958±0.109	0.134
IMA-2 (ABSU), mean±SD	0.867±0.091	0.861±0.096	0.922
Albumin (g/dL), mean±SD	4.45±0.45	4.15±0.23	0.116
IMAR (ABSU), mean±SD	0.2±0.03	0.23±0.03	***0.037***
Adj-IMA, median (Q1-Q3)	0.864 (0.709-1.398)	0.873 (0.802-1.128)	0.986

ABSU: absorbance units, Adj-IMA: albumin-adjusted ischemia-modified albumin, IMA: ischemia-modified albumin, IMAR: ischemia-modified albumin ratio, IQR: interquartile range, SD: standart deviation, WBC: white blood cell.

Table III. The area under the curve, cut-off levels, specifity, sensitivity, positive predictive values and negative predictive value of IMA-1.

	AUC	Cut-off level	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)
IMA-1	0.867	0.848	90.2	75.6	88.5	78.7

AUC: area under the curve, IMA: ischemia-modified albumin, NPV: negative predictive value, PPV: positive predictive value

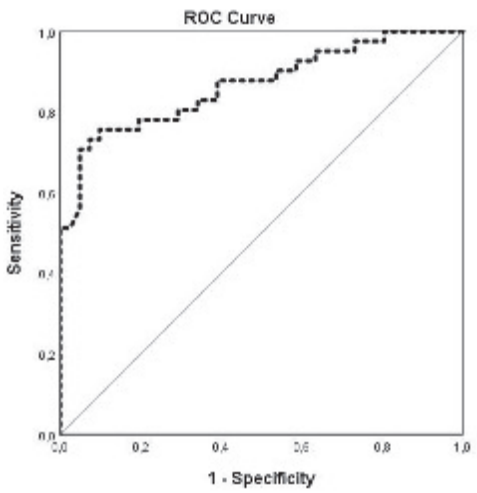

Fig. 3. Receiver operating characteristic (ROC) curves for patients with COVID-19 versus controls; ischemia-modified albumin (IMA).

of 75.6% and specificity of 90.2% (area under the curve 0.867, p<0.001) (95% CI=0.789-0.946). ROC curves of patients with COVID-19 versus controls are depicted in Figure 3 and Table III.

Discussion

The main result of this study was that IMA levels were higher in the COVID-19 group compared to the controls. However, there was no significant difference between groups in predicting clinical severity. In the study of Ducastel et al.[7], which included 160 cases of COVID-19, it was reported that the severity of the disease and the increase in the level of IMA were parallel. In a study on 74 adults and 79 children with COVID-19, IMA levels were found to be similar between patients

with COVID-19 and healthy controls. Similar to our study, IMA levels were not statistically significant between groups according to disease severity in children.[3] One of the remarkable results we obtained in the study for evaluating clinical severity was that IMAR was another marker that may be used. Studies with a larger number of cases are needed to investigate the importance of IMAR in assessing clinical severity. Laboratory findings including C-reactive protein (CRP) and procalsitonin have an irreplaceable role in the diagnosis and evaluation of COVID-19. Likewise, laboratory tests have an important role in evaluating disease severity and prognosis.

Significant changes in hematological values, which are among the basic biomarkers, include leukopenia and lymphopenia. However, in severe and critical COVID-19 disease, an increase in leukocyte, neutrophil and neutrophil-to-lymphocyte ratio values were detected.[9] Abnormal coagulation and fibrinolysis biomarkers are other important markers used in COVID-19 disease. It is associated with a poor prognosis and the most typical finding is the increased concentration of D-dimer. Because this disease causes an inflammatory storm, associated cytokines rise sharply, resulting in an increase in levels of certain inflammatory biomarkers such as CRP, ferritin, serum amyloid-A, and procalcitonin.[10] However, the search for new markers that can be used in the diagnosis and follow-up of children with COVID-19 continues worldwide. A study from Spain examined changes observed in adenosine deaminase and isoenzymes in saliva samples of individuals with COVID-19.[11] In another study from India, Viral Bacterial (VB10), a 10-gene serum-based biomarker, was discovered and investigated in COVID-19 cases.[12] This study aimed to identify the possible role of IMA as a new biomarker in the diagnosis of COVID-19.

IMA is a biomarker formed as a result of the modification of albumin by reactive oxygen species. Initially, although IMA levels were specific to ischemia, some factors such as acidosis, superoxide-radical damage, energy-dependent membrane degradation, and exposure to free iron and copper have been shown to cause IMA formation.[13] Depending on these factors, it has been found that IMA levels increase in inflammatory diseases in addition to ischemia-related diseases. Studies have shown that serum IMA levels increase in infectious diseases such as bacteremia, neonatal sepsis, and pneumonia in adults and children.[3-5] Based on the data in our study, IMA levels were statistically significantly higher in patients with COVID-19 than in the control group. ROC curve analysis revealed an IMA-1 value higher than 0.848 on presentation to have a sensitivity of 75.6%, a specificity of 90.2%, a positive predictive value (PPV) of 88.5%, and a negative predictive value (NPV) of 78.7% for COVID-19 diagnosis. In a study in which IMA levels were significantly higher in the patient group compared to healthy controls, the Area under the curve (AUC) value was found to be quite high in the ROC analysis, as in our study (0.937).[14] In our study, ROC analysis was found to be good. Based on this, evaluation of IMA levels in the diagnosis of COVID-19 may be considered.

Oxidative stress is defined as the disturbance of the balance between reactive oxygen species and antioxidants and is one of the well-established pathological conditions in various diseases. There is clinical evidence in the literature that oxidative stress is increased in COVID-19 patients and that this worsening redox state could potentially contribute to disease progression.[15] CRP has been previously reported as a reliable marker of oxidative stress and systemic inflammation. Specifically, CRP exhibits superior diagnostic value for bacterial infections with high plasma concentrations. However, CRP levels remain normal or increase only slightly during most viral infections.[16] Therefore, it can be thought that the role of CRP level in the evaluation of COVID-19 will be limited. This was not our main purpose, but in our study, by comparing CRP levels of COVID-19 patients according to clinical severity, we managed to demonstrate a statistically

significant difference between disease severity. Other biomarkers i.e., ferritin and IMA/albumin were determined to be statistically significantly higher in severe clinical course.

Free radicals formed due to tissue damage cause IMA levels to increase within minutes and remain high for 6-12 hours before returning to their normal value. In the study of Sinha et al.[17], it was shown that IMA levels increase early in ischemia and can be measured earlier than other markers. This situation is beneficial in the diagnosis of the disease when applied early.[17] However, our study observed that IMA-2 levels in the COVID-19 group did not decrease to similar levels as those of the control group. It may be thought that more than 48-72 hours are needed to re-evaluate the IMA-2 levels.

Hypoalbuminemia has been identified as a risk factor associated with poor clinical outcomes in the early stages of the disease. It has been reported that serum IMA levels can be misleading in patients with extremely low or high serum albumin levels.[18] In our study, the albumin levels of the participants were not within pathological limits. However, the corrected IMA level (IMAR) was also calculated for the data to be reliable. The formula was locally tested and verified in a cohort consisting of patients with autoimmune liver disease.[19] Our results also support this, and a significant relationship was found between the clinical severity of COVID-19 and IMAR. These data can be supported by large-scale studies.

Our study has several limitations. First, the number of patients with moderate/severe COVID-19 was low, so the comparison of the IMA according to disease severity may be affected. Also, as a control group, comparisons with non-COVID-19 patients with the same disease severity could not be made. Because, during the study, there were no previously healthy patients with similar severity due to other infectious factors. Second, IMA-2 was taken 48-72 hours after admission and it was noticed that the IMA-2 level did not decrease to the levels of the children in the control group. If we had taken the IMA-2 later than 48-72 hours, we might have seen lower levels similar to those of the control group. Finally, SARS CoV-2 IgM antibody levels could not be measured in the control group. Despite the limitations, our study has provided useful and significant insight into the new biomarkers of COVID-19 for diagnosis.

As studies on IMA's clinical benefits are still ongoing, we believe that future prospective studies may help elucidate whether IMA could be used in the diagnosis of COVID-19 patients, particularly for the evaluation of clinical severity. In our study, the sample size of the patient group may have been insufficient to reach general results. In addition, due to the limited number of patients in the moderate/severe group in clinical classification, the assessment may have been insufficient. Therefore, new studies including larger case numbers are required to analyze the usefulness of IMA and IMAR in the diagnosis and clinical severity of COVID-19.

Ethical approval

This study was approved by the Health Sciences University, İzmir Tepecik Training and Research Hospital Ethical Committee in accordance with the Helsinki Declaration (Decision number: 2020/14-70). Informed consent was obtained from the families of the participants for the study.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: EKO, AET, YEK, AS, GU; data collection: TKA, IK, BIB; analysis and interpretation of results: EKO, AKA, SN; draft manuscript preparation: DYC, OE. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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