Coronavirus Pandemic

Could ischemia-modified albumin levels predict the severity of disease in SARS-CoV-2 infection?

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Abstract

Introduction: Ischemia-modified albumin (IMA) level increases in inflammatory conditions. We aimed to investigate the association between IMA levels and the severity of coronavirus disease 2019 (COVID-19) infection in adult patients.

Methodology: We grouped adult patients with COVID-19 infection: Group A - mild symptoms, but normal computed tomography (CT), Group B - mild/moderate illness, and Group C - severe or critical illness. We measured IMA levels at the time of diagnosis of COVID-19 infection.

Results: Mean age of the total number of patients (n = 90) was 54.43 (± 8.11) year, and 46.7% (n = 42) were female. IMA levels were highest in Group C and lowest in A (p < 0.001). The most important factor predicting COVID-19 disease severity was IMA. Type 2 diabetes was more frequent in Group C and lowest in A (p < 0.001). The most important factor predicting COVID-19 disease severity was IMA. Type 2 diabetes was more frequent in Group C than in Group A (n = 29) and B (p = 0.009). Duration of hospitalization was highest in Group C (p < 0.001).

Conclusions: We analyzed a sample of patients with COVID-19 infection and found that IMA predicted severe COVID-19 disease. Disease severity grouping was based on patients' clinical and radiological features. IMA level measured when SARS-CoV-2 infection is diagnosed may be a useful marker in predicting likely disease severity or intensive care need.

Key words: Ischemia-modified albumin; COVID-19; SARS-CoV-2; pandemic; IMA; severity.


(Received 27 September 2022 – Accepted 16 March 2023)

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Introduction

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) on 11 March 2020. To date more than 476 million people have been affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and more than 6 million have died [1]. The severity of COVID-19 infection ranges from asymptomatic infection detected by polymerase chain reaction (PCR) positivity to more severe illness, sometimes leading to respiratory insufficiency or death [2]. A number of studies have been conducted to explain the pathogenesis of the disease in pulmonary or systemic involvement in COVID-19 infection [3]. The severity of inflammatory response in COVID-19 infection was found to be associated with the severity of clinical disease [4-6]. Similarly, cytokine storm has been demonstrated to be a major factor related to organ failure in COVID-19 infection [7].

Inflammatory process seems to be closely associated with oxidative stress (OS) [8]. Release of reactive oxygen species (ROS), neutrophil migration and decreased levels of antioxidant mechanisms were important factors in the development of viral infections [9–11]. These factors were also shown to be related with microvascular dysfunction [9,10]. OS was shown to have an important role in the pathogenesis of various pulmonary diseases, such as asthma, acute bronchiolitis, cystic fibrosis, and also COVID-19 infection [8,12–15]. In severe COVID-19 cases, the effect of OS was shown to contribute to hypoxic...
respiratory failure by affecting the alveolar epithelium [16].

ROS and natural antioxidant defense mechanisms, which act against ROS production, exist in balance. OS occurs if the balance is impaired towards the predominance of ROS [17]. ROS induces structural changes in the N-terminal region of albumin, which may be measured by spectrophotometry using the albumin cobalt binding test [18]. The structurally modified form of albumin, ischemia-modified albumin (IMA), has been studied in various clinical conditions, such as in polycystic ovary syndrome, renal failure, myocardial and mesenteric ischemia, acute ischemic stroke, depression, and bipolar disorder [19].

A few studies have revealed the relationship between SARS-CoV-2 pneumonia and IMA level [13,20,21]. In one study, IMA level was found to be higher in patients with SARS-CoV-2 pneumonia than in healthy controls, and to be related with the severity of COVID-19 pneumonia [21]. In another study, in contrast to other OS parameters, IMA levels were shown not to be associated with COVID-19 or the severity of infection [13]. We aimed to investigate the association between IMA levels and the severity of COVID-19 infection in adult patients.

**Methodology**

**Study design**

This prospective study was conducted in SANKO University Faculty of Medicine, and approved by the local Ethics Committee of SANKO University Faculty of Medicine (Date: 2021, Decision No: 2). The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all the participants.

Data for adult patients diagnosed and followed up with COVID-19 infection in SANKO University Faculty of Medicine hospital since April 1, 2020 were analyzed prospectively. COVID-19 diagnosis was made by polymerase chain reaction (PCR) test analyzed from nasal swab samples taken from patients suspected with COVID-19 infection. Upon admission, all patients underwent clinical and radiological evaluation either in the outpatient clinics or emergency department. Patients with chronic inflammatory bowel diseases such as ulcerative colitis or Crohn’s disease, chronic kidney disease, diabetic nephropathy, chronic liver failure, psychiatric or neurological diseases, malignancy and collagen vascular disorders were not included in the study because IMA levels might be affected by these conditions.

**Data collection**

Demographic parameters (age, gender, and body mass index [BMI], smoking status), clinical parameters (symptoms, chronic illnesses [hypertension, type 2 diabetes mellitus, asthma, chronic obstructive pulmonary disease, and coronary artery disease], oxygen saturation (SaO₂ %), duration of hospitalization [days]), and laboratory findings (C-reactive protein [CRP], ferritin, D-dimer, procalcitonin, fibrinogen, lactate dehydrogenase [LDH], IMA levels, lymphocyte, neutrophil and leukocyte counts) were electronically and manually recorded.

Complete blood count was studied with an automated analyzer. Neutrophil to lymphocyte ratio (NLR), neutrophil to leukocyte ratio (NLER), and lymphocyte to leukocyte ratio (LLR) were calculated as neutrophil divided by lymphocyte, neutrophil divided by leukocyte, and lymphocyte divided by leukocyte counts, respectively.

**Patient groups**

The patients were grouped on admission and follow-up based on their clinical symptoms and pulmonary imaging findings from chest computed tomography (CT). We grouped them as Group A - outpatient (mild symptoms of COVID-19 infection and no CT findings); Group B - mild/moderate illness (fever and respiratory tract symptoms of COVID-19 infection together with pneumonia on CT); Group C - severe (respiratory rate > 30/minute, or oxygen saturation at room air of < 93%, or PaO₂/FiO₂ of < 300, or increase in CT findings more than 50% in 1-2 days) or critical illness (shock, or respiratory insufficiency requiring mechanical ventilation, or organ failure necessitating intensive care).

The patients, who were grouped in Group A at diagnosis, but who developed a more severe disease later in the disease course were re-classified as Group B or C.

**IMA measurement**

IMA levels in collected serum samples, which were obtained from the patients at the time of diagnosis of SARS-CoV-2 infection were measured by a previously reported method [22]. The IMA levels were calculated as absorbance units and defined as IU/mL.

**Statistical analysis**

Data obtained in the study were analyzed statistically using SPSS 25.0 (IBM Corporation, Armonk, New York, United States). The conformity of
the data to normal distribution was evaluated using the Shapiro-Wilk Francia test. Homogeneity of variance was evaluated with the Levene test. When comparing more than 2 independent groups of quantitative data we used parametric One-Way ANOVA (Robust Test, Brown-Forsythe) with post-hoc analysis of Tukey HSD and Games-Howell tests, or non-parametric Jonckheere-Terpstra test with post-hoc analysis of Dunn’s test. When comparing categorical variables, the Pearson Chi-Square and Fisher-Freeman-Holton tests with Monte Carlo simulation technique were used. Comparison of column ratios was expressed by Benjamini-Hochberg corrected p values. The partial correlation test was used to analyze the correlation of IMA with the clinical and laboratory variables, after adjusting by age and BMI. Counselling machine learning methods such as Logistic Regression, Discriminant Analysis, Support Vector Machine, Random Forest, K-nearest Neighbor Algorithm, Simple (Native) Bayes Classification and Neural Network (Multilayer Perceptron-Radial Basis) were used to find and estimate the most important variable for the groups. Results of analysis of Neural Network (Multilayer Perceptron), as the most successful method, were used. Gradient Descent was used for the optimization algorithm, hyperbolic tangent for hidden layer

Table 1. Comparison of demographic, clinical and laboratory parameters among the patient groups.

<table>
<thead>
<tr>
<th>Total (n = 90)</th>
<th>Outpatient (A) (n = 29)</th>
<th>Mild or Moderate Illness (B) (n = 30)</th>
<th>Severe or Critical Illness (C) (n = 31)</th>
<th>P</th>
<th>Pairwise Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean (SD)</td>
<td>mean (SD)</td>
<td>mean (SD)</td>
<td></td>
<td>A vs B</td>
</tr>
<tr>
<td>Age</td>
<td>54.43 (8.11)</td>
<td>50.90 (7.70)</td>
<td>54.39 (8.64)</td>
<td>0.003&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.190, 0.002, 0.181</td>
</tr>
<tr>
<td>BMI</td>
<td>35.69 (2.90)</td>
<td>35.56 (2.43)</td>
<td>35.55 (3.12)</td>
<td>0.820&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ns, ns, ns</td>
</tr>
<tr>
<td>Gender (Female)</td>
<td>42 (46.7)</td>
<td>16 (55.2)</td>
<td>15 (48.4)</td>
<td>0.356&lt;sup&gt;c&lt;/sup&gt;</td>
<td>ns, ns, ns</td>
</tr>
<tr>
<td>Smoking</td>
<td>52 (57.8)</td>
<td>17 (58.6)</td>
<td>17 (54.8)</td>
<td>0.927&lt;sup&gt;c&lt;/sup&gt;</td>
<td>ns, ns, ns</td>
</tr>
<tr>
<td>HT</td>
<td>45 (50)</td>
<td>15 (51.7)</td>
<td>14 (45.2)</td>
<td>0.865&lt;sup&gt;c&lt;/sup&gt;</td>
<td>ns, ns, ns</td>
</tr>
<tr>
<td>T2D</td>
<td>36 (40)</td>
<td>11 (37.9)</td>
<td>8 (25.8)</td>
<td>0.047&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.313, 0.224, 0.042</td>
</tr>
<tr>
<td>Asthma</td>
<td>20 (22.2)</td>
<td>9 (31)</td>
<td>10 (32.3)</td>
<td>0.009&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.919, 0.008, 0.008</td>
</tr>
<tr>
<td>COPD</td>
<td>2 (2.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.217&lt;sup&gt;I&lt;/sup&gt;</td>
<td>ns, ns, ns</td>
</tr>
<tr>
<td>CAD</td>
<td>15 (16.7)</td>
<td>0 (0)</td>
<td>2 (6.5)</td>
<td>&lt;0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>0.164, &lt;0.001, 0.002</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>61 (67.8)</td>
<td>0 (0)</td>
<td>30 (100)</td>
<td>&lt;0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>&lt;0.001, &lt;0.001, 0.999</td>
</tr>
<tr>
<td>Duration of Hospitalization (days)</td>
<td>4 (0/14)</td>
<td>0 (0/0)</td>
<td>4 (3/5)</td>
<td>0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>&lt;0.001, &lt;0.001, &lt;0.001</td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>93 (89/98)</td>
<td>98 (98/99)</td>
<td>93 (93/94)</td>
<td>&lt;0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>&lt;0.001, &lt;0.001, &lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>16 (8/75)</td>
<td>3 (2/8)</td>
<td>15 (12/27)</td>
<td>&lt;0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>&lt;0.001, &lt;0.001, &lt;0.001</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>120 (46/385)</td>
<td>56 (40/112)</td>
<td>100 (39/139)</td>
<td>&lt;0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>0.230, &lt;0.001, &lt;0.001</td>
</tr>
<tr>
<td>D-dimer (ng/mL)</td>
<td>0.43 (0.34/0.58)</td>
<td>0.34 (0.27/0.42)</td>
<td>0.41 (0.37/0.51)</td>
<td>&lt;0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>0.015, &lt;0.001, &lt;0.001</td>
</tr>
<tr>
<td>Procalcitonin (μg/L)</td>
<td>0.04 (0.02/0.08)</td>
<td>0.03 (0.01/0.04)</td>
<td>0.02 (0.02/0.04)</td>
<td>0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>0.999, &lt;0.001, &lt;0.001</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>400.50 (324/538)</td>
<td>324 (285/383)</td>
<td>382 (323/493)</td>
<td>&lt;0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>0.012, &lt;0.001, &lt;0.001</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>260 (206/385)</td>
<td>200 (172/221)</td>
<td>260 (237/283)</td>
<td>&lt;0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>&lt;0.001, &lt;0.001, &lt;0.001</td>
</tr>
<tr>
<td>Lymphocyte (/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>1480 (840/1860)</td>
<td>1830 (1460/2100)</td>
<td>1720 (1500/1990)</td>
<td>0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>0.656, &lt;0.001, &lt;0.001</td>
</tr>
<tr>
<td>Neutrophil (/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>5055 (3720/6388)</td>
<td>4640 (3560/5310)</td>
<td>4120 (3330/4710)</td>
<td>0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>0.406, &lt;0.001, &lt;0.001</td>
</tr>
<tr>
<td>Leukocyte (/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>7512.5 (6110/8770)</td>
<td>7430 (6110/8080)</td>
<td>6420 (5450/7530)</td>
<td>0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>0.197, 0.001, &lt;0.001</td>
</tr>
<tr>
<td>NLR</td>
<td>3.31 (2.8/0.5)</td>
<td>2.06 (1.66/3.33)</td>
<td>2.32 (1.64/3.30)</td>
<td>0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>0.859, &lt;0.001, &lt;0.001</td>
</tr>
<tr>
<td>NLER</td>
<td>0.67 (0.13)</td>
<td>0.61 (0.11)</td>
<td>0.63 (0.12)</td>
<td>&lt;0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>0.085, &lt;0.001, &lt;0.001</td>
</tr>
<tr>
<td>LLR</td>
<td>0.22 (0.12)</td>
<td>0.28 (0.09)</td>
<td>0.29 (0.09)</td>
<td>&lt;0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>0.979, &lt;0.001, &lt;0.001</td>
</tr>
<tr>
<td>IMA (IU/mL)</td>
<td>0.45 (0.31)</td>
<td>0.15 (0.08)</td>
<td>0.36 (0.15)</td>
<td>&lt;0.001&lt;sup&gt;τ&lt;/sup&gt;</td>
<td>&lt;0.001, &lt;0.001, &lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup> One-Way ANOVA (Robust Statistic: Brown-Forsythe) post hoc test: Tukey HSD, Games Howell, <sup>τ</sup> Jonckheere-Terpstra test (Monte Carlo); post hoc test: Dunn’s Test; SD: standard deviation; q1: percentile 25; q3: percentile 75; NLR: neutrophil to lymphocyte ratio; NLER: neutrophil to leukocyte ratio; LLR: lymphocyte to leukocyte ratio; IMA: ischemia modified albumin; LDH: lactate dehydrogenase; CRP: C-reactive protein; T2D: type 2 diabetes mellitus; CAD: coronary artery disease.
activation function, and Softmax as the output layer activation function. To select training data, the Mini-Batch method was used using a 70% Training set and 30% Testing set. Quantitative variables were stated as mean (standard deviation), and median (percentile 25[q1]/percentile 75[q3]) values, and categorical variables as number (n) and percentage (%). Variables were evaluated at a 95% confidence level, and a value of \( p < 0.05 \) was accepted as statistically significant.

**Results**

Of the total number of patients (\( n = 90 \)), mean age was \( 54.43 \pm 8.11 \) (41-79) with higher mean age in Group C than in Group A (\( p = 0.002 \)). Mean BMI was \( 35.69 \pm 2.90 \) kg/m\(^2\) with no significant difference among the groups (\( p = 0.820 \)). Female/male ratio was 42/48 (46.7/53.3%), and was similar in the three groups (\( p = 0.356 \)). The frequency of type 2 diabetes mellitus (T2D) was higher in Group C than in Group A (\( p = 0.002 \)). Duration of hospitalization, and levels of CRP, ferritin, D-dimer, procalcitonin, fibrinogen, LDH, neutrophil, leukocyte, NLR, and NLER (\( p < 0.001 \)). IMA was negatively correlated with levels of CRP, ferritin, D-dimer, procalcitonin, fibrinogen, LDH, neutrophil, leukocyte, NLR, and NLER (\( p < 0.001 \)). IMA was positively correlated with levels of CRP, ferritin, D-dimer, procalcitonin, fibrinogen, LDH, neutrophil, leukocyte, NLR, and NLER (\( p < 0.001 \)). IMA was negatively correlated with SaO2, lymphocyte count and LLR (\( p < 0.001 \)).

IMA was positively correlated with levels of CRP, ferritin, D-dimer, procalcitonin, fibrinogen, LDH, neutrophil, leukocyte, NLR, and NLER (\( p < 0.001 \)). IMA was negatively correlated with SaO2, lymphocyte count and LLR (\( p < 0.001 \)).

The most important factor predicting disease severity was IMA with an importance level of 100%. The other important factors were LDH, levels of procalcitonin, ferritin, NLR, neutrophils, leukocytes and lymphocytes count (Table 2).

IMA was positively correlated with levels of CRP, ferritin, D-dimer, procalcitonin, fibrinogen, LDH, neutrophil, leukocyte, NLR, and NLER (\( p < 0.001 \)). IMA was negatively correlated with SaO2, lymphocyte count and LLR (\( p < 0.001 \)).

### Table 2: Importance of laboratory parameters in the prediction of severe disease.

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Normalized Importance</th>
<th>Independent Variable</th>
<th>Normalized Importance</th>
<th>Sample (Holdout)</th>
<th>Predicted</th>
<th>Percent Correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training (%70)</td>
<td>Training (%70)</td>
<td>Training (%70)</td>
<td>Training (%70)</td>
<td>Training (%70)</td>
<td>Training (%70)</td>
<td>Training (%70)</td>
</tr>
<tr>
<td>Outpatient A</td>
<td>Mild-Moderate Illness B</td>
<td>Severe-Critical Illness C</td>
<td>Percent Correct</td>
<td>41.4%</td>
<td>27.6%</td>
<td>31.0%</td>
</tr>
</tbody>
</table>

Neural network (multilayer perceptron); hidden layer activation function: hyperbolic tangent output layer activation function: Softmax; dependent variable: groups; IMA: ischemia modified albumin; LDH: lactate dehydrogenase; CRP: C-reactive protein; T2D: type 2 diabetes mellitus; CAD: coronary artery disease; NLR: neutrophil to lymphocyte ratio; NLER: neutrophil to leukocyte ratio; LLR: lymphocyte to leukocyte ratio.
Discussion

T2D and CAD were associated with severe COVID-19 disease. Patients without any CT findings were not hospitalized, and IMA levels were lowest in this group. Higher IMA levels were associated with more severe disease. The most important factor predicting disease severity was IMA with an importance level of 100%. The other important factors predicting disease severity were LDH, levels of procalcitonin, ferritin, NLR, neutrophil, leukocyte and lymphocyte. CRP or fibrinogen was not a significant predictor for disease severity.

ROS are produced by inflammatory cells activated in infectious processes, and have important functions in signal transduction and the immune system [22–24]. A minimal increase in the production of ROS may evoke normal immune function, but higher levels of ROS were shown to increase inflammatory cytokines, and to disrupt biomolecules such as lipids, proteins, nucleic acids leading to a loss of immune function [25,26]. Antioxidant defense mechanisms act to keep ROS at a certain level. Disruption of the balance in favor of ROS may be involved in diabetes mellitus or cancer [26]. As shown in previous studies, viral infections may induce ROS production and decrease antioxidant defenses as a result of oxidative stress [20,27,28]. Bacterial and viral pneumonia were shown to increase oxidative stress markers such as malondialdehyde and advanced oxidation protein products [29].

OS and ROS levels increase in COVID-19 infection, and seem to be associated with disease severity or co-existing diseases such as diabetes mellitus or obesity [30,31]. The effect of ROS on alveolar epithelium may contribute to respiratory failure in severe COVID-19 pneumonia [16]. ROS injury may lead to changes in the N-terminal region of albumin, which may be defined as IMA. IMA was shown to be an indicator of endogenous ROS production [20]. It was seen that IMA levels were higher in a number of clinical conditions such as renal failure or myocardial infarction [19]. Studies regarding the clinical importance of IMA in COVID-19 infection are limited. In one study analyzing IMA levels in 60 patients with PCR positivity for COVID-19 infection and 24 controls, infected patients were divided into early infection (IgG anti-S1 protein negative) and acute infection (IgG anti-S1 protein positive) [32]. They found that IMA levels were higher in infected patients than those in controls, and higher in early infection than those in acute infection. They proposed a cut-off value of > 59.26 mg/mL to discriminate early infection (area under curve, AUC: 0.94); the method of IMA measurement was different from that in our study. We included only infected patients and did not measure antibody titers in our patients. Similarly, in another study, the IMA levels were found to be higher in SARS-CoV-2 pneumonia than those in controls [20]. These findings suggest increased endogenous oxidative damage in COVID-19 infection. Hypoxia and tissue ischemia were shown to be a part of the pathophysiological process developed in SARS-CoV-2 infection [33]. Increased IMA levels in COVID-19 infection may be explained by tissue ischemia.

Beside the discriminating role of IMA in COVID-19 infection, it was shown to be important also in the detection of severe COVID-19 infection [20]. In the study analyzing IMA levels in SARS-CoV-2 pneumonia, they found that IMA was higher in SARS-CoV-2 pneumonia patients than in the control group [20]. In addition, there was an increase in other endogenous markers of OS, such as NOX 4 (nicotinamide adenine dinucleotide phosphate oxidase 4) or malondialdehyde or coenzyme Q10, in SARS-CoV-2 pneumonia. They also grouped the patients according to radiological findings, and found that CoQ10, malondialdehyde and IMA levels were higher in those COVID-19 patients with severe pulmonary involvement. Our findings also suggest that IMA level was associated with the severity of COVID-19 infection. In contrast, we grouped our patients not only in accordance with radiological findings, but on a combination of clinical and radiological findings. In another study analyzing 160 patients with COVID-19 infection, IMA levels were found to be an important predictor for intensive care unit (ICU) admission or increased oxygen need, but not for mortality [21]. In receiver operating characteristic (ROC) curve analysis for ICU admission, they found that inflammatory biomarkers had a higher area under curve (AUC) level than that for IMA. In that study, the cut-off value of IMA for prediction of ICU admission was found to be 0.17 absorbance units which was lower than that for most of our patients not requiring ICU admission. They also found that thiol, advanced oxidation protein products, IL-6, presepsin, or calprotectin might predict increased oxygen need. We could not analyze these parameters. In our study, some patients in the severe/critical disease group were also admitted to the ICU, and had higher IMA levels. In a previous study, some patients had elevated levels of IL-6, and some patients had elevated levels of calprotectin, while in some cases both were elevated [21]. The measurement of various parameters of ROS and inflammation together with IMA may be important. The combination
of IMA and pregnancy-associated plasma protein-A (PAPP-A) was shown to increase prediction sensitivity for early stage COVID-19 infection [32].

IMA was found to be correlated with other endogenous OS markers, such as CoQ10, malondialdehyde, and NOX4 in SARS-CoV-2 pneumonia [21]. In that report, CoQ10 was also found to be correlated with CRP and ferritin levels [21]. We did not measure other OS markers, but analyzed inflammatory markers. We revealed that LDH, procalcitonin, ferritin, NLR, neutrophil, leukocyte and lymphocyte were important factors in predicting disease severity, but that IMA was the most important predictor for severe disease. NLR was shown to be associated with disease course in various clinical conditions such as diabetes mellitus, sarcopenia, malignancy, pneumonia, or thyrotoxicosis [34–37]. NLR was also found to be an important predictor for severity of disease and mortality in SARS-CoV-2 pneumonia [38–42]. We revealed that IMA was positively correlated with CRP, ferritin, D-dimer, procalcitonin, fibrinogen, LDH, levels of neutrophil, leukocyte, NLR and NLER. These findings suggest that endogenous oxidative damage may play an important role in the pathogenesis of SARS-CoV-2 pneumonia, and IMA, as an OS marker, may be used to predict the severity of the pneumonia. However, in a study that included 40 adults and 46 children with COVID-19 infection, IMA levels did not predict the presence or the severity of COVID-19 in either the adults or children [43]. They found that lower levels of thiols were associated with severe COVID-19 infection. This may indicate that a higher number of patients with COVID-19 infection may be necessary to observe the net effect of oxidative damage on the structure of albumin, in which the level may be significantly altered as a result of inflammation. In a study analyzing ICU admissions in patients with COVID-19 infection, it was found that there was a negative correlation between IMA levels and serum albumin levels [21]. In that study, IMA was found to be positively correlated with fibrinogen, calprotectin, CRP, presepsin, leukocyte and neutrophil levels. Albumin is a negative acute phase reactant, and the level decreased in more than half of the patients with COVID-19 infection [21]. It may also preclude the correct measurement of IMA levels in COVID-19 infection. We did not analyze the correlation between IMA and albumin levels. Albumin is synthesized by the liver, and its level decreases in liver failure as an indicator of defect in liver synthetic capacity. Due to the possibility of alteration in the levels of IMA, we excluded those patients with a diagnosis of chronic liver failure. In one study, IMA levels were found to be higher in cirrhotic patients when compared to controls [44]. They also analyzed the ratio of IMA/serum albumin level, and found that it was higher in cirrhosis. It is unclear whether IMA might be a prognostic factor for SARS-CoV-2 infection or disease severity in those patients, who developed liver insufficiency. In our study, organ failure developed in some patients with severe or critical illness. If possible, repeated measurement of IMA might be beneficial both in predicting the actual risk of progression in the course of the infection and in detecting the effect of organ failure on IMA levels.

Strengths and limitations of the study

One strength of our study was that we analyzed the severity of COVID-19 infection based not only on radiological, but also clinical findings. While the sample size appears to be small, the number is greater than that in the previous reports. We could not analyze other parameters of OS, or measure antioxidant status. We did not measure SARS-CoV-2 antibodies, because we analyzed IMA levels when the infection was diagnosed.

Conclusions

We analyzed a significant number of patients with COVID-19 infection, and found that IMA predicted severe disease. We grouped the severity of the disease based on both the clinical and radiological features of the patients. The IMA level measured at the diagnosis of SARS-CoV-2 infection may serve as a clinically useful marker in predicting disease severity or ICU admission. Repetitive measurements of IMA levels might also be important in ascertaining the predictive role of IMA in the progression of infection. In future studies, IMA levels could be analyzed in conjunction with serum albumin levels, and other markers of inflammation and OS. Future prospective studies with large sample sizes including patients with nephropathy or liver failure will reveal the prognostic value of IMA in SARS-CoV-2 infection in which patients suffered from organ failure.

Acknowledgements

We would like to thank all the authors and laboratory staff who contributed to the study. We are also grateful to our patients who participated in our study.

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Conflict of interests: No conflict of interests is declared.