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Research article

Value of thiol and ischemia modified albumin (IMA) in predicting mortality in serious COVID-19 pneumonia

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ABSTRACT

Background/aim: Viral infections of the respiratory tract are generally related to many factors such as excessive production of cytokines, inflammation, cellular death, redox imbalance or oxidative stress. The aim of this study was to determine the serum levels of thiol and IMA in patients with severe COVID-19 pneumonia to evaluate oxidative stress.

Study design: This was a prospective, sectional cohort study conducted at a pandemics hospital between 01.01.2022 and 01.02.2022.

Methods: A total of 153 patients who had been confirmed with severe COVID-19 pneumonia in the emergency unit were prospectively analyzed. The control group was formed by 50 healthy volunteers with similar age and no chronic disease history. Thiol and IMA levels were statistically compared both in the patient and the control groups, and within the patient groups (survived and non-survival).

Results: While 96 out of 153 patients had survived, 57 patients had non-survival. There was a statistically significant distinction between the survived and non-survival patients with regard to Thiol and IMA levels ($p < 0.001$). The thiol levels in the patient group were significantly lower compared to the control group, and the IMA levels were significantly higher ($p < 0.001$). The sensitivity, specificity and NPV were 70.2%, 86.5% and 83% when thiol cut-off value was ≤345.2 μmol/L (AUC: 0.886, $p < 0.001$). The sensitivity, specificity and NPV were 70.2%, 85.4% and 82.8% when the IMA cut-off was >302.9 ABSU (AUC: 0.875, $p < 0.001$).

Conclusions: Our results demonstrate that thiol and IMA levels may be used as bioindicators for risk classification and mortality in patients with serious COVID-19 pneumonia.

1. Introduction

Clinical progression of Coronavirus disease-2019 (COVID-19) varies from mild flu-like symptoms to severe pneumonia and even death. In order to reduce hospitalization and mortality rates, to predict the development of severe pneumonia and to determine the patients at risk, the pathogenesis of the disease should be understood in detail [1]. Viral infections of the respiratory tract are generally related to many factors such as excessive production of cytokines, inflammation, cellular death, redox imbalance or oxidative stress (OS) [2]. Cytokine storm that develops in patients with COVID-19, leads to serious tissue damage and triggers a pro-inflammatory response [3]. In many pulmonary diseases including coronavirus infection, there is a connection between pro-inflammatory elements and reactive oxygen species (ROS) [4]. The increase in the levels of ROS and reduction in antioxidant defense demonstrated in animal studies have suggested the possible role of OS in the pathogenesis of COVID-19 [5].

Human receptor angiotensin-converting enzyme- 2 (ACE-2) is the functional receptor for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) entering the host cells. Angiotensin-II (a potent vasoconstrictor and a potent OS activator) increases the ROS formation through NADPH oxidase activation and peroxynitrite anion production [6]. Since ACE-2 has an important role in improving OS, the interaction of viral spike proteins and ACE-2 is critical for the viral replication cycle [7]. The reduction of angiotensin-II to angiotensin 1-7 by ACE-2 reduces the OS, as it inhibits NADPH oxidase [8]. When ACE-2 is bound to the spike protein, the cellular concentration of angiotensin-II increases; thereby, the risk for severe disease will also increase [9].

ROS are bound to thiols and thiols are converted to a disulfide. Disulfide may be re-converted to thiols and thereby, thiol-disulfide

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homeostasis (TDH) may be preserved [10]. Dynamic TDH plays an important role in metabolism and homeostasis [11]. The impairment of TDH may be demonstrated by changes in the levels of oxidant or antioxidant molecules [12]. ROS may oxidize the cysteine remnants in the peptidase field of ACE-2 receptors and a receptor-binding domain (RBD) of virus spike proteins and may keep them in oxidized (disulfide) forms on the contrary to reduced (thiol) forms [13]. Hati et al. have seen that when all disulfide bonds are reduced to thiol groups, the binding affinity of both ACE-2 and SARS-CoV-2 spike proteins is significantly impaired [14]. The increased ROS may produce the chemical modification of albumin resulting in an IMA increase. Since serum IMA levels are associated with oxidative balance, when the antioxidant source is decreased, the IMA levels will also increase. Hence, IMA may be used as an effective OS marker [15].

Thiols are the basic components of the antioxidant defense network, as well as the main regulators of the response to oxidants [16]. Furthermore, they are major indicators of cellular proliferation, apoptosis, immune response, and cellular redox reaction [17, 18]. The role of thiol level in the progression of COVID-19 has been of interest recently [19]. Aykaç K et al. have supported the suggestion that the levels of thiol may be used as a marker in predicting the severity of COVID-19 [1]. Studies have also demonstrated that ischemia-modified albumin (IMA) has had an important potential in OS and in patients with community-acquired pneumonia (CAP) [20, 21]. Ducastel M et al. suggested that the imbalance between antioxidant (thiol) and pro-antioxidant (IMA) biomarkers may be correlated to the severity of COVID-19, and that it may predict hospitalization in an intensive care unit (ICU) and mortality [22].

The aim of this study was to determine the serum levels of thiol and IMA in patients with severe COVID-19 pneumonia to evaluate OS, and to investigate their relationship with the prognosis.

2. Materials and method

2.1. Study design

This was a prospective, sectional cohort study conducted at a pandemics hospital between 01.01.2022 and 01.02.2022.

2.2. Patient and control group population

Patients who were clinically, hematologically, biochemically, microbiologically and radiologically diagnosed to have COVID-19 infection, those who fulfilled the inclusion criteria and those who have given written informed consent, were prospectively included in the study. The age and gender of the patients, vital findings on admission and the Glasgow Coma Score (GCS) were recorded on the previously designed forms. In the emergency unit (EU), blood samples were obtained from patients for arterial blood gases analysis and for hematological and biochemical analysis. For confirmation of COVID-19 diagnosis, real-time reverse transcriptase polymerase-chain reaction (PCR) test was performed, in order to evaluate the pulmonary involvement, non-contrast mediated computed thoracic tomography (CT) was performed. Duration of hospitalization, need for mechanical ventilation (MV) (non-invasive/invasive/high-flow nasal cannula oxygen) and outcomes observed in the clinics (discharge/in-hospital mortality) were followed-up and recorded in the forms. For mortality evaluation, the in-hospital mortality was considered.

The diagnosis of severe/critical COVID-19 pneumonia was confirmed according to current directories [23, 24]. PCR positive patients with a thoracic CT report approved by a radiologist were included in the study [25].Those younger than 18 years of age, pregnant women, patients with cardiovascular diseases, chronic portal failure, bacterial pneumonia, bacterial sepsis or renal failure, cancers, immunosuppressed patients, those who were exposed to trauma and those who had not given informed consent, were excluded from the study.

The control group was formed by 50 healthy volunteers with similar age and no chronic disease history. All patients were grouped as those who survived and non-survival. Thiol and IMA levels were statistically compared both in the patient and the control groups, and within the patient groups (survived and non-survival). Additionally, the correlation of thiol and IMA levels were evaluated with the remaining inflammatory indicators.

2.3. Hematological and biochemical analysis

The blood samples obtained in the EU were analyzed for White blood cell count (WBC), neutrophil, lymphocyte, thrombocyte (PLT) count, D-dimer, CRP, procalcitonin (PRC) and albumin levels. 10 cc venous blood samples were obtained from patients with confirmed COVID-19 pneumonia diagnosis within the first 24 h into an EDTA tube, centrifuged at 2000 $\times$g for 10 min and the sera were separated. The serum samples were then stored at 80 °C until analysis for thiol and IMA levels. The thiol levels were analyzed via colorimetric and -5,5' -dithiobis (2-nitrobenzoic acid) methods using the Biotek ® Microplate Reader Kıt (Winooski, Vermont, U.S.A.). IMA levels were studied using the BT-Lab ® IMA ELISA Kit (Shanghai, China.) and ELISA methods. Albumin-adjusted IMA (AAIMA) was calculated according to the formula = [(ındividual serum albumin concentration/median albumin concentration of the population) $\times$ IMA value [26].

2.4. Ethical situation

The study was approved by the Local Ethics Committee of Necmettin Erbakan University Faculty of Medicine [date: 03/09/2021 and number: 2021/3326 (6903)]. We declare that this study is compatible with the ethical standards of Helsinki Declaration. Prior to the study, all patients and volunteers were informed about the study and written consents were obtained.

2.5. Statistical analysis

Descriptive analyses were carried out. The categorical data were given as rates and numbers. The categorical data were compared with the Chi-square test. The distribution of the numerical data was analyzed using the visual (histogram and likelihood plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). The normally distributed data were given as mean $\pm$ standard deviation and the non-normally distributed data were given as median and interquartile range (IQR). The normally distributed groups were compared using the Student's t test and the non-normally distributed groups were compared using the Mann-Whitney U test. The correlation coefficients of Thiol and IMA levels with other markers and the statistical significance were calculated with the Spearman correlation test. The likelihood of mortality prediction of the Thiol and IMA levels was analyzed with the receiver operating characteristics (ROC) curve analysis. In the assessment of the area under the curve (AUC), the diagnostic value of the test was interpreted to be statistically significant when the type 1 error level was below 5%. The AUC values of ROC analyses were compared with the DeLong method using the MedCalc program. Cut-off values were calculated with the Youden index. The sensitivity, specificity, and negative predictive values (NPV) of the cut-off values were calculated. A p level of <0.05 was accepted to be statistically significant in all tests. Statistical analyses were performed using the IBM SPSS version 22 and MedCalc version 20 programs.

3. Results

Table 1 demonstrates the comparison of the age, gender, vital and laboratory findings of the patients in the groups who survived and the group who non-survival. Among the 153 patients, 96 survived and 57 non-survival. The mean age of the patients was 64 years (IQR 26). The number of male patients was 86 (75.4%). The mean age among the dying

Table 1. Characteristics of patients enrolled in the study.

Variables		All patients (n = 153)	Survivors (n = 96)	Non-survivors (n = 57)	p-Value
Age, (years)[a]		64 (48–74)	58.65 (46–72)	67.35 (55.7–82)	**0.001**
Gender[c]	Male	86 (75.4)	51 (36–37)	35 (37.6–38.2)	0.318
	Female	67 (75.3)	45 (67.2)	22 (32.8)	
Fever, (°C)[a]		37 (36.5–37.8)	36.5 (1)	37.9 (0.7)	**<0.001**
Heart rate, (min.)[a]		85 (66.7–115)	74 (65–85)	125 (113.7–135)	**<0.001**
Saturation, (%)[a]		75 (68–78)	76 (75–80)	67 (59–75)	**<0.001**
Respiratory rate, (minute)[a]		18 (16–28)	16 (14–18)	30 (26–35)	**<0.001**
SBP, (mmHg)[a]		124 (85–145)	138 (125–150)	78 (72–85)	**<0.001**
PaCO2, (mmHg)[a]		42 (35–49.2)	38 (34–43.5)	51 (43.7–57.2)	**<0.001**
PaO2, (mmHg)[a]		62 (50–65)	64.3 (55–68)	53 (50–62)	**<0.001**
GCS[a]		13 (11–14)	14 (13–15)	11 (10–12)	**<0.001**
WBC, (10^3/mL)[a]		9.6 (6, 5–15)	7.7 (5.65–10)	16.2 (13.1–19.5)	**<0.001**
Neutrophil, (10^3/mL)[a]		8.6 (6–13.6)	6.5 (5.2–8.6)	15.4 (12–18)	**<0.001**
Lymphocyte, (10^3/mL)[a]		0.7 (0.4–1.225)	0.5 (0.3–0.8)	1.3 (0.7–1.525)	**<0.001**
PLT, (10^3/mL)[a]		188 (135–256.7)	144 (113.5–185)	273 (234–334.7)	**<0.001**
Albumin, (g/L)[a]		30.2 (25.3–35)	34.4 (31–36.3)	25 (23.3–26.5)	**<0.001**
D-dimer, (μg/mL)[a]		980 (345–3432.5)	372.5 (300.5–1110)	4690 (1847.7–6870)	**<0.001**
CRP, (mg/L)[a]		78 (4–198.5)	5.5 (2.4–66.5)	240 (176–334)	**<0.001**
PRC, (ng/ml)[a]		1 (0.3–23.2)	0.5 (0.2–1.1)	29 (18.8–38)	**<0.001**
THİOL, (μmol/L)[b]		363 ± 45	386 ± 35	325 ± 33	**<0.001**
IMA, (ABSU)[b]		268 ± 76	231 ± 62	330 ± 55	**<0.001**
AAIMA, (ABSU)[b]		265 ± 70	260 ± 72	273 ± 66	0.270
Length of stay in hospital, (day)[a]		14 (7)	14 (6)	15 (8)	0.033
MV support[c]		76 (49.7)	22 (28.9)	54 (71.1)	**<0.001**

[a] Data are presented as median (IQR), [b] Data are presented as mean ± standard deviation, [c] Data are presented as n (%), IQR: interquartile range, SBP: systolic blood pressure, GCS: Glascow Coma Scale, WBC: White blood cell, PLT: Platelet, CRP: C-reactive protein, PRC: procalcitonin, IMA: ischemia-modified albumin, MV: mechanical ventilation, AAIMA: albumin-adjusted ischemia-modified albumin.

group was significantly higher between the groups and no significant difference was observed with regard to gender ($p < 0.001$ and $p = 0.318$, respectively). Oxygen saturation, systolic tension, GCS, PaO2 and albumin and thiol levels were significantly lower in the dying group ($p < 0.001$ for all). Furthermore, the temperature, pulse, and respiratory rate, PaCO2, WBC, neutrophil, lymphocyte and thrombocyte counts, D-dimer, CRP, PRC, IMA levels and MV support were significantly higher in the dying group ($p < 0.001$ for all). However, no significant difference could be found between the two groups with regard to AAIMA ($p = 0.270$).

The mean levels of thiol, IMA and AAIMA were 342 ± 43 μmol/L, 301 ± 76 ABSU and 276 ± 71 ABSU among patients who received MV support, and 385 ± 37 μmol/L, 235 ± 61 ABSU and 263 ± 69 ABSU among those who did not receive MV support. The thiol level was significantly lower, and the IMA level was significantly higher among patients who received MV support ($p < 0.001$ for all). However, no significant difference could be found between the two groups with regard to AAIMA ($p = 0.649$).

Table 2 demonstrates the comparison of age, gender and thiol and IMA levels between the patients and the healthy controls, where the Thiol level was significantly lower and IMA level was significantly higher in the patient group ($p < 0.001$ for all).

Figure 1a and 1b demonstrates the ROC analysis of thiol and IMA levels in the patient and the control groups, and the cut-off and AUC values of thiol and IMA have been demonstrated in Table 3. Accordingly, the sensitivity, specificity and NPV were 82.4%, 90% and 62.5% when the thiol cut-off was ≤411.2 μmol/L (AUC: 0.931, $p < 0.001$). The sensitivity, specificity and NPV were 77.8%, 88% and 56.4% when the IMA cut-off was >201.2 ABSU (AUC: 0.928, $p < 0.001$).

Table 4 demonstrates the sensitivity, specificity and NPV calculated according to the cut-off values and AUC values of thiol and IMA in predicting mortality. Accordingly, the sensitivity, specificity and NPV were 70.2%, 86.5% and 83% when AUC value of thiol was 0.886, and the cut-off value was ≤345.2 μmol/L. The sensitivity, specificity and NPV were 70.2%, 85.4% and 82.8%, and AUC value was 0.875 when the IMA cut-off was >302.9 ABSU ($p < 0.001$ for all). Figure 2a and 2b demonstrates the ROC analysis of thiol and IMA in predicting mortality.

In the correlation analysis, a positive and strong correlation was observed between thiol and albumin ($r = 0.810$, $p < 0.001$). Furthermore, a negative and moderate correlation was determined between thiol and IMA, WBC, neutrophil, lymphocyte, PLT, D-dimer, CRP, and PRC (Table 5).

4. Discussion

Acute inflammation, cytokine storm, acute thromboembolic events and impaired oxidant-antioxidant balance indicate a possible relationship between the pathophysiology of COVID-19 and OS [27]. There is a strong relationship between inflammation and OS; one is easily induced by the other [28]. This relationship may importance in the severity of COVID-19 [29]. Furthermore, it is known that OS, which develops as a result of increased ROS level and impaired antioxidant balance, has a valuable role in the pathogenesis of viral replication and virus-related

Table 2. Comparison of Thiol and IMA values for patient and control group.

		Patient (n = 153)	Control (n = 50)	P value
Age, (years)[a]		64 (48–74)	46 (41–53)	**<0.001**
Gender[c]	Male	86 (75.4)	28 (24.6)	0.318
	Female	67 (75.3)	22 (24.7)	
Thiol, (μmol/L)[b]		363 ± 45	448 ± 32	**<0.001**
IMA, (ABSU)[b]		268 ± 76	120 ± 60	**<0.001**

[a] Data are presented as median (IQR).
[b] Data are presented as mean ± standard deviation.
[c] Data are presented as n (%), IQR: interquartile range, IMA: ischemia-modified albumin.

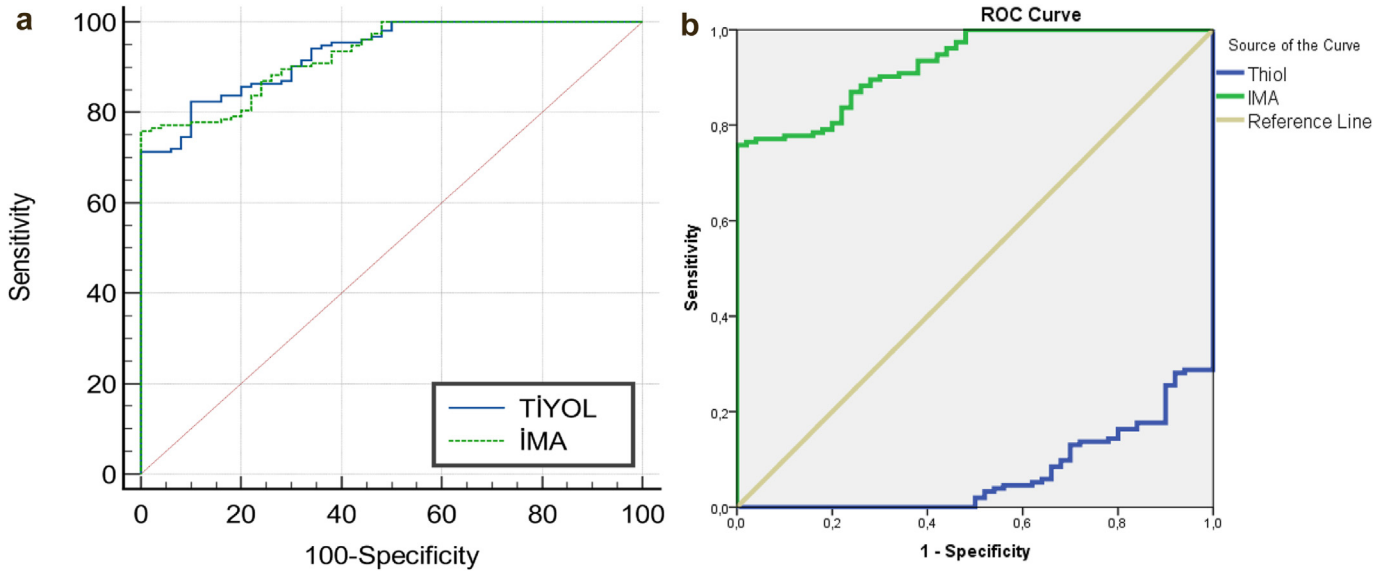

Figure 1. Receiver operating characteristic analysis for the best cutoff values of Thiol and IMA values in patient and control group. 1a: ROC analysis was performed with Medcalc program [X-axis label (100-specificity)]. 1b: ROC analysis was performed with the SPSS program [X-axis label (1-specificity)].

Table 3. Predictive value of the Thiol and IMA for patient and control group.

	AUC	95% CI		Cut-off	Sensitivity (%)	Specificity (%)	NPV	P
		Lower limit	Upper limit					
Thiol, μmol/L	0.931	0.897	0.964	≤411.2	82.4	90	62.5	<0.001
IMA, ABSU	0.928	0.894	0.962	>201.2	77.8	88	56.4	<0.001

IMA: ischemia-modified albümin, AUC: Areas under the ROC curve, CI: confidence interval, NPV: negative predictive value.

Table 4. Predictive value of the Thiol and IMA in predicting mortality.

	AUC	95% CI		Cut-off	Sensitivity (%)	Specificity (%)	NPV	P
		Lower limit	Upper limit					
Thiol, μmol/L	0.886	0.833	0.939	≤345.2	70.2	86.5	83	<0.001
IMA, ABSU	0.875	0.818	0.932	>302.9	70.2	85.4	82.8	<0.001

IMA: ischemia-modified albümin, AUC: Areas under the ROC curve, CI: confidence interval, NPV: negative predictive value.

diseases [30]. Many studies have suggested that OS indicators may be used in the early prediction of COVID-19-related negative outcomes [2, 29, 31]. Doğan et al. demonstrated significantly high total oxidant status (TOS) levels and significantly low total antioxidant status (TAS) levels in the patients with COVID-19 compared to the control group [32]. Erel et al. reported that a 0,949 AUC value of thiol could perfectly discriminate patients with COVID-19 from healthy controls and was related to the severity of the disease [33]. In our study, the thiol levels in the patient group were significantly lower compared to the control group, and the IMA levels were significantly higher ($p < 0.001$). Besides, the AUC values calculated for both indicators were high for the patient and control groups (0.931 and 0.928, respectively). Therefore, thiol and IMA may be used as useful indicators to estimate the severity and risk classification of COVID-19.

Thiol levels decrease in many infectious/inflammatory processes and when OS is increased [1, 34]. It has been demonstrated in recent studies that thiol levels are lower in patients with severe COVID-19, related to its consumption [1, 12, 22, 33]. Kalem et al. reported that reduced levels of thiol was effective in predicting both the diagnosis and the severity of COVID-19. They added that thiol may be used in the triage and early management of these patients [12]. Ducastel et al. concluded that thiol was the best bioindicator that predicts referral to the ICU when its cut-off value was 154 μmol/L (AUC = 0.762, 80% sensitivity, 65% specificity) [22]. In our study, thiol levels were observed to be significantly lower in the non-surviving group compared to the surviving group ($p < 0.001$). Likewise, thiol levels were different between patients receiving and not receiving MV support ($p < 0.001$). Therefore, thiol levels measured in the first 24 h may predict the possible need for intensive care in the future and the severity of COVID-19. Additionally, it may be used in predicting mortality when its cut-off value is ≤345.2 μmol/L, with a 70.2% sensitivity, 86.5% specificity, 83% NPV and 0.886 AUC value.

Many infectious diseases lead to inflammation, including COVID-19 pneumonia [35]. It has been reported that antioxidant defense is decreased in addition to neutrophil infiltration and increased ROS levels in viral infections [31]. It is known that inflammation indicators such as CRP, PRC, D-dimer, and ferritin are increased in patients with COVID-19, which are related to the severity of the disease [36, 37]. In two recent studies, a strong correlation was demonstrated between these indicators and thiol and TOS [32, 33]. Ducastel et al. reported a negative correlation between IMA and thiol levels ($r: -0.506$, $p < 0.001$) [22]. In our study, a moderate negative correlation was detected between thiol and IMA levels, compatible with the literature. This seems to be due to the relationship between OS and inflammation that is observed in patients with severe COVID-19.

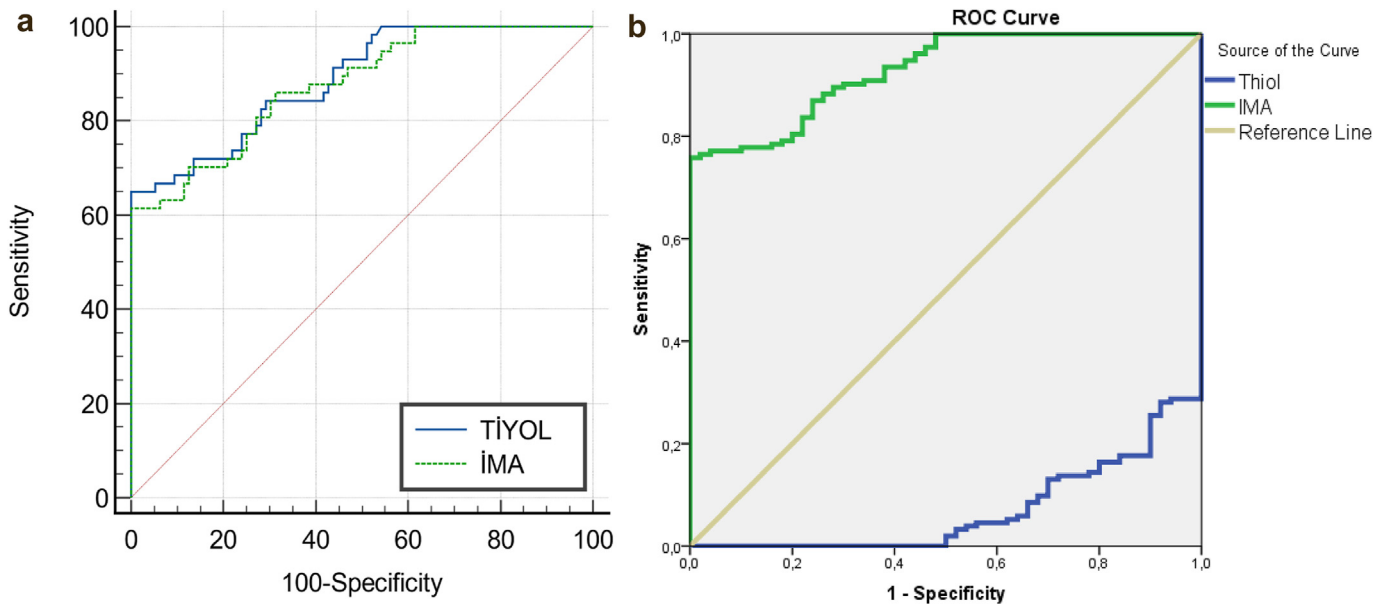

Figure 2. Receiver operating characteristic analysis for the best cutoff values of Thiol and IMA values in predicting mortality. 2a: ROC analysis was performed with Medcalc program [X-axis label (100-specificity)]. 2b: ROC analysis was performed with the SPSS program [X-axis label (1-specificity)].

The plasma compartment has relatively low concentrations of thiols and plenty of albumin. As in COVID-19, in increased inflammation and OS-related pathophysiological processes, albumin is irreversibly oxidized [38, 39]. It has been suggested in many studies that, hypoalbuminemia detected on admission could be predictive of the negative outcomes of COVID-19 [40, 41]. Ducastel et al. demonstrated lower albumin levels in the patient group with critical COVID-19, and a significant correlation between thiol and albumin ($r = 0.615$, $p < 0.001$) [22]. In our study, we detected a moderate negative correlation between thiol and WBC, neutrophil, lymphocyte and PLT count, D-dimer, CRP and PRC, and a strong positive correlation with albumin. These outcomes indicate the role of thiol, as well as OS parameters, in the pathophysiology of COVID-19, as in the inflammation parameters.

IMA is formed as a result of the modification of N-terminal cobalt binding region due to the secretion of ROS from ischemic tissue. This new albumin with impaired Cobalt-binding ability, is one of the earliest predictors of ischemia [42]. IMA may play a role in many pathological processes including pneumonia where the balance between oxidant and antioxidant systems are impaired. Bolatkale et al. reported significantly high levels of IMA in adult patients with CAP and a positive correlation with CRP [21]. Recent studies also demonstrate high IMA levels in patients with COVID-19 compared to control groups [1, 43]. In our study, the IMA levels were observed to be higher in the patient group compared to the control group. Likewise, it was significantly higher among the non-surviving group compared to the surviving group ($p < 0.001$). Since IMA has high sensitivity, specificity, and AUC values for predicting mortality according to the ROC analysis, we believe that the power of IMA in predicting mortality in patients with severe COVID-19 pneumonia should not be underestimated.

Table 5. Correlation between Thiol, IMA and other markers.

	THİOL		IMA	
Markers	Correlation coefficient	p value	Correlation coefficient	p value
Thiol	1	-	−0.631	<0.001
IMA	−0.631	<0.001	1	-
WBC	−0.504	<0.001	0.908	<0.001
Neutrophil	−0.541	<0.001	0.877	<0.001
Lymphocyte	−0.505	<0.001	0.806	<0.001
PLT	−0.560	<0.001	0.886	<0.001
Albumin	0.810	<0.001	−0.510	<0.001
D-dimer	−0.557	<0.001	0.865	<0.001
CRP	−0.574	<0.001	0.875	<0.001
PRC	−0.563	<0.001	0.882	<0.001

Correlation coefficient: Spearman's rho, IMA: ischemia-modified albümin, WBC: White blood cell, PLT: Platelet, CRP: C-reactive protein, PRC: procalcitonin.

5. Limitations

Our study is a single-center study with relatively low sample size and including only critical/serious cases; therefore, the outcomes cannot be generalized. The second limitation was smoking, alcohol consumption, daily energy or protein need, nutritional support, body mass index and routine medications prior to hospitalization may have affected the inflammatory and OS parameters [44]. The third limitation was that due to its high cost, the dynamic changes in the levels of thiol and IMA could not be followed-up. Studies with longer follow-up periods and daily measurements are required.

6. Conclusion

Our results demonstrate that thiol and IMA levels may be used as indicators for risk classification and mortality in patients with severe COVID-19 pneumonia. Furthermore, correlations of thiol and IMA with other indicators of inflammation support their relationship with the severity of COVID-19.

Declarations

Author contribution statement

Tarık Acar: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Birsen Ertekin: Conceived and designed the experiments; Performed the experiments; Wrote the paper.

Mehmet Yortanlı: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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