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Predictive Value of Thiol-Disulfide Homeostasis and Ischemia-Modified Albumin on Survival in Patients with Sepsis

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ABSTRACT

Objective: Sepsis is a dysregulated systemic inflammatory and oxidative response to infection. Thiol–disulfide homeostasis (TDH) has a crucial role in the protection from oxidative stress and is a reliable indicator of oxidative stress. Furthermore, ischemia-modified albumin (IMA) is an indicator of oxidative-stress-related tissue damage. In this study, we determined the predictive value of TDH and IMA on 28-day mortality in patients undergoing sepsis.

Materials and Methods: We collected blood samples from adult patients undergoing sepsis at the time of admission to the intensive care unit to determine TDH and IMA levels. Concurrently, we calculated Sequential Organ Failure Assessment (SOFA) scores to weigh the severity of sepsis. Moreover, we followed up the patients for 28-day intra-hospital mortality. We statistically analyzed the study parameters of the patients in both the survivor and non-survivor groups.

Results: Forty-six patients with sepsis were enrolled. Among them, 27 survived at the end of the 28-day follow-up period. The mean age of the patients was 73.07±13.87 years, and 43.5% of them were female. The mean SOFA score was significantly higher in the non-survivor group ($p<0.05$). However, no significant differences in the total thiol, native thiol, disulfide, and IMA levels at baseline were observed between the survivor and non-survivor groups ($p>0.05$ for all). Receiver operator characteristics (ROC) and area under the curve (AUC) analysis revealed that IMA and thiol parameters had no predictive power on the survival of patients with sepsis.

Conclusion: This study showed that baseline TDH parameters and IMA levels were not significantly different between survivors and non-survivors of sepsis and were not related to the prediction of mortality.

Keywords: Sepsis, oxidative stress, protein disulfide reductase, survival, mortality

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INTRODUCTION

Sepsis is defined as fatal organ dysfunction induced by the dysregulated systemic inflammatory response of the host to infection (1). The incidence of sepsis is approximately 6% among patients admitted to the hospital (2). The mortality rate of patients with sepsis is 28.6%, which is increasing with age and reaches up to 38.4% in patients aged over 85 years (2).

In the early stages of sepsis, increased production of inflammatory mediators remarkably increases the oxidative stress state of the patient. In the second stage, while the inflammatory mediator production continues, synthesis and secretion of anti-inflammatory mediators co-occur to maintain a steady state between pro-inflammatory and anti-inflammatory mechanisms. If this balance cannot be obtained and the inflammatory and oxidative state predominates, devastating outcomes such as multiple organ failure or death may occur due to sepsis.

The discovery of survival-related biomarkers in sepsis has long been of interest. In this sense, an increasing number of publications have focused on oxidative stress-related predictors of a worse outcome in sepsis. We have learned that oxidative stress causes loss of function in proteins, which have vital intracellular and extracellular functions. In a recent study, thiol–disulfide homeostasis (TDH) has increasingly become a reliable indicator of oxidative stress (3). TDH significantly contributes to protecting molecules from oxidative damage (4). This physiologically prime pathway plays essential roles in maintaining intracellular signaling, protein synthesis, and preserving the genomic structure (5). Several studies have shown that increasing disulfide levels are related to increased oxidative stress in infectious conditions such as pneumonia (6) and neonatal sepsis (7). Alternatively, disruption of TDH has been implicated in the pathogenesis of noninfectious conditions such as ankylosing spondylitis (8), parathyroid disorders (9), and coronary artery disease (10), though some controversial findings have been reported (11).

Recently, ischemia-modified albumin (IMA) has attracted attention in terms of oxidative stress-related damage to tissues (12). Under normal conditions, albumin itself has antioxidant properties. The cause of IMA production in tissues is the oxidative stress occurring after acute ischemia. Conversely, the recovery from the ischemic state returns

Table 1. General characteristics and baseline laboratory findings of the patients

	Total (n=46)	Survivors (n=27)	Non-survivors (n=19)	p
Age, mean (SD)	73.07 (13.87)	71.89 (13.82)	74.74 (14.13)	0.499
Gender, n (%)				
Female	20 (43.5)	11 (23.9)	9 (19.6)	0.655
Hypertension, n (%)	32 (69.6)	20 (43.5)	12 (26.1)	0.428
Diabetes mellitus, n (%)	13 (28.3)	7 (15.2)	6 (13.0)	0.675
Dyslipidemia, n (%)	6 (13.0)	2 (4.3)	4 (8.7)	0.213
Chronic kidney disease, n (%)	11 (23.9)	5 (10.9)	6 (13.0)	0.484
Congestive heart disease, n (%)	19 (41.3)	12 (26.1)	7 (15.2)	0.606
Coronary artery disease n, (%)	9 (19.6)	5 (10.9)	4 (8.7)	1.000
COPD, n (%)	9 (19.6)	5 (10.9)	4 (8.7)	1.000
WBC (cells/uL), median (IQR)	14700 (12250)	15850 (10138)	13400 (16350)	0.668
Hemoglobin (g/dL), median (IQR)	9.9 (2.6)	9.9 (2.8)	9.9 (2.5)	0.635
Platelets (cellsx103/uL), median (IQR)	191 (199.5)	188 (140.8)	212 (290.0)	0.835
Glucose (mg/dL), median (IQR)	140 (105.5)	131.5 (143)	148 (94.5)	0.709
Urea (mg/dL), median (IQR)	120 (95.5)	121 (108.5)	119 (92.0)	0.618
Creatinine (mg/dL), median (IQR)	1.54 (1.63)	1.44 (1.53)	1.72 (2.50)	0.247
AST (U/L), median (IQR)	30 (23.5)	32 (22.5)	28 (26.5)	0.459
ALT (U/L), median (IQR)	20 (19.5)	20 (32.8)	20 (16.5)	0.262
Potassium (mmol/L), median (IQR)	4.21 (1.65)	4.24 (1.67)	4.21 (1.39)	0.720
Sodium (mmol/L), median (IQR)	141 (10.5)	137 (14.0)	141.5 (8.3)	0.123
Procalcitonin, (ng/ml) median (IQR)	3.11 (9.84)	2.74 (7.54)	8.32 (27.46)	0.164
CRP (mg/L), median (IQR)	150 (128.3)	126.3 (124.9)	174.1 (128.9)	0.138

SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; IQR: Interquartile range; WBC: White blood cell count; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CRP: C-reactive protein

the IMA level to normal. Therefore, IMA is considered a sensitive indicator of oxidative stress-related conditions (13). In patients with severe sepsis, a higher baseline level of IMA was an independent predictor of short-term mortality (14); however, other noninfectious conditions, such as heart failure (15), aorta dissection (16), and acute pancreatitis (17), also increased circulating IMA levels.

In this study, we determine whether alterations in TDH and IMA metabolism can be used to estimate the likelihood of 28-day mortality in patients with sepsis admitted to the intensive care unit (ICU).

MATERIALS and METHODS

Study Design and Patients

This study prospectively enrolled patients diagnosed with sepsis or septic shock admitted to an ICU of a tertiary hospital. The diagnosis of sepsis or septic shock was based on the criteria accepted in the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) published jointly by the Society of Critical Care Medicine and European Society of Intensive Care Medicine in 2016 (18) and the International Sepsis and Septic Shock Management Guidelines updated by the same institutions in 2017 (1). Patients with the following conditions were excluded from the study: a history of advanced dementia, end-stage cancer, cirrhosis, and incomplete data. The institutional review board approved the study protocol (ethics committee approval number: 46418926-18/55). Informed written consent was obtained for each patient. All procedures followed the ethical standards of the Turkish Ministry of Health and Good Clinical Practices Guidelines published by the Turkish Medicine and Medical Devices Agency.

Venous blood samples were collected on the day of sepsis diagnosis, centrifuged at 12,000 rpm for 15 min, and stored at −800°C. All samples were run in a single session to measure native thiol, total thiol, disulfide, and IMA levels.

Data on demographics, anthropometrics, and chronic diseases were obtained from the patients' electronic health records. Sequential Organ Failure Assessment (SOFA) scores were calculated at baseline to determine the severity of sepsis (19).

The predefined follow-up period was 28 days, and the primary outcome measure was mortality from any cause.

Determination of Serum TDH Status

We used an automatic and spectrophotometric method to measure serum native thiol and serum total thiol levels and to determine the exact thiol–disulfide status (20). In this method, dynamic disulfide bonds (- S – S -) are reduced to functional thiol groups (- SH) using sodium borohydride (NaBH4). After complete removal of remnant NaBH4 molecules using formaldehyde, the modified Ellman re-

Table 2. Study parameters and their comparisons

	Survivors (n=27)	Non-survivors (n=19)	p
SOFA, mean (SD)	9.93 (3.40)	12.63 (3.73)	**0.014**
Total thiol (μmol/L), mean (SD)	174.90 (41.70)	188.16 (51.86)	0.342
Native thiol (μmol/L), mean (SD)	154.61 (43.89)	165.06 (50.45)	0.459
Disulfide (μmol/L), mean (SD)	10.14 (3.84)	11.55 (5.31)	0.302
Disulfide/native thiol, median (IQR)	6.77 (5.62)	7.02 (3.79)	0.956
Disulfide/total thiol, median (IQR)	5.96 (4.42)	6.16 (2.92)	0.956
Native thiol/total thiol, median (IQR)	88.08 (8.84)	87.68 (5.85)	0.956
IMA (ABSU), median (IQR)	0.70 (0.26)	0.73 (0.22)	0.354

SD: Standard deviation; SOFA: Sequential Organ Failure Assessment; IMA: Ischemia-modified albumin; IQR: Interquartile range; ABSU: Absorbance unit

agent was used to quantify the total thiol content in the samples. Following the serum extraction, the test took approximately 12 min to obtain all parameters. Half of the difference between the native thiol and total thiol levels indicates the dynamic disulfide levels. Finally, the following indices were calculated:

Index 1: (disulfide/native thiol ratio)*100

Index 2: (disulfide/total thiol ratio)*100

Index 3: (native thiol/total thiol ratio)*100

Determination of Serum IMA Levels

To determine IMA levels, we used the albumin cobalt binding test. In this test, serum samples were mixed with 50 mL of 0.1% cobalt (II) chloride and incubated for 10 min. Subsequently, 50 mL of 1.5 mg/mL dithiothreitol was added to the mixture, which was incubated for an additional 2 min. Then, to reduce the binding capacity, 1 mL of 0.9% sodium chloride was added. In addition, we prepared blanks using a similar method; however, we used distilled water instead of dithiothreitol. Finally, we used a 470-nm spectrophotometer to measure the absorbance of samples and expressed the results as absorbance units (13).

Statistical Analysis

Categorical data were presented as absolute numbers and a percentage of the total. The normality of distribution was tested using the Shapiro–Wilk test. Normally distributed data were expressed as mean±standard deviation (SD), and data that are not normally distributed were expressed as median (interquartile range). The differences between the survivor and non-survivor groups were tested using either Student's t-test, the Mann–Whitney U test, or the chi-square test depending on the type and distribution of variables. Not normally distributed continuous variables were log-transformed as necessary. Simple correlations between the study variables and age and gender were calculated using the Pearson correlation (r) test. We performed a receiver operator characteristics (ROC) analysis and calculated the area under the curve (AUC) to assess the ability of the parameters in the study to estimate the 28-day mortality rate. In addition, the cut-off values of the study variables and their sensitivity and specificity to estimate mortality in the ICU were estimated using ROC analysis. P values of less than 0.05 were used to denote statistical significance. Statistical analyses were performed using Statistical Package for the Social Sciences (version 23.0; IBM Corp., Armonk, NY, USA).

RESULTS

The study enrolled 46 patients with sepsis, and 27 of them survived at the end of the 28-day follow-up period. The mean age of the patients was 73.07±13.87 years, and 43.5% of them were female. No statistical difference in age, gender, and comorbidities including hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, congestive heart failure, coronary artery disease, and chronic obstructive pulmonary disease was found between the survivor and non-survivor groups (Table 1). The mean SOFA score of the non-survivors of sepsis was significantly higher than that of the survivors ($p<0.05$) (Table 2).

No significant differences in total thiol, native thiol, and disulfide levels and their indices at baseline were observed between survivors and non-survivors ($p>0.05$ for all parameters). Furthermore, no significant difference in the baseline IMA level was found between the two groups ($p>0.05$ for all parameters).

ROC–AUC analysis revealed that the IMA and thiol parameters had no predictive power on the survival of patients with sepsis (Table 3). ROC curve diagrams are illustrated in Figure 1.

Moreover, patients with above median total thiol, native thiol, disulfide, all three TDH indices, and IMA values at baseline were not different from those having below-median values in terms of 28-day survival ($p>0.05$ for all parameters) (Table 4).

The correlations between age and gender and the study parameters are shown in Table 5. However, none of any study parameters showed any correlation with age or gender. In addition, we studied whether IMA or TDH is correlated with laboratory findings; however, results showed no significant correlations.

DISCUSSION

Although diagnostic and therapeutic interventions have improved recently, sepsis remains the leading cause of mortality in the ICU (1). Therefore, new studies and evidence on the pathophysiology of sepsis continue to accumulate, and most recent studies have focused on the different aspects of inflammation, including the oxidative stress components. In this study, we examined the predictive value of the oxidative stress biomarkers, dynamic TDH and IMA, on 28-day survival among adult patients with sepsis admitted to the ICU. The

Table 3. ROC analyses of patient survival across thiol, disulfide, and IMA results

	ROC			
	Cut-off	**Sensitivity/specificity**	**AUC, CI**	**P**
Total thiol (µmol/L)	166.95	0.704/0.316	0.564, 0.391–0.738	0.462
Native thiol (µmol/L)	177.95	0.370/0.632	0.567, 0.395–0.740	0.441
Disulfide (µmol/L)	10.25	0.556/0.421	0.576, 0.403–0.749	0.384
Disulfide/native thiol	6.31	0.593/0.421	0.505, 0.333–0.676	0.956
Disulfide/total thiol	5.61	0.593/0.421	0.505, 0.333–0.676	0.956
Native thiol/total thiol	86.98	0.593/0.421	0.495, 0.324–0.667	0.956
IMA (ABSU)	0.67	0.667/0.421	0.419, 0.249–0.589	0.355

ROC: Receiver operator characteristics; AUC: Area under the curve; CI: Confidence interval; IMA: Ischemia-modified albumin; SD: Standard deviation; ABSU: Absorbance unit

Table 4. The survival rates of the patients with above- and below-median values

	Median values		**Survivors (n=27)**	**Non-survivors (n=19)**	**p**
Total thiol (µmol/L), n (%)	0.704	Above median	12 (26.1)	12 (26.1)	0.211
		Below median	15 (32.6)	7 (15.2)	
Native thiol (µmol/L), n (%)	185.25	Above median	12 (26.1)	11 (23.9)	0.369
		Below median	15 (32.6)	8 (17.4)	
Disulfide (µmol/L), n (%)	170.25	Above median	13 (28.3)	10 (21.7)	0.765
		Below median	14 (30.4)	9 (19.6)	
Disulfide/native thiol, n (%)	10.48	Above median	13 (28.3)	10 (21.7)	0.765
		Below median	14 (30.4)	9 (19.6)	
Disulfide/total thiol, n (%)	6.90	Above median	13 (28.3)	10 (21.7)	0.765
		Below median	14 (30.4)	9 (19.6)	
Native thiol/total thiol, n (%)	6.06	Above median	13 (28.3)	10 (21.7)	0.765
		Below median	14 (30.4)	9 (19.6)	
IMA (ABSU), n (%)	87.88	Above median	13 (28.3)	10 (21.7)	0.765
		Below median	14 (30.4)	9 (19.6)	

N: Absolute number; %: Percentage of the total; IMA: Ischemia-modified albumin; ABSU: Absorbance unit

Table 5. Correlation between age and gender and TDH, their indices, and IMA measurements

	Age		**Gender**	
	r	**P**	**r**	**p**
Total thiol (µmol/L)	-0.207	0.168	-0.021	0.892
Native thiol (µmol/L)	-0.157	0.297	0.048	0.753
Disulfide (µmol/L)	-0.247	0.098	-0.352	0.057
Disulfide/native thiol	-0.065	0.667	-0.200	0.183
Disulfide/total thiol	-0.067	0.658	-0.198	0.186
Native thiol/total thiol	0.045	0.767	0.187	0.212
IMA (ABSU)	-0.213	0.153	-0.116	0.443

TDH: Thiol–disulfide homeostasis; IMA: Ischemia-modified albumin; ABSU: Absorbance unit; *: Log-transformed value

relationship between oxidative stress markers and sepsis is well established, and several anti-inflammatory agents have been tested for their therapeutic potential (21). In this study, we observed no difference in the baseline blood levels of TDH and IMA between the 28-day survivors and non-survivors of sepsis. To the best of our knowledge, this is the first study to examine the predictive role of TDH in adult sepsis.

Sepsis is a clinical entity dominated by inflammation. In addition, the inflammatory environment worsens oxidative stress. Increased reactive oxygen species in septic shock have been previously reported (22). In addition, TDH is linked to the antioxidant mechanisms of inflammatory environments (6). Similarly, in a recently published study involving neonatal patients, Aydogan et al. (7) have demonstrated that patients with sepsis had lower native thiol and total thiol levels and a higher serum disulfide/total thiol ratio than healthy controls. We failed to include a healthy control group in this study. However, both the survivors and non-survivors had higher native thiol and total thiol levels and a lower disulfide/total

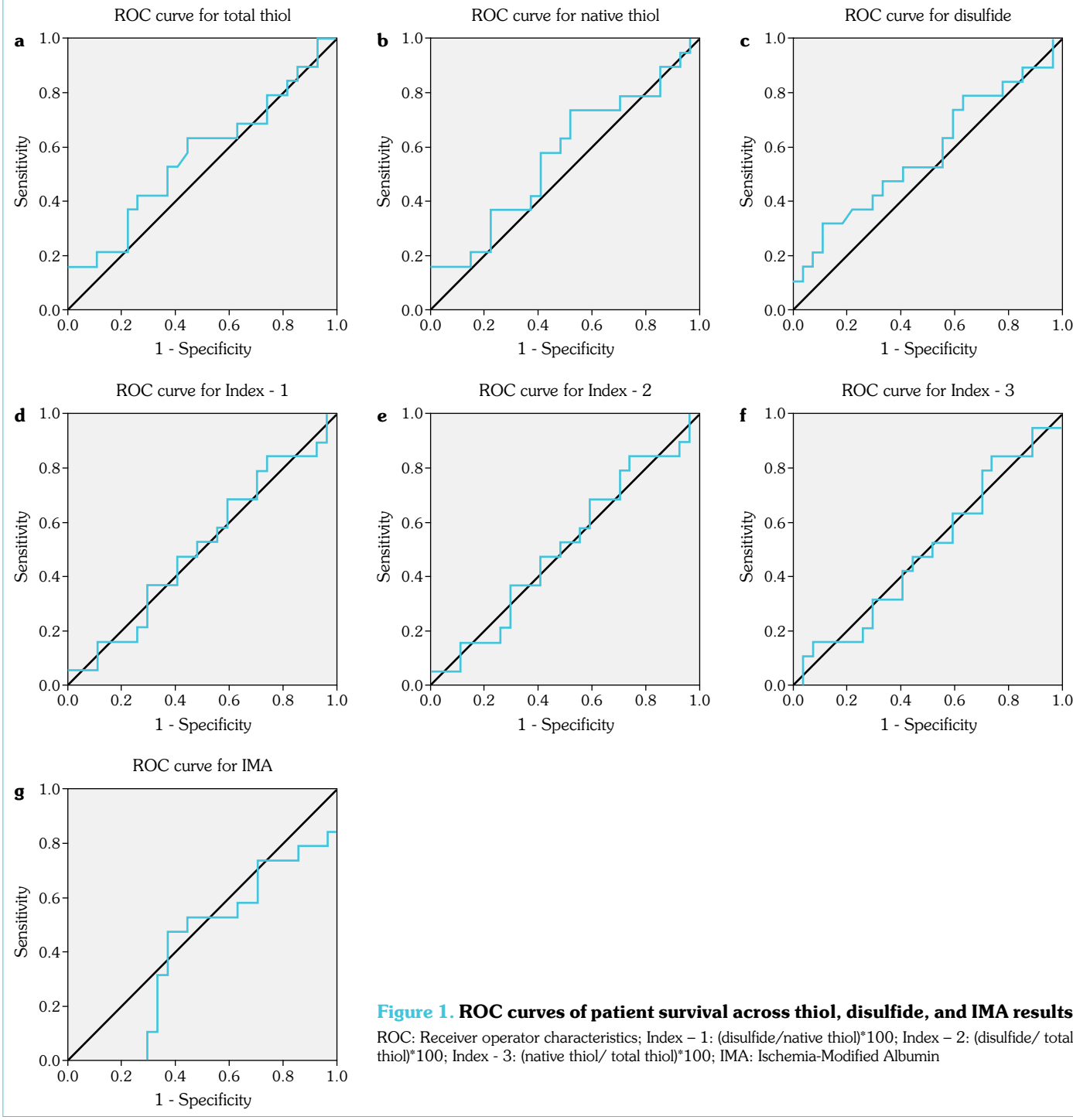

Figure 1. ROC curves of patient survival across thiol, disulfide, and IMA results

ROC: Receiver operator characteristics; Index – 1: (disulfide/native thiol)*100; Index – 2: (disulfide/ total thiol)*100; Index - 3: (native thiol/ total thiol)*100; IMA: Ischemia-Modified Albumin

thiol ratio than healthy individuals in studies that used the same measurement technique as in this study (3, 4, 6). Alternatively, we found no significant differences in the level of thiols and their indices between the survivor and non-survivor groups. These results suggest that despite the association between the dynamic TDH and oxidative responses, these variables do not have a potential predictive value in estimating survival among adult patients with sepsis.

Thiols are a family of organic compounds in the cytoplasm and mitochondria containing a sulfhydryl group (-SH) that specifically binds to cysteine proteins (5). Cysteine residues in the active regions of proteins neutralize reactive oxygen molecules, while thiol level decreases and disulfide bonds increase. These bonds can be reduced by the formation of thiol groups again, and TDH continues (23). The distribution of total thiol occurs in the intracellular and extracellular components. During their distribution, the free form may be oxidized or reduced by glutathione. In addition, thiols can be detected in protein-bound forms. The thiol pool in the plasma is often identified as albumin-bound thiols, while fewer low-molecular-weight thiols can also be present. In conditions with high oxidative stress, the number of thiols decreases to neutralize reactive oxygen molecules, in which sulfhydryl groups play an essential role (5).

In addition to TDH metabolism, we studied IMA for its potential value in predicting survival in patients with sepsis. A study with a similar design as this study has reported that a higher baseline IMA level predicts short-term mortality in patients with sepsis (14). However, that study enrolled patients with severe sepsis and did not report any findings regarding non-severe cases. Similarly, findings from another study involving adult patients with severe sepsis aged younger than 65 years have suggested that IMA is a potential prognostic biomarker (24). In that study, however, the mean age of the patients was 47.5±13.1 years, much younger than the patients in this study (mean age, 73.1±13.9 years). As age plays a key role in the metabolism of albumin (25), the discrepancy between this study and other studies may be related to the age of the recruited patients. With increases in ischemia and reactive oxygen derivatives in the environment, reversible changes occur in albumin, a necessary acute phase reactant with antioxidant properties (26). In clinical situations where inflammation is intense, the N-terminal residue of albumin molecules gains the ability to temporarily bind ions such as copper and cobalt (27). This modified album is called IMA. IMA is considered a marker for diseases characterized by increased oxidative stress (28), particularly sepsis (29). In addition, IMA has a prognostic significance for many clinical conditions such as heart failure (15), aortic dissection (16), and acute pancreatitis (17).

The difference in results between this study and previously published studies (14, 24) may also be caused by the enrollment of patients with different grades of sepsis severity. It is likely that patients with severe sepsis, but not all patients with sepsis, are more prone to die in the ICU when they have serious albumin modification responses on admission.

This study has several limitations. First, we did not include a healthy control group to make firm conclusions about the baseline comparisons. Second, our study was limited by the number of patients enrolled that we could not perform subgroup and adjusted analyses. Third, since we did not have blood culture results, we could not have any information about the microbial sources of sepsis, which have a critical impact on survival.

CONCLUSION

In contrast to what has been reported in some studies on serious conditions, this study showed no significant differences in baseline TDH parameters and IMA levels between survivors and non-survivors of sepsis in a broad range of severity. Studies with more extensive patient series are warranted to confirm the findings in this study.

Ethics Committee Approval: The institutional review board approved the study protocol (ethics committee approval number: 46418926-18/55).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – BBB, RA, MBA, SN, ÖE, HLY, İT; Design – BBB, RA, SN, ÖE, HLY, İT; Supervision – BBB, RA, HLY, İT; Resource – BBB, RA, MBA, SN, ÖE, HLY, İT; Materials – BBB, RA, SN, ÖE, HLY; Data Collection and/or Processing – BBB, RA, MBA, SN, ÖE, HLY, İT; Analysis and/or Interpretation – BBB, İT; Literature Search – BBB, MBA, İT; Writing – BBB, RA, MBA, SN, ÖE, HLY, İT; Critical Reviews – BBB, RA, MBA, SN, ÖE, HLY, İT.

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