RESEARCH

IS DYNAMIC THIOL/DISULFIDE HOMEOSTASIS ASSOCIATED WITH THE PROGNOSIS OF GERIATRIC PATIENTS WITH SEPSIS IN THE INTENSIVE CARE UNIT?

Turkish Journal of Geriatrics
DOI: 10.31086/tjgeri.2022.307
2022; 25(4): 495-503

■ Esra YAKIŞIK ÇAKIR[1]
■ Gamze GÖK[2]
■ Özcan EREL[2]
■ Işıl ÖZKOÇAK TURAN[1]

CORRESPONDANCE

[1] Esra YAKIŞIK ÇAKIR

Phone : +903125085175
e-mail : pavulonmouse@hotmail.com

Received : Jun 21, 2022
Accepted : Nov 27, 2022

[1] Ankara Bilkent City Hospital, Department of Anesthesiology and Clinical of Critical Care, Ankara, Turkey

[2] Ankara Bilkent City Hospital, Department of Biochemistry, Ankara, Turkey

Abstract

Introduction: Sepsis is an important cause of mortality, especially in geriatric patients hospitalized in the intensive care unit. Our study aims to evaluate the effectiveness of thiol / disulfide homeostasis in determining the mortality of geriatric patients admitted to intensive care unit due to sepsis.

Materials and Method: Our study was designed prospectively in patients aged 65 years and older with geriatric sepsis hospitalized in the intensive care unit between January 2018 and March 2019. Thiol-disulfide homeostasis was measured at the time of hospitalization. Demographic and clinical characteristics and thiol – disulfide homeostasis levels were compared in patients with mortality and surviving.

Results: 252 geriatric patients with sepsis were included in the study. A total of 148 (58.7%) of the patients died, 104 (41.3%) were discharged alive. In the group with mortality, native-thiol, total-thiol and disulfide levels were found to be significantly lower compared to the surviving group ($p < 0.05$). In geriatric patients with sepsis; levels of native-thiol less than 209 µmol / L, total-thiol lesss than 248 µmol / L and disulfide being less than 20.4 µmol / L was found as the cut-off value for mortality ($p=0.0001$).

Conclusion: This study showed that low native-thiol, total-thiol and disulfide levels may be associated with mortality in patients with geriatric sepsis hospitalized for the first time in the intensive care unit.

Keywords: Aged; Intensive Care Units; Sepsis; Sulfhydryl Compounds.

INTRODUCTION

Sepsis is the leading cause of morbidity and mortality in patients hospitalized in the intensive care unit (ICU) (1). Older patients have a higher risk for mortality (2). In addition to the age factor in patients developing sepsis, determining other risk factors for patient mortality in ICU is imperative to sepsis prognosis (2,3). Age, vital sign assessment, and other scoring systems are used for evaluation of the mortality data of patients hospitalized in ICU. It is difficult to determine patient mortality in ICU owing to various causative agents and underlying diseases that lead to ICU hospitalization. Therefore, additional parameters are crucial for the evaluation of ICU mortality (3).

Activation of free radicals, reactive oxygen species (ROS), oxidant, and pro-oxidant systems are associated with negative clinical outcomes in aging individuals with sepsis (4); both advanced age and sepsis increase the morbidity and mortality (4,5). Therefore, evaluation of oxidant systems in patients hospitalized in ICU could aid determination of sepsis prognosis (5).

The plasma thiol level is usually measured by using the classical 5,5′-dithiobis-(2-nitrobenzoic) acid (DTNB) and Ellman reagent. This compound is stoichiometrically decreased by free thiols in an exchange reaction, forming disulphide and releasing one molecule of 5-thionitrobenzoic acid. Dynamic thiol/disulfide homeostatis is critical for a number of processes: antioxidant protection, detoxification, signal transmission, apoptosis, regulation of enzymatic activity, transcription factor regulation, and cellular signaling mechanisms (6). Low thiol levels are associated with decreased inflammatory processes, decreased antioxidant activity, and adverse clinical outcomes (7). Furhtermore, dynamic thiol disulphide homeostasis is being increasingly implicated in many disorders. There is also a growing body of evidence demonstrating that an abnormal thiol disulphide homeostasis state is involved in the pathogenesis of a varietyof diseases, including diabetes, cardiovascular disease, malignancy, rheumatoid arthritis, chronic kidney disease, infection diseases, neorological diseases, and liver disorder. Therefore, determination of dynamic thiol disulphide homeostasis can provide valuable information on various normal or abnormal biochemical processes (6).

In this respect, evaluation of thiol/disulfide homeostasis, which is one of the oxidant systems, may be effective in the prognosis of severe sepsis in geriatric patients admitted to ICU (5). There are no previous studies evaluating thiol/disulfide homeostasis in geriatric patients with sepsis. Therefore, the aim of our study was to evaluate the possible relationship of thiol/disulfide homeostasis with mortality in geriatric patients (aged ≥65 years) hospitalized in ICU.

MATERIALS AND METHOD

Ethics committee approval and study design

This study was planned prospectively in geriatric patients (aged ≥65 years) with sepsis; they were hospitalized in the ICU in the Health Sciences University, Anesthesiology and Clinical of Critical Care, Ankara Numune Education and Research Hospital between January 2018 and March 2019. Inpatients were diagnosed with sepsis based on their clinical findings as well as according to the "Third International Consensus Definitions" criteria (8). ICU patients who were <65 years of age and diagnosed with causes other than primary sepsis (trauma, intoxication, metabolic disorders, cardiovascular, and respiratory reasons, etc.) were excluded from the study. Patients' age, sex, number of comorbid disease (diabetes mellitus, hypertension, malignancy/immunodeficiency, respiratory system disease, heart disease, renal disease, central nervous system disease), acute physiology chronic health evaluation (APACHE II) score, sepsis-related organ failure assessment (SOFA) score, duration of mechanical

ventilation (MV), ICU stay, and mortality data were recorded (9,10).

This study was approved by the ethics Committee at Ankara Numune and Research Hospital (date: 28/12/2017, no: E-17-1478). Verbal and written consent was obtained from patients or their legal representative before the study. Our study was conducted in accordance with the Helsinki Declaration principles. In this study, while sampling the geriatric elderly patient group, the definition of "elderly" for age ≥65 years was taken into account, which is the criteria of World Health Organization and the Organization for Economic Co-operation and Development (11,12).

Blood sampling and determination of white blood cell counts and serum levels of C–reactive protein and thiol–disulfide

Venous blood samples were obtained for the determination of white blood cell (WBC) counts, C-reactive protein (CRP) levels, and thiol-disulphide homeostasis status during hospitalization. WBC count was determined with a Cell-Dyn 3700 automated hemocytometer (Abbott, Abbott Park, IL, USA) by drawing the blood into tubes containing ethylenediamine tetra-acetic acid. Serum was separated after blood samples were centrifuged at 1200 rpm for 15 minutes. Serum samples were stored at -80°C until use for thiol-disulfide analysis. Serum CRP concentrations were measured on the Roche Modular P analyzer with a Tinaquant CRP (Latex) high-sensitive immuno-turbidimetric assay (CRP latex HS, Roche kit, Roche Diagnostics, GmbH, Mannheim, Germany). Serum total thiol and native thiol levels were determined by the automated method developed by Erel and Neselioğlu (Roche cobas-c501 automated analyzer, Mannheim, Germany) (6). Thiol/disulfide homeostasis tests were performed using the automatic and spectrophotometric method. The principle of the thiol/disulfide measurement method is the reduction of dynamic disulfide bonds (-S-S-) to functional thiol groups (-SH) with $NaBH_4$. The unused $NaBH_4$ remnants were completely dissociated using formaldehyde; this prevented further reduction of the 5,5'-dithiobis-2-nitrobenzoic acid (DTNB) as well as the disulfide bonds that were formed by the reaction with DTNB. The modified Ellman reagent was used to measure the total thiol content in samples. After serum extraction, it took approximately 12 minutes to measure all the parameters. Dynamic disulfide content was calculated by taking half of the difference between the amount of total thiol and native thiol. Ratio formulas (Index 1: disulfide/native thiol ratio, index 2: disulfide/total thiol ratio, and index 3: native thiol/total thiol disulfide) were used to calculate the dynamic disulfide content.

Data analysis

Statistical analysis of the patient data was performed using SPSS software 17.0 (SPSS, Chicago, IL) and p values <0.05 were considered significant. The conformity of the data to the normal distribution was evaluated with histogram and Kolmogorov-Smirnov test. Mann-Whitney's U-test was used to compare for non-parametric continuous variables and the chi-square test was used to compare for categorical variables. The results were specified as the mean and standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR,25-75) for continuous variables with abnormal distribution. Categorical variables were expressed as frequency and percentage distribution. The thiol / disulfide homeostasis were compared between the mortality groups and the surviving group using multiple logistic regression. The odds ratios (ORs) and 95% confidence interval (CI) were defined in multiple logistic regression analysis. Diagnostic screening tests were used to determine the cut-off for thiol/disulfide homeostasis; additionally, receiver operating characteristic (ROC) curve analysis was also performed (sensitivity, specificity, positive predictive value, and negative predictive value). The area under the curve (AUC) was calculated.

RESULTS

During the study period, 793 patients were admitted in our ICU. According to the inclusion criteria, 252 (31.7%) patients were included in the study; 148 (58.7%) patients died and 104 (41.3%) were discharged. The total mean age of 252 geriatric patients included in the study was 78.2 ± 10.1 (mean ± SD) years. Patients who succumbed to mortality were higher in age, experienced a greater number of comorbid diseases, and had higher APACHE II and SOFA scores; in addition to this, the patients had increased duration of MV and ICU stay. The results were similar between the groups in terms of gender (Table 1). Results were similar between groups with mortality and surviving in terms of WBC counts and indices -1, -2, and -3 (p>0.05). In the surviving group, native-thiol, total-thiol, and disulfide levels were found to be significantly higher and CRP significantly lower, than those in the mortality group (p<0.05) (Table 2).

In addition to thiol / disulfide homeostasis, confounding factors such as age, comorbid disease, and CRP levels can also impact mortality. After adjusting for confounding factors using multiple logistic analysis, patients with mortality had lower levels of native-thiol [OR = 5.15, 95% CI (1.745–8.322), p = 0.002], total-thiol [OR = 2.09, 95% CI (1.119–4.244), p = 0.005], and disulfide [OR = 3.65, 95% CI (2.124–8.103), p < 0.001] than those surviving.

The cut-off value for mortality in geriatric patients with sepsis was 209 (μmol/L) for native-thiol, ≤248 (μmol/L) for total-thiol, and ≤20.4 (μmol/L) for disulfide. The AUC level between 0.7-0.9 is assumed to have moderate accuracy in predictive value. In our results, we found that AUC levels of native-thiol, total-thiol, and disulfide were between 0.7 ile 0.9 which were assumed as moderate accuracy (13). The results are presented in Table 3 as AUC, p-value, sensitivity, specificity, positive predictive value, and negative predictive value. ROC analyses for native-thiol, total-thiol, and disulfide mortality prediction are given in Figure 1.

DISCUSSION

In geriatric patients hospitalized for sepsis, native-thiol, total-thiol, and disulfide levels were significantly lower in the mortality group than in the

Table 1. Comparison of demographic and clinical features of the geriatric patients

Variables	Surviving (n=104)	Mortality (n=148)	P value
Age, (years), [a]	76.1±10.9	81.1±8.0	<0.001*
Male gender, n (%)	46 (44.2)	64 (43.2)	0.489
Comorbid disease, [b]	1 (1-3)	2 (1-4)	<0.001*
APACHE II score, [b]	24 (17-28)	29 (19-38)	<0.001*
SOFA score, [b]	7 (6-10)	10 (8-16)	<0.001*
Duration of MV, (days), [b]	5 (3-18)	7 (4-28)	0.015*
ICU stay, (days), [b]	15 (6-83)	17 (7-96)	0.001*

[a] mean ± standard deviation, [b] median (interquartile range (IQR, 25-75))

*Statistically significant p values are highlighted.

APACHE II: acute physiology and chronic health evaluation score, SOFA: sepsis-related organ failure assessment score, ICU: intensive care unit, MV: mechanical ventilation

Table 2. Comparison of laboratory features of the geriatric patients.

Variables	Surviving (n=104)	Mortality (n=148)	P value
WBC (x10^3/μL), [a]	10 (5-12)	12 (6-14)	0.416
CRP (mg/L), [a]	75 (41-110)	161 (51-214)	<0.001*
Native-thiol, (μmol/L) [b]	218.8±102.9	158.4±71.1	<0.001*
Total-thiol, (μmol/L) [b]	264.1±110.1	192.7±74.3	<0.001*
Disulfide, (μmol/L) [b]	22.5±5.3	17.1±7.0	<0.001*
Index-1, [b]	12.2±5.1	13.5±9.2	0.151
Index-2, [b]	9.5±3.1	9.9±5.2	0.531
Index-3, [b]	80.9±6.2	80.2±10.5	0.531

[a] median (interquartile range (IQR, 25-75)), [b] mean ± standard deviation
*Statistically significant p values are highlighted.
WBC: white blood cell, CRP: C-reactive protein level

surviving group. In addition, the level of native-thiol (<209 μmol/L), total-thiol (<248 μmol/L), and disulfide (<20.4 μmol/L) was determined as the cut-off value for mortality. Our results support the information that thiol is an important antioxidant, and decrease in the native-thiol, total-thiol, and disulfide levels shortens the cellular life span, which leads to increase in the mortality rate (5). To the best of our knowledge, this is the first study that provides data concerning the relationship between thiol/disulfide homeostasis and clinical outcome of sepsis in geriatric patients hospitalized in ICU.

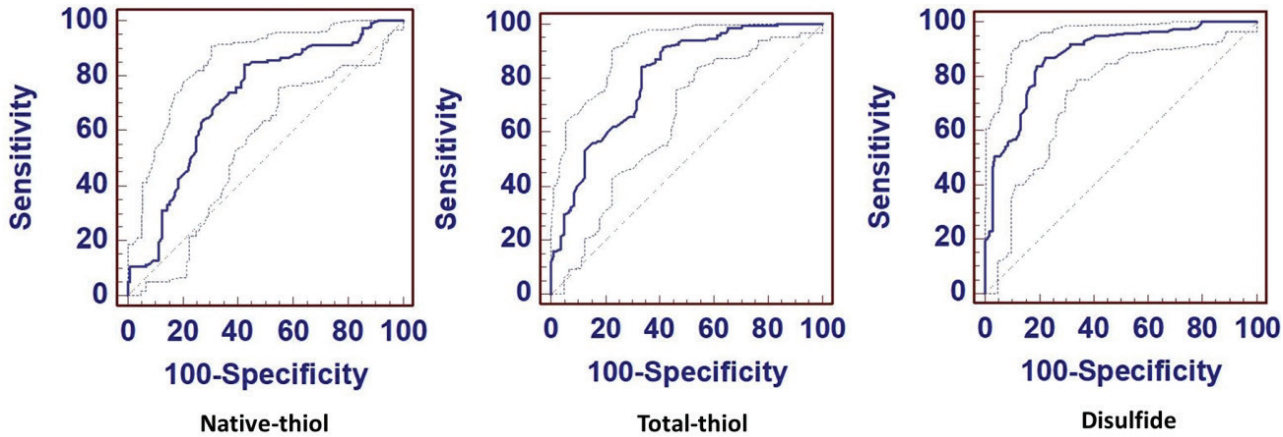
The aging of the population is a global phenomenon; the population aged 65 and above is growing faster than all other age groups. As the population demography changes, there will likely be an increase in the number of geriatric patients admitted to the ICU. According to literature, elderly patients account for 26-51% of ICU admissions. In addition, mortality rates in patients hospitalized in ICU vary between 20% and 58% (11,14,15). In patients with

Table 3. The area under the curve, cutoff level, sensitivity, specificity, PPV, and NPV of native-thiol, total-thiol and disulfide for mortality

	AUC	95% Confidence interval	p values	Cutoff level	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Native-thiol (μmol/L)	0.713	0.653-0.768	0.0001	≤209	84	61	74	72
Total-thiol (μmol/L)	0.803	0.749-0.850	0.0001	≤248	84	70	78	75
Disulfide (μmol/L)	0.878	0.831-0.916	0.0001	≤20.4	87	78	84	81

AUC: area under the curve, PPV: positive predictive values, NPV: negative predictive values

Figure 1. ROC curve for native-thiol, total-thiol and disulfide levels, predicting mortality in intensive care unit



ROC: receiver operating characteristic

sepsis, the rate of mortality increases with age; hence, age is considered as an independent predictor of mortality (16). Therefore, patients with an average age of 78.2 years were included in our study, which explains why the patient mortality rate in our study was close to the upper limit of 58.7%. Studies have suggested that there are different predictors of mortality in geriatric ICU patients. APACHE II and SOFA scores have been frequently used for this purpose, and as in our results, increased scores were associated with an increased mortality rate (11,14,15,17,18). However, available evidence is still not sufficient for physicians to determine clinical results and mortality rate in geriatric patients (11). Therefore, new studies are needed to predict clinical outcomes in elderly patients who are at a risk for mortality.

Although the pathophysiology of sepsis is not fully understood, clinical studies have revealed an imbalance between oxidants and antioxidants (19). Lorente et al. demonstrated that antioxidant capacity in sepsis determines the course of the disease and indicates a possible relationship between the total antioxidant capacity and mortality (20). Other causes of increased mortality in patients with sepsis are uncontrolled inflammatory response against pathogens, persistent oxidative stress, impaired oxygen use due to mitochondrial dysfunction, energy deficiency, and organ failure. Organ failure worsens the outcome of sepsis and is associated with 70% ICU mortality (17,21).

Based on existing scientific literature and our results, it can be concluded that low levels of native-thiol, total-thiol, and disulfide, which are indicators of antioxidant capacity, can help predict negative clinical outcomes, particularly mortality, in patients with sepsis (5,17,22,23). Oxidative stress contributes to the pathophysiology of sepsis by disrupting cellular redox homeostasis, which is the cause for lower thiol levels in patients who succumb to mortality. In addition, low disulfide levels in patients who succumb to mortality may be due to the reversible conversion of disulfide products to S-nitrosothiol and sulfenic acid (24), because when oxidative stress persistently occurs in a patient, irreversible sulfonic acid concentration increases and causes permanent loss of protein activity (25). Therefore, more research on the measurement of reversible and irreversible modifications is imperative.

Kozanhan et al. compared the status of thiol/disulfide homeostasis of 44 adult patients with sepsis with that of 44 control patients. While native-thiol, total-thiol, and disulfide levels were significantly lower in the sepsis group than in the control group, there was no difference between the groups in terms of indices -1, -2, and -3. Additionally, in the non-survivor group (18 patients), native-thiol, total-thiol, and disulfide levels were insignificantly lower than those in the survivor group (26 patients) (17). Ayar et al. compared 40 healthy children and 38 children with sepsis and reported that native-thiol, total-thiol, and disulfide levels and index-3 in the sepsis group were significantly lower than those in the control group, whereas indices -1 and -2 were higher in the sepsis group than in the control group. In addition, similar results were obtained when native-thiol, total-thiol, and disulfide levels and indices -1, -2, and -3 were compared between 27 survivor and 11 non-survivor patients (22). The probable reason for the similar results obtained may be the small number of patients included in the study. In our study, native-thiol, total-thiol, and disulfide levels in the mortality with sepsis and were significantly lower than those in the surviving group. Therefore, change in thiol/disulfide homeostasis may help us to better evaluate clinical outcomes of patients with sepsis. In order to reach this goal, sufficient number of patients should be included in the study. In another study evaluating the neonatal age group, similar results were obtained when native-thiol, total-thiol, index-3, index-2, disulfide, and index-1 levels were compared between the newborns with sepsis (66 patients) and the healty control group (51 newborn patients) (23). The balance of antioxidant and oxidant systems, including thiol/disulfide homeostasis, can change with age. Due to the age groups of the patients in these studies, thiol/disulfide homeostasis results may vary. Therefore, it would be more accurate to interpret the results according to age (5). In addition, other reasons for the difference in results obtained in terms of thiol/disulfide homeostasis may be due to difference in level of sepsis severity and the difference between the groups compared (control versus sepsis and mortality versus survivor).

Thiol/disulfide homeostasis levels normally vary during life-time. We see increase in the levels of native-thiol, total-thiol, and disulfide up to 3rd decades of age and then, these levels gradually starts to decrease from these decades up to 7th decades of life. The rate of diminish in the levels of native-thiol, total-thiol, and disulfide may increase due to secondary morbidities such as alcohol abuse, smoking, infections and genetic factor. Decrease in the levels of native-thiol, total-thiol, and disulfide increase the rate of mortality (5,6). The variables such as age, level of CRP and comorbid disease, were found to be higher in mortality group. Multiple logistic analysis was done in order to evaluate variables such as age, comorbid diseases and level of CRP which affect the mortality. Multiple logistic analysis revealed that low levels of native-thiol, total-thiol, and disulfide were isolated risk factors for mortality other than age, comorbid diseases and level of CRP. The levels of native-thiol, total-thiol, and disulfide do not change after 7th decades of life. Both of our groups have similar mean ages over 70. So this variable-age-does not directly explain the difference between groups. We speculate that the degree of severity of sepsis might effect the levels of native-thiol, total-thiol, and disulfide which increase the mortality. High levels of CRP due to severe sepsis and higher frequency in comorbid diseases may increase mortality. Multiple logistic analysis revealed these results. In conclusion, our study showed that low levels of native-thiol, total-thiol, and disulfide were found to be directly related with rate of mortality in geriatric-sepsis patients.

There is no previous study determining the cut-off values of native-thiol, total-thiol, and disulfide levels to predict mortality in geriatric patients with sepsis. According to our results, cut-off value of native-thiol for mortality in geriatric patients with sepsis was ≤209 (μmol/L); total-thiol, ≤248 (μmol/L);

and disulfide, ≤20.4 (μmol/L). In addition, the AUC value for all three parameters was between 0.7 and 0.9 and had a moderate accuracy predictive value (13). Our results are valid for geriatric patients with sepsis. To confirm our findings, further studies defining cut-off values for different age groups and AUC values are crucial.

Our study has few limitations. Thiol/disulfide homeostasis was tested at the time of the patient's hospitalization, and the values during patient's follow-up could not be measured. Therefore, the change in thiol/disulfide homeostasis during the follow-up for sepsis and its effect on clinical results are unknown. Additionally, thiol/disulfide homeostasis level could not be compared between sepsis and control groups owing to the absence of the control group.

CONCLUSION

Our study is the first to demonstrate the efficacy of thiol/disulfide homeostasis on the clinical outcome i.e. the prognosis of sepsis in geriatric patients hospitalized in ICU. Low levels of native-thiol, total-thiol, and disulfide were shown to be related with higher mortality in geriatric septic patients. Further studies with larger cohorts are needed to validate our current findings and to comprehensively understand the pathophysiology of oxidative stress in the sepsis process.

Conflict of Interest, Disclosure Statement

The authors declare that they have no conflicts of interest. The authors have indicated they have no financial relationships relevant to this article to disclose

Ethical Approval: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Acknowledgement: none

REFERENCES

1. van Vught LA, Klein Klouwenberg PM, Spitoni C, et al. Incidence, risk factors, and attributable mortality of secondary infections in the intensive care unit after admission for sepsis. JAMA 2016; 315(14): 1469-79. (PMID: 26975785).
2. Ghimire RH, Budhathoki S, Shreewastav RK. Scenario of sepsis in intensive care unit in a tertiary care hospital. J Nepal Health Res Counc 2020; 18(1): 99-102. (PMID: 32335601).
3. Zeng A, Song X, Dong J, et al. Mortality in relation to frailty in patients admitted to a specialized geriatric intensive care unit. J Gerontol A Biol Sci Med Sci 2015; 70(12): 1586-94. (PMID: 26400736).
4. Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. BMJ 2016; 353(5): i1585. (PMID: 27217054).
5. Dröge W. Aging-related changes in the thiol/disulfide redox state: implications for the use of thiol antioxidants. Exp Gerontol 2002; 37(12): 1333-45. (PMID: 12559403).
6. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem 2014; 47(18): 326-32. (PMID: 25304913).
7. Erel Ö, Erdoğan S. Thiol-disulfide homeostasis: an integrated approach with biochemical and clinical aspects. Turk J Med Sci 2020; 50(SI-2): 1728-38. (PMID: 32233181).
8. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315(8): 801-10. (PMID: 26903338).
9. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13(10): 818-29. (PMID: 3928249).
10. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the

Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996; 22(7): 707-10. (PMID: 8844239).

11. Martin-Loeches I, Guia MC, Vallecoccia MS, et al. Risk factors for mortality in elderly and very elderly critically ill patients with sepsis: a prospective, observational, multicenter cohort study. Ann Intensive Care 2019; 9(1): 26. (PMID: 30715638).
12. Metnitz PG, Moreno RP, Almeida E, et al. SAPS 3-From evaluation of the patient to evaluation of the intensive care unit. Part 1: Objectives, methods and cohort description. Intensive Care Med 2005; 31(10): 1336-44. (PMID: 16132893).
13. Akobeng AK. Understanding diagnostic tests 3: Receiver operating characteristic curves. Acta Paediatr 2007; 96(5): 644-7. (PMID: 17376185).
14. Sodhi K, Singla MK, Shrivastava A, Bansal N. Do Intensive care unit treatment modalities predict mortality in geriatric patients: An observational study from an Indian intensive care unit. Indian J Crit Care Med 2014; 18(12): 789-95. (PMID: 25538413).
15. Bo M, Massaia M, Raspo S, et al. Predictive factors of in-hospital mortality in older patients admitted to a medical intensive care unit. J Am Geriatr Soc 2003; 51(4): 529-33. (PMID: 12657074).
16. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. Crit Care Med 2006; 34(1): 15-21. (PMID: 16374151).
17. Kozanhan B, Eğilmez A, Tok Cekmecelioglu B, et al. Novel oxidative stress biomarker in sepsis: dynamic thiol-disulfide homeostasis. Cukurova Med J 2020; 45(1): 63-70. (DOI: 10.17826/cumj.637127).
18. Stein Fde C, Barros RK, Feitosa FS, et al. Prognostic factors in elderly patients admitted in the intensive care unit. Rev Bras Ter Intensiva 2009; 21(3):255-61. (PMID: 25303546).
19. Kumar S, Gupta E, Kaushik S, Kumar Srivastava V, Mehta SK, Jyoti A. Evaluation of oxidative stress and antioxidant status: Correlation with the severity of sepsis. Scand J Immunol 2018; 87(4): e12653. (PMID: 29484685).
20. Lorente L, Martín MM, Almeida T, et al. Association between serum total antioxidant capacity and mortality in severe septic patients. J Crit Care 2015; 30(1): 217.e7-12. (PMID: 25307978).
21. Galley HF. Oxidative stress and mitochondrial dysfunction in sepsis. Br J Anaesth 2011; 107(1): 57-64. (PMID: 21596843).
22. Ayar G, Sahin S, Men Atmaca Y, Uysal Yazici M, Neselioglu S, Erel O. Thiol-disulphide homeostasis is an oxidative stress indicator in critically ill children with sepsis. Arch Argent Pediatr 2019; 117(3): 143-8. (PMID: 31063297).
23. Aydogan S, Akduman H, Dilli D, et al. The role of thiol-disulfide homeostasis in neonatal sepsis. J Matern Fetal Neonatal Med 2021; 34(10): 1522-8. (PMID: 31268367).
24. Turell L, Radi R, Alvarez B. The thiol pool in human plasma: the central contribution of albumin to redox processes. Free Radic Biol Med 2013; 65(12): 244-53. (PMID: 23747983).
25. Schieber M, Chandel NS. ROS function in redox signaling and oxidative stress. Curr Biol 2014; 24(10): R453-62. (PMID: 24845678).