





Evaluation of Serum Selenium Levels in Sepsis Patients Hospitalized in Tabriz

Hamid Owaysee Osquee¹ , Peyman Eini², Saleh Bahramnezhad¹, Mehdi Haghdooost^{1*} 

Abstract

Objectives: Selenium (Se) is one of the elements of the body whose deficiency causes immune system weakness. Given that a weak immune system is one of the main causes of sepsis, in this study, it was decided to increase the serum Se level in sepsis patients in hospitals affiliated to Tabriz University of Medical Sciences.

Materials and Methods: In this cross-sectional descriptive study, 82 patients with sepsis (common, severe, and septic shock) were selected using a two-year census sampling ending on March 21, 2019 from Sina and Imam Reza hospitals in Tabriz. Data related to the etiology of the disease, underlying diseases, comorbidities, and inpatient testing were collected for each patient, and serum Se levels were assessed by atomic absorption spectroscopy. To analyze the data, chi-square, t test, and Mann-Whitney U tests were run using SPSS, version 20, and a P value less than 0.05 was considered statistically significant.

Results: The results of a review revealed that the history of underlying diseases [diabetes ($P=0.009$), hypertension ($P=0.019$), and malignancies ($P=0.029$)], comorbidities [pneumonia ($P=0.001$), malignancy and chemotherapy ($P=0.012$), and meningitis ($P=0.009$)], and disease etiology [bacteremia of uncertain origin ($P=0.001$), pneumonia ($P=0.001$), urinary tract infection ($P=0.009$), and skin infection ($P=0.005$)] was significantly higher in patients with septic shock compared to those with sepsis and severe sepsis. On the other hand, the severity of the disease was significantly associated with a decrease in the serum Se level ($P=0.010$).

Conclusions: In general, serum Se levels decrease with the increased severity of sepsis. Thus, measuring Se levels may be helpful in rejecting the progression of the disease.

Keywords: Severe sepsis, Septic shock, Prediction, Etiology, Selenium

Introduction

Sepsis, severe sepsis, and septic shock is a life-threatening clinical disease that globally affects 27 million people each year. The incidence of sepsis is still increasing considering about 10%-30% of patients admitted to intensive care units (1). A key point in the treatment of this dangerous disease is the early identification and early treatment before the onset of symptoms such as hypotension (2,3).

Sepsis, as a systemic inflammatory response to severe infection, is one of the major causes of mortality in hospitalized patients. Sepsis, severe sepsis (a patient with sepsis with the hypoperfusion of end organs responding to normal saline administration), and septic shock (a condition of sepsis in which the patient has hypotension and requires vasopressor) may occur following infection. Two stages of severe sepsis and septic shock are the leading causes of mortality following sepsis (4-7).

The etiology of this disease includes the weakness of the immune system, nosocomial infections, bacteremia, age over 65 years, acquired pneumonia from the community and genetic factors, and the like (8,9). However, more research has recently focused on changes in serum

selenium (Se) levels in immunocompromised patients (10-12). Recent studies have shown that the serum levels of this substance significantly reduce in critically ill patients, and the reduction of serum Se levels in patients with sepsis has been confirmed as well (13,14).

The prevalence of severe sepsis and septic shock has dramatically increased over the last 30 years, imposing high hospital costs. Its prevalence is reported to be between 10 and 27% in different countries and has increased in recent decades (6,15,16). This complication has increased in the last decade and has led to an increase in-hospital death. Thus, the present study was conducted given the lack of knowledge on the exact role of Se in the development of this complication and different degrees of this complication. With the aim of investigating the serum level of Se in patients with sepsis in hospitals affiliated to Tabriz University of Medical Sciences, the results of this study can pave the way for various interventions to timely identify this complication and treatment methods to improve the condition of these patients while reducing hospital deaths.

Received 16 March 2020, Accepted 27 June 2020, Available online 31 July 2020

¹Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. ²School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran.

*Corresponding Author: Mehdi Haghdooost, Tel: +989143137387, Email: Drmehdihaghdooost@yahoo.com



Key Messages

- ▶ Hospital infections can be a risk factor for sepsis.
- ▶ Se deficiency can worsen the disease.
- ▶ Patients with septic shock have extremely low levels of Se.

Materials and Methods

Study Design

This cross-sectional descriptive study was conducted from March 21, 2018 until March 21, 2019 in Sina (Infectious disease ward) and Imam Reza (Infectious disease ward) Hospitals affiliated to Tabriz University of Medical Sciences. The minimum sample size was calculated based on the study by Keshtkari et al (17), and 45 individuals were considered for the study of sepsis in the adult Iranian population. Considering that the census sampling method was performed (throughout the study and in both hospitals) during one year, the sample size was increased to enhance the validity of the results. Finally, 82 sepsis patients admitted to the mentioned wards were included in this study. The inclusion criteria included having at least 18 years (Because factors affecting sepsis in adults differ from those in children) of age, sepsis, severe sepsis, and septic shock. On the other hand, the exclusion criteria were patients with previous sepsis, pre-hospitalization medication supplementation, and autoimmune diseases, and intravenous total parenteral nutrition. Patients were entered into the study after obtaining informed consent (18).

Clinical record data including age, gender, patient's main complaint, type of underlying disease, current illness, and disease etiology were completed by an infectious disease assistant (a research team member) for each patient in the relevant tool (designed for research purposes). All patients were examined by two infectious disease specialists (faculty members), and the final diagnosis was confirmed by the two specialists. All patients also had routine tests for sepsis (the type of tests will be reported in the Result Section).

Selenium Measurement

Blood tests were performed by a skilled nurse by taking 5 cc of blood from the available veins, and then blood samples were transferred to the respective hospital laboratory for relevant investigations. The tests were performed daily for each individual. The serum levels of Se were also measured after taking the blood sample and transferring it to the Chemistry Laboratory of Tabriz University of Chemistry using the spectrAA 220 VARIAN Se (#5610127000) method. In this method, which is known as Se atomic absorption spectroscopy, Se was extracted from the blood samples. To measure the concentration of the extracted Se, an atomic absorption spectrophotometer was used with a stagnant graphite furnace with a ground absorber modifier. In this method, 20 μL of the sedimentary extraction phase of carbon tetrachloride was injected into

the platform furnace by a sampler. The concentration of Se in the samples was calculated by comparing the signals from the absorption of Se atoms in the samples that were not added to the standard. Considering that Se compounds strongly evaporate inside the graphite kiln at different stages of drying and ash formation, a corrector was used to avoid this. Iridium 1000 ppm solution and the existing temperature program were used to modify (19).

The type of comorbidities and the confirmation of its etiology were performed by appropriate consultations with specialists in urology, orthopedics, neurology, cardiology, dermatology, internal medicine, gastrointestinal, lung diseases, and nephrology wards. Finally, the disease etiology was confirmed with the advice of the relevant consultant and the treating physician (infectious specialty).

Statistical Analysis

The data were entered into SPSS 20 and were compared by chi-square, *t* test, and Mann-Whitney U tests at $P < 0.05$.

Results

During the mentioned period, there were 94 patients in the mentioned hospitals, and by examining the criteria for entering and leaving the study, 12 people did not have the criteria for entering the study. The study began with 80 patients and ended with 82 patients. Sample shedding in this study was zero (Figure 1). Of the 82 studied patients, 32 (39.04%), 29 (35.36%), and 21 (25.60%) cases had

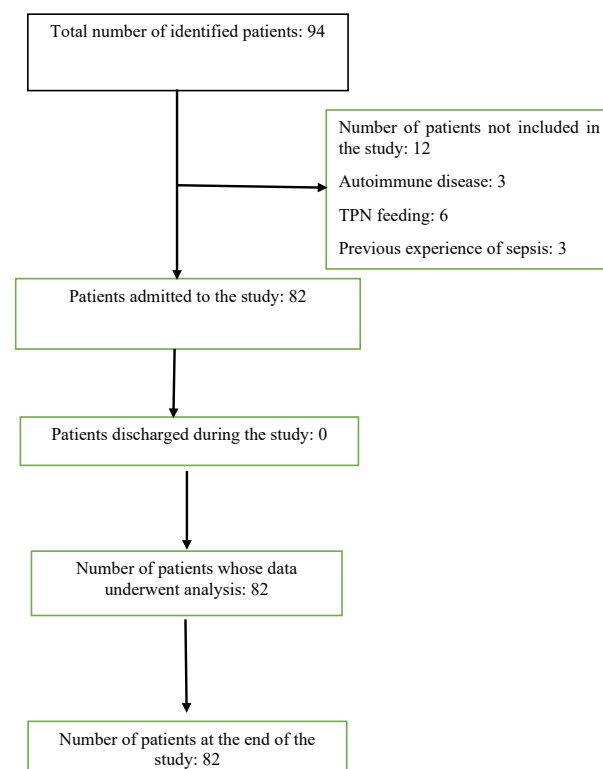


Figure 1. Entry and Exit of Patients Participating in the Study. Note. TPN: Total parenteral nutrition.

sepsis, severe sepsis, and septic shock, respectively. Based on demographic data the mean age (\pm standard deviation) of the participants was 38.14 (\pm 29.50) years (mean (SD) of the sepsis and severe sepsis groups was 49.55 \pm 14.41 and 50.88 \pm 14.13, respectively).

Based on the results, 44 (65.53%) participants were males including 13, 17, and 14 cases in the sepsis, severe sepsis, and septic shock groups, respectively. The comparison of the frequency of the main complaints in the three groups showed that fever, chills, weakness, and fatigue were the most common symptoms in both groups. No statistically significant difference was found between the three groups (the χ^2 test) based on the comparison of patients' main complaints ($P > 0.05$, Figure 2).

Laboratory findings and the comparison between the three groups indicated that mean arterial pressure

($P = 0.003$) and platelet ($P = 0.031$) levels were significantly higher in patients with septic shock compared to other patients (Table 1).

The comparison of underlying diseases in patients with sepsis demonstrated that diabetes ($P = 0.009$), hypertension ($P = 0.019$), and malignancies ($P = 0.029$) were significantly higher in patients with septic shock in comparison with the other two groups. On the other hand, the prevalence of comorbidities showed that pneumonia ($P = 0.001$), malignancy and chemotherapy ($P = 0.012$), and meningitis ($P = 0.009$) were significantly higher in patients with septic shock compared to the other two groups (Table 2).

Finally, examining the etiology of sepsis in patients participating in the study, it was revealed (Figure 3) that the frequencies of the bacteremia of unknown

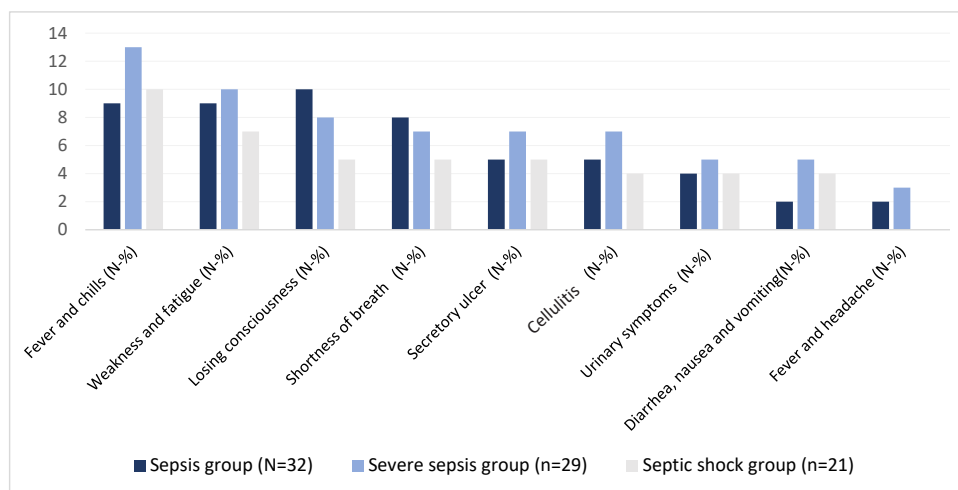


Figure 2. Comparison of the Frequency of the Major Complaints of Sepsis, Severe Sepsis, and Septic Shock Groups.

Table 1. Comparison of Laboratory Findings in Patients With Severe Sepsis and Septic Shock Groups

Related Experiment	Sepsis Group (n=32)	Severe Sepsis Group (n=29)	Septic Shock Group (n=21)	P Value
MAP (mm Hg)	99.15 \pm 75.13	115.42 \pm 86.10	159.85 \pm 79.19	0.003*
BT (degree)	37.67 \pm 01.10	37.91 \pm 01.10	38.21 \pm 01.15	0.203
PR (beats/minute)	98.79 \pm 20.15	99.90 \pm 20.04	100.03 \pm 21.12	0.119
RR (beats/minute)	25.91 \pm 08.30	26.85 \pm 08.09	26.98 \pm 08.33	0.510
WBC	15.19 \pm 02.53	15.08 \pm 02.92	16.14 \pm 03.00	0.119
PLT	195.59 \pm 15.46	226.70 \pm 19.60	259.19 \pm 21.21	0.031*
Procalcitonin	23.20 \pm 03.11	23.15 \pm 03.89	23.59 \pm 03.19	0.500
Cr	01.97 \pm 02.15	01.98 \pm 02.77	01.98 \pm 02.01	0.541
ALT	45.15 \pm 05.10	47.55 \pm 05.19	50.11 \pm 05.37	0.463
AST	50.18 \pm 06.15	51.70 \pm 06.36	53.93 \pm 05.14	0.346
ALK	271.15 \pm 83.19	275.42 \pm 85.19	276.15 \pm 86.19	0.473
CPK	51.15 \pm 08.15	53.65 \pm 08.87	55.60 \pm 08.56	0.293
LDH	478.15 \pm 60.36	482.42 \pm 59.54	490.15 \pm 60.16	0.207

Note. MAP: Mean arterial pressure; BT: Body temperature; PR: pulse rate; RR: Respiration rate; WBC: White blood cell; PLT: Platelet; Cr: Creatinine; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALK: Alkaline; CPK: Creatinine phosphokinase; LDH: Lactic dehydrogenase. Applied test: t test; *Significant.

Table 2. Comparison of the Underlying Diseases of the Study Participants

The Main Complaint of the Patient	Sepsis Group (n=32)	Severe Sepsis Group (n=29)	Septic Shock Group (n=21)	P Value
Underlying disease				
Diabetes, No. (%)	14%-35.89	10%-34.48	13%-61.90	0.009*
Cancer, No. (%)	14%-35.89	10%-34.48	10%-47.61	0.019*
Hypertension, No. (%)	10%-25.64	7%-24.13	8%-38.09	0.029*
Ischemic heart disease, No. (%)	8%-20.51	5%-17.24	3%-14.28	0.115
Thyroid disease, No. (%)	5%-12.82	3%-10.33	2%-09.52	0.419
Convulsion, No. (%)	3%-07.69	2%-06.89	1%-04.16	0.213
ESRD, No. (%)	2%-05.12	2%-06.89	1%-04.16	0.213
Cirrhosis, No. (%)	2%-05.12	1%-03.44	0%-00.00	0.501
Pneumonia, No. (%)	10%-25.64	10%-34.48	15%-71.42	0.001*
Cancer and chemotherapy, No. (%)	9%-23.07	10%-34.48	10%-47.61	0.012*
Meningitis, No. (%)	8%-20.51	7%-24.13	9%-42.85	0.009*
Pyelonephritis, No. (%)	8%-20.51	7%-24.13	5%-23.80	0.112
Cellulitis, No. (%)	6%-15.38	5%-17.24	3%-14.28	0.256
Osteomyelitis, No. (%)	5%-12.82	4%-13.79	3%-14.28	0.231
Gastroenteritis, No. (%)	5%-12.82	4%-13.79	2%-09.52	0.119

Note. ESRD: End-stage renal disease.

Applied test: χ^2 test; *Significant.

origin ($P=0.001$), pneumonia ($P=0.001$), urinary tract infection ($P=0.009$), and skin infection ($P=0.005$) were significantly higher in the group of patients with septic shock compared to the group with severe sepsis (Mann-Whitney test).

As regards the main part of the study comparing serum Se levels between the three groups, the results represented that serum Se levels significantly reduced following septic shock such that the serum levels of Se reduced by moving toward septic shock (Table 3).

Discussion

The aim of this study was to evaluate the serum Se level in sepsis patients admitted to Tabriz hospitals. The prevalence of bacteremia of unknown origin, pneumonia, urinary tract infection, and skin infection was significantly higher

in the septic shock group compared to severe sepsis and sepsis groups. Regarding the origin of sepsis, Artero et al investigated the effects of bacterial disease on hospitalized patients in the intensive care unit (20) and concluded that bacteremia can predispose patients to sepsis. As time goes on, the severity of sepsis increases, which is consistent with the results of the current study. The results of other studies (21-23) conducted in this area are consistent with those of our study. It is believed that other diseases and infections can predispose a patient to varying degrees of sepsis.

On the other hand, with regard to comorbidities, the results also revealed that the prevalence of pneumonia, malignancy, and chemotherapy and meningitis was significantly higher in patients with septic shock in comparison with those with severe sepsis and sepsis. In

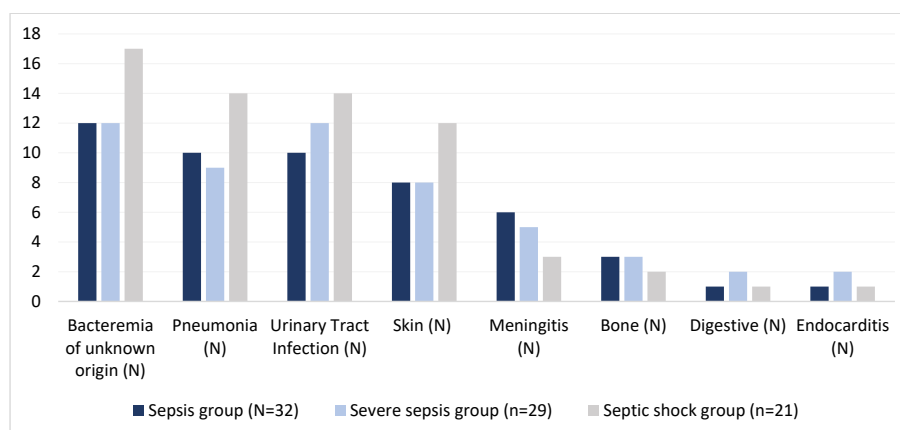


Figure 3. Comparison of Disease Etiology in Severe Sepsis and Septic Shock Groups.

Table 3. Comparison of Serum Selenium Levels in the Study Groups

Variable	Sepsis Group (n=32)	Severe Sepsis Group (n=29)	Septic Shock Group (n=21)	P Value
Selenium	50.87 ± 23.38	43.35 ± 19.50	34.80±13.58	0.010*

Note. Applied test: *t* test; *Significant.

this regard, our findings corroborate with the results of the latest articles of other researchers (24-26). In this context, it is indicated that contracting these diseases leads to a person prone to septic shock, and the patient's involvement in these diseases can lead the patient to dangerous stages. Therefore, identifying patients with such diseases can be helpful in predicting the worsening of the disease for physicians, and physicians should pay attention to this issue.

Concerning serum Se levels, it was found that as the amount of this substance decreased, the disease worsened such that in patients with septic shock, serum Se levels reduced by 30% compared to those with sepsis. In this respect, the results of our study are in conformity with those of other studies (27,28). It can be mentioned that in severe inflammatory conditions such as sepsis (with all degrees), the antioxidant system of the body weakens, which can lead to severe oxidative conditions, and the disease condition worsens in case of reduced intake of antioxidants such as Se. Moreover, the results of using Se-containing supplements have shown that sepsis patients show improved recovery after Se supplementation. This finding is in line with our theory that low Se levels deteriorate the disease.

These differences in disease etiology and comorbidities in the three groups of sepsis, severe sepsis, and septic shock seemed to act as predictors of disease deterioration. In other words, by identifying the origin and associated diseases in individuals, it can be determined that a person will develop septic shock from severe sepsis and sepsis, and thus it can be effective in the survival of patients. In another similar study conducted (29) examining the administration of high levels of Se in patients with septic shock, it was found that the administration of this substance did not reduce the high mortality rate of the disease. The accompanying ones also had no effect in this regard. The results of their study contradict those of our study.

Based on the results of our study, patients with more Se deficiency were significantly more likely to develop other diseases, meaning that lower Se levels of patients increase the risk of further illness. It worsens the condition of sepsis in addition to lowering the level of this substance and increases complications. In this regard, our results are in line with the findings of Brodska et al (30), representing that Se was directly linked to inflammatory responses and disease and lower levels of the substance in the body led to higher levels of mortality and morbidity.

The findings of the current study also demonstrated that low levels of Se in the blood were associated with a

variety of infections and diseases. In other words, it was found that low levels of Se made a person more susceptible to other diseases. The results of the study by Chelkeba et al (31), which was conducted with the same purpose as our study, are similar to those of our study. In their study of clinical trials, they found that high doses of Se could reduce the risk of infections in ICU patients. It seems that this substance has a protective and preventive role in various diseases and its deficiency aggravates the disease.

Suggestions for Further Research

The researchers recommend further studies with larger sample sizes and drug interventions such as the use of Se-containing medication supplements for patients with septic shock to prevent mortality. We also recommend that Se and other salts be measured for at-risk patients for sepsis in the first few days of hospitalization, and that courses be provided for infectious disease physicians regarding the role of mineral salts in septic shock.

Study Limitations

The small sample size, the effects of drug therapy on the disease process, and the lack of attention to the type of treatment and microbial resistance in individuals are the limitations and weaknesses of the present study. Additionally, other weaknesses of our study included the lack of examining the family history, the role of heredity in patients participating in the study, and the records of previous diseases in these patients.

Conclusions

Septic shock is a dangerous stage of sepsis and can cause death. Therefore, early detection and diagnosis, as well as early treatment can greatly reduce mortality. Considering the disease etiology and comorbidities in sepsis patients can help predict the progression of the disease. In this cross-sectional study, there was a decrease in Se levels as the disease progressed, which could be considered as a treatment plan. The results of this study can be used for patients who are hospitalized in the ICU so that the level of Se is measured at the beginning of admission to the ward, and supplements containing Se should be prescribed in the case of the deficiency of this substance in the body.

Authors' Contribution

HOO: Study design, intervention; PE: follow-up; SB: Study design; MH: article writing, article submission.

Conflict of Interests

None declared.

Ethical Issues

A code of ethics was obtained from the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1397.295). In addition, information confidentiality was respected, and the patients were not prevented from receiving the main treatments to obtain the expected results of the study. The permission of the patient and his/her family was obtained to perform the tests, and written informed consent was obtained from the patient and a member of his/her family.

Financial Support

This study was financially supported by Tabriz University of Medical Sciences.

Acknowledgments

This study is the result of a small portion of Mr. Saleh Bahramnezhad's general practitioner course. The researchers are grateful to Mr. Saleh Bahramnezhad for collecting information, patients for participating in the study, and financial support from the Vice-president of Research and Technology of Tabriz University of Medical Sciences.

References

1. Quenot JP, Binquet C, Kara F, et al. The epidemiology of septic shock in French intensive care units: the prospective multicenter cohort EPISS study. *Crit Care*. 2013;17(2):R65. doi:10.1186/cc12598
2. Butler T, Levin J. Sepsis and septic shock: a review of definitions, pathogenesis, and treatment. In: Williams K, ed. *Endotoxin Detection and Control in Pharma, Limulus, and Mammalian Systems*. Cham: Springer; 2019:807-835. doi:10.1007/978-3-030-17148-3_22
3. Park SK, Shin SR, Hur M, Kim WH, Oh EA, Lee SH. The effect of early goal-directed therapy for treatment of severe sepsis or septic shock: a systemic review and meta-analysis. *J Crit Care*. 2017;38:115-122. doi:10.1016/j.jcrc.2016.10.019
4. Simpson SQ, Gaines M, Hussein Y, Badgett RG. Early goal-directed therapy for severe sepsis and septic shock: a living systematic review. *J Crit Care*. 2016;36:43-48. doi:10.1016/j.jcrc.2016.06.017
5. Fujii T, Ganeko R, Kataoka Y, et al. Polymyxin B-immobilized hemoperfusion and mortality in critically ill adult patients with sepsis/septic shock: a systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2018;44(2):167-178. doi:10.1007/s00134-017-5004-9
6. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013;369(9):840-851. doi:10.1056/NEJMra1208623
7. Dadkhah A, Fatemi F, Mohammadi Malayeri MR, Rasooli A, Karvin Ashtiani MH. The effects of *Mentha spicata* on oxidative stress and COX-2 gene expression in prevention of sepsis. *Journal of Cellular and Molecular Research (Iranian Journal of Biology)*. 2019;31(4):484-499. [Persian].
8. Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. *BMJ*. 2016;353:i1585. doi:10.1136/bmj.i1585
9. Martín S, Pérez A, Aldecoa C. Sepsis and immunosenescence in the elderly patient: a review. *Front Med (Lausanne)*. 2017;4:20. doi:10.3389/fmed.2017.00020
10. Belsky JB, Wira CR, Jacob V, Sather JE, Lee PJ. A review of micronutrients in sepsis: the role of thiamine, l-carnitine, vitamin C, selenium and vitamin D. *Nutr Res Rev*. 2018;31(2):281-290. doi:10.1017/s0954422418000124
11. Li S, Tang T, Guo P, et al. A meta-analysis of randomized controlled trials: efficacy of selenium treatment for sepsis. *Medicine (Baltimore)*. 2019;98(9):e14733. doi:10.1097/md.00000000000014733
12. Garg BD, Bansal A, Kabra NS. Role of selenium supplementation in prevention of late onset sepsis among very low birth weight neonates: a systematic review of randomized controlled trials. *J Matern Fetal Neonatal Med*. 2019;32(24):4159-4165. doi:10.1080/14767058.2018.1481039
13. Braunstein M, Kusmenkov T, Zuck C, et al. Selenium and selenoprotein P deficiency correlates with complications and adverse outcome after major trauma. *Shock*. 2020;53(1):63-70. doi:10.1097/shk.0000000000001344
14. Lipinski B. Redox-active selenium in health and disease: a conceptual review. *Mini Rev Med Chem*. 2019;19(9):720-726. doi:10.2174/1389557517666161104125022
15. De Backer D, Cecconi M, Lipman J, et al. Challenges in the management of septic shock: a narrative review. *Intensive Care Med*. 2019;45(4):420-433. doi:10.1007/s00134-019-05544-x
16. Hariri G, Joffre J, Leblanc G, et al. Narrative review: clinical assessment of peripheral tissue perfusion in septic shock. *Ann Intensive Care*. 2019;9(1):37. doi:10.1186/s13613-019-0511-1
17. Keshkari A, Parsa G, Ghafarian Shirazi H, Koleini P. The evaluation of microorganisms and risk factors of neonatal sepsis in patients with suspected sepsis in Imam Sajjad hospital, Yasuj. *Armaghane Danesh*. 2017;22(1):118-128. [Persian].
18. Shirani K, Akhoundi R, Safaei A. Demographic and some underlying factors in patients with sepsis in Alzahra hospital, Isfahan, Iran. *Journal of Isfahan Medical School*. 2017;35(418):42-49. [Persian].
19. Farajzadeh M, Mardani A. Determination of benzene, toluene, ethylbenzene and xylenes by headspace spectrophotometry with an atomic absorption apparatus. *Anal Sci*. 2001;17(9):1059-1062. doi:10.2116/analsci.17.1059
20. Artero A, Inglada L, Gómez-Belda A, et al. The clinical impact of bacteremia on outcomes in elderly patients with pyelonephritis or urinary sepsis: a prospective multicenter study. *PLoS One*. 2018;13(1):e0191066. doi:10.1371/journal.pone.0191066
21. da Silva Santos MC, Sanches CT, de Oliveira Moraes UR, et al. Clinical aspects and the origin of sepsis patients treated at a university hospital. *Acta Paul Enferm*. 2019;32(1):65-71. doi:10.1590/1982-0194201900009
22. Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. Carbapenem resistance, inappropriate empiric treatment and outcomes among patients hospitalized with Enterobacteriaceae urinary tract infection, pneumonia and sepsis. *BMC Infect Dis*. 2017;17(1):279. doi:10.1186/s12879-017-2383-z
23. Lee YC, Hsiao CY, Hung MC, et al. Bacteremic urinary tract infection caused by multidrug-resistant Enterobacteriaceae are associated with severe sepsis at admission: implication for empirical therapy. *Medicine (Baltimore)*. 2016;95(20):e3694. doi:10.1097/md.0000000000003694
24. Kim YJ, Kang J, Ryoo SM, Ahn S, Huh JW, Kim WY. Platelet-lymphocyte ratio after granulocyte colony stimulating factor administration: an early prognostic marker in septic shock patients with chemotherapy-induced febrile neutropenia. *Shock*. 2019;52(2):160-165. doi:10.1097/shk.0000000000001256
25. Tofas P, Skiada A, Angelopoulou M, et al. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections in neutropenic patients with haematological malignancies or aplastic anaemia: analysis of 50 cases. *Int J Antimicrob Agents*. 2016;47(4):335-339. doi:10.1016/j.ijantimicag.2016.01.011
26. Llitjos JF, Gassama A, Charpentier J, et al. Pulmonary infections prime the development of subsequent ICU-acquired pneumonia in septic shock. *Ann Intensive Care*. 2019;9(1):39. doi:10.1186/s13613-019-0515-x
27. Leite HP, de Lima LF. Metabolic resuscitation in sepsis: a necessary step beyond the hemodynamic? *J Thorac Dis*.

- 2016;8(7):E552-557. doi:10.21037/jtd.2016.05.37
28. Gärtner R. Selenium in immune response and intensive care. In: Michalke B, ed. Selenium. Cham: Springer; 2018:363-371.
 29. Bloos F, Trips E, Nierhaus A, et al. Effect of sodium selenite administration and procalcitonin-guided therapy on mortality in patients with severe sepsis or septic shock: a randomized clinical trial. *JAMA Intern Med.* 2016;176(9):1266-1276. doi:10.1001/jamainternmed.2016.2514
 30. Brodska H, Valenta J, Malickova K, Kohout P, Kazda A, Drabek T. Biomarkers in critically ill patients with systemic inflammatory response syndrome or sepsis supplemented with high-dose selenium. *J Trace Elem Med Biol.* 2015;31:25-32. doi:10.1016/j.jtemb.2015.02.005
 31. Chelkeba L, Ahmadi A, Abdollahi M, et al. The effect of parenteral selenium on outcomes of mechanically ventilated patients following sepsis: a prospective randomized clinical trial. *Ann Intensive Care.* 2015;5(1):29. doi:10.1186/s13613-015-0071-y

Copyright © 2021 The Author(s); This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.