Zinc as a Predictor of Sepsis in Critically Ill Patients

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Receive date: 21/8/2024
Revise date:14/10/2024
Accept date:6/11/2024
Publish date:16 /11/2024
Keywords: Zinc, sepsis accuracy, ferritin

Background and study aim: Any delay in diagnosis and treatment of sepsis may lead to significant organ failure and can be associated with elevated mortality rates. The aim of the study is to evaluate the diagnostic role of serum zinc as a marker for the detection of sepsis in critically ill patients.

Patients and Methods: The current study enrolled 60 patients who were admitted to the critical care unit. Those patients were subdivided into two groups each group enrolled 30 patients either with sepsis or without sepsis. All patients were subjected to thorough history taking and clinical evaluation. In addition to, C-reactive protein, ferritin, and zinc were also, done and blood culture.

Results: Patients with sepsis had significantly higher mean age (58.34 ± 14.69 vs. 46.75 ± 14.83 (years), C-reactive protein (112.93 ± 79.67 vs. 14.86 ± 5.19 (mg/dl)) and ferritin (1231.17 ± 176.11 vs. 123.96 ± 87.82 (mcg/l)) with significantly lower serum albumin (31.01 ± 0.22 vs. 35.67 ± 1.10 (g/dl)) and serum zinc (31.45 ± 6.78 vs.75.55 ± 12.45 (µg/dl). For the prediction of sepsis in critically ill patients; serum zinc at cutoff < 28.90 µg/dl, had the best diagnostic accuracy (88%).

Conclusion: Routine determination of serum zinc may improve the management of critically ill patients at critical care unit. It had higher accuracy in the prediction of sepsis in such patients in comparison to ferritin and C-reactive protein. Further multicenter studies are needed to confirm the current results.

INTRODUCTION

Sepsis in patients who were admitted to critical units would badly affect their prognosis **[1]**. Immune cells require sufficient minerals, vitamins, and energy to function properly. Zinc deficiency disrupts macrophages, and neutrophils and immunological function. Its shortage causes a range of alterations in DNA repair pathways, cytokine gene expression, and zinc transporters **[2]**. In the current study, we aimed to evaluate serum zinc as a predictor of sepsis.

PATIENTS/MATERIALS AND METHODS

Study setting & design:

This case-control study was carried out in the Critical Care Unit (CCU) of the Internal Medicine Department, Assiut University Hospital during the period from 1st August 2022 to 30th May 2023.

Selection criteria

Adult 60 (30 patients with sepsis and 30 patients without sepsis) patients with ages ranging between 18-70 years old with symptoms of systemic infection and with a clinical suspicion of sepsis as diagnosed by the CCU physician. Patients who received antibiotic therapy within three days before sample collection were excluded. Sepsis-related organ failure assessment (SOFA) score was used to define sepsis (patients required two points to be considered to have sepsis) **[3]**.

Methodology

Each patient was subjected to, a full history and clinical examination including vital signs such as pulse, blood pressure, respiratory rate, and temperature. The following investigations were done; complete blood count, liver function tests, kidney function tests, and arterial.

Blood gases. Serum ferritin, C-reactive protein, and serum zinc.

Blood culture

Cultures were drawn before administration of antibiotics, if possible, and if not, a resin-containing bottle was used. Blood cultures were drawn via venepuncture, not from lines. Two samples were drawn via different sites per set to exclude contamination. Collection of the sample as mentioned above and incubated in BacT/ALERT 3D system (bioMérieux, France).

Data analysis

Data was collected and analyzed by using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). The Shapiro test was used to determine the compliance of the data to normal distribution. Quantitative data mean ± standard deviation (SD) and range. These data were compared with the Student t-test. Nominal data were given as number (n) and percentage (%). The Chi2 test was implemented on such data.

The receiver operator characteristic curve was used to determine the accuracy of serum zinc, CRP, and serum ferritin in the prediction of sepsis in critically ill patients. The level of confidence was kept at 95% and hence, the P value was considered significant if < 0.05.

RESULTS

Baseline data in the studied patients based on the development of sepsis (table 1):

Both groups had insignificant differences as regards baseline data (p> 0.05) except patients with sepsis had a significantly higher mean age (58.34 ± 14.69 vs. 46.75 ± 14.83 (age); p< 0.001). ***Baseline laboratory data in patients based on the development of sepsis (table 2, figures 1-3):***

Patients with sepsis had significantly higher leucocytes, neutrophils, CRP, and ferritin with significantly lower serum albumin. Serum zinc (31.45 ± 6.78 vs.75.55 ± 12.45 (µg/dl); p < 0.001) was lower in patients with sepsis. ***Results of culture among patients with sepsis (table 3):***

The most frequent isolated organisms were Staphylococcus hemolyticus (33.3%) and Klebsiella pneumonia (23.3%). Each of Staphylococcus epidermidis and Staphylococcus hominis was isolated in 4 (13.3%) patients. ***Correlation of zinc, CRP, and ferritin with other variables (table 4):***

It was found that CRP had a positive correlation with leucocytes (r= 0.51), neutrophils (r= 0.46), ESR (r= 0.23), and ferritin (r= 0.21) with a negative correlation serum zinc (r= -0.53). ***Zinc level based on possible risk factors for sepsis and types of infection (table 5):***

We found that different risk factors for sepsis showed no significant difference as regards zinc level. Also, zinc levels showed insignificant differences between types of infection either pneumonia or urinary tract infection.

Accuracy of serum zinc, CRP, and ferritin in the diagnosis of sepsis (table 6, figure 4):

For the prediction of sepsis in critically ill patients; serum zinc at cutoff < 28.90 µg/dl, had the best diagnostic accuracy in comparison to other markers (88%). Meanwhile, CRP at cutoff > 23.45 mg/dl had 67.5% accuracy while serum ferritin at cutoff > 997.67 mcg/l had 60% overall accuracy.

Outcome among the studied patients based on development of sepsis (table 7):

CCU's stay was significantly longer among patients with sepsis (15.83 ± 1.87 vs. 9.14 ± 2.17 (days); p< 0.001). Also, a total of 6 (20%) patients with sepsis and only one patient without sepsis deteriorated and died.

DOI: 10.21608/aeji.2024.314252.1407

Table 1: Baseline data in the studied patients based on the development of sepsis

	Development of sepsis		***P* value**
	Yes (n= 30)	No (n= 30)	
Age (years)	58.34 ± 14.69	46.75 ± 14.83	< 0.001
Sex			0.59
Male	20 (66.7%)	21 (70%)	
Female	10 (33.3%)	9 (30%)	
Smoking	9 (30%)	10 (33.3%)	0.80
Comorbidities			
Diabetes mellitus	10 (33.3%)	11 (36.7%)	0.06
Hypertension	5 (16.7%)	6 (20%)	0.43
Chronic kidney disease	3 (10%)	4 (13.3%)	0.55
Ischemic heart disease	4 (13.3%)	5 (16.7%)	0.98
COPD	3 (10%)	4 (13.3%)	0.55
Malignant lesions	1 (3.3%)	2 (6.7%)	0.54
Previous hospital admission	5 (20%)	9 (30%)	0.13
Cause of admission			0.09
Acute pancreatitis	14 (46.7%)	12 (40%)	
DKA	9 (30%)	10 (33.3%)	
Uremic encephalopathy	3 (10%)	4 (13.3%)	
Myocardial infarction	2 (6.7%)	3 (10%)	
AE-COPD	2 (6.7%)	1 (3.3%)	
Risk factors for sepsis			
Catheter insertion	15 (50%)	16 (53.3%)	0.22
Ryle insertion	9 (30%)	11 (36.7%)	0.15
Mechanical ventilation	6 (20%)	4 (13.3%)	0.19
Hemodialysis	3 (10%)	4 (13.3%)	0.50
TPN	2 (6.7%)	3 (10%)	0.33

Data expressed as frequency (percentage), and mean (SD). *P* value was significant if < 0.05. COPD: chronic obstructive pulmonary disease; AE-COPD: acute exacerbation of chronic obstructive lung disease; DKA: diabetic ketoacidosis; TPN: total parenteral nutrition

Table 2: Baseline laboratory data based on the development of sepsis

	Development of sepsis		***P* value**
	Yes (n= 30)	No (n= 30)	
Hemoglobin (g/dl)	11.09 ± 1.20	11.10 ± 0.76	0.11
Platelets (10^3/ul)	167.01 ± 19.39	178.19 ± 40.13	0.70
Leucocyte (10^3/ul)	16.45 ± 3.33	4.39 ± 1.10	< 0.001
Neutrophils (10^3/ul)	10.44 ± 1.20	2.67 ± 0.55	< 0.001
Bilirubin (mmol/l)	16.01 ± 3.30	15.55 ± 3.90	0.11
Aspartate transaminase (u/l)	29.09 ± 12.98	30.01 ± 14.90	0.45
Alanine transaminase (u/l)	31.99 ± 19.87	32.34 ± 22.22	0.18
Alkaline phosphatase (u/l)	90.11 ± 13.67	89.01 ± 23.45	0.07
Gamma-glutamyl transpeptidase (u/l)	45.01 ± 5.11	57.78 ± 9.13	0.65
Albumin (mg/dl)	31.01 ± 0.22	35.67 ± 1.10	0.04
Proteins (mg/dl)	70.11 ± 18.19	71.11 ± 19.10	0.20
Creatinine (mg/dl)	0.81 ± 0.13	0.88 ± 0.19	0.06
Urea (mg/dl)	9.22 ± 1.80	10.91 ± 0.90	0.90
INR	1.10 ± 0.12	1.21 ± 0.01	0.67
Sodium (mmol/l)	133.40 ± 0.10	133.50 ± 0.22	0.07
Potassium (mg/dl)	3.99 ± 0.12	4.01 ± 0.12	0.16
Magnesium (mmol/l)	1.01 ± 0.04	0.99 ± 0.09	0.87
Random blood sugar (mmol/L)	5.83 ± 2.03	6.47 ± 1.87	0.15
C-reactive protein (mg/dl)	112.93 ± 79.67	14.86 ± 5.19	< 0.001
ESR (ml/hour)	39.82 ± 16.98	34.06 ± 18.09	0.33
Ferritin (mcg/l)	1231.17 ± 176.11	123.96 ± 87.82	0.02
Zinc (µg/dl)	31.45 ± 6.78	75.55 ± 12.45	< 0.001

Data expressed as mean (SD). *P* value was significant if < 0.05. INR: international randomized ratio; ESR: erythrocyte sedimentation rate.

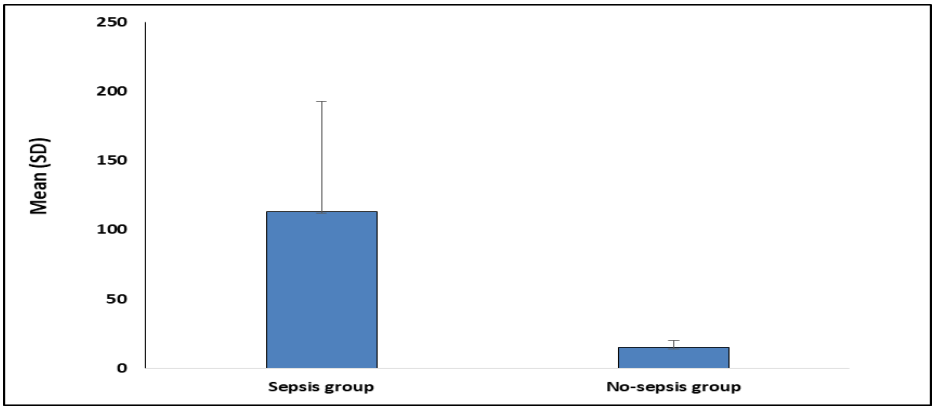

Figure 1: Mean C-reactive proteins in the studied patients based on the development of sepsis.

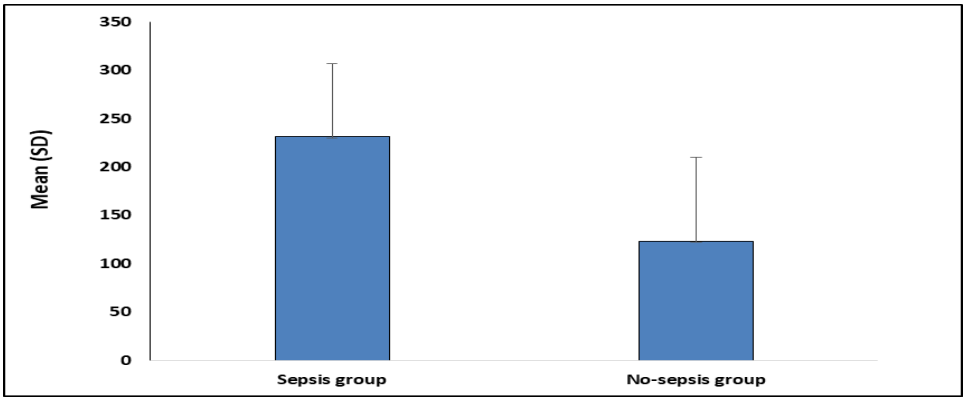

Figure 2: Mean ferritin among the studied patients based on the development of sepsis.

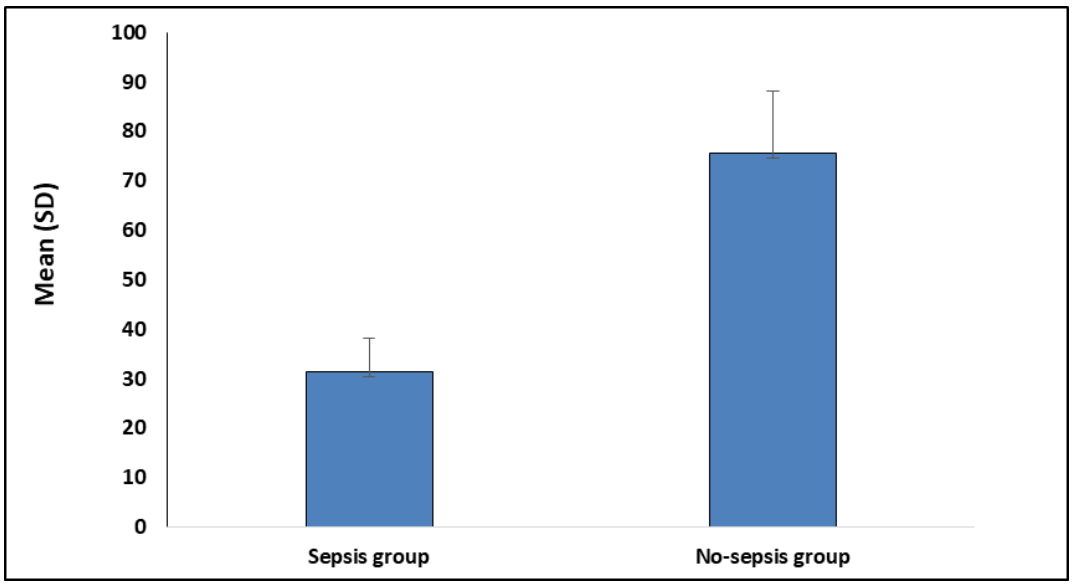

Figure 3: Mean serum zinc among the studied patients based on the development of sepsis.

Table 3: Results of culture among the studied patients with sepsis

	N= 30
Staphylococcus hemolytic	10 (33.3%)
Klebsiella pneumonia	7 (23.3%)
Staphylococcus epidermidis	4 (13.3%)
Staphylococcus hominins	4 (13.3%)
Enterococcus faecalis	2 (6.7%)
Acinetobacter species	2 (6.7%)
Staphylococcus aureus	1 (3.3%)

Data expressed as frequency (percentage).

Table 4: Correlation of zinc, CRP, and ferritin with other variables

	CRP	Ferritin	Zinc
Age (years)	0.10 (0.73)	0.10 (0.34)	-0.02 (0.82)
Hemoglobin (g/dl)	0.03 (0.77)	-0.05 (0.64)	0.07 (0.51)
Platelets (10^3/ul)	0.24 (0.03)	0.02 (0.80)	0.02 (0.84)
Leucocyte (10^3/ul)	0.51 (0.001)	-0.10 (0.35)	-0.50 (0.001)
Neutrophils (10^3/ul)	0.46 (0.001)	0.07 (0.53)	-0.49 (0.001)
Bilirubin (mmol/l)	0.22 (0.05)	-0.10 (0.34)	-0.02 (0.81)
Aspartate transaminase (u/l)	0.11 (0.33)	-0.13 (0.25)	-0.05 (0.62)
Alanine transaminase (u/l)	0.04 (0.76)	-0.03 (0.56)	-0.08 (0.15)
Alkaline phosphatase (u/l)	0.11 (0.09)	-0.09 (0.40)	-0.01 (0.86)
Gamma-glutamyl transpeptidase (u/l)	0.09 (0.88)	-0.06 (0.55)	-0.02 (0.80)
Albumin (mg/dl)	-0.19 (0.08)	0.01 (0.89)	0.06 (0.54)
Proteins (mg/dl)	0.04 (0.73)	-0.24 (0.92)	-0.15 (0.17)
Creatinine (mg/dl)	0.05 (0.62)	0.05 (0.64)	-0.15 (0.17)
Urea (mg/dl)	-0.08 (0.48)	-0.29 (0.81)	-0.18 (0.10)
INR	-0.02 (0.79)	0.25 (0.62)	-0.09 (0.41)
Sodium (mmol/l)	-0.05 (0.62)	-0.08 (0.47)	0.09 (0.55)
Potassium (mg/dl)	-0.19 (0.09)	-0.09 (0.39)	0.12 (0.26)
Magnesium (mmol/l)	-0.06 (0.56)	-0.02 (0.84)	0.03 (0.78)
Random blood sugar (mmol/L)	-0.1 (0.93)	0.03 (0.76)	-0.04 (0.69)
ESR (ml/hour)	0.23 (0.04)	-0.03 (0.74)	-0.02 (0.80)
C-reactive protein (mg/dl)		0.21 (0.03)	-0.53 (0.001)
Ferritin (mcg/l)	0.13 (0.23)		0.06 (0.58)
Zinc (µg/dl)	-0.53 (0.001)	0.06 (0.58)	

Data expressed as *r* (strength of correlation) and *P* value (significance of correlation). *P* value was significant if < 0.05. ESR: erythrocyte sedimentation rate; INR: international randomized ratio.

Table 5: Zinc level based on possible risk factors and site of sepsis in the current study

	Zinc (µg/dl)
Risk factors	
Catheter insertion	31.99 ± 5.34
Ryle insertion	29.45 ± 5.55
Mechanical ventilation	33.01 ± 4.44
Hemodialysis	28.10 ± 2.01
TPN	32.29 ± 4.98
***P* value**	0.45
Site of infection	
Pneumonia	33.10 ± 7.18
Urinary tract infection	30.61 ± 3.76
***P* value**	0.51

Data expressed as mean (SD). *P* value was significant if < 0.05. TPN: total parenteral nutrition.

Table 6: Accuracy of serum zinc, CRP, and ferritin in the diagnosis of sepsis

	CRP (mg/dl)	Ferritin (mcg/l)	Zinc (µg/dl)
Sensitivity	70%	66%	89%
Specificity	65%	54%	87%
PPV	66.7%	81.8%	87.2%
NPV	68.4%	61.4%	88.7%
Accuracy	67.5%	60%	88%
Cutoff point	> 23.45	> 997.67	< 28.90
AUC	0.62	0.51	0.87
***P* value**	0.04	0.56	< 0.001

CRP: C-reactive protein; PPV: positive predictive value; NPV: negative predictive value; AUC: area under curve. *P* value was significant if < 0.05

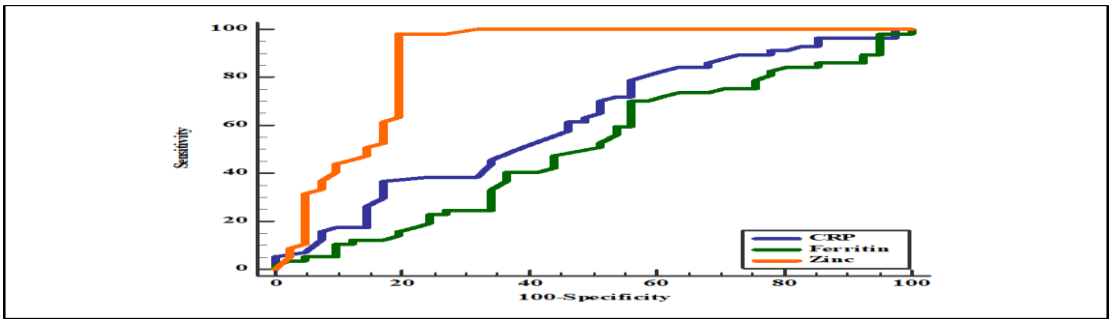

Figure 4: Accuracy of serum zinc, CRP, and ferritin in diagnosis of sepsis.

Table 7: CCU's stay and outcome based on the development of sepsis in the current study

	Development of sepsis		***P* value**
	Yes (n= 30)	**No (n= 30)**	
Stay (days)	15.83 ± 1.87	9.14 ± 2.17	< 0.001
Outcome			0.01
Alive	24 (80%)	29 (96.7%)	
Died	6 (20%)	1 (3.3%)	

Data expressed as mean (SD), range, frequency (percentage). *P* value was significant if < 0.05. CCU: Critical care unit.

DISCUSSION

In the current study, we found that baseline data including sex-different comorbidities and different diagnoses showed no significant differences between those who developed sepsis and those who did not develop sepsis. Meanwhile, patients with sepsis had a significantly higher mean age (58.34 ± 14.69 vs. 46.75 ± 14.83 (years); p< 0.001). Previous studies noticed similar findings **[4]**.

Another finding in the current study, the most frequent risk factor for development of sepsis was catheter insertion (50% vs. 53.3%; p= 0.22), ryle tube insertion (30% vs. 36.7%; p= 0.15), mechanical ventilation (20% vs. 13.3%; p= 0.09), hemodialysis (10% vs. 13.3%; p= 0.50) and total parenteral nutrition (6.7% vs. 10%; p= 0.33). **Ahiawodzi et al (2018)** stated similar data **[5]**.

The Sepsis group had significantly higher, neutrophils, CRP, and ferritin with significantly lower serum albumin and serum zinc. Previous research concluded that patients with raised CRP had poor prognosis **[6].** Many previous reports were consistent with our findings **[7][8-11]**. Also, others noticed lower zinc levels in the sepsis group **[12][2, 13-15]**.

Here, the most frequently isolated organisms were Staphylococcus hemolyticus (33.3%) and Klebsiella pneumonia (23.3%). Gram-negative bacteria were detected in up to 58% of sepsis group **[16]**.

We found that for the prediction of sepsis in critically ill patients; serum zinc at cutoff < 28.90 µg/dl, had the best diagnostic accuracy in comparison to other markers (88%). Meanwhile, CRP at cutoff > 23.45 mg/dl had 67.5% accuracy while serum ferritin at cutoff > 997.67 mcg/l had 60% overall accuracy.

Similarly, a previous study stated that the sensitivity and specificity of using serum zinc of 70.6 µg/dL as a cut-off to predict the severity of sepsis were 90.2 % and 59.2 % **[17]**. Serum zinc level correlated with the prognosis of early-onset neonatal sepsis. A high zinc serum is associated with a better prognosis **[18]**.

Yet, there is a paucity of literature that discusses the role of serum zinc in such issues. This point is considered a point of strength in our study.

Unfortunately, the current study had some limitations including a low number of patients, and being conducted in a single center. We didn't assess the level of inflammatory biomarkers such as IL-6, presepsin, and PCT. But the latter biomarkers, although they had more sensitivities, were more expensive. Also, we didn't study the role of zinc supplementation in such patients. Future studies are warranted to draw firm conclusions.

CONCLUSION:

Routine determination of serum zinc may improve the management of critically ill patients at critical care unit. It had higher accuracy in the prediction of sepsis in such patients in comparison to ferritin and C-reactive protein. Further multicenter studies are needed to confirm the current results.

Conflict of interest: none

Funding: None.

Conflict of Interest: None.

Ethical consideration:

This work was conducted after obtaining approval by the Medical Ethics Committee of the Faculty of Medicine at Assiut University with IRB: 17101600 Also, written informed consent was obtained from all participants before being enrolled in the study. The study was registered on *www. Clinicaltrials.gov* Identifier: NCT05112406.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Acknowledgments: Not applicable

Authors' contribution

All authors read the manuscript, revised it, and approved it for publication

HIGHLIGHTS:

- Sepsis in critically ill patients greatly affects the outcome
- Results of blood culture usually take a long time to obtain the growth
- Serum zinc may play an important role in the early prediction of sepsis in critically ill patients

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Cite as: El-Hefny, N., Noshy, M., El-Masry, M. Zinc as a Predictor of Sepsis in Critically Ill Patients. *Afro-Egyptian Journal of Infectious and Endemic Diseases*, 2024;14(4):477-486. doi: 10.21608/aeji.2024.314252.1407