Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.285207.3354 Volume 30, Issue 5, August 2024
Manuscript ID ZUMJ-2404-3354
DOI 10.21608/ZUMJ.2024.285207.3354

ORIGINAL ARTICLE

Role of Serum Hepcidin as A Diagnostic and Prognostic Marker for Sepsis among Critically ill Patients

Ahmed Noaman Elsayed [1], Yasser A A El hendy[1],Islam Ehab[1*], Ghada Elsayed Amr[2], Amira Hamed Mohamed Afifi[2], Michael Edwar[1], Usama Ragab[1]
1 Internal Medicine Department, Faculty of Medicine, Zagazig University
2 Clinical Pathology Department, Faculty of Medicine, Zagazig University

***Corresponding author:**
Islam Ehab Fikry Salem

Email:
Islamehab15@gmail.com

Submit Date 2024-04-25
Accept Date 2024-04-29

ABSTRACT

Background: In the last decade hepcidin which was previously known to have a significant role in iron metabolism, has gained attention as a possible marker of bacterial sepsis in adults. This research aimed to evaluate the role of hepcidin as a biomarker for diagnosis and prognosis of sepsis among critically ill patients.

Methods: In a cohort study, 62 emergency medical patients who were admitted to the ICU within 24 hours and were divided into two groups: those with sepsis (Group A) and those without (Group B). Hepcidin levels were measured using an ELISA kit, and patient assessments included SOFA, SAPS 3, and APACHE II scores.

Results: Septic patients had significantly higher hepcidin than the non-septic patients ($p<0.001$). Hepcidin was a significant diagnostic marker for sepsis with sensitivity (91.89%) and specificity (70.97%) at cutoff point of 2.52 ng/ml with AUC was (0.922). Multivariate regression analysis revealed that alongside traditional sepsis markers, hepcidin and SAPS3 scores were independent predictors of mortality, with ORs of 2.09 (95% CI: 1.31–3.33, $p=0.002$) and 1.21 (95% CI: 1.04–1.4, $p=0.01$), respectively.

Conclusion: Serum hepcidin, combined with clinical scoring systems, proves to be a reliable diagnostic tool for sepsis and could serve as a predictor of mortality in critically ill septic patients.

Keywords: Serum Hepcidin, Predictor, Mortality, Sepsis, critically ill

INTRODUCTION

Globally, sepsis—defined as malfunction of many organs as a result of an uncontrolled immune response to infection—is a leading cause of death and disability and a drain on healthcare systems' and governments' financial resources [1].

Despite the 2016 agreement statement on sepsis-3 criteria, diagnosing critically ill people is still difficult. Worldwide, sepsis was the leading cause of death in 2017, with an estimated 50 million cases and a mortality rate of 22% across sub-Saharan Africa, Oceania, and substantial areas of Asia. But in countries with high per capita wealth, the death rate from sepsis is declining [2].

Sequential Organ Failure Assessment (SOFA) scores and microbial identification are the main tools used by clinicians to differentiate sepsis from other critical illnesses. In bacteria-induced sepsis, additional highly sensitive and specific biomarkers might be useful for diagnosis, disease progression monitoring, and antibiotic efficacy evaluation. As a result, the risk of antibiotic resistance can be reduced, and the therapy for bacterial sepsis can be reduced [3].

Hepcidin is mainly known for its role in iron homeostasis, but it also has antibacterial and antifungal properties. When serum iron levels are high, hepatocytes produce more hepcidin. In reaction to lipopolysaccharide and under the control of IL-6, hepcidin initiates the acute phase reaction. Within a few hours of receiving an intravenous injection of IL-6, patients exhibit a decline in blood

iron and transferrin saturation levels together with an increase in urine hepcidin levels [4].

While multiple studies have demonstrated the importance of biomarkers such as CRP, WBCs, and procalcitonin for recognizing sepsis, the possible relevance of hepcidin remains unknown. Considering this gap, our study focuses on a complete evaluation of hepcidin's utility as a diagnostic and predictive biomarker for sepsis in the critical care setting among patients at Zagazig University Hospitals.

PATIENTS AND METHODS

Between August 2023 to February 2024, we performed this cohort study on 62 patients presented with medical emergency within 24h of arrival to Medical Intensive Care Unit (MICU) of the Internal Medicine Department Zagazig University Hospitals. Written informed consent was obtained from all participants after explaining the procedure and medical research. The research was conducted under the World Medical Association's Code of Ethics (Helsinki Declaration) for human research. This study was carried out after the approval of the Institutional Review Board (IRB) (#101066-30-8-2023).

Inclusion criteria were as follows: individuals aged 18 or older admitted to the MICU due to any medical emergency within 24 hours of arrival at the hospital, patients with a SOFA score of two or higher, and those requiring ICU admission for a minimum of three days. We excluded patients with incomplete data or loss of follow-up while in the ICU, those who had received blood transfusions, individuals who had undergone surgery within the last seven days prior to their hospital stay, and patients with an anticipated ICU stay of less than two days or who declined to participate in the study.

All included patients were subjected to full history taking and thorough clinical examination. Patients were allocated into two groups based on the presence of sepsis (31 cases in each group): Group A: critically ill patients admitted to ICU due to sepsis, and Group B: critically ill patients who did not have sepsis. Diagnosis of sepsis was done based on Sequential Organ Failure Assessment (SOFA) score [5].

Laboratory investigations included complete blood count, Liver function tests, Kidney function tests, coagulation profile, serum electrolytes, Urine output, Arterial blood gases, Blood glucose level, Urine output, and measurement of serum lactate and procalcitonin. Measurement of serum Hepcidin: Serum Hepcidin was evaluated using an enzyme-linked immune sorbent assay (ELISA) kit (Catalogue number: DLR-Hepc-Hu), according to the instruction of the manufacturer BioVision's Human Hepcidin ELISA Kits. Time of sampling: Group A: on 1st and 5th days of being admitted, Group B: on 1st day of being admitted. The normal Reference range of Hepcidin was 6.32-46.06 ng/ml for males and 3.44-24.78 ng/ml for females [6].

The SOFA score was used to monitor patients' conditions during hospitalization to determine the extent of organ function or failure. Scores were assigned for neurological, coagulation, cardiovascular, hepatic, and renal systems, with an overall average of six [3].

Acute Physiology and Chronic Health Evaluation II (APACHE II): Twelve admission physiologic characteristics were used to determine the point score, including the patient's age, chronic health status, and Acute Physiology Score.

Simplified Acute Physiology Score (SAPS 3): Twenty variables made up the SAPS 3 score; they included physiological measures, patient characteristics before admission in the ICU, and circumstances surrounding the admission to the ICU [7]. Follow-up: was done until discharge from ICU for routine laboratory investigations, ICU mortality, and Duration of ICU stay.

Statistical analysis

Statistical analysis was performed on all data using SPSS 24.0 for Windows after it was gathered tabulated, and organized (SPSS Inc., Chicago, IL, USA). To ensure that the data followed a normal distribution, the Shapiro Walk test was employed. The results of the qualitative analysis were shown using relative percentages and frequency counts. The difference between the qualitative variables was calculated using the chi-square test ($\chi 2$) and Fisher exact tests. A Mann Whitney test was used for non-parametric variables and an independent T-test for parametric ones. We used Pearson's test for parametric variables and Spearman's test for non-parametric ones to determine their correlation. Logistic regression can determine if an outcome is present or not by using a set of independent factors. Statistical significance was determined by a P-value less than 0.05, and non-significant by a P-value greater than 0.05.

RESULTS

There was no difference in age, sex, and other comorbidities among the septic and non-septic groups at baseline (Table 1).

The median neutrophil to lymphocyte ratio, CRP, procalcitonin, serum lactate, and hepcidin levels

were higher in group A ((P<0.001)). Further differences were identified in the scores; the mean SOFA score, APACHE II score, and SAPS 3 score were higher in group A ((P<0.001)). A significant difference was also identified between different stages of sepsis and initial hepcidin levels; mean hepcidin levels were higher among septic shock patients compared to those with sepsis without shock ((P<0.001)) (Table 2).

We studied the correlation between serum hepcidin level and different study parameters among patients with sepsis (Group A). Significant positive correlations were revealed between serum hepcidin and age *(r=0.503, P=0.009)*, SOFA score *(r=0.521, P=0.006)*, APACHE score *(r=0.518, P=0.007)*, SAPS3 score *(r=0.670, P<0.001)*, serum creatinine *(r=0.579, P=0.002)* and CRP *(r=0.559, P=0.003)* as summarized in Table(3).

On conducting Receiver operation Curve (ROC) analysis for assessment of the optimal cutoff value to discriminate sepsis patients from non-sepsis patients, analysis showed that serum Hepcidin had highest sensitivity (91.89%) and specificity (70.97%) at 2.52 ng/ml with (AUC) was (0.922), CRP had highest sensitivity (91.89%) and specificity (80.65%) at 70 mg/dL with (AUC) was (0.946), Procalcitonin had highest sensitivity (94.59%) and specificity (96.77%) at 0.8 *μg/L* with (AUC) was (0.992), and serum lactate had highest sensitivity (75.68%) and specificity (93.55%) at 1.7 mmol/l with area under the curve was (0.912) (Table 4, Figure 1)

Further ROC analysis compared different sepsis markers as predictors of mortality. Serum hepcidin exhibited the highest specificity among them, with specificity of 78.05% and a sensitivity of 70.37% at a cutoff of 3.619 ng/ml and an AUC of 0.799. CRP had a sensitivity of 81.48% and specificity of 60.98% at 75 mg/dL with an AUC of 0.729, and procalcitonin showed a sensitivity of 92.59% and specificity of 60.98% at 1 μg/L with an AUC of 0.790 (Table 5, Supplementary Figure 1).

Multivariate regression analysis showed that SAPS3 score with odd ratio (OR)=1.21, 95 % confidence interval (CI)=1.04 – 1.4, P=0.01, and Hepcidin (OR = 2.09, 95 % CI = 1.31–3.33, P = 0.002) can be used as independent factors for predicting mortality (Table 6).

ICU outcome and different sepsis markers exhibited statistically significant difference between the studied groups; as median of neutrophil to lymphocyte ratio, CRP, Procalcitonin, serum lactate and serum hepcidin were higher among patients who died *(P<0.001)*, *(P=0.006)*, *(P<0.001)*, *(P=0.004)* and *(P=0.01)* respectively (Supplementary Table 1).

Table 1: Demographic data among the studied groups

Variables	Group A (n=31)	Group B (n=31)	P value
Age *(years)* *Mean ± SD* *Range*	 57.8 ± 16.8 (25 – 90)	 55 ± 17.2 (15 – 78)	 0.66[1]
Sex *(N. %)* Male Female	 14 (45.2%) 17 (54.8%)	 14 (45.2%) 17 (54.8%)	 1.00[2]
BMI *(Kg/m²)* *Mean ± SD* *Range*	 25.6 ± 2.58 (21 – 30)	 26.4 ± 2.25 (21 – 29)	 0.18[1]
Diabetes mellitus	11 (35.5%)	18 (58.1%)	0.08[1]
Hypertension	16 (51.6%)	19 (61.3%)	0.44[1]
Chronic liver disease	1 (3.2%)	7 (22.6%)	0.053[2]
Chronic obstructive pulmonary disease	0 (0%)	4 (12.9%)	0.11[2]
Ischemic heart disease	2 (6.5%)	7 (23.3%)	0.08[2]
Chronic kidney disease	5 (16.7%)	4 (12.9%)	0.73[2]

**[1]Mann-Whitney U test, [2]Chi-square test, Non-significant: P >0.05, Significant: P ≤0.05*

**BMI=body mass index*

Table 2: Initial Laboratory, Sepsis markers, Different scores of assessments among the studied groups on admission, and Comparison of stages of sepsis and Initial hepcidin level among sepsis patients

Variable		**Group A (n=31)**	**Group B (n=31)**	**P Value**
WBC *($10^3/mm^3$)*	*Median (IQR)*	17.35 (20.2)	8.6 (3.65)	**0.001**[2]
	Range	(0.2 – 73)	(2.6 – 19.4)	
Neutrophil to lymphocyte ratio	*Median (IQR)*	15.8 (15.25)	3.2 (2.9)	**<0.001**[2]
	Range	(0 – 85)	(1.3 – 21)	
Platelet to lymphocyte ratio	*Median (IQR)*	138 (206)	97.8 (93.5)	0.14[2]
	Range	(4.1 – 1195)	(22 – 523)	
CRP *(mg/dL)*	*Median (IQR)*	222 (183.5)	22 (33.5)	**<0.001**[2]
	Range	(21 – 550)	(3 – 207)	
Procalcitonin *(µg/L)*	*Median (IQR)*	6.6 (29.5)	0.1 (0.1)	**<0.001**[2]
	Range	(0.5 – 100)	(0.01 – 1.4)	
Serum lactate *(mmol/l)*	*Median (IQR)*	2.2 (1.35)	1.2 (0.5)	**<0.001**[2]
	Range	(1.1 – 4.4)	(0.9 – 2)	
Hepcidin *(ng/ml)*	*Mean ± SD*	4.06 ± 1.05	2.85 ± 1.68	**0.002**[1]
	Range	(2.28 – 5.67)	(0.24 – 5.3)	
SOFA score	*Mean ± SD*	11.07 ± 3.36	0.16 ± 0.37	**<0.001**[1]
	Range	(4 – 19)	(0 – 1)	
APACHE II score	*Mean ± SD*	25.9 ± 7.29	12.74 ± 6.82	**<0.001**[1]
	Range	(12 – 48)	(4 – 27)	
SAPS 3 score	*Median (IQR)*	75 (16.5)	54 (12.5)	**<0.001**[2]
	Range	(50 – 106)	(39 – 89)	

Variable		**Sepsis (n=3)**	**Severe sepsis (n=14)**	**Septic shock (n=14)**	***P Value**	**Post Hock**
Hepcidin *(ng/ml)*	*Mean ± SD*	2.7 ± 0.29	3.89 ± 0.77	4.95 ± 0.85	**<0.001**	**P1=0.03 P2<0.001 P3=0.008**
	Range	(2.28 – 2.98)	(3.08 – 5.35)	(2.72 – 5.67)		

**[1]Student's T test, [2]Mann-Whitney U test, Non-significant: P >0.05, Significant: P ≤0.05*
WBC: white blood cell, CRP: C-reactive protein, APACHE: Acute Physiology and Chronic Health Evaluation, SAPS: Subacromial Pain Syndrome, SOFA: Sequential Organ Failure Assessment

Table 3: Correlation of Serum hepcidin with different parameters among sepsis group

Variable	**Hepcidin**	
	r	***P***
Age	0.503	**0.009**[2]
SOFA score	0.521	**0.006**[1]
APACHE II score	0.518	**0.007**[1]
SAPS3 score	0.670	**<0.001**[2]
Serum Creatinine	0.579	**0.002**[2]
CRP	0.559	**0.003**[1]

**[1]Pearson correlation, [2]Spearman rank correlation test, Non-significant: P >0.05, Significant: P ≤0.05*

**CRP=C reactive protein, SOFA: Sequential Organ Failure Assessment, APACHE: Acute Physiology and Chronic Health Evaluation, SAPS: Simplified Acute Physiology Score*

Table 4: ROC curve analysis of different sepsis markers in predicting sepsis diagnosis

Variables	Cut-point	Sensitivity (%)	Specificity (%)	PPV (%)	NPP (%)	AUC (%)	P Value
Hepcidin	**2.52**	91.89%	70.97%	79.07%	88%	0.922	**<0.001**
CRP	**70**	91.89%	80.65%	85%	89.29%	0.946	**<0.001**
Procalcitonin	**0.8**	94.59%	96.77%	97.22%	93.75%	0.992	**0.001**
Serum Lactate	**1.7**	75.68%	93.55%	93.33%	76.32%	0.912	**<0.001**
WBCs	**15.2**	75%	83.87%	84.38%	74.29%	0.758	**<0.001**
Neutrophile to lymphocyte ratio	**6**	78.38%	83.87%	85.29%	76.47%	0.850	**<0.001**
Platelets to lymphocyte ratio	**165**	51.35%	77.42%	73.08%	57.14%	0.657	**0.02**

CRP: C-reactive protein, WBCs: white blood cells, PPV: Positive predictive value, NPP: Negative predictive value, AUC: Area Under the Curve

Table 5: ROC curve analysis of different sepsis markers in predicting mortality

Variables	Cut-point	Sensitivity (%)	Specificity (%)	PPV (%)	NPP (%)	AUC (%)	P Value
Hepcidin	**3.613**	70.37%	78.05%	67.86%	80%	0.806	**<0.001**
CRP	**75**	81.48%	60.98%	57.89%	83.33%	0.729	**0.01**
Procalcitonin	**1**	92.59%	60.98%	60.98%	92.59%	0.790	**0.04**
Serum Lactate	**1.8**	74.07%	65.85%	58.82%	79.41%	0.736	**0.02**
WBCs	**16**	80.77%	68.29%	61.76%	84.85%	0.758	**0.03**
Neutrophile to lymphocyte ratio	**4.25**	88.89%	56.1%	57.14%	88.46%	0.768	**0.04**
Platelets to lymphocyte ratio	**97.8**	66.67%	46.34%	45%	67.86%	0.575	0.15

CRP: C-reactive protein, WBCs: white blood cells, PPV: Positive predictive value, NPP: Negative predictive value, AUC: Area Under the Curve

Table 6: Logistic regression analysis for predictors of Mortality

Variables	Univariate analysis		Multivariate analysis	
	P value	Odds (CI 95%)	P value	Odds (CI 95%)
Age	0.49	0.99 (0.97 – 1.02)	-	-
Pneumonia	**<0.001**	12.39 (3.55 – 43.19)	0.12	3.57 (0.73 – 17.47)
Pyelonephritis	**0.009**	4.15 (1.43 – 12.07)	0.74	0.78 (0.18 – 3.33)
SOFA score	**<0.001**	1.34 (1.18 – 1.53)	0.18	0.78 (0.54 – 1.13)
APACHE II	0.18	1.08 (0.97 – 1.19)	-	-
SAPS 3	**0.003**	1.22 (1.07 – 1.38)	**0.01**	1.21 (1.04 – 1.4)
WBCs	**0.03**	1.05 (1.01 – 1.1)	0.39	1.03 (0.96 – 1.099)
Neutrophile to lymphocyte ratio	**0.04**	1.04 (1.003 – 1.083)	0.12	1.09 (0.98 – 1.23)
Platelet to				

Variables	Univariate analysis		Multivariate analysis	
	P value	Odds (CI 95%)	P value	Odds (CI 95%)
lymphocyte ratio	0.15	1.002 (0.99 – 1.005)	-	-
CRP	**0.01**	1.005 (1.001 – 1.009)	0.52	1.002 (0.99 – 1.007)
Procalcitonin	**0.05**	1.017 (1 – 1.035)	0.54	1.006 (0.99 – 1.027)
Serum lactate	**0.02**	2.11 (1.14 – 3.89)	0.22	1.56 (0.77 – 3.79)
Hepcidin	**<0.001**	2.19 (1.47 – 3.27)	**0.002**	2.09 (1.31 – 3.33)
Serum Albumin	**0.03**	0.4 (0.17 – 0.93)	0.4	0.64 (0.22 – 1.82)
ICU stay	**0.02**	1.67 (1.11 – 2.51)	0.65	1.03 (0.91 – 1.17)
Hospital stay	**0.02**	1.55 (1.08 – 2.23)	0.2	0.93 (0.83 – 1.04)

SOFA: Sequential Organ Failure Assessment, APACHE: Acute Physiology and Chronic Health Evaluation, SAPS: Simplified Acute Physiology Score, WBCs: white blood cells, CRP: C-reactive protein, ICU: Intensive Care Unit

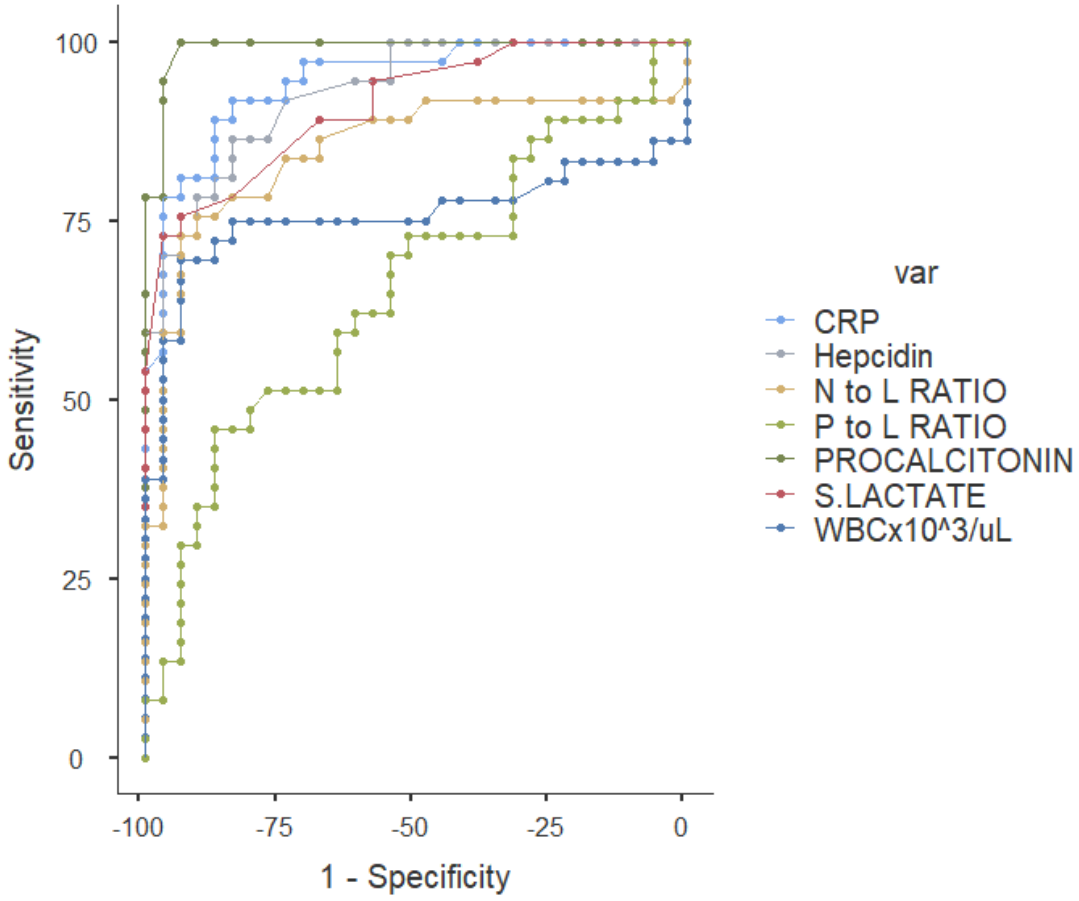

Figure 1: ROC curve analysis of different sepsis markers in predicting sepsis diagnosis

DISCUSSION

Sepsis is a huge financial burden on healthcare systems and governments worldwide. It is defined by a dysregulated host response to infection that causes several organs to malfunction. Age, co-morbidities, and immunological status are some of the host factors that determine sepsis severity; pathogen factors include virulence, microbial species, and infectious load. In extremely sick individuals, the diagnosis can be difficult even when using the sepsis-3 criteria that were published in 2016 [4]. A number of biomarkers have been studied as possible markers for sepsis, such as lactate, procalcitonin, C-reactive protein, and white blood cell count [8].

Not only Hepcidin has primarily been studied in relation to anemia since its discovery, but it also has been extensively studied in critically ill adult patients, particularly those with infectious disorders like sepsis [9]. Thus, we aimed to

evaluate the role of hepcidin as a biomarker for diagnosis and prognosis of sepsis among critically ill patients.

According to our observations, both the septic and non-septic groups had comparable baseline characteristics when looking at age, sex, and comorbidities.

In our study, we found that the septic patients had significantly higher WBCs, NLR, PLR, CRP, PCT, and serum lactate compared to the non-septic patients. In consistent, Qiu et al. [10] revealed that the septic patients had significantly higher levels of PCT, and serum lactate compared to those in the non-sepsis group.

Yeşilbaş et al. [11] found that PCT and hepcidin levels were more precise in differentiating between infected and non-infected than CRP and WBCs in research involving pediatric patients.

In the present study, we found that septic patients had significantly higher serum hepcidin levels than the non-septic patients. These findings were in line with Olinder et al. [4] as they revealed that Serum hepcidin levels are higher in people with infection compared to those without infections. Also, Qiu et al. [10] and Yeşilbaş et al. [11] found that the sepsis group had significantly higher serum Hepcidin levels than those of the non-sepsis group. Our findings also agreed with the results of Wakakuri et al. [9] and van Eijk et al. [12] as severe sepsis was associated with elevated serum hepcidin levels.

Olinder et al. [4] detected a marked decline in hepcidin levels following the start of antibiotic treatment, which could indicate a reduction of the bacterial load. So, it's possible that early on in treatment, the dynamics of hepcidin levels indicate therapeutic efficacy. However, in our study serum hepcidin level didn't significantly decrease in fifth day of treatment compared to initial measurement. This may be explained due to multi drug resistant bacteremia which were found in most septic patients.

The present study findings were in line with Tacke et al. [13] who demonstrated that hepcidin levels in the blood are increased according to severity of sepsis, where patients with septic shock had a higher level of Hepcidin than those without shock.

Moreover, in our study septic patients had significantly higher SOFA score, APACHE II, and SAPS 3 were significantly higher among septic patients compared to non-septic patients. Similarly, Qiu et al. [10] reported that the sepsis group had significantly higher APACHE II and SOFA scores compared to the non-sepsis group.

The current study revealed significant positive correlations between serum hepcidin and age, SOFA score, APACHE score, SAPS3 score, serum creatinine, and CRP among septic patients. In accordance, Qiu et al. [10] documented a significantly positive correlation between Hepcidin APACHE II, PCT, and SOFA in the sepsis patients. Also, Olinder et al. [4] and Cherry-Bukowiec et al. [14] reported that hepcidin significantly correlated with CRP and SAPS3 score.

In our study, we found that hepcidin was a significant diagnostic marker for sepsis with sensitivity (91.89%) and specificity (70.97%) at cutoff value (2.52 ng/dl) with AUC of (0.922) as we compared different sepsis markers (CRP, Procalcitonin, Serum Lactate, WBCs, Hepcidin). Procalcitonin had the highest sensitivity (94.59%) in predicting sepsis in critically ill patients followed by Hepcidin and CRP (91.89%). Hepcidin was comparable to CRP in its sensitivity thus we can use hepcidin to rule out sepsis among critically ill patients. Our finding was compared to Qiu et al. [10] who reported that the ROC curve (AUC) of Hepcidin in diagnosis of sepsis were 0.865 (CI) = 0.807-0.911 with specificity of 66.67%, sensitivity for sepsis diagnosis was 95.56%, positive and negative predictive values were 73.51% and 93.94%, respectively. On top of that, compared to the standard biomarkers CRP and WBCs, Hepcidin had a significantly higher AUC for sepsis detection.

It's interesting that our results reported that serum hepcidin level at cut off value (3.619 ng/dl) had the highest specificity (78.05%) among all sepsis markers in predicting mortality with AUC of (0.799) followed by WBCs (68.29%), Serum lactate (65.85%). This means that serum hepcidin level is the most valuable predictor of mortality among septic patients.

Similarly, Olinder et al. [4] revealed a strong correlation between hepcidin levels and the risk of death within 180 days in patients with septic shock.

We found that SAPS3 score and Hepcidin can be used as independent factors for predicting mortality. We performed multivariant logistic model for predicting mortality including different variables that could affect mortality among critically ill patients. Only SAPS 3 score and

serum hepcidin level could be used as predictor of mortality.

Similarly, Qiu et al. [10] demonstrated that Elevated levels of serum hepcidin, procalcitonin, lactate, APACHE II, and SOFA were associated with a significantly higher risk of 28-day mortality.

This study has some points of strength, first we included most sepsis markers in our study. We compared septic patients with non-septic patients. Serum hepcidin level was measured in two sets at first and fifth day of admission. We utilized ROC curve analysis and logistic regression model to find the best predictors of mortality. However our study has some limitations, it's single center study and has small sample size. We recommend carrying out large scale studies to determine the best cutoff value of serum hepcidin in diagnosis of sepsis and prediction of mortality, and to conduct additional prospective studies to follow up serum hepcidin level during hospital stay to evaluate the effect of different interventions on serum hepcidin and its relation to outcome.

CONCLUSION

Seum hepcidin level when combined with clinical scores may serve as a good tool for diagnosis of sepsis among critically ill patients who might require more care and supervision. Serum hepcidin level could be a good predictor for mortality among critically ill patients who had sepsis.

REFRENCES

1. Paoli CJ, Reynolds MA, Sinha M, Gitlin M, Crouser E. Epidemiology and Costs of Sepsis in the United States-An Analysis Based on Timing of Diagnosis and Severity Level. Crit Care Med. 2018;46(12):1889-97.
2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395(10219):200-11.
3. van Engelen TSR, Wiersinga WJ, Scicluna BP, van der Poll T. Biomarkers in Sepsis. Crit Care Clin. 2018;34(1):139-52.
4. Olinder J, Börjesson A, Norrman J, West T, Carlström J, Gustafsson A, et al. Hepcidin discriminates sepsis from other critical illness at admission to intensive care. Sci Rep. 2022;12(1):14857.
5. Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med*. 1998;26(11):1793-1800.
6. Singh A, Pandey HC, Chaudhary R. Establishment of normal reference range of serum hepcidin in Indian blood donors. Asian J Transfus Sci. 2023;17(1):1-6.
7. Moreno RP, Metnitz PG, Almeida E, Jordan B, Bauer P, Campos RA, et al. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission [published correction appears in Intensive Care Med. 2006;32(5):796]. Intensive Care Med. 2005;31(10):1345-55.
8. Kandil M, Khalil G, El-Attar E, Shehata G, Hassan S. Accuracy of heparin binding protein: As a new marker in prediction of acute bacterial meningitis. Braz. J. Microbiol. 2018;49(Suppl 1):213–9.
9. Wakakuri H, Hyodo H, Ohara T, Yasutake M. Serum Hepcidin-25 Levels Reflect the Presence of Bacteremia in Patients with Systemic Inflammatory Response Syndrome. J Nippon Med Sch. 2019;86(2):91
10. Qiu Z, Shen K, Shu M, Xu D, Deng X, Chen D. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2018;30(7):652-7.
11. Yeşilbaş O, Şevketoğlu E, Bursal Duramaz B, Kıhtır HS, Gedikbaşı A, Talip Petmezci M, et al. Role of hepcidin in the diagnosis of sepsis and septic shock in children. Turk J Med Sci. 2018;48(3):517-24.
12. van Eijk LT, Kroot JJ, Tromp M, van der Hoeven JG, Swinkels DW, Pickkers P. Inflammation-induced hepcidin-25 is associated with the development of anemia in septic patients: an observational study. Crit Care. 2011;15(1): R9.
13. Tacke F, Nuraldeen R, Koch A, Strathmann K, Hutschenreuter G, Trautwein C,et al. Iron Parameters Determine the Prognosis of Critically Ill Patients. Crit Care Med. 2016;44(6):1049-58.
14. Cherry-Bukowiec JR, Engoren M, Wiktor A, Raghavendran K, Napolitano LM. Hepcidin and Anemia in Surgical Critical Care: A Prospective Cohort Study. Crit Care Med. 2018;46(6):567-74.

Table S1: Comparison between sepsis markers according to ICU outcome among the studied groups

Variable		Discharged (n=40)	Died (n=22)	P Value
Neutrophil to lymphocyte ratio	*Median (IQR)*	3.95 (3.95)	15.4 (12.88)	**<0.001[1]**
	Range	(0.5 – 85)	(0 – 85)	
Platelet to lymphocyte ratio	*Median (IQR)*	110.3 (105.6)	138 (187.75)	0.29[1]
	Range	(22 – 523)	(4.1 – 1195)	
CRP *(mg/dL)*	*Median (IQR)*	27 (172.75)	159 (217)	**0.006[1]**
	Range	(3 – 452)	(4 – 550)	
Procalcitonin *(µg/L)*	*Median (IQR)*	0.15 (2.9)	4.5 (24)	**<0.001[1]**
	Range	(0.01 – 100)	(0.1 – 100)	
Serum lactate *(mmol/l)*	*Median (IQR)*	1.4 (0.55)	2 (0.78)	**0.004[1]**
	Range	(0.9 – 4.4)	(1 – 4)	
Hepcidin *(ng/ml)*	*Mean ± SD*	3.07 ± 1.52	4.17 ± 1.34	**0.01[1]**
	Range	(0.24 – 5.29)	(1.02 – 5.67)	

*[1]*Mann-Whitney U test, Non-significant: P >0.05, Significant: P ≤0.05*

**CRP=C reactive protein, IQR: Interquartile Range*

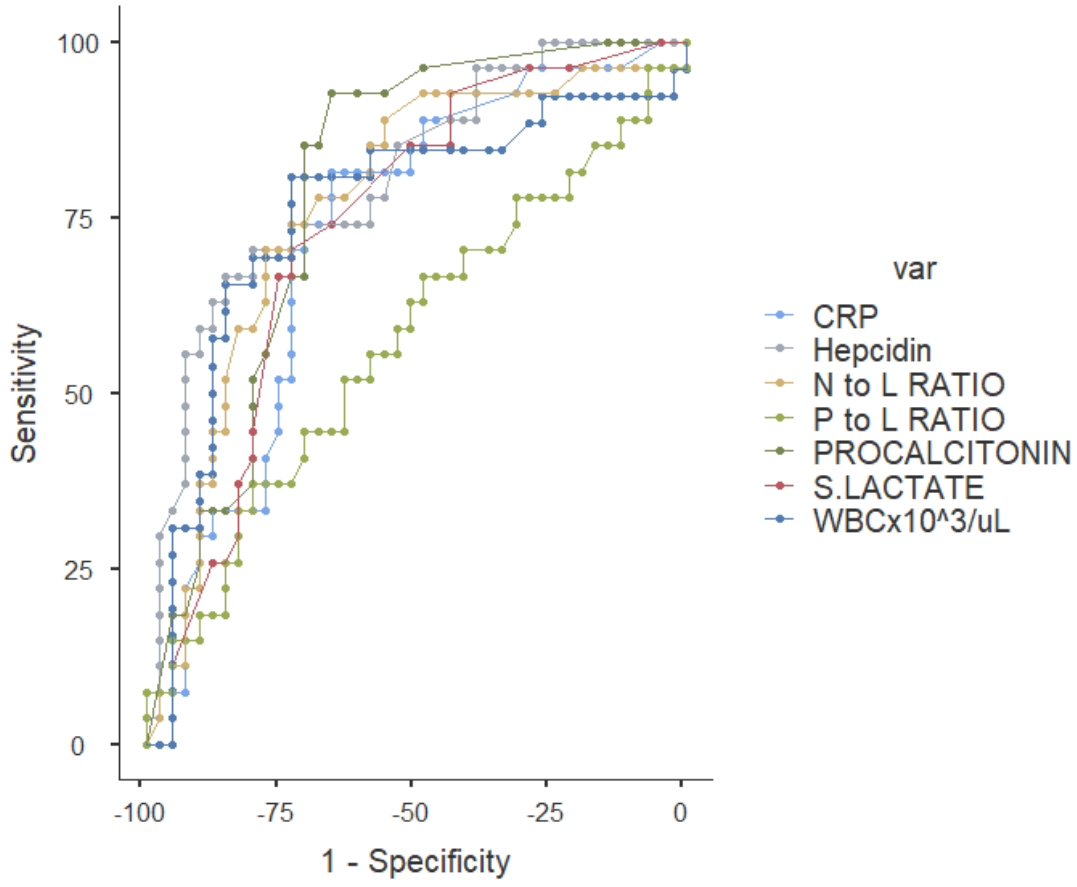

Figure S1: ROC curve analysis of different sepsis markers in predicting mortality

To Cite:

Elsayed, A., El hendy, Y., Ehab, I., Amr, G., Afifi, A., Edwar, M., Ragab, U. Role Of Serum Hepcidin as A Diagnostic and Prognostic Marker For Sepsis among Critically ill Patients. *Zagazig University Medical Journal*, 2024; (1783-1792): -. doi: 10.21608/zumj.2024.285207.3354