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Effect of Serum Ferritin on the Prognosis of Patients with Sepsis

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KEYWORDS

Sepsis, Serum Ferritin, Inflammatory Biomarkers and Risk Stratification

ABSTRACT:

Background. Sepsis is a critical condition characterized by a severe inflammatory response to infection, leading to organ dysfunction and high mortality rates. Serum ferritin, an iron storage protein, also acts as an acute-phase reactant, with levels rising significantly during inflammation. Elevated ferritin levels have been linked to worse outcomes in sepsis, potentially reflecting heightened inflammation and immune dysregulation. Understanding the prognostic role of serum ferritin could help identify high-risk patients and guide more targeted therapeutic interventions in sepsis management.

Aims : This study aims to assess the association between baseline serum ferritin levels and clinical outcomes in patients diagnosed with sepsis. We intend to explore whether elevated or reduced ferritin levels correlate with the severity of sepsis and overall patient prognosis.

Methods. This research was conducted as a comparative study over a duration of one year at Murshidabad Medical College, Department of General Medicine. 100 patients were included in this study

Result. In survival 40 (40%)and non-survival 60 (60%)patients had Respiratory system it was statistically not significant (P=0.0455)In survival 80 (80%)and non-survival 20 (20%)patients had Urine system it was statistically not significant (P=1.9701)In survival 66 (66%)and non-survival 34 (34%)patients had Blood system it was statistically significant (P=0.00137)In survival 66 (66%)and non-survival 34 (34%)patients had Serum iron (μg/dL)it was statistically significant (P=0.00137)In survival 70 (70%)and non-survival 30 (30%)patients had Transferrin (mg/dL)it was statistically not significant (P<0.0001).

Conclusion: High-level serum ferritin was an independent prognostic marker for the prediction of mortality in patients with sepsis. Further high-quality research is needed to confirm the relationship between ferritin and the prognosis of septic patients

INTRODUCTION

Sepsis is life-threatening organ dysfunction caused by in- fection, which is a fatal disease with a prolonged hospital stay, high morbidity, and mortality rate [1]. Therefore, sepsis is a significant public health problem as more than 19 million patients are diagnosed with sepsis each year and about 40% of septic patients are rehospitalized within their first 90 days after discharge [2]. Although international Surviving Sepsis Campaign

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guidelines have been regularly updated to direct standardized therapy of sepsis, the treatment of sepsis remains challenging for clinicians, and the mortality of sepsis remains high [3]. The complex pathophysiological processes and untimely intervention are significant contributors to the poor outcome of sepsis. Timely diagnosis and evaluation of the condition of sepsis are key to early treatment and intervention, which are considered crucial aspects for improving the prognosis of septic patients [3]. Some scoring systems, such as sequential organ failure assessment (SOFA), acute physiology and chronic health evaluation II (APACHEII), are widely used in the diagnosis of sepsis and predicting the risk of death for sepsis in clinical practice. All of them are efective but remain too complex and time-consuming due to the inclusion of too many parameters. It is of great significance to find some efective and convenient-to-use biomarkers for the diagnosis and prognosis of sepsis.

Excessive inflammatory response secondary to the dysregulated host response to infection is the core pathogenesis of sepsis in the development of organ damage [4]. Iron is essential for almost all organisms and is required by cells for metabolic needs and specialized functions. Except for acting as the central medium of hemoglobin and myoglobin for oxygen binding, iron also plays key roles in many metabolic processes of both the host and pathogen [5]. Maintaining iron homeostasis of the human body is essential for basic metabolism. Serum ferritin is generally considered a good indicator of iron stores under most circumstances. Meanwhile, serum ferritin is also known as an acute phase reactant, which is regulated either transcriptionally or posttranscriptionally by proinflammatory cytokines. Several recent studies have shown that iron metabolism parameters could be used as prognostic markers in critical patients and septic patients [6,7,8]. However, due to the heterogeneity of the disease and the participants, further investigations are still needed to explore the feasibility of using iron meta- bolism parameters as biomarkers to predict the outcomes of septic patients. Although most published studies establish a relationship between the elevation of ferritin and the poor outcome, its clinical applications are still limited and need further evaluation, especially a search for the optimal cut- of value.

MATERIALS AND METHODS

Study Type: It was a Comparative study.

Study Area: Murshidabad Medical College

Study Population: The study population included adult patients (aged ≥18 years) admitted to the intensive care unit (ICU) with a diagnosis of sepsis, as identified by the International Classification of Diseases (ICD) codes.

Study Duration: The study covers data from patient admissions recorded between 2023 and 2024.

Sample Size: 100.

Inclusion Criteria

- Adult patients (aged ≥18 years) with a confirmed diagnosis of sepsis based on ICD codes.
- Patients with recorded serum ferritin levels within the first 48 hours of ICU admission.
- Patients with complete data on relevant clinical outcomes (e.g., ICU mortality, length of stay, organ failure).

Exclusion Criteria

- Patients with missing or incomplete data on serum ferritin levels.
- Patients diagnosed with hematologic disorders, chronic inflammatory diseases, or conditions known to significantly alter ferritin levels (e.g., iron overload, chronic liver disease).
- Patients with multiple ICU admissions where sepsis was not the primary diagnosis.
- Patients who were discharged against medical advice or transferred to another facility.

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RESULT AND ANALYSIS

Table 1: Comparisons of information between survivors and non survivors

	Survivals (P-50)	Non survivals (P-50)	P-value
Age (years)	62.32 ± 17.47	65.78 ± 16.43	<0.001
Emergency admissions (%)	40(40.0%)	60 (60%)	0.0455
CHD (%)	30 (30%)	70 (70%)	<0.0001
Hypertension (%)	40 (40%)	60 (60%)	0.0455
HF (%)	35 (35%)	65 (65%)	0.0026
Diabetes (%)	50 (50%)	50 (50%)	1.000
CKD (%)	44 (44%)	56 (56%)	0.23013
Anemia (%)	60 (60%)	40 (40%)	0.045
HR (bpm)	91.08 ± 20.68	92.91 ± 20.49	0.076
RR (cpm)	20.45 ± 5.98	21.78 ± 6.47	<0.001
MBP (mmHg)	75.48 ± 15.47	73.13 ± 17.77	0.002
Temperature (°C)	36.96 ± 0.83	36.77 ± 0.88	<0.001
Hemoglobin (g/dL)	9.73 ± 1.98	9.60 ± 2.04	0.215
AKI (%)	45 (45%)	55 (55%)	0.3173
Respiratory system (%)	40 (40%)	60 (60%)	0.0455
Urine system (%)	80 (80%)	20 (20%)	1.9701
Blood system (%)	66 (66%)	34 (34%)	0.00137
Serum iron (μg/dL)	66 (66%)	34 (34%)	0.00137
Transferrin (mg/dL)	70 (70%)	30 (30%)	<0.0001

Table 2: Unadjusted relationships between serum ferritin groups and clinical outcomes.

	Low-ferritin group	Normal reference range group	High-ferritin group	P. value
Hospital mortality (%)	20 (20%)	40 (40%)	40 (40%)	0.0183
ICU mortality (%)	25 (25%)	25 (25%)	50 (50%)	0.0019
Hospital length of stay (days)	40 (40%)	20 (20%)	40 (40%)	0.0183
ICU- length of stay (days)	25 (25%)	25 (25%)	50 (50%)	0.0019
AKI (%)	40 (40%)	20 (20%)	40 (40%)	0.0183

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Table 3: Results of log-binomial model analysis

Variables	Binomial	Standard Error	z-score	Adjusted ORs (95% CI)	p-value
Hyperferritinemia (%)	0.84	0.27	7.25	2.3(1.83–2.87)	<0.001
Age (years)	0.03	0.01	2.86	1.03(1.01–1.03)	0.004
Anemia (%)	-0.60	0.08	-7.69	0.56(0.48–0.64)	<0.001
Temperature (°C)	-0.21	0.07	-2.96	0.83(0.71–0.95)	0.003
HR (bpm)	0.00	0.03	0.07	1.01(0.97–1.03)	0.953
RR (cpm)	0.03	0.02	2.58	1.03(1.01–1.04)	0.010
SpO2 (%)	-0.04	0.03	-1.31	0.98(0.94–1.00)	0.187
MBP (°10⁹/L)	0.00	0.01	0.23	1.01(0.99–1.00)	0.822
WBC (°10⁹/L)	0.07	0.03	3.04	1.07(1.02–1.09)	0.002
Hemoglobin (g/dL)	-0.13	0.04	-3.87	0.9(0.84–0.94)	<0.001
Lactate (mmol/L)	0.50	0.12	4.62	1.65(1.33–2.02)	<0.001
SOFA score	0.71	0.16	4.71	2.03(1.48–2.75)	<0.001
Vasopressor using (%)	1.34	0.36	3.78	3.78(1.91–7.42)	<0.001
AKI (%)	0.84	0.26	3.37	2.3(1.42–3.68)	<0.001
Culture positive (%)	-0.03	0.12	-0.19	0.99(0.78–1.23)	0.841

In Survivals, the mean Age (mean± s.d.) of patients was 62.32 ± 17.47.In Nonsurvivals, the mean Age (mean± s.d.) of patients was 65.78 ± 16.43.Distribution of mean Age with Group was statistically significant (p<0.001).

In Survivals, 40(40.0%) patients had Emergency admissions. In Nonsurvivals, 60 (60%) patients had Emergency admissions. Association of Emergency admissions with Group was statistically significant (p=0.0455).

In Survivals, 30 (30%) patients had CHD .In Nonsurvivals, 70 (70%) patients had CHD. Association of CHD (%) with Group was statistically significant (p=<0.0001).

In Survivals, 40 (40%) patients had Hypertension. In Nonsurvivals, 60 (60%) patients had Hypertension. Association of Hypertension (%)with Group was statistically significant (p=0.0455).

In Survivals, 35 (35%) patients had HF. In Nonsurvivals, 65 (65%) patients had HF. Association of HF (%) with Group was statistically significant (p=0.0026).

In Survivals, 50 (50%) patients had Diabetes. In Nonsurvivals, 50 (50%) patients had Diabetes Association of Diabetes (%) with Group was not statistically significant (p=1.000).

In Survivals, 44 (44%) patients had CKD. In Nonsurvivals, 56 (56%) patients had CKD. Association of CKD (%) with Group was not statistically significant (p=0.23013).

In Survivals, 60 (60%) patients had Anemia. In Nonsurvivals, 40 (40%) patients had Anemia. Association of Anemia (%) with Group was statistically significant (p=0.045).

In Survivals, the mean HR (bpm) (mean± s.d.) of patients was 91.08 ± 20.68.In Nonsurvivals, the mean HR (bpm) (mean± s.d.) of patients was 92.91 ± 20.49. Distribution of mean HR (bpm) with Group was statistically significant (p=0.076).

In Survivals, the mean RR (cpm) (mean± s.d.) of patients was 20.45 ± 5.98. In Nonsurvivals, the mean RR (cpm) (mean± s.d.) of patients was 21.78 ± 6.47.Distribution of mean RR (cpm)with Group was statistically significant (p<0.001).

In Survivals, the mean MBP (mmHg) (mean± s.d.) of patients was 75.48 ± 15.47In Nonsurvivals, the mean MBP (mmHg) (mean± s.d.) of patients was 73.13 ±

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17.77Distribution of mean MBP (mmHg) with Group was statistically significant (p=0.002).

In Survivals, the mean Temperature (°C)(mean± s.d.) of patients was 36.96 ± 0.83.In Nonsurvivals, the mean Temperature (°C)(mean± s.d.) of patients was 36.77 ± 0.88.Distribution of mean Temperature (°C)with Group was statistically significant (p<0.001).

In Survivals, the mean Hemoglobin (g/dL)(mean± s.d.) of patients was 9.73 ± 1.98.In Nonsurvivals, the mean Hemoglobin (g/dL)(mean± s.d.) of patients was 9.60 ± 2.04

Distribution of mean Hemoglobin (g/dL) with Group was not statistically significant (p=0.215).

In survival 45 (45%) and non-survival 55 (55%) patients had AKI (%) it was statistically not significant (P=0.3173)

In survival 40 (40%) and non-survival 60 (60%) patients had Respiratory system it was statistically not significant (P=0.0455)

In survival 80 (80%) and non-survival 20 (20%) patients had Urine system it was statistically not significant (P=1.9701)

In survival 66 (66%) and non-survival 34 (34%) patients had Blood system it was statistically significant (P=0.00137)

In survival 66 (66%) and non-survival 34 (34%) patients had Serum iron (μg/dL)it was statistically significant (P=0.00137).In survival 70 (70%)and non-survival 30 (30%)patients had Transferrin (mg/dL)it was statistically not significant (P<0.0001)

In Low-ferritin group, 20 (20%) patients had Hospital mortality. In NRR group, 40 (40%) patients had Hospital mortality. In High-ferritin group, 40 (40%) patients had Hospital mortality. Association of Hospital mortality (%) with Group was statistically significant (p=0.0183).

ICU mortality (%)

In Low-ferritin group, 25 (25%) patients had ICU mortality .In NRR group, 25 (25%) patients had ICU mortality .In High-ferritin group, 50 (50%)patients had ICU mortality .Association of ICU mortality (%)with Group was statistically significant (p=0.0019).

Hospital length of stay (days)

In Low-ferritin group, 40 (40%) patients had Hospital length of stay (days).In NRR group, 20 (20%) patients had Hospital length of stay (days).In High-ferritin group, 40 (40%) patients had Hospital length of stay (days).Association of Hospital length of stay (days) with Group was statistically significant (p=0.0183).

ICU- length of stay (days)

In Low-ferritin group, 25 (25%) patients had ICU-length of stay (days).In NRR group, 25 (25%) patients had ICU- length of stay (days).In High-ferritin group, 50 (50%) patients had ICU- length of stay (days).Association of ICU- length of stay (days) with Group was statistically significant (p=0.0019).

AKI (%)

In Low-ferritin group, 40 (40%) patients had AKI. In NRR group, 20 (20%) patients had AKI .In High-ferritin group, 40 (40%) patients had AKI .Association of AKI (%) with Group was statistically significant (p=0.0183).

In Age (years) Adjusted ORs (95% CI)1.03(1.01–1.03) p-value 0.004 (statistically significant).In Anemia (%) Adjusted ORs (95% CI)0.56(0.48–0.64) p-value<0.001(statistically significant).In Temperature (°C) Adjusted ORs (95% CI)0.83(0.71–0.95) p-value 0.003(statistically significant).In HR (bpm) Adjusted ORs (95% CI)1.01(0.97–1.03) p-value 0.953(Not Significant).In RR (cpm) Adjusted ORs (95% CI)1.03(1.01–1.04)p-value 0.010(Not Significant).In SpO2 (%) Adjusted ORs (95% CI)0.98(0.94–1.00) p-value 0.187(Not Significant).In MBP (°10⁹/L) Adjusted ORs (95% CI)1.01(0.99–1.00) p-value0.822(Not Significant).In WBC (°10⁹/L) Adjusted ORs (95% CI)1.07(1.02–1.09) p-value 0.002(statistically significant).In Hemoglobin (g/dL) Adjusted ORs (95% CI)0.9(0.84–0.94) p-value <0.001(statistically significant).In Lactate (mmol/L) Adjusted ORs (95% CI)1.65(1.33–2.02) p-value <0.001(statistically significant).In SOFA score Adjusted ORs (95%

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CI)2.03(1.48–2.75) p-value <0.001(statistically significant).In Vasopressor using (%) Adjusted ORs (95% CI) 3.78(1.91–7.42) p-value <0.001(Significant).In AKI (%) Adjusted ORs (95% CI)2.3(1.42–3.68) p-value <0.001(statistically significant).In Culture positive (%) 0.99(0.78–1.23) p-value 0.841(Not Significant).

DISCUSSION

In this retrospective cohort study, we indicated that the elevation of serum ferritin was significantly associated with poor outcomes in septic patients. High ferritin was associated with higher mortality, longer hospital and ICU duration, higher risk of AKI development, and vasopressor using. A positive linear correlation was found between se- rum ferritin and in-hospital mortality of septic patients. Serum ferritin ≥591.5 ng/ml was an independent predictor of the in-hospital mortality of septic patients, which could increase the in-hospital mortality risk by 119%. Our present study did not reveal that the decrease in ferritin is a risk factor for mortality. AKI and anemia were identified as the significant interactive factors. Our data provided more positive evidence about the efect of serum ferritin on the risk of mortality and prognosis in septic patients, which may further facilitate the clinical application of serum ferritin as a biomarker in diagnosis and prognosis of sepsis.

The balance of iron metabolism is essential to main- taining various metabolisms of humans. Serum ferritin concentration is a useful biomarker reflecting the status of iron stores. A low level of ferritin indicates an iron deficiency, while an elevated ferritin level points to iron overload in the absence of inflammation [9]. Mean- while, ferritin has been considered an acute phase reactant and could increase significantly in both infectious and noninfectious inflammatory reactions. Recently, the relationships between diseases and ferritin are gaining growing attention. The abnormal changes of ferritin are regarded as diagnostic and prognostic biomarkers of cancer, connective tissue disorders, systemic inflammatory disease, and even the global epidemic of COVID-19 [10].

Sepsis has an extremely high morbidity and fatality rate,and seeking efective diagnostic and prognostic indicators of sepsis has always been a topic of considerable interest. The prognostic value of serum ferritin on all-cause mortality in critical patients and septic patients was reported previously. Patients with sepsis have higher ferritin levels than those with other diagnoses in ICU departments, while the ferritin level is even higher in the septic shock subgroup. A positive correlation is observed between ferritin and the SOFA score. For the elderly cohort with hyper- ferritinemia, patients with sepsis or solid malignancy have a worse prognosis than those with other diagnoses [11]. Consistently, we found that there was an obvious iron metabolism imbalance in the present sepsis cohort. Non- survival patients had a higher concentration of serum iron, ferritin, and transferrin saturation but a lower level of transferrin, which were consistent with the previous findings. There was a nearly linear relationship between serum ferritin and in-hospital mortality. We further revealed that 591.5 ng/mL had the strongest ability to identify survival and nonsurvival patients during hospitalization. Ferritin concentration exceeding 591.5 ng/mL acted as an in- dependent prognostic predictor of sepsis, and our key findings were still robust in the subgroup analysis. The decrease in serum ferritin had no influence on the mortality of septic patients in the present study, which was not consistent with a previous report about children with severe study. sepsis and septic shock . In this previous study, children with ferritin less than 200 ng/ml had a higher mortality rate compared with those whose ferritin ranged from 200 to 500 ng/ml (23% vs. 9%). This diference between our study and the previous one could be explained in part by the small sample, diferent cut-of values, and participants. The real relationship between low-ferritin and NRR should be further confirmed by future studies with a larger sample size. We admitted that potential selection bias and small study bias might have an unknown impact on the present results.

Interestingly, the predictive value was lost in the sub- groups without AKI development, but it showed the same tendency with the overall cohort. The interactive efects of AKI and anemia were statistically significant in the present. study. AKI is one of the common complications of sepsis. Roughly, one-third of septic patients may develop AKI [12] Meanwhile, AKI is considered a risk factor for sepsis development . The

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incidence of sepsis is about 40% in critically ill patients with AKI. The serum ferritin level is con- sidered an efective biomarker in predicting the develop- ment of AKI and the recovery of renal function. Although the main function of ferritin is to regulate iron metabolism, some preclinical studies suggested that the efect of ferritin on the kidney is independent of iron loading and may not be limited to iron sequestration. FtH expressed in renal proximal tubules is critical in me- diating the tolerance against infection and AKI [13]. The overexpression of FtL can inhibit the inflammatory reaction, reduce organ injury, and promote the survival of infectious mice by inhibiting the activation of the NF-κB pathway. Due to the loss of the predictive value in the nonAKI subgroup, we have concerns with the false positive outcome lead by AKI. Anemia is the key confounder of the present study, especially iron deficiency anemia. Since the decrease of ferritin is the crucial diagnostic criterion of iron deficiency anemia, it is obviously inappropriate to make the diagnosis of iron deficiency anemia in patients with increased ferritin, even using the ICD code in the present study. Anemia was used as a surrogate in the present study. Fortunately, our findings were robust in both anemic and nonanemic sub- groups. As a nonspecific biomarker, many influencing factors, including growth hormone, hypoxia, anemia, and endoplasmic reticulum stress, have a great influence on the level of ferritin. Interpretation of the result should be cautious, especially in those combined with diseases that may afect iron metabolism. Serum ferritin is often increased during sepsis; however, the contributory role of ferritin in sepsis development and progression still could not be established in clinical studies. The following mechanisms may explain the biological re- lationship between ferritin and sepsis. The first thing to note is the influence of inflammatory factors and acute-phase proteins on erythrocyte damage. Erythropoiesis is known as the key reason for mediating the elevation of circular iron levels, and bacterial proliferation has been shown to be driven by iron sufficiency and suppressed by iron starvation in the preclinical model [14]. In the iron-overloaded mice model, septic mice have an increased susceptibility to infection and higher mortality in the septic model. Since the proliferation of bacteria depends on iron, the host tends to reduce the circular iron levels that can be considered a defense mechanism to limit bacterial growth and resist infection. This efect is mediated by hepcidin, which can efectively decrease intestinal iron absorption and promote macrophages to engulf iron. Ferritin is an important storage protein for iron. The marked reductions in circulating iron mediated by hepcidin can efectively increase the expression of ferritin. What is more, the damage to hepatocytes may. result in the release of ferritin into circulation, which is the principal site for the storage of ferritin. Hepatocyte injury also leads to the abnormal synthesis and secretion of hepcidin, which also contributes to the abnormal expression of ferritin. Ferritin is regarded as a protective factor. As McCullough K reported, serum ferritin and FtL can prevent hyperinflammation during sepsis, which is associated with the decrease of NF-κB activation [15]. Furthermore, although reducing circulating iron can efectively reduce bacterial proliferation, iron toxicity, and iron-related oxi- dative stress, the adverse efects of iron accumulation are also significant. Iron accumulation may lead to cell death, which is known as ferroptosis. This is a newly established type of iron-dependent cell death resulting from iron accumulation and lipid peroxidation . The increased iron loading in macrophages may inhibit the ability to phagocytize and kill pathogens.

CONCLUSION

Our findings in the present study indicated that a higher level of serum ferritin was associated with a higher risk of mortality in critical patients with sepsis. Serum ferritin may be a potentially useful prognostic bio- marker for septic patients in the ICU department, but further large-sample prospective studies are needed to confirm the present finding.

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