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Association Between Serum Ferritin and In-hospital Mortality in Critical Ills with Sepsis-Associated Acute Kidney Injury: A Retrospective Cohort Study

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Abstract

Background: The association between serum ferritin (SF) and in-hospital mortality in sepsis-associated acute kidney injury (SAAKI) remains unclear. The study explored the relationship between SF and in-hospital mortality in SAAKI patients. Methods: A retrospective cohort study was conducted using data from the Medical Information Mart for Intensive Care-IV2.2 database. The primary outcome was all-cause, in-hospital mortality. Multivariable adjusted Cox regression models were utilized to determine the hazard ratio (HR) and 95% confidence interval (95% CI). The natural logarithm of SF (SF(ln)) was employed for restricted cubic spline regression and threshold effects analyses. Stratified and interaction analyses in different subgroups were performed to assess the relationship's stability.

Results: The study included 2,806 SAAKI patients in the intensive care unit, with a 54.1% male enrollment rate and a mean age of 64.8 ± 16.6 years. After adjusting for potential confounders, SF(ln) was found to be associated with in-hospital mortality among SAAKI patients (HR 1.27; 95% CI, 1.18-1.36; p <0.001). Patients in the highest SF quantile (Q4, SF≥1056.2ng/mL) had an adjusted HR for in-hospital mortality of 1.64 (95% CI, 1.23-2.19; p=0.001). Non-linear associations between SF(ln) and in-hospital mortality were observed, with higher SF levels corresponding to increased mortality risk. Sensitivity analyses across different subgroups yielded consistent results.Conclusion: A nonlinear association was observed between SF and in-hospital mortality among SAAKI patients. Individuals admitted with SF ≥1056.2ng/mL had substantially increased in-hospital mortality. However, additional prospective studies are required to validate these findings.

Keywords: acute kidney injury, inflammation, mortality, sepsis, serum ferritin

1. Introduce

Sepsis, a dangerous condition associated with a high mortality rate in the intensive care unit (ICU)[1], is characterized by life-threatening organ dysfunction resulting from a dysregulated host response to infection[2]. Sepsis-associated acute kidney injury (SAAKI), a common complication of sepsis, is associated with high morbidity and fatality rates in critical illness[3]. Therefore, the immediate identification of SAAKI patients with a poor prognosis is crucial.

Currently, there are no specific rapid diagnostic indicators in clinical practice to guide the decision-making in the treatment of SAAKI patients. While some indicators are helpful in the diagnosis of sepsis, these are inadequate in the evaluation of SAAKI patients.

Serum ferritin (SF), one of the indicators for differentiating anemia[4], reportedly reflected the cellular defensive response to inflammation[5]. Increased ferritin levels were identified as a response to immune dysregulation, caused by infection[6]. SF was also linked to the prognosis of sepsis with the potential to predict outcomes[7].

Additionally, elevated SF levels were predictive of renal function recovery among patients with acute kidney injury[8]. Consequently, a retrospective cohort study was conducted to investigate the relationship between SF levels and in-hospital mortality among patients with SAAKI, using the Medical Information Mart for Intensive Care IV2.2 (MIMIC-IV2.2) database.

2. Methods

2.1 Data Sources

This retrospective cohort study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[9]. The MIMIC-IV2.2 database is a freely accessible public database, containing comprehensive clinical data of patients at Beth Israel Deaconess Hospital in Boston, Massachusetts, United States, from 2008 to 2019. Ming Lu conducted this study and was granted access to the MIMIC-IV2.2 database after completing the "Protecting Human Research Participants" examination (ID:12473926) as part of a learning program offered by the National Institutes of Health. All experimental protocols were approved by the institutional review boards of Beth Israel Deaconess Medical Center (Boston, Massachusetts, United States) and the Massachusetts Institute of Technology (Cambridge, Massachusetts, United States) (Record ID: 57688587).

2.2 Participants

Patients with SAAKI, who were hospitalized and admitted to the ICU for the first time between 2008 and 2019, were included in this study. Sepsis was defined as a two-point increase in the sequential organ failure assessment (SOFA) score in a patient with a documented or suspected infection[10]. Acute kidney injury was determined using serum creatinine (SCr) and urine output, based on the Kidney Disease Improving Global Outcomes criteria[11]. SAAKI patients are referred to patients with sepsis, who developed acute kidney injury (AKI) within seven days of ICU admission[12]. If a patient had multiple ICU admissions, only data from the first admission were analyzed. The flowchart for participant enrollment is presented in Figure 1.

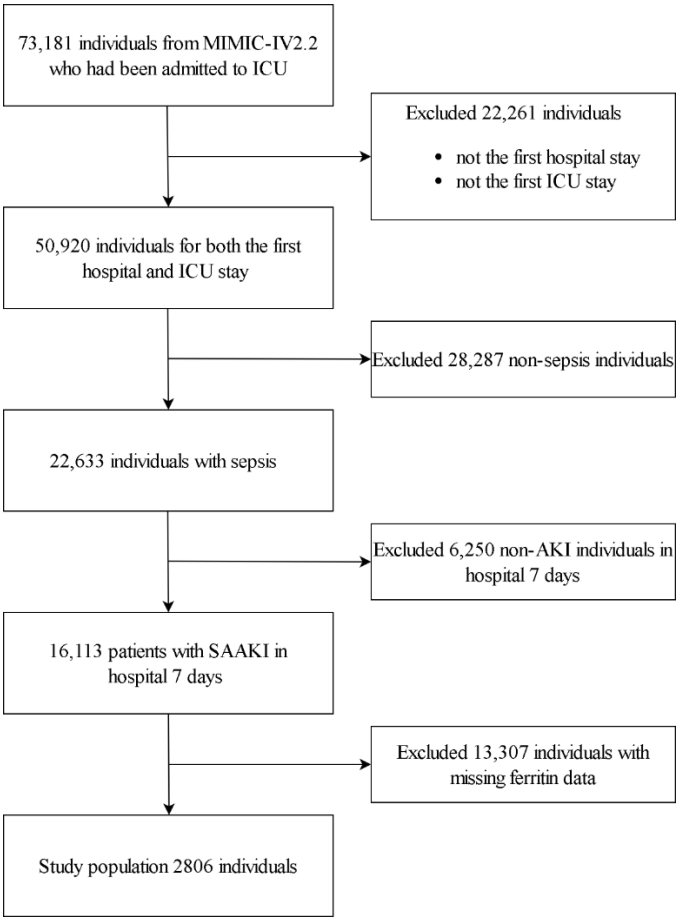

Figure 1. Flowchart of the study population

Abbreviations: MIMIC-IV2.2, Medical Information Mart for Intensive Care-IV2.2; ICU, intensive care unit; AKI, acute kidney injury; SAAKI, sepsis-associated acute kidney injury.

2.3 Variables

This study involved the following variables. The demographic and admission data included age, gender, ethnicity, and admission score. The latter consisted of the Charlson comorbidity index (CCI), simplified acute physiology score II (SAPS II), and SOFA score. Upon ICU admission, the individual's vital signs, including heart rate, temperature (T), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and pulse oximetry saturation (SaO2), were evaluated. Within the initial 24 hours of ICU admission, laboratory tests, including SF, hematocrit (HCT), hemoglobin (HGB), platelet count (PLT), white blood cell (WBC) count, blood urea nitrogen (BUN), SCr, glucose (Glu), prothrombin time (PT), and partial thromboplastin time (PTT), were conducted. Comorbidities included congestive heart failure, chronic pulmonary disease, and renal disease. In cases where multiple results were obtained within 24 hours of ICU admission, the initial dataset was utilized.

2.4 The Management of Missing Data

The main analysis variable SF and in-hospital mortality excluded missing data. Covariables with less than 4% missing data, such as T (2.6%), heart rate (0.18%), SBP (0.57%), DBP (0.57%), MBP (0.18%), SaO2 (0.25%), WBC (0.18%), HGB (0.18%), PLT (0.18%), HCT (0.11%), PT (3.67%), PPT (3.96%), BUN (0.11%), SCr (0.11%), and Glu (0.18%), were supplied using the median value. Covariables, such as lactate and total bilirubin, which had more than 20% missing data, were excluded.

2.5 Study Endpoint

The primary outcome was all-cause, in-hospital mortality.

2.6 Statistical Analyses

Continuous variables with normal or skewed distributions were presented as mean ± standard deviation or median (interquartile range [IQR]), respectively. Meanwhile, categorical variables were presented in percentages. In the analysis of the baseline characteristics, continuous variables with normally distributed values were tested using one-way analysis of variance or t-tests, while those with non-normally distributed values were tested using the Kruskal-Wallis H test. Categorical variables were subject to Chi-square tests. The links between risk factors and in-hospital mortality were demonstrated using univariate Cox regression models. Multivariate Cox proportional hazards models were utilized to assess the association between SF and in-hospital mortality. Kaplan-Meier in-hospital survival curves were constructed to determine the cumulative survival of the different SF groups. The natural logarithm of SF(SF(ln)) was calculated to identify its nonlinear relationship with in-hospital mortality using a Cox regression model with a cubic spline function and a smoothed curve fit. Additionally, the inflection point was determined via a recursive algorithm. A two-piecewise Cox regression model was developed, including the values on both sides of the inflection point. Finally, subgroups were analyzed to detect any interaction effect of SF(ln) in different subgroups. Statistical analyses were conducted using R 4.1.1 software and Free Statistics software version 1.9. All tests were two-tailed, and the significance level was set at $p < 0.05$.

3. Results

3.1 Population and Baseline Characteristics

A total of 16,113 eligible patients were identified in the MIMIC-IV2.2 database. After excluding those with missing clinical data, the remaining 2,806 patients were included in this study (**Figure 1**). The 2,086 SAAKI patients were divided into four groups based on SF quantiles (Q1 <218 ng/mL, 218 ng/mL ≤ Q2 < 479.5 ng/mL, 479.5 ng/mL ≤ Q3 < 1056.2 ng/mL, Q4 ≥1056.2 ng/mL). The individuals' baseline characteristics are shown in **Table 1**. Among the study population, 54.1% were male, and 63.7% were Caucasians. The mean age was 64.8 ± 16.6 years. The in-hospital mortality rate of SAAKI patients was 17.0% in this study. The patients in the highest SF group (Q4) had higher values for heart rate, T, BUN, SCr, PT, PPT, CCI, SAPS II, SOFA score, and in-hospital mortality. Meanwhile, they had lower values for SBP, MBP, SaO2, HCT, HGB, PLT, and Glu. They were more likely to have renal disease but not congestive heart failure or chronic pulmonary disease.

Table 1. Baseline demographic characteristics of the study population stratified by serum ferritin levels.

		Serum Ferritin (ng/ml)				
Variables	Total(n= 2806)	Q1 (n = 700)	Q2 (n = 703)	Q3 (n = 701)	Q4 (n = 702)	P value
Age(years)	64.8 ± 16.6	67.2 ± 16.7	66.5 ± 16.6	63.8 ± 16.2	61.7 ± 16.5	< 0.001
Gender, n (%)						< 0.001
Female	1289 (45.9)	400 (57.1)	335 (47.7)	281 (40.1)	273 (38.9)	
Male	1517 (54.1)	300 (42.9)	368 (52.3)	420 (59.9)	429 (61.1)	

Race, n (%)						0.054
White	1787 (63.7)	465 (66.4)	459 (65.3)	443 (63.2)	420 (59.8)	
Non-white	1019 (36.3)	235 (33.6)	244 (34.7)	258 (36.8)	282 (40.2)	
Vital signs						
HR (beats/min)	74.9 ± 17.3	72.8 ± 17.1	72.6 ± 16.3	76.4 ± 17.4	77.7 ± 17.7	< 0.001
SBP (mmHg)	87.6 ± 17.0	88.8 ± 16.6	88.4 ± 17.0	87.3 ± 16.0	85.9 ± 18.3	0.006
DBP (mmHg)	44.2 ± 11.3	44.0 ± 11.0	44.0 ± 11.4	44.6 ± 11.3	44.2 ± 11.6	0.706
MBP (mmHg)	55.6 ± 14.1	56.1 ± 13.4	55.8 ± 13.6	55.3 ± 14.3	55.2 ± 14.9	0.606
T (°C)	37.6 ± 0.9	37.5 ± 0.8	37.6 ± 0.8	37.7 ± 0.9	37.7 ± 1.0	< 0.001
SpO_2 (%)	90.7 ± 7.5	90.9 ± 7.3	91.1 ± 5.9	90.6 ± 7.5	90.0 ± 8.9	0.037
Laboratory parameters						
HCT (%)	28.6 ± 6.4	29.1 ± 6.0	29.2 ± 6.0	28.6 ± 6.3	27.6 ± 6.9	< 0.001
HGB (g/dL)	9.4 ± 2.1	9.3 ± 2.0	9.6 ± 2.0	9.5 ± 2.1	9.2 ± 2.4	0.001
PLT ($\times 10^9$/L)	159.0 (101.0, 232.0)	184.0 (129.8, 253.0)	172.0 (111.5, 243.0)	152.0 (101.0, 225.0)	126.0 (69.0, 201.0)	< 0.001
WBC ($\times 10^9$/L)	13.7 (9.4, 19.2)	12.9 (8.9, 17.2)	13.6 (9.8, 18.6)	14.5 (9.9, 20.3)	14.2 (9.0, 20.3)	< 0.001
BUN (mg/dL)	31.0 (19.0, 53.0)	28.0 (17.0, 46.0)	30.0 (18.0, 50.0)	31.0 (19.0, 56.0)	35.0 (22.0, 58.0)	< 0.001
Crea (mg/dL)	1.5 (1.0, 2.8)	1.3 (0.9, 2.2)	1.3 (0.9, 2.5)	1.8 (1.0, 3.1)	2.0 (1.1, 3.8)	< 0.001
Glu (mg/dL)	118.8 ± 45.1	121.1 ± 47.6	118.4 ± 42.3	119.2 ± 44.1	116.7 ± 46.2	0.324
PT (seconds)	15.8 (13.5, 20.3)	15.0 (12.9, 20.1)	15.5 (13.4, 20.3)	15.7 (13.7, 20.1)	16.7 (14.0, 23.6)	< 0.001
PTT (seconds)	35.6 (29.0, 51.0)	33.2 (27.9, 49.0)	36.9 (29.3, 53.3)	35.5 (29.2, 50.9)	37.2 (29.7, 54.8)	< 0.001
Comorbidities, n (%)						
CHF	1060 (37.8)	332 (47.4)	275 (39.1)	239 (34.1)	214 (30.5)	< 0.001
CPD	831 (29.6)	249 (35.6)	209 (29.7)	195 (27.8)	178 (25.4)	< 0.001
RD	848 (30.2)	213 (30.4)	207 (29.4)	210 (30)	218 (31.1)	0.926
In-hospital mortality	477 (17.0)	77 (11)	86 (12.2)	117 (16.7)	197 (28.1)	< 0.001
Severity scores						
CCI	6.3 ± 3.0	6.4 ± 2.8	6.2 ± 3.0	6.1 ± 3.0	6.3 ± 3.1	0.247
SAPS II	44.1 ± 14.5	40.6 ± 13.2	42.7 ± 13.8	45.0 ± 14.3	48.2 ± 15.6	< 0.001
SOFA	3.0 (2.0, 5.0)	3.0 (2.0, 4.0)	3.0 (2.0, 5.0)	4.0 (3.0, 5.0)	4.0 (3.0, 6.0)	< 0.001

Notes: Data presented are Mean ± SD, Median (IQR), or N (%).

Abbreviations: Q, quantile; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; T, temperature; SpO_2, pulse oximetry saturation; HCT, hematocrit; HGB, hemoglobin; PLT, platelets; WBC, white blood cell; BUN, blood urea nitrogen; Crea, creatinine; Glu, glucose; PT, prothrombin time; PTT, partial thromboplastin time; CHF, congestive heart failure; CPD, chronic pulmonary disease; RD, renal disease; CCI, Charlson comorbidity index; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment

3.2 Univariate and Multivariable Cox Regression Analysis

The univariate analysis of risk factors, associated with in-hospital mortality, among SAAKI patients was summarized in **Table 2**. Based on the results of the univariate analysis, the SF(ln), age, race, DBP, SBP, MBP, T, SaO2, HCT, HGB, PLT, WBC, BUN, PT, PPT, CCI, SAPS II, and SOFA score were significantly associated with in-hospital mortality (all p <0.01). Multivariable-adjusted Cox regression models were used to determine the hazard ratio (HR) and 95 % confidence interval (95% CI) for in-hospital mortality concerning the different SF levels (**Table 3**). After adjusting for potential confounders, the SF(ln) was associated with in-hospital mortality among SAAKI patients (HR, 1.27; 95%CI, 1.18-1.36; p <0.001). Concerning the Q1 reference group in the unadjusted model, the HRs for in-hospital mortality of the patients in the Q2, Q3, and Q4 groups were 0.93 (95% CI: 0.69-1.27, p=0.669), 1.09 (95% CI: 0.69-1.27, p=0.55), and 1.87 (95% CI: 1.43-2.44, p <0.001), respectively. Concerning the participants in the first quantile (Q1) of SF, those in the highest quantile (Q4) had an all-variable adjusted HR for in-hospital mortality of 1.64 (95% CI, 1.23-2.19; p=0.001).

Table 2. Association of covariates and in-hospital mortality in sepsis-associated acute kidney injury patients

Variable	**HR[a] (95%CI)**	***P* value**
SF(ln)	1.29 (1.22,1.38)	< 0.001
Gender: F vs M	0.93 (0.77,1.11)	0.41
Age (years)	1.01 (1.01,1.02)	< 0.001
Race: nW vs W	1.31 (1.09,1.57)	0.003
HR[b] (beats/min)	0.9982 (0.9931,1.0034)	0.502
SBP (mmHg)	0.99 (0.98,0.99)	< 0.001
DBP (mmHg)	0.98 (0.97,0.98)	< 0.001
MBP (mmHg)	0.99 (0.98,0.99)	< 0.001
T (°C)	0.79 (0.71,0.87)	< 0.001
SpO_2 (%)	0.98 (0.97,0.99)	< 0.001
HCT (%)	0.98 (0.97,0.99)	0.002
HGB (g/dL)	0.93 (0.90,0.97)	0.001
PLT ($\times10^9$/L)	0.998 (0.9971,0.9989)	< 0.001
WBC ($\times10^9$/L)	1.0042 (1.001,1.0074)	0.01
BUN (mg/dL)	1.0063 (1.0038,1.0088)	< 0.001
Crea (mg/dL)	1.02 (0.98,1.06)	0.284
Glu (mg/dL)	0.9994 (0.9972,1.0015)	0.552
PT (seconds)	1.01 (1.01,1.02)	< 0.001
PTT (seconds)	1.0063 (1.004,1.0086)	< 0.001
CHF	1.15 (0.96,1.39)	0.132
CPD	1.19 (0.98,1.44)	0.086
RD	1.06 (0.87,1.29)	0.541
CCI	1.09 (1.06,1.12)	< 0.001
SAPS II	1.03 (1.03,1.04)	< 0.001
SOFA score	1.07 (1.04,1.10)	< 0.001

Abbreviations: HR[a], hazard ratio; CI, confidence interval; SF(ln), natural logarithm of serum ferritin; F, female; M, male; nW, non-white; W, white; HR[b], heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; T, temperature; SpO_2 , pulse oximetry saturation; HCT, hematocrit; HGB, hemoglobin; PLT, platelets; WBC, white blood cell; BUN, blood urea nitrogen; Crea, creatinine; Glu, glucose; PT, prothrombin time; PTT, partial thromboplastin time; CHF, congestive heart failure; CPD, chronic pulmonary disease; RD, renal disease; CCI, Charlson comorbidity index; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

Table 3. Relationship between different serum ferritin levels and in-hospital mortality in different models.

	Non-adjusted Model		Model I		Model II		Model III	
Variable	HR (95%CI)	***P* value**	HR (95%CI)	***P* value**	HR (95%CI)	***P* value**	HR (95%CI)	***P* value**
SF(ln)	1.29 (1.22~1.38)	<0.001	1.33 (1.25~1.42)	<0.001	1.31 (1.22~1.40)	<0.001	1.28 (1.20~1.37)	<0.001
SF (ng/ml)								
Q1	reference		reference		reference		reference	
Q2	0.93 (0.69~1.27)	0.669	0.94 (0.69~1.28)	0.705	0.89 (0.65~1.22)	0.476	0.84 (0.61~1.15)	0.278
Q3	1.09 (0.82~1.46)	0.550	1.15 (0.86~1.54)	0.351	1.12 (0.83~1.52)	0.447	1.01 (0.75~1.37)	0.939
Q4	1.87 (1.43~2.44)	<0.001	1.97 (1.50~2.58)	<0.001	1.86 (1.41~2.47)	<0.001	1.64 (1.23~2.19)	0.001
***P* for Trend**		<0.001		<0.001		<0.001		<0.001

Notes: The data presented are HRs and 95% CIs. SF quantiles: Q1<218 ng/ml, 218 ng/ml≤Q2＜479.5 ng/ml, 479.5 ng/ml≤Q3＜1056.2 ng/ml, Q4≥1056.2 ng/ml.

Model I: adjusted for age, gender, race, heart rate, temperature, systolic blood pressure, diastolic blood pressure, mean blood pressure, and pulse oximetry saturation;

Model II: adjusted for Model I + hematocrit, hemoglobin, platelets, white blood cell, blood urea nitrogen, creatinine, glucose, prothrombin time, and partial thromboplastin time;

Model III: adjusted for Model II + congestive heart failure, chronic pulmonary disease, renal disease, Charlson comorbidity index, Simplified Acute Physiology Score II, and Sequential Organ Failure Assessment score.

Abbreviations: HR, hazard ratio; CI, confidence interval; SF(ln), the natural logarithm of serum ferritin; SF, serum ferritin; Q, Quantile.

3.3 The Nonlinear Relationship between SF and In-Hospital Mortality

The multivariable restricted cubic spline showed a non-linear relationship between SF(ln) and in-hospital mortality among SAAKI patients (p <0.001) (Figure 2). Based on the two-piecewise multivariate Cox regression models, the adjusted HR of in-hospital mortality was 1.393 (95% CI, 1.282-1.512; p <0.001) among participants with SF(ln) ≥5.517. Meanwhile, there was no association between SF(ln) and in-hospital mortality in the group with SF(ln) <5.517 (HR, 0.803; 95% CI, 0.571,1.129; p=0.2072) (Table 4).

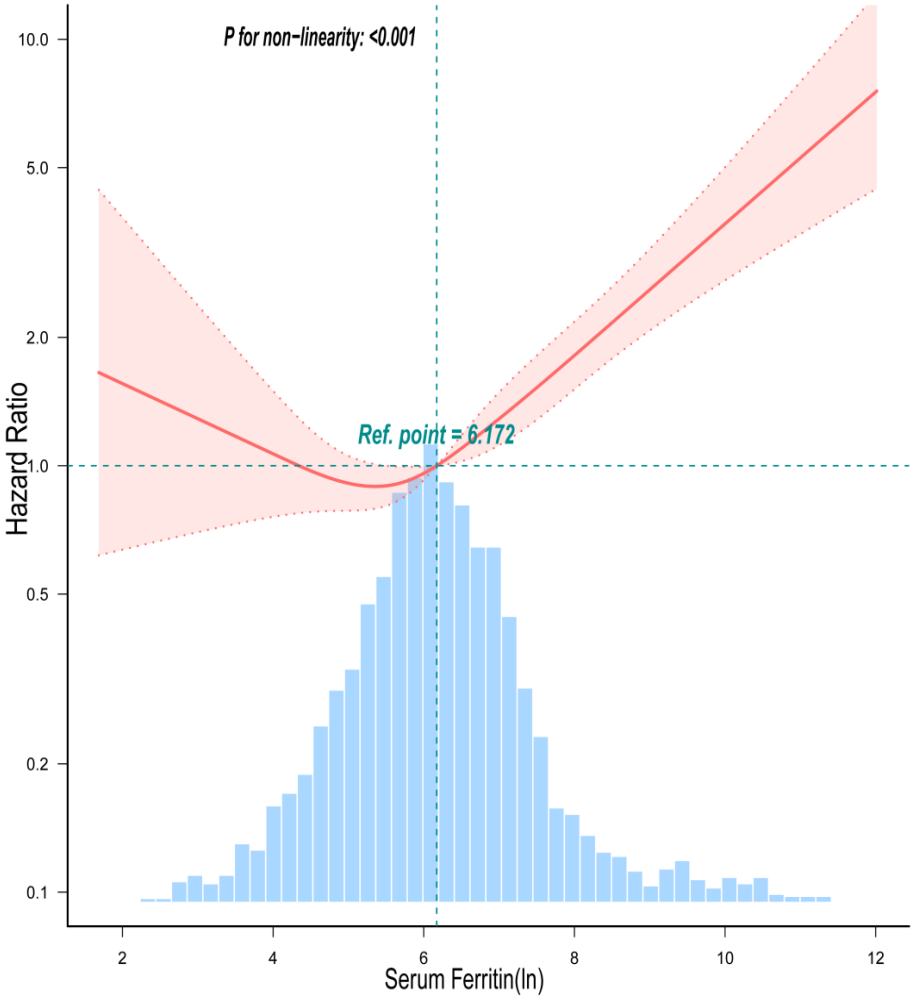

Figure 2. The nonlinear relationship between SF(ln) and in-hospital mortality in sepsis-associated acute kidney injury patients in ICU.

Notes: The serum ferritin levels were transformed by the natural logarithm. The data took the upper limit of 99.9%. Adjusted for all of the factors included in **Model III** in **Table 3**

Table 4 Threshold effect analysis of SF levels and in-hospital mortality of sepsis-associated AKI using Cox regression models.

	HR	**95%CI**	***P* value**
Turning point	5.517		
SF(ln) < 5.517	0.803	0.571,1.129	0.2072
SF(ln) ≥ 5.517	1.393	1.282,1.512	< 0.001
Likelihood Ratio test			0.005

Notes: The serum ferritin levels were transformed by the natural logarithm. The data took the upper limit of 99.9%. It was adjusted for all the factors included in Model III in Table 3.

Abbreviations: HR, hazard ratio; CI, confidence interval; SF(ln), the natural logarithm of serum ferritin.

3.4 Kaplan–Meier Curves

To determine the cumulative survival for the different SF groups, in-hospital survival curves were created for individuals with SAAKI by categorizing them, based on the SF quantiles. The KM survival curve revealed that individuals in Q4 with SF ≥1056.2 ng/mL had substantially poorer in-hospital survival. Additionally, in-hospital survival decreased with baseline SF (Figure 3).

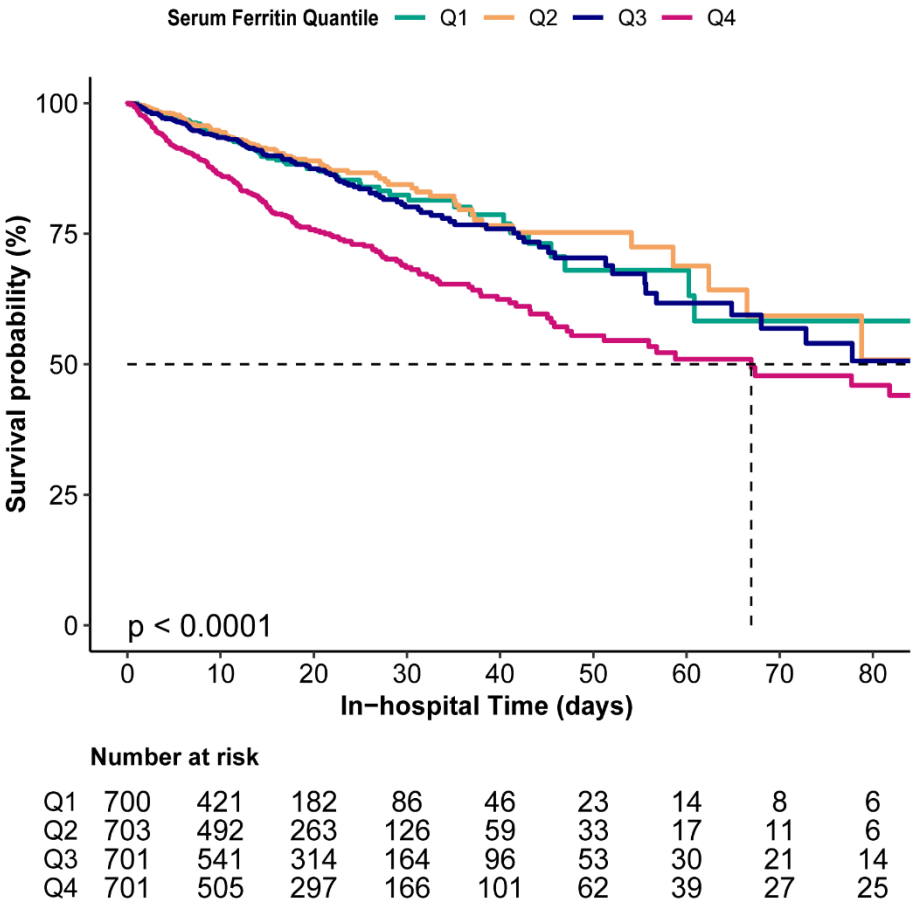

Figure 3. Kaplan-Meier analysis of in-hospital survival according to different SF groups

Notes: SF quantiles: Q1<218 ng/ml, 218 ng/ml≤Q2＜479.5 ng/ml, 479.5 ng/ml≤Q3＜1056.2 ng/ml, Q4≥1056.2 ng/ml.

3.5 Subgroup Analyses of Factors Influencing the Association between SF and In-Hospital Mortality

In the subgroup analysis, stratified by gender (female, male), age (years; <65, ≥65), WBC (×109/L; <12, ≥12), HGB (g/dL; <9, ≥9), BUN (mg/dL; <30, ≥30), SCr (mg/dL; <1.5, ≥1.5), SOFA score (<4, ≥4), CCI (<6, ≥6), congestive heart failure (yes, no), and chronic pulmonary disease (yes, no), the association between SF(ln) and the in-hospital mortality was explored in Figure 4. The effect size of SF(ln) on the in-hospital mortality subgroups was stable. The subgroup interaction analysis, regarding the in-hospital mortality, was not significant (all p >0.05).

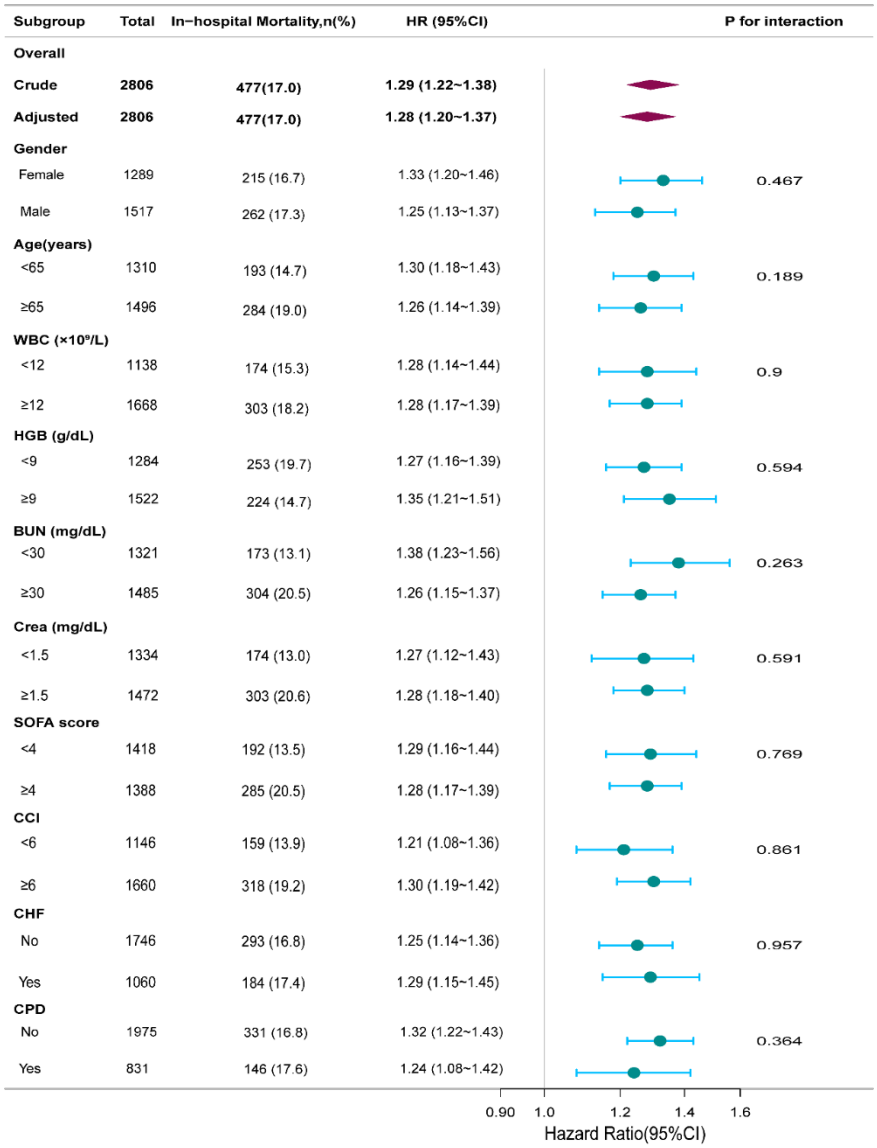

Figure 4. The relationship between SF and in-hospital mortality in the subgroup analysis

Notes: The serum ferritin levels were transformed by the natural logarithm.

Abbreviations: HR, hazard ratio; CI, confidence interval; WBC, white blood cell; HGB, hemoglobin; BUN, blood urea nitrogen; Crea, creatinine; SOFA, Sequential Organ Failure Assessment; CCI, Charlson comorbidity index; CHF, congestive heart failure; CPD, chronic pulmonary disease.

4. Discussion

The findings of this retrospective cohort study demonstrated a J-shaped nonlinear relationship between SF and all causes of in-hospital mortality in ICU patients with SAAKI. In these patients, the survival rate significantly decreased with increasing SF ≥1056.2 ng/mL. The subgroup analysis further reinforced the findings, ensuring the strength and validity of our results.

The effect of ferritin on critically ill patients remains controversial. The findings of our study indicated no statistically significant correlation between ferritin levels below 1056.2 ng/mL and in-hospital mortality. However, a meaningful increase in the mortality of SAAKI patients was observed as the ferritin levels rose. A review focused on the role of ferritin in kidney health and disease, highlighted the role of ferritin in the physiology and pathophysiology. Based on this review, SF, specifically the ferritin light chain, prevented the cytokine storm and consequently SAAKI[13]. A similar outcome was found in another article, which observed an association between elevated SF levels on admission and favorable renal outcomes among patients with acute kidney injury[8].

Moreover, another study indicated that the ability to tolerate disease in sepsis depended on the interaction between iron and glucose metabolism. In particular, ferritin supported the liver's glucose production to maintain blood glucose levels within a range compatible with survival in response to infection[14]. Based on this conclusion, SF improved the outcomes of patients with sepsis. Abolfazl Zarjou et al. demonstrated that circulating ferritin played a crucial immunomodulatory role. It protected against lipopolysaccharide-induced endotoxemia in the cecal ligation and puncture-induced model of sepsis. This finding was supported by reduced cytokine levels, multi-organ dysfunction, and mortality[15].

However, there have been conflicting results among several clinical researchers. Ferritin is elevated during sepsis, and many studies indicated its crucial role in infection and inflammation processes[16,17]. Consequently, the SF level was considered a significant indicator for infectious and inflammatory diseases, and increased SF levels were closely associated with a poor prognosis in sepsis patients[18]. A study revealed a significant correlation between the ratio of ferritin to albumin(FAR) and the 28-day mortality rate in patients with sepsis. Higher FAR values were strongly associated with increased mortality rates within 28 days[19]. Ferritin levels, however, did not have a linear correlation with illness severity or hospital mortality in septic shock patients[20]. He et al. established non-linear relationships between SF and clinical outcomes in sepsis. In addition, SF had a predictive value for short-term and long-term outcomes in sepsis[21]. In the present study, similar outcomes were observed in SAAKI patients. There was a J-shaped association between SF and in-hospital mortality, even after adjusting for confounding factors. Therefore, an elevated SF level is a valuable predictor of in-hospital mortality. Overall, the paper was improved by providing more specific details, clarifying the associations, and emphasizing the need for further research.

Some limitations of our study must be considered. First, this was a retrospective study with inevitable bias. Variables were adjusted to ensure the accuracy of the results. Second, only the first SF values after ICU admission were used, and its trends were not followed. However, the first SF was likely a more accurate prognosticator for SAAKI. Finally, only patients, admitted to the ICU for the first time, were included, possibly leading to selection bias. Therefore, prospective studies are needed to validate the conclusions of the present study. Despite these drawbacks, this study on the relationship between SF and the prognosis of patients with SAAKI was remarkable.

5. Conclusion

SF was a viable predictor of the prognosis of SAAKI patients since it exhibited a nonlinear relation with in-hospital mortality. An increasing level of SF ≥1056.2 ng/mL was positively associated with an elevated risk of in-hospital mortality among SAAKI patients.

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Ethics Statement

The Massachusetts Institute of Technology review boards evaluated and authorized the experiments involving human volunteers. According to national law and institutional regulations, written informed consent was not required to participate in this study.

Author Contributions

Xuezhi Zhang and Taotao Luo contributed to the research planning, the assessment of the findings, and the editing of the paper. Xuezhi Zhang, Taotao Luo, and Yating Luo performed data mining and text editing. Ming Lu and Yongle Xie contributed to the study design. All authors revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Disclosure Statement

There is no potential conflict of interest reported by the authors.

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Data Availability Statement

In this study, MIMIC-IV2.2, a publicly accessible database, was investigated. This database is available at https://physionet.org/content/mimiciv/2.2/.

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