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Serum iron levels are an independent predictor of in-hospital mortality of critically ill patients: a retrospective, single-institution study

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Abstract

Objective: This study aimed to examine the relationship between serum iron levels and in-hospital mortality in critically ill patients.

Methods: We retrospectively studied 250 critically ill patients who received treatment at the intensive care unit between June 2015 and May 2017. Blood chemistry and hepatic and renal function were measured. Kaplan–Meier survival curves were plotted according to serum iron levels. Correlations between serum iron levels and other variables were analyzed.

Results: A total of 165 (66.0%) patients had abnormally low serum iron levels (<10.6 μmol/L). Patients who died during hospitalization had markedly higher Acute Physiology and Chronic Health Evaluation II scores and significantly lower serum iron levels compared with those who survived. Cumulative survival was significantly lower in patients with low serum iron levels than in those with normal serum iron levels in subgroup analysis of older patients (n = 192). Multivariate regression analysis showed that, after adjusting for relevant factors, low serum iron levels

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remained an independent risk for in-hospital mortality (odds ratio 2.014; 95% confidence interval 1.089, 3.725).

Conclusions: Low serum iron levels are present in a significant proportion of critically ill patients and are associated with higher in-hospital mortality, particularly in older patients.

Keywords

Critical illness, serum iron, mortality, prognosis, survival analysis, intensive care unit

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Introduction

Altered iron metabolism plays an important role in development of anemia in critically ill patients and may also adversely affect normal functioning of critical organs.[1] Parameters of iron metabolism, such as transferrin saturation, which reflects serum iron availability, are strong outcome predictors in intensive care unit (ICU) patients.[2] Serum iron is soluble and non-toxic under physiological conditions.[3] However, under stressful conditions, iron may inflict tissue and cellular damage when non-transferrin bound iron increases in the plasma after the iron binding capacity of transferrin becomes saturated.[3] Iron undergoes the Fenton reaction[4] and free radicals and active groups generated by the Fenton reaction further aggravate oxidative stress.[5]

A variety of parameters of iron metabolism have been investigated in critically ill patients, including serum iron levels, serum ferritin levels, transferrin levels, total iron binding capacity, transferrin saturation, and soluble transferrin receptor.[2] Serum iron levels are one of the most commonly measured markers in critically ill patients. Serum iron levels are closely associated with anemia,[6] severity of infection,[7] and cardiac failure,[8] all of which are common complications in critically ill patients and may affect the prognosis of patients.

This retrospective, single-center study aimed to determine the relationship between serum iron levels and in-hospital mortality of critically ill patients in the ICU.

Methods

Study population

In this retrospective study, we analyzed the clinical data of critically ill patients who received treatment at the ICU of Shanghai Jiading District Central Hospital of Shanghai University of Medicine and Health Sciences between June 2015 and May 2017. Patients who were aged > 18 years were included. Major exclusion criteria were hematological diseases, including iron deficiency anemia due to long-term insufficient iron intake, severe chronic hepatic and renal diseases or severe chronic heart failure, malignancy, and pregnancy. Patients who received long-term iron supplementation or took gastric acid inhibitors (e.g., proton pump inhibitors or H2 receptor antagonists) were excluded. Patients who were admitted to the ICU because of severe trauma were not included in the analysis.

The study protocol was approved by the Ethics Review Board of Jiading District Central Hospital (2017-ZD-03). Written

informed consent was waived by the Ethics Review Board because of the retrospective nature of the study. Patients' data were anonymized.

Data on demographics (including sex, age, and others), medical history (hypertension, diabetes, and others), mechanical ventilation, and use of vasoactive drugs were obtained from all of the study patients. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores at 24 hours post-admission were calculated and recorded.

Laboratory studies

Venous blood was obtained within 24 hours post-admission and blood chemistry was measured using the Sysmex xs-800i Automatic Hematology Analyzer (SYSMEX Corp., Kobe, Japan). Hepatic and renal function was examined using a Vitros350 Automatic Biochemical Analyzer (Johnson & Johnson, New Brunswick, NJ, USA). High-sensitivity C-reactive protein (hs-CRP) levels were determined using an avidin-biotin-horseradish peroxidase complex enzyme-linked immunosorbent assay.

Statistical analysis

Normally distributed data are expressed as mean ± standard deviation (SD) and were compared using the Student's *t*-test. Non-normally distributed data are expressed as the median (interquartile range [IQR]) and were compared using the non-parametric Mann–Whitney test. Trends in changes were examined using the Jonckheere–Terpstra test. Numerical data are expressed as frequency and were compared using the χ^2 test. Kaplan–Meier survival analysis was performed and survival was counted from the date of admission until death of any cause in hospital. Patients' survival was examined using Kaplan–Meier curves followed by the log-rank test. Correlations between serum iron levels and other variables were analyzed by Spearman correlation analysis. Serum iron levels were analyzed as a continuous variable or as a bivariate variable (normal *versus* low serum iron levels). $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 19.0 software (IBM Corp., Armonk, NY, USA).

Results

Demographic and baseline characteristics

Three hundred forty-nine patients were admitted to the ICU at our hospital during the study period (Figure 1). Twenty-six patients were excluded because of iron deficiency anemia from inadequate iron intake and 73 patients were excluded for other reasons. Finally, 250 patients were eligible for this retrospective analysis. There were 155 (62%) men and 95 (38%) women, and their mean age was 74.1 ± 15 years. The median serum iron level was 7.3 μmol/L (IQR: 4.5–12.1 μmol/L) (normal reference values: 10.6–32 μmol/L) and 66.0% (165/250) had low serum iron levels (<10.6 μmol/L). The mean APACHE II score was 22.1 ± 7.5. Moreover, 54.4% of patients required mechanical ventilation and 40.4% patients used vasoactive drugs. Demographic and baseline characteristics of the patients are shown in Table 1.

Patients' characteristics stratified by survival status

In-hospital mortality was 36.4% (91/250) for the study population. Non-survivors had markedly higher Apache II scores compared with survivors ($P = 0.005$). Non-survivors also had significantly lower median serum iron levels compared with survivors ($P = 0.019$). The rate of abnormally low serum iron levels was

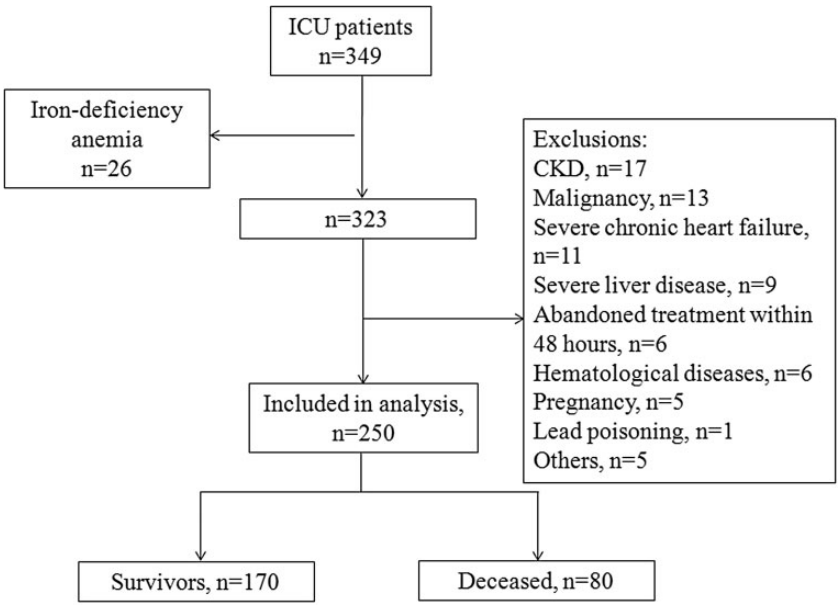

Figure 1. Flowchart of the study

significantly higher in non-survivors than in survivors ($P = 0.018$). A significantly greater percentage of non-survivors received mechanical ventilation ($P < 0.001$) and vasoactive drugs ($P = 0.013$) than did survivors (Table 1). Additionally, non-survivors had significantly lower albumin levels ($P = 0.001$) and estimated glomerular filtration rate ($P < 0.001$), and higher hs-CRP levels ($P = 0.003$) than did survivors.

Low serum iron levels are an independent risk for in-hospital mortality

Multivariate regression analysis that included serum iron levels as a continuous variable failed to show a significant association between serum iron levels and in-hospital mortality (hazard ratio 0.992; 95% confidence interval 0.963, 1.021; $P = 0.585$). When serum iron levels were included as a bivariate variable (abnormally low *versus* normal), we found that low serum iron levels were an independent risk for in-hospital mortality (crude $P = 0.016$) (Table 2). In subgroup analysis that only included older patients (age $\geq$65 years, n = 192), patients with abnormally low serum iron levels had a significantly higher in-hospital mortality rate than did those with normal serum iron levels (45.3% *versus* 25.0%, $P = 0.006$) (Figure 2a). Such an association was not significant in younger patients (age < 65 years, n = 58). In analysis of the trend of change, in-hospital mortality decreased with rising serum iron levels (P for trend = 0.002) (Figure 2b).

Cumulative survival was significantly lower in older patients with abnormally low serum iron levels than in older patients with normal serum iron levels ($P = 0.013$) (Figure 3a), with no difference in younger patients (Figure 3b).

Correlation analysis

Spearman correlation analysis showed that serum iron levels were negatively correlated

Table 1. Demographic and baseline characteristics of the study population

Variables	All patients (n = 250)	Survivors (n = 159)	Non-survivors (n = 91)	*P*
Male sex, n (%)	155 (62.0)	93 (58.5)	62 (68.1)	0.131
Age (y), mean ± SD	73.5 ± 15.4	72.2 ± 16.1	75.7 ± 13.9	0.082
≥65 years, n (%)	192 (76.8)	118 (74.2)	74 (81.3)	0.217
APACHE II score, mean ± SD	22.1 ± 7.5	20.9±7.9	23.8 ± 6.4	0.005
<25, n (%)	164 (65.6)	114 (71.7)	50 (54.9)	
25–35, n (%)	79 (31.6)	42 (26.4)	37 (40.7)	0.019
>35, n (%)	7 (2.8)	3 (1.9)	4 (4.4)	
Presenting disease, n (%)				
Lung infection	134 (53.6)	93 (58.5)	41 (45.1)	
MODS	46 (18.4)	25 (15.7)	21 (23.1)	
Stroke	32 (12.8)	19 (11.9)	13 (14.3)	0.156
Myocardial infarction and heart failure	26 (10.4)	13 (8.2)	13 (14.3)	
Others	12 (4.8)	9 (5.7)	3 (3.3)	
Comorbidities, n (%)				
Hypertension	144 (57.6)	95 (59.7)	49 (53.8)	0.364
Diabetes	64 (25.6)	35 (22.0)	29 (31.4)	0.086
Use of vasoactive drugs, n (%)	101 (40.4)	55 (34.6)	46 (50.5)	0.013
Mechanical ventilation, n (%)	136 (54.4)	70 (44.0)	66 (72.5)	<0.001
Hemoglobin (g/L), mean ± SD	111.3 ± 24.2	111.9 ± 24.6	110.3 ± 23.7	0.617
Hematocrit (%), mean ± SD	32.5 ± 9.2	32.8 ± 9.3	32.1 ± 9.0	0.588
White blood cells (10^9/L), median (IQR)	10.4 (7.7–13.8)	10.3 (7.7–13.9)	10.8 (7.8–13.8)	0.625
Platelets (10^9/L), median (IQR)	143 (97–200)	148 (107–206)	134 (88–189)	0.058
ALT (U/L), median (IQR)	23.1 (12.8–45)	21 (12–44)	23.7 (15.1–46.5)	0.146
Total bilirubin (μmol/L), median (IQR)	11 (7.3–17.6)	9.9 (7.2–16.8)	12.7 (8.0–17.9)	0.167
Albumin (g/L), mean ± SD	30.7 ± 6.2	31.6 ± 5.8	29.0 ± 6.5	0.001
hs-CRP (mg/dL), median (IQR)	49 (16–115)	38 (11.6–101)	65 (22.5–145)	0.003
eGFR (mL/min), median (IQR)	68.7 (37.1–96.4)	81 (51.1–102.6)	42.3 (20.4–85.5)	< 0.001
Serum iron (μmol/L), median (IQR)	7.3 (4.5–12.1)	8.3 (4.7–13.1)	5.9 (4.1–10.2)	0.019
<10.6 μmol/L, n (%)	165 (66.0)	96 (60.4)	69 (75.8)	0.018

APACHE II: Acute Physiology and Chronic Health Evaluation II; MODS: multiple organ dysfunction syndrome; SD: standard deviation; IQR: interquartile range; ALT: glutamate-pyruvate transaminase; hs-CRP: high-sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate

with mechanical ventilation ($r = -0.132$, $P = 0.040$) and hs-CRP levels ($r = -0.461$, $P < 0.001$). Serum iron levels were negatively correlated with the use of vasoactive drugs ($r = -0.181$, $P = 0.013$) in older patients, but not in younger patients. Serum iron levels were correlated with hs-CRP levels in older patients ($r = -0.471$, $P < 0.001$) and younger patients ($r = -0.404$, $P = 0.002$) (Table 3).

Discussion

The present study showed that approximately two thirds (66.0%) of critically ill ICU patients had low serum iron levels. Furthermore, low serum iron levels were associated with an increased risk of in-hospital mortality, particularly in older patients.

The study of iron metabolism has been traditionally limited to iron deficiency

Table 2. Cox multivariate regression analysis of risks of hospital mortality in older (age $\geq$ 65 years) critically ill patients

	Crude				Adjusted[1]				Adjusted[2]			
Variables	HR	95% CI		*P*	HR	95% CI		*P*	HR	95% CI		*P*
Age	1.053	1.017	1.090	0.004	1.048	1.011	1.087	0.012	1.046	1.010	1.084	0.011
eGFR	0.987	0.980	0.994	<0.001	0.991	0.983	0.999	0.023	0.990	0.982	0.997	0.008
Abnormal serum iron	1.980	1.136	3.452	0.016	2.014	1.089	3.725	0.026	2.047	1.132	3.704	0.018

Adjusted[1]: adjusted for sex, diabetes, presenting disease, use of vasoactive drugs, mechanical ventilation, APACHE II score (as continuous variable), albumin levels, and hs-CRP levels

Adjusted[2]: adjusted for the APACHE II score categorized as <25, 25–35, or >35; all other factors remained identical to adjusted[1]

HR: hazard ratio; CI: confidence interval; eGFR: estimated glomerular filtration rate

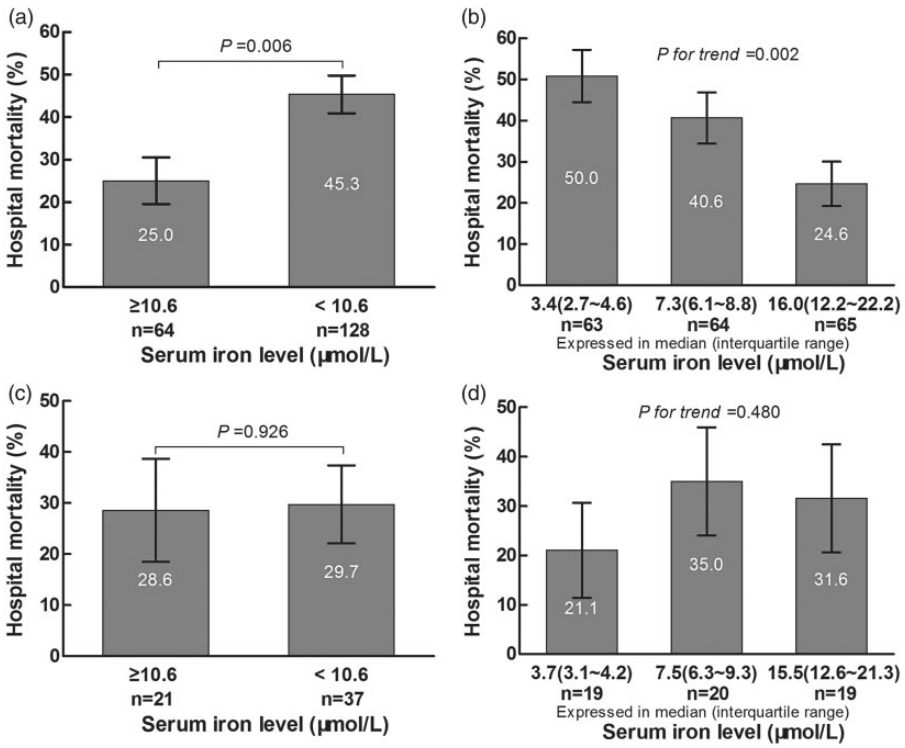

Figure 2. Serum iron levels and in-hospital mortality. (a) Comparison of in-hospital mortality in patients with normal *versus* low serum iron levels in older patients. (b) Comparison of in-hospital mortality in patients with low (<5.5 μmol/L, n = 83), intermediate (5.5–11.0 μmol/L, n = 84), and high serum iron (>11.0 μmol/L, n=83) levels in older patients. (c) Comparison of in-hospital mortality in patients with normal *versus* low serum iron levels in younger patients. (d) Comparison of in-hospital mortality in patients with low, intermediate, and high serum iron levels in younger patients

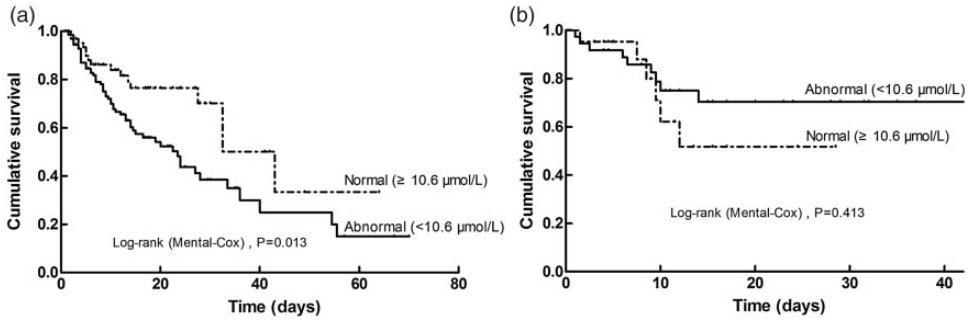

Figure 3. Cumulative survival in patients with low *versus* normal serum iron levels in older and younger patients

Table 3. Correlation of serum iron levels with other factors

	Overall sample (n = 250)		Age ≥ 65 years (n = 192)		Age < 65 years (n = 58)	
Variables	r	*P*	r	*P*	r	*P*
Male sex	0.076	0.237	0.092	0.209	0.021	0.877
Age	0.003	0.961	0.019	0.801	0.077	0.568
Diabetes	−0.040	0.561	−0.070	0.376	0.136	0.355
Use of vasoactive drugs	−0.123	0.054	−0.181	0.013	0.082	0.539
Mechanical ventilation	−0.132	0.040	−0.100	0.172	−0.254	0.061
APACHE II score	−0.104	0.122	−0.062	0.427	−0.233	0.093
Albumin	0.088	0.167	0.127	0.084	−0.030	0.823
hs-CRP	−0.461	<0.001	−0.471	<0.001	−0.404	0.002
eGFR	0.068	0.291	0.033	0.658	0.147	0.271

APACHE II: Acute Physiology and Chronic Health Evaluation II; hs-CRP: high-sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate

diseases and iron overload diseases. Recent evidence has suggested that altered iron metabolism is also implicated in the development of anemia in critically ill patients and may affect the clinical outcome in such patients.[2] Our finding that a significant proportion of critically ill ICU patients had low serum iron levels indicates that altered iron metabolism is common in these patients. These patients face multiple stressors[9] that may activate the inflammation cascade, including release of proinflammatory cytokines, which in turn causes release of serum ferritins[10] and a reduction in serum iron levels.[11–13] Elevated serum ferritin levels are correlated with the prognosis of critically ill patients[14] and lower serum iron levels may be associated with an adverse outcome of critically ill patients. Limited evidence suggests that low serum iron levels, high transferrin levels, and low transferrin saturation are associated with morbidity and mortality of critically ill patients in the ICU.[2]

Consistent with previous findings,[15–17] we also found that a higher percentage of patients who died underwent mechanical ventilation and used vasoactive drugs compared with those who survived. Non-survivors also had significantly higher

APACHE II scores than did survivors, which indicated that these patients had more severe illness than those who survived. We found that patients who died during hospitalization had significantly lower serum iron levels than did patients who survived. This finding suggests that low serum iron levels are a poor prognostic factor in addition to the factors that have already been established.[18,19] Multivariate analysis that included serum iron levels as a continuous variable failed to show a significant association between in-hospital mortality with low serum iron levels. This finding suggests that a reduction in serum iron levels is clinically meaningful only when reaching a breaking point. Cumulative survival in patients with low serum iron levels was significantly lower than that in those with normal serum iron levels in the current study. Spearman correlation analysis showed that serum iron levels were negatively correlated with mechanical ventilation. Higher stress levels in patients on mechanical ventilation[20] may result in lower serum iron levels, which in turn inhibits immune function and further aggravates underlying diseases.[21,22] Proinflammatory actions of tumor necrosis factor-α, and interleukin-1, -6, and -10 can cause disturbances in homeostasis of iron metabolism, leading to reduced serum iron levels.[23] The current study did not examine levels of proinflammatory cytokines in the patients. However, we observed a negative association between serum iron levels and clinical inflammatory parameters (e.g., Hs-CRP). This finding also suggests that serum iron levels in critically ill patients are mainly subject to the influence of the stress response and inflammatory reactions. In subgroup analysis that included only older subjects, serum iron levels were negatively associated with the use of vasoactive agents, which likely reflected a poor general condition of the patients. This finding provides an alternative explanation to the association between low serum iron levels and high mortality. We failed to identify such a correlation in younger patients, which was most likely due to the small sample size.

The current study has several limitations. First, our study was retrospective and thus we were not able to establish a causal relationship. Second, our hospital is a suburban secondary care institute. Patients with a severe condition were often transferred to tertiary hospitals. Therefore, patients who were included in this analysis generally had less severe diseases (average Apache II score of 22). Consequently, extrapolation of our findings to other settings requires caution. Third, the sample size was relatively small. Fourth, because serum ferritin and transferrin levels are not routinely measured at the hospital, data on these two important parameters were lacking. We were unable to analyze the correlation of these two important parameters with the clinical outcome of critically ill patients in the ICU. The level of serum iron is only one, albeit important, measure that reflects iron metabolism. Monitoring other variables (e.g., ferritin, transferrin, and hepcidin) could have led to further insight. Unfortunately, we did not measure these variables for the majority of the patients included in this study, but plan to follow up on this important issue in future studies. Finally, our findings were subject to bias by many confounding factors. Examples of this possible bias are that serum iron levels are closely associated with oxidative stress,[24] and critically ill patients often require mechanical ventilation and other therapeutic measures that are associated with oxidative stress.[20]

In conclusion, low serum iron levels correlate with a poor prognosis in critically ill patients in the ICU, particularly in older patients. However, our findings must be considered preliminary. Further studies with a larger sample size and more careful

delineation of confounding factors are required.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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