

# Elevated serum iron level is a predictor of prognosis in ICU patients with acute kidney injury

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## Research article

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# Abstract

**Background** Accumulation of iron is associated with oxidative stress (OS), inflammation and regulated cell death. The above three reactions contribute to the development of acute kidney injury (AKI). Here we aimed to investigate the association between the serum iron level and prognosis in severe patients with AKI.

**Methods** A total of 483 patients with AKI defined by Kidney Disease: Improving Global Guidelines (KIDGO) were included in this retrospective study. The data was extracted from the single-center Medical Information Mart for Intensive Care III (MIMIC-III) database. The max serum iron concentration measured after Intensive Care Unit (ICU) admission was defined as the serum iron in the study and divided into three groups (Low group, Middle group, High group). We plotted boxplots and Kaplan–Meier curves and used cox regression analysis to analyze data.

**Results** In univariable Cox regression analysis, serum iron levels were significantly correlated to the prognosis of AKI patients. After adjusting for confounding variables, higher serum iron level was remained to associate with the increase in 90-day mortality in the multivariable Cox regression analysis. Moreover, the risk of 90-day mortality stepwise increased as the groups of serum iron levels increased in AKI patients.

**Conclusions** From our study, we investigated that high serum iron level was associated with the increased mortality in severe patients with AKI. Serum iron levels on admission can be a predictor for predicting the prognosis of AKI patients.

## Background

Acute kidney injury (AKI) is a severe syndrome with high morbidity and significant mortality risk. It is a common complication in patients admitted to hospitals (10–15% of all hospitalizations) [1] and intensive care units (more than 50%) [2]. Increasing AKI severity is associated with a stepwise increase in mortality [2]. However, no targeted therapy can reliably prevent or treat AKI. It is needed to choose appropriate biological indicators to predict the prognosis of AKI for preventing and treating.

Iron plays an essential role in many critical cellular functions such as hypoxia signaling, mitochondrial function, erythropoiesis, cell cycle progression, DNA synthesis and repair, and regulation of inflammation. Nevertheless, excess iron is toxic to cells and tissues, including kidney due to its ability to cause oxidative stress (OS), cause mitochondrial dysfunction, promote inflammation, and regulate cell death.

Moreover, OS, inflammation, and regulated cell death mechanisms are thought to have important roles in AKI [3]. And the persistence of OS, mitochondrial dysfunction, and inflammation are considered as reasons to promote the development of AKI to chronic kidney disease (CKD) [3]. The relationship between iron-related parameters and AKI has been confirmed in many preclinical trials, but few clinical trials researching in prognosis of AKI are available. Therefore, we hypothesized that elevated serum iron level

was positively associated with a poor prognosis in patients with AKI. We aimed to investigate the prognostic role of serum iron in short- and long-term mortality in ICU patients with AKI.

## Methods

### Data source

The data in our study was acquired from a large, single-center database named Medical Information Mart for Intensive Care (MIMIC-III). It integrates clinical information of 53,423 patients (aged 16 years or above) who were admitted to critical care units of the Beth Israel Deaconess Medical Center in Boston, Massachusetts from 2001 to 2012 [4]. Clinical information includes coded data, interventions, demographic detail, laboratory test results, medications, and survival data.

### Study patients

A total of 483 adult patients with AKI were included in the final analysis after excluding patients with missing serum iron measurements and repetitive admissions. AKI was defined by Kidney Disease: Improving Global Outcomes (KDIGO) criteria: serum creatinine increases greater than 50% from baseline or has 0.3 mg/dL or more increase within 48 hours.

Iron-related parameters such as serum iron, ferritin, and transferrin were acquired. For iron-related parameters were repeatedly measured after admission, the maximum value was used. Other information including age (categorized into 16–59 and 60 years or above), gender, admission type, comorbidities, other laboratory measurements, and survival data were extracted. All the above data were extracted using structure query language (SQL).

### Outcomes

The primary outcome was the association between serum iron levels and 28-day, 90-day, and one-year mortality of ICU patients with AKI. The secondary outcomes included the roles of ferritin and transferrin in the prognosis of ICU patients with AKI.

### Statistical analyses

Shapiro-Wilk tests were performed and density maps were drawn to determine the normality of the distribution of the continuous variables. Normally distributed continuous variables were reported as mean  $\pm$  SD, while skewed variables were expressed as medians and interquartile ranges (IQRs). AKI patients were stratified according to the bar chart of the mortality rates of serum iron deciles (Figure 1) and

divided into three groups (low group:  $\leq 53.2$   $\mu\text{g/dl}$ ; middle group:  $53.2\text{-}98.6$   $\mu\text{g/dl}$ ; High group:  $>98.6$   $\mu\text{g/dl}$ ). Boxplots were generated to show the correlation between serum iron levels and different survival status. Differences between the death group and survival group were assessed using a Wilcoxon test or T test. And We used log-rank tests to compare the 28-day, 90-day, and one-year survival rates among different groups and expressed the results as Kaplan–Meier curves. Correlations between iron-related parameters and short- and long-term mortality were determined by the univariate Cox proportional hazards model. Moreover, variables with  $P < 0.05$  in the univariate analysis were finally incorporated into multivariate Cox proportional hazards models to determine the independent effects of serum iron levels on short- and long-term mortality. The hazard ratio (HR) and its 95% confidence interval (CI) were calculated. All comparisons were two-tailed, with  $P < 0.05$  considered significant. All statistical analyses were performed using R 3.5.1.

## Results

A total of 483 patients with AKI (246 males and 237 females) defined by KDIGO were identified into the final analysis. The demographics, laboratory measurements, and comorbidities were shown in Table 1. More than half of the patients were older than 60 years. And the majority of the patients were admitted from emergency clinic. Most of the patients had a SOFA score greater than 2 points. Patients in the low, middle, and high group were 290, 96, and 97, respectively. The medians of transferrin and ferritin were 2.1 mg/dl (IQR: 1.1-3.75) and 347 ng/ml (IQR: 122-770), respectively.

The total mortality rates of 28-day, 90-day, and one-year were 30.8%, 39.5% and 49.3%, respectively (Table 2). As shown in the boxplots, significant associations were observed between the survival status of 28-day, 90-day, and one-year and serum iron levels ( $P = 0.0011$ ,  $P = 0.0026$  and  $P = 0.002$ , respectively) (Figure 2). The mortality risks on days 28, 90 and one year stepwise increased as serum iron levels increased ( $P < 0.001$ ,  $P = 0.002$  and  $P = 0.003$ , respectively) (Figure 3). After adjusting the possible confounding variables, significant correlations were remained between higher serum iron level and 28-day, 90-day, and one-year mortality risks (HR = 2.031, 95%CI: 1.378-2.994,  $P < 0.001$ ; HR = 2.297, 95%CI: 1.592-3.314,  $P < 0.001$ ; and HR = 2.144, 95%CI: 1.532-3.000,  $P < 0.001$ , respectively) in multivariate Cox proportional hazards models (Table 3, Table 4 and Table 5). As for the other iron-related measurements, transferrin negatively correlated with 28-day, 90-day, and one-year mortality risks in ICU patients with AKI (HR = 0.994, 95% CI: 0.991-0.997,  $P < 0.001$ ; HR = 0.993, 95% CI: 0.990-0.996,  $P < 0.001$ ; and HR = 0.995, 95% CI: 0.992-0.997,  $P < 0.001$ , respectively). While ferritin had no significant correlation with 28-day, 90-day, and one-year mortality risks ( $P > 0.05$ ,  $P > 0.05$  and  $P > 0.05$ , respectively) (Table 3, Table 4 and Table 5).

## Discussion

In this retrospective study, we investigated that higher serum iron level was significantly associated with increased short- and long-term mortality in ICU patients with AKI. Moreover, transferrin exerted a beneficial effect on the short- and long-term mortality of ICU patients with AKI.

Catalytic iron is a transitional pool of non-transferrin bound iron (NTBI). It readily participates in redox cycling and causes damage to cell membranes, proteins, and DNA through redox reaction such as Fenton reaction [5-7]. The catalytic iron as a critical player in different types of AKI has been demonstrated in many animal models [8, 9]. A study in a rat model of ischemia/reperfusion injury (IRI) showed that no significant changes in total iron, non-heme or ferritin iron levels were observed, but catalytic iron level significantly increased after reperfusion [10]. In IRI, there are possible self-protection mechanisms for regulating iron homeostasis [11]. In a rat of the cisplatin-induced nephrotoxicity model, research supported the key role of iron in mediating tissue damage through hydroxyl radicals (or similar oxidants) [12]. Another study demonstrated the protective effects of hydroxyl radical scavengers and iron chelators on penicillin-induced acute renal failure [13]. Moreover, the protective effect of iron chelator deferoxamine on renal function was identified in rat models [14]. And Ikeda Y et al. showed that restricting dietary iron could inhibit oxidative stress and inflammatory changes, thereby reducing renal tubular interstitial damage [15].

In recent years, researches on iron related measurements have gradually been carried out in humans. Several studies have shown that elevated levels of catalytic iron were associated with the increased incidence of AKI caused by different causes [5, 16-19]. Heparin is an essential regulator in iron homeostasis. It reduces extracellular iron levels through downregulating iron absorption in duodenal and ferroportin expression and cellular iron release in macrophages [18, 20]. And the protective role of hepcidin in AKI provides evidence on the key role of iron in mediating AKI [21]. Meanwhile, a study involving 807 patients showed that plasma catalytic iron and hepcidin possibly be useful prognostic indicators in AKI patients [9]. At present, most of the studies are about the relationships between iron-related measurements and morbidity of AKI rather than mortality. Few studies have reported the roles of iron-related measurements in mortality of AKI in humans. Our study investigated that higher serum iron level was significantly associated with short- and long-term mortality of patients with AKI. Clinically, serum iron levels on admission may be used as a prognostic marker for predicting prognosis of AKI, thereby taking interventions in advance to reduce mortality. In addition, our study found that the transferrin was a protective factor in short- and long-term mortality of patients with AKI. As the main protein that binds and transports iron into circulatory, transferrin increases its binding with overloaded iron. The potential mechanisms of transferrin protective role in AKI need further study.

In humans, the role of ferritin in AKI is conflicting. Several studies investigated that ferritin heavy chain had a protective effect on renal function [17, 22]. And some studies showed that lower level of ferritin was associated with increased morbidity of AKI after cardiopulmonary bypass [23, 24]. Dimitrijevic ZM et al. reported that elevated serum ferritin level was favorable for renal function recovery [8]. However, this association has not been observed in a research of 120 patients [25]. It was consistent with our study, in which ferritin had no significant correlation with the mortality in ICU patients with AKI.

Disturbances in cellular and systemic iron balance and AKI may affect each other. The kidney is an important player in preventing iron loss from the body by reabsorption [3]. Different tubular segments play different roles in handling iron. Proximal tubule has the majority of the reabsorption capacity [26,

27]. The kidney reabsorbs iron, even when systemic iron levels are high [3]. Studies have shown that level of catalytic iron in urine increased, rather than decreased in AKI patients [28-30]. However, body iron stores are not low in AKI patients [19, 31]. The iron-mediated mechanisms in AKI are complex and may include multiple pathways. Excess iron is associated with OS, and production of oxygen free radicals causes damage to lipids, DNA, and proteins [6]. While renal tubular epithelial cells are particularly vulnerable to OS due to the high number of mitochondria [32]. In a rat model of acute ischemia, mitochondrial dysfunction caused by OS led to the production of proinflammatory cytokines [3]. Free iron can amplify the inflammatory response through the intracellular uptake and catabolism of damaged, stored red blood cells by the monocyte-macrophage system [33]. What's worse, inflammatory response is important in the pathogenesis of AKI [3, 34]. Iron mediates OS, mitochondrial dysfunction, and inflammatory may be the potential mechanisms of AKI. Moreover, ferroptosis has been considered as a central player in AKI, characterized by the accumulation of lethal lipid ROS produced by iron-mediated lipid peroxidation [18, 35, 36]. As for the excess iron in AKI, degraded red blood cells, iron release from ferritin, and origination from mitochondria rich in heme and nonheme iron are the possible sources [37].

In terms of iron targeted therapy in AKI, the therapeutic effects of hepcidin, deferoxamine, apolipoprotein, and pharmacologic therapy with apotransferrin and hydroxyl radical scavengers have been reported in animal models [37, 38]. Combined with our study results, iron targeted therapy in patients with AKI needs further study.

Our study has several limitations. Firstly, this is a retrospective study with confounding bias due to missing values in the database and some indicators not recorded in the MIMIC-III database. Secondly, MIMIC-III is a signal center database between 2001 to 2012, so information may be relatively old while the sample size of our study is large. In addition, we selected the maximum values of iron-related parameters on ICU admission as research indicators and did not monitor the dynamic trend of serum iron levels changes. These may cause impacts on the results.

## Conclusions

We clarified the relationship between elevated serum iron level and increased mortality in ICU patients with AKI. And the protective effect of transferrin on prognosis of AKI. Serum iron levels can give suggestions on the severity and prognosis of the AKI, guide clinical decision making, and monitor disease progression. Further clinical studies of iron targeted therapy in AKI are needed.

## Abbreviations

AKI	Acute kidney injury
CI	Confidence interval
CKD	Chronic kidney disease

HR	Hazard ratio
ICU	Intensive Care Unit
IQR	Interquartile range
IRI	Ischemia/reperfusion injury
KIDGO	Kidney Disease: Improving Global Guidelines
OS	Oxidative stress
SQL	Structure query language

## **Declarations**

### **Ethics approval and consent to participate**

Not applicable.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

### **Competing Interests**

All authors declare no competing interests.

### **Funding**

Not applicable.

## Author's Contributions

J.S. contributed to the design of the study, data extraction and analysis and drafted the manuscript. Y.H. and X.Y. assisted in data collection and analysis. J.C. and W.X. contributed to prepare the manuscript. JYP designed and supervised this study and obtained funding. All authors read and approved the final manuscript.

## Acknowledgements

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## Tables

**Table 1: Baseline characteristics of the study cohort.** Values are number (%) and median (IQR). SOFA Score, Sequential Organ Failure Assessment score; IQR, interquartile range.

<b>Characteristics</b>	<b>Values</b>
<b>Gender, n (%)</b>	
Female	237(49.07)
Male	246(50.93)
<b>Admission type, n (%)</b>	
Elective	8(1.66)
Emergency	457(94.62)
Urgent	18(3.73)
<b>Comorbidity, n (%)</b>	
Congestive heart failure	198(40.99)
Hypertension	255(52.80)
<b>Age</b>	
16-59	196(40.58)
≥60	287(59.42)
<b>SOFA score</b>	
<2	39(8.07)
≥2	444(91.93)
<b>Laboratory measurements</b>	
Creatinine, median (IQR)(mg/dl)	2.1(1.10-3.75)
Transferrin, median (IQR)(mg/dl)	155.5(115.75-203.00)
Ferritin, median (IQR)(ng/ml)	347(122.00-770.00)

**Table 2. Survival outcomes of patients in different serum iron levels groups.**

Outcomes	Total(n=483)	Low iron group(n=290)	Median iron group(n=96)	High iron group(n=97)	P Value
28-day mortality(n%)	149[30.8]	73(25.2)	32[33.3]	44[45.4]	< 0.001
90-day mortality(n%)	191[39.5]	101(34.8)	39[40.6]	51[52.6]	< 0.001
one-year mortality(n%)	238[49.3]	128[44.1]	52[54.2]	58[59.8]	0.016
Hospital mortality(n%)	141[29.2]	62(21.4)	35[36.5]	44[45.4]	< 0.001

**Table 3. The results of Cox proportional hazards models exploring the relationship between different serum iron levels and 28-day mortality of AKI.**

Factors	Univariate model			Multivariate model		
	Hazard ratio	95%CI	p value	Hazard ratio	95%CI	p value
Gender(M)	1.436	1.037-1.990	0.029	1.197	0.855-1.675	0.294
Age						
16-59	Reference	—	—	Reference	—	—
≥60	1.217	0.871-1.699	0.250	—	—	—
Congestive heart failure	0.823	0.590-1.146	0.248	—	—	—
Hypertension	0.759	0.550-1.047	0.092	—	—	—
SOFA score						
<2	Reference	—	—	Reference	—	—
≥2	3.653	1.353-9.866	0.011	2.652	0.974-7.225	0.056
Creatinine	0.984	0.934-1.036	0.528	—	—	—
Transferrin	0.994	0.991-0.997	<0.001	0.994	0.991-0.997	<0.001
Ferritin	1.000	1.000-1.000	0.883	—	—	—
Iron group						
Low iron group	Reference	—	—	Reference	—	—
Median iron group	1.421	0.938-2.154	0.097	1.327	0.867-2.030	0.192
High iron group	2.112	1.453-3.071	<0.001	2.031	1.378-2.994	<0.001

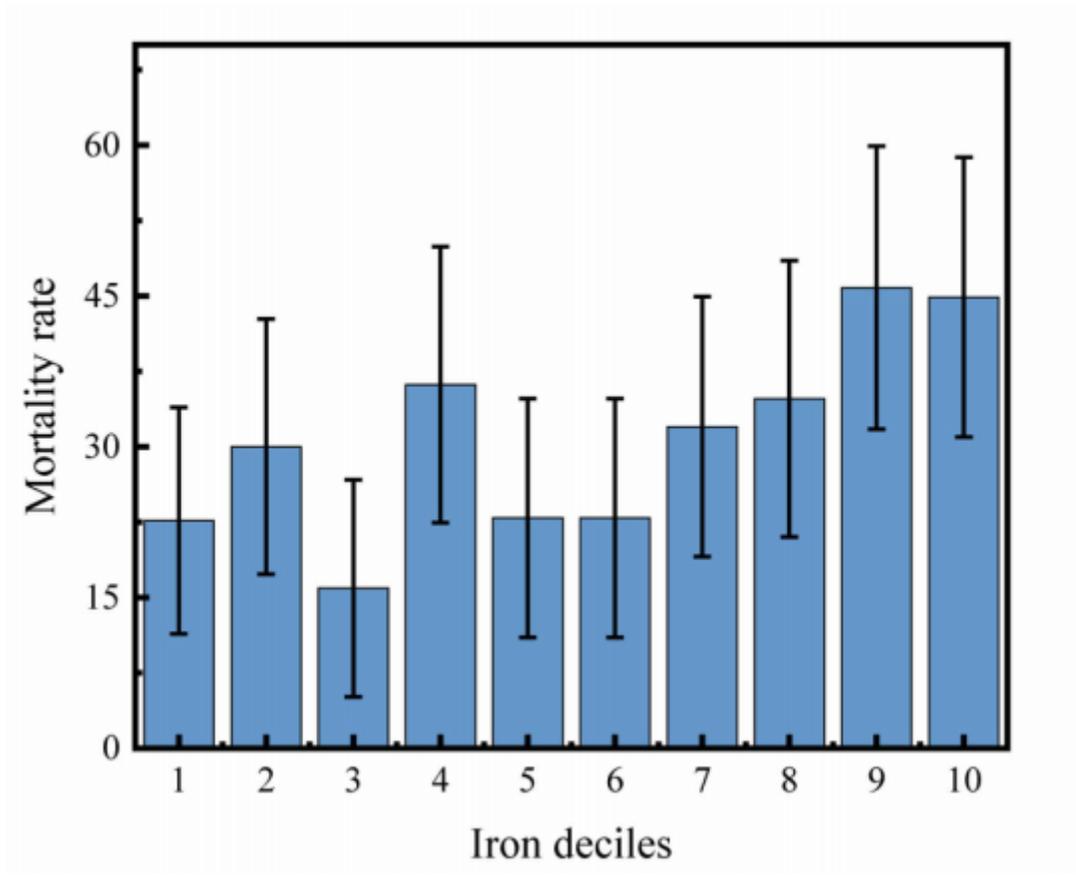
**Table 4. The results of Cox proportional hazards models exploring the relationship between different serum iron levels and 90-day mortality of AKI.**

Factors	Univariate model			Multivariate model		
	Hazard ratio	95%CI	P value	Hazard ratio	95%CI	P value
Gender(M)	1.524	1.142- 2.034	0.004	1.315	0.977- 1.772	0.071
Age						
16-59	Reference	—	—	Reference	—	—
≥60	1.440	1.065- 1.947	0.018	1.972	1.417- 2.746	<0.001
Congestive heart failure	1.012	0.759- 1.348	0.936	—	—	—
Hypertension	0.782	0.589- 1.039	0.090	—	—	—
SOFA score						
<2	Reference	—	—	Reference	—	—
≥2	2.760	1.297- 5.872	0.008	2.083	0.971- 4.468	0.059
Creatinine	0.985	0.943- 1.030	0.513	—	—	—
Transferrin	0.993	0.990- 0.995	<0.001	0.993	0.990- 0.996	<0.001
Ferritin	1.000	1.000- 1.000	0.709	—	—	—
Iron group						
Low iron group	Reference	—	—	Reference	—	—
Median iron group	1.271	0.879- 1.840	0.203	1.242	0.848- 1.820	0.266
High iron group	1.835	1.310- 2.570	<0.001	2.297	1.592- 3.314	<0.001

**Table 5. The results of Cox proportional hazards models exploring the relationship between different serum iron levels and one-year mortality of AKI.**

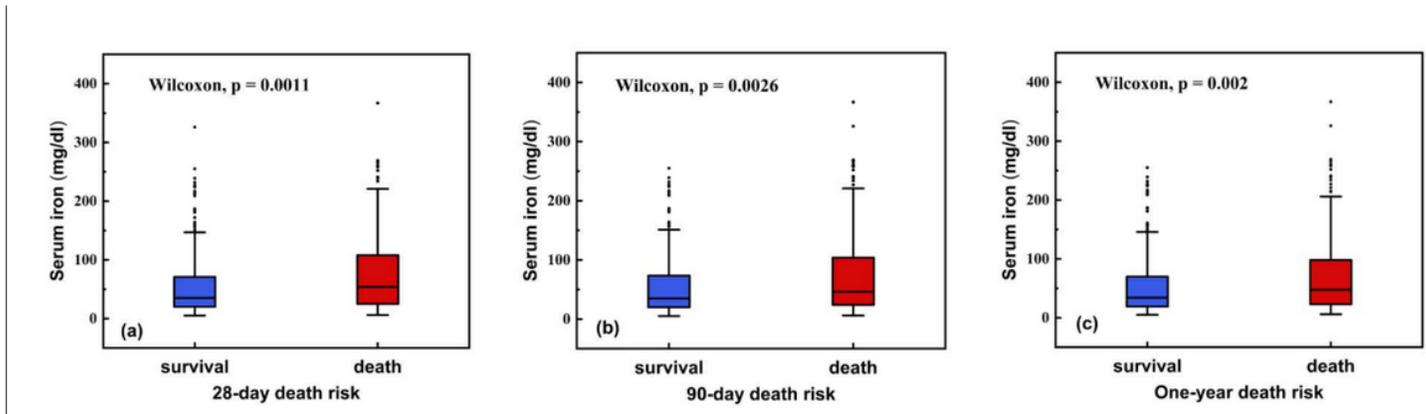
Factors	Univariate model			Multivariate model		
	Hazard ratio	95%CI	P value	Hazard ratio	95%CI	P value
Gender(M)	1.362	1.054-1.759	0.018	1.231	0.945-1.604	0.123
Age						
16-59	Reference	—	—	Reference	—	—
≥60	1.621	1.233-2.132	0.001	2.157	1.601-2.907	<0.001
Congestive heart failure	1.159	0.898-1.497	0.257	—	—	—
Hypertension	0.866	0.672-1.117	0.268	—	—	—
SOFA score						
<2	Reference	—	—	Reference	—	—
≥2	1.887	1.079-3.302	0.026	1.499	0.850-2.642	0.162
Creatinine	1.000	0.965-1.035	0.989	—	—	—
Transferrin	0.995	0.992-0.997	<0.001	0.995	0.992-0.997	<0.001
Ferritin	1.000	1.000-1.000	0.402	—	—	—
Iron group						
Low iron group	Reference	—	—	Reference	—	—
Median iron group	1.359	0.984-1.876	0.062	1.389	0.997-1.935	0.052
High iron group	1.684	1.235-2.297	0.001	2.144	1.532-3.000	<0.001

# Figures



**Figure 1**

Bar chart showing the different mortality rates of serum iron deciles. Serum iron levels less than or equal to the sixth decile were defined as the low group ( $\leq 53.2 \mu\text{g/dl}$ ), greater than the six decile and less than or equal to the eighth decile were defined as the middle group ( $53.2-98.6 \mu\text{g/dl}$ ), and greater than the eighth decile were defined as the high group ( $>98.6 \mu\text{g/dl}$ ).



**Figure 2**

Boxplots exploring the relationship between serum iron levels and different survival status. Serum iron levels were significantly higher in patients with death.

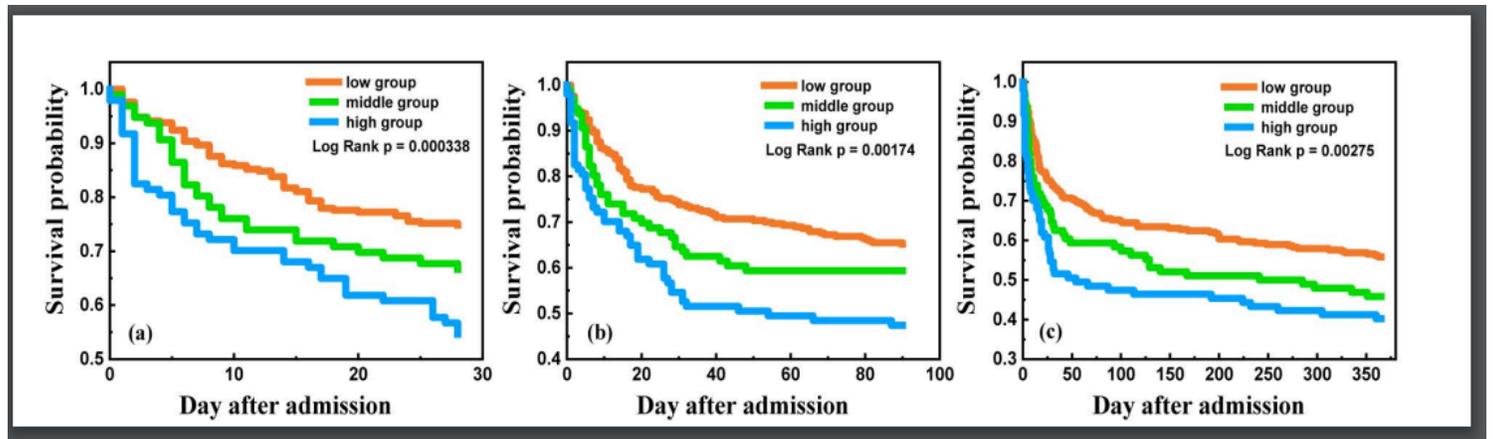


Figure 3

Kaplan-Meier curves demonstrating the association of different serum iron levels and short- and long-term mortality. The short- and long-term mortality stepwise increased as serum iron levels increased.