

# Elevated serum iron level is a predictor of prognosis in severe 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  $\times$  (MIMIC- $\times$ ) 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 serious 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]. And there was a stepwise increase in mortality with increasing AKI severity [2]. However, no targeted 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 important 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 cell 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 were thought to have important roles in AKI [3]. And the persistence of OS, mitochondrial dysfunction and inflammation were considered as reasons to promote the development of AKI to chronic kidney disease (CKD) [3]. The relationship between iron-related parameters and AKI had been confirmed in many preclinical trials, but few clinical trials researching in prognosis of AKI were available. Therefore, we hypothesized that elevated serum iron

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

## 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 integrated clinical information relating to 53,423 patients (aged 16 years or above) admitted to critical care units of the Beth Israel Deaconess Medical Center in Boston, Massachusetts during 2001 to 2012 [4]. Clinical information included 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 0.3 mg/dL or more increase within 48 hours.

Iron related parameters such as iron serum iron, ferritin, transferrin and creatinine were acquired. When the iron related parameters were repeatedly measured after admission, the maximum value was taken into the final analysis. And 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 above data was extracted using structure query language (SQL).

### Outcomes

The primary outcome was the association between serum iron level and 28-day mortality, 90-day mortality and one-year mortality of AKI patients. The secondary end point was the role of ferritin and transferrin in the prognosis of AKI patients.

### Statistical Analyses

Shapiro-Wilk test was performed and a density map was drawn to determine the normality of the continuous variables distribution. Normally distributed continuous variables were reported as mean  $\pm$  SD, while skewed distributed variables were expressed as median and interquartile range (IQR). The grouping of serum iron levels was based on the bar chart of mortality of serum iron decile. Serum iron levels were divided into three groups (Low group:  $\leq 53.2$   $\mu\text{g/dl}$ ; Middle group: 53.2–98.6  $\mu\text{g/dl}$ ; High group:  $>98.6$   $\mu\text{g/dl}$ ). Comparison of serum iron levels between AKI patients who had different prognosis was

assessed using Wilcoxon test or T test. And boxplots were generated to show the correlation between serum iron level and mortality risks. We used log-rank tests to compare the 28-day, 90-day and one-year survival rates for groups with different serum iron levels and expressed the results as Kaplan–Meier curves. Correlations between iron-related parameters and short-time and long-time mortality risk were determined by the univariate Cox proportional hazards model. Moreover, the variables with a  $P < 0.05$  in the univariate analysis were finally incorporated into a multivariate Cox proportional hazards model to determine the independent effects of different serum iron levels on short-time and long-time mortality risk. 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 showed in Table 1. More than half of patients were older than 60 years. And the majority of patients were admitted from emergency clinic. SOFA scores were divided into two parts at a cut of 2 points, and most patients were greater than 2 points. Patients in the low, middle and high serum iron group were 290, 96 and 97, respectively. The median of transferrin and ferritin were 2.1 mg/dl (IQR: 1.1–3.75) and 347 ng/ml (IQR: 122–770).

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)

The total mortality of 28-day, 90-day and one-year were 30.8%, 39.5% and 49.3%, respectively (Table 2). As shown in the boxplots, the survival status of 28-day, 90-day and one-year were significantly associated with serum iron level ( $P = 0.0011$ ,  $P = 0.0026$  and  $P = 0.002$ , respectively) (Fig. 1). To explore the relationship between short-term and long-term mortality and different serum iron levels. We plotted the Kaplan–Meier curves, in which we could see the risk of 28-day mortality, 90-day mortality and one-year mortality stepwise increased as the groups of serum iron levels increased in AKI patients ( $P < 0.001$ ,  $P = 0.002$  and  $P = 0.003$ , respectively) (Fig. 2). After adjusting the possible confounding variables, a

significant correlation remained between high serum iron level with 28-day, 90-day and one-year mortality risk (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 model. As for other iron related measurements, transferrin negatively correlated with 28-day, 90-day and one-year mortality risk of 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 risk (P > 0.05) (Table 3).

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

<b>Outcomes</b>	<b>Total(n = 483)</b>	<b>Low iron group(n = 290)</b>	<b>Median iron group(n = 96)</b>	<b>High iron group(n = 97)</b>	<b>P Value</b>
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

## Discussion

In this retrospective study, we evaluated the prognostic role of different serum iron levels in short-term and long-term mortality of AKI patients. We investigated that high serum iron was significantly

associated with the short-time and long-time mortality risk of severe AKI patients. Moreover, transferrin exerted a beneficial effect on the short-time and long-time mortality risk of patients with AKI.

Catalytic iron, labile iron, was a transitional pool of non-transferrin bound iron (NTBI). It readily participated in redox cycle and caused 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 was demonstrated in many animal models [8, 9]. Study in a rat model of ischemia/reperfusion injury (IRI) shown that no significant changes in total iron, non-heme and ferritin iron levels were observed, but rather catalytic iron significantly increased after reperfusion [10]. In IRI, there were possible self-protection mechanism for regulating iron homeostasis [11]. In a rat of cisplatin-induced nephrotoxicity model, research supported that 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]. Consistent with this study, the protective effect of iron chelator deferoxamine on renal function was identified in rat models of intramuscular glycerol injection and intravenous hemoglobin injection induced acute renal failure [14]. And animal experiment had shown that restricting dietary iron can inhibit oxidative stress and inflammatory changes, thereby reducing renal tubular interstitial damage [15].

In recent years, researches on iron-related measurements had gradually been carried out in humans. Several studies have shown that elevated levels of catalytic iron were associated with increased incidence of AKI caused by different causes [5, 16–19]. Hepcidin was an essential regulator in iron homeostasis through downregulating iron absorption in duodenal and ferroportin expression and cellular iron release in macrophage to reduce extracellular iron levels [18, 20]. And the protective role of hepcidin in AKI provided evidence on the key role of iron in mediating AKI [21]. Meanwhile, a study involving 807 patients showed plasma catalytic iron and hepcidin possibly be useful indicators for prognosing the mortality of AKI [9]. At present, most studies are about the relationship between iron related measurements and morbidity of AKI, rather than mortality. Few studies had predicted the role of iron-related indicators in AKI mortality in humans. Our study investigated that high concentrations of excess serum iron levels and 90-day mortality of AKI were significantly correlated. Clinically, the prognosis of AKI can be assessed by measuring serum iron for taking interventions in advance to reduce mortality. In addition, this study found that the transferrin was a protective factor in 28-day, 90-day and one-year mortality of AKI. The mechanism may be that transferrin, as the main protein that bound and transported iron in blood, increased bonding with iron when it overloaded.

In humans, the role of ferritin in AKI were conflicting. Study investigated that ferritin heavy chain had protective effect on renal function [17, 22]. And some study showed that low level of ferritin was associated with increased morbidity of AKI after cardiopulmonary bypass [23, 24]. Elevated serum ferritin levels were favourable for renal function recovery [8]. However, this association was not seen in a 120 patients research[25]. It was consistent with our study, ferritin was no significant correlation with the mortality of AKI.

Disturbances in cellular and systemic iron balance and AKI may affect each other. The kidney was an important player in preventing iron loss from the body by reabsorption [3]. Different tubular segments play different roles in handling iron. Proximal tubule had majority of the reabsorption capacity [26, 27]. The kidney reabsorbed iron even when systemic iron levels were high [3]. Level of catalytic iron in urine increased, rather than decreased in AKI patients [28–30]. However, body iron stores were not low in AKI patients [19, 31]. The iron-mediated mechanisms in AKI were complex and may include multiple pathways. Excess iron was associated with OS, and production of oxygen free radicals caused damage to lipids, DNA and proteins [6]. While, renal tubular epithelial cells were 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]. And free iron could 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 was important in the pathogenesis of AKI [3, 34]. Iron mediated OS, mitochondrial dysfunction and inflammatory may be the potential mechanism of AKI. Moreover, ferroptosis was recently considered as a central player in AKI, which characterized by the accumulation of lethal lipid ROS produced through 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 were the possible sources [37].

In terms of iron targeted therapy in AKI, the therapeutic effects of hepcidin, deferoxamine, apolipoprotein, pharmacologic therapy with apotransferrin and hydroxyl radical scavengers were reported in animal models [37, 38]. Combined with our study results, it showed further study on taking interventions of serum iron concentration for improving the prognosis in AKI needed completed.

We also acknowledged several limitations of this study. Firstly, this was a retrospective study with confounding bias due to missing values in the database and some indicators not recorded in MIMIC-III database. Secondly, this was a signal center database between 2001 to 2012, so information may relatively old while the sample size of our study was large. In addition, we selected the largest measurements of serum iron and other iron-related indicators after admission as research indicators. Meanwhile we 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 levels and the increased mortality of severe AKI patients, and the protective effect of transferrin on prognosis of AKI. Serum iron level 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.

## **Conflict of Interest Statement**

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.

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## Figures

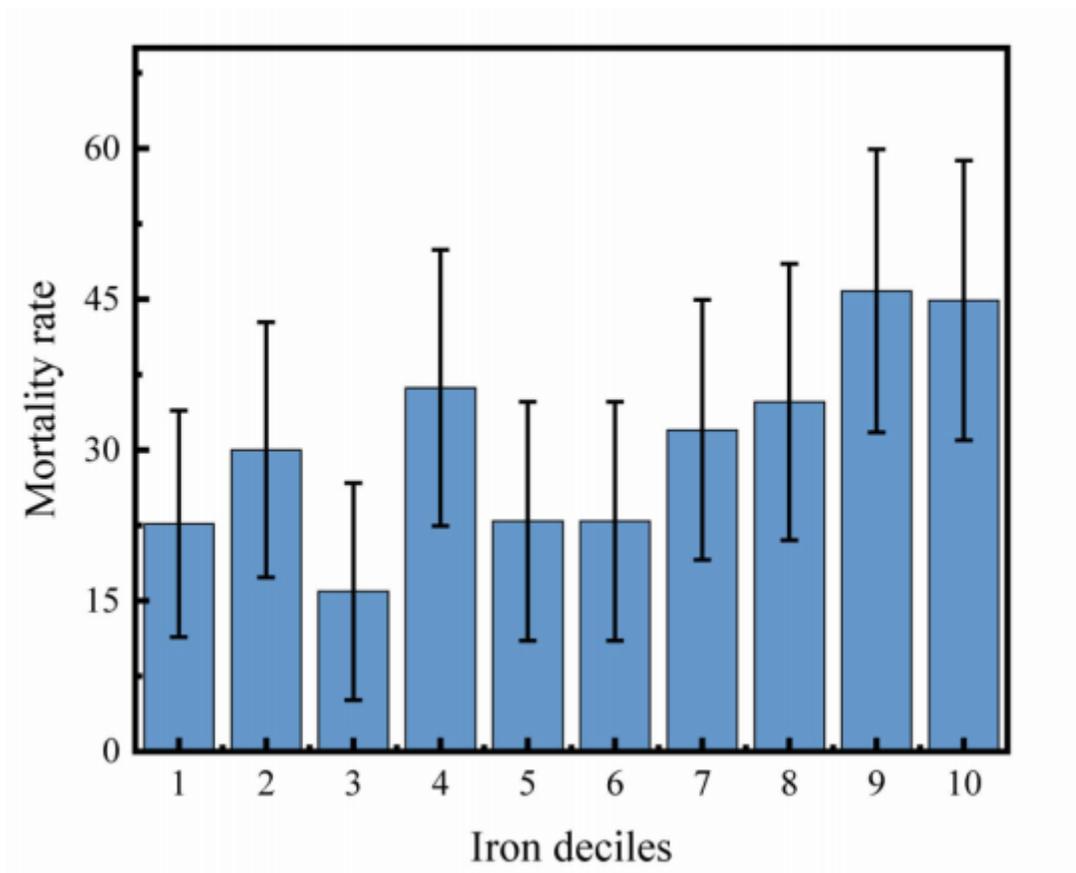


Figure 1

Bar chart showing the different mortality of serum iron decile

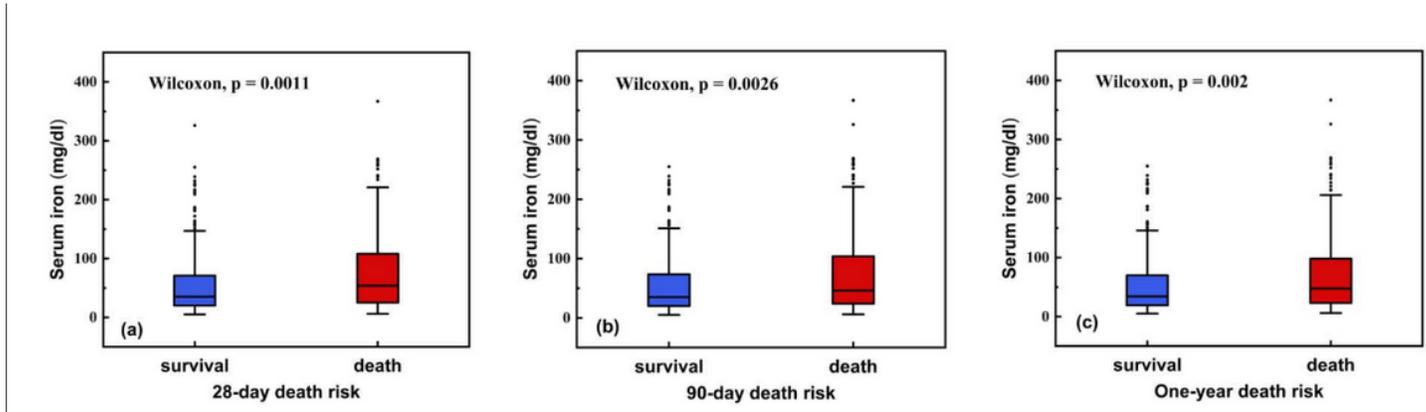
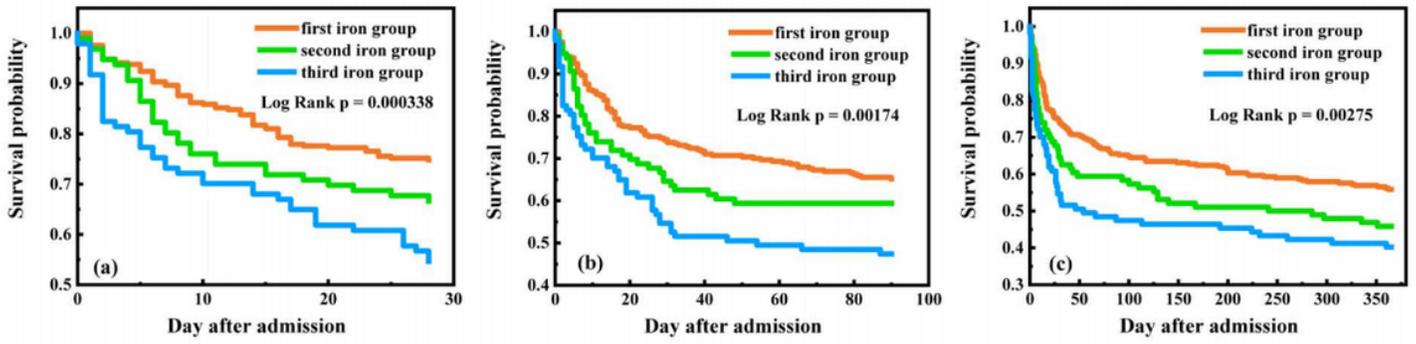


Figure 2

Boxplots exploring the relationship between serum iron level and different survival status



**Figure 3**

Kaplan-Meier curves demonstrating the association of different serum iron levels and short and long mortality