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Iron and ferritin effects on intensive care unit mortality: A meta-analysis

Iron and ferritin on icu mortality
Abstract

BACKGROUND
The effect of serum iron or ferritin parameters on mortality among critically ill patients is not well characterized.

AIM
To determine the association between serum iron or ferritin parameters and mortality among critically ill patients.

METHODS
Web of Science, Embase, PubMed, and Cochrane Library databases were searched for studies on serum iron or ferritin parameters and mortality among critically ill patients. Two reviewers independently assessed, selected, and abstracted data from studies reporting on serum iron or ferritin parameters and mortality among critically ill patients. Data on serum iron or ferritin levels, mortality, and demographics were extracted.

RESULTS
Nineteen studies comprising 125,490 patients were eligible for inclusion. We observed a slight negative effect of serum ferritin on mortality in the US population (RR, 1.002; 95% CI, 1.002 - 1.004). In patients with sepsis, serum iron had a significant negative effect on mortality (RR, 1.567; 95% CI, 1.208 - 1.925).

CONCLUSION
This systematic review presents evidence of a negative correlation between serum iron levels and mortality among patients with sepsis. Furthermore, it reveals a minor yet adverse impact of serum ferritin on mortality among the US population.

Key Words: iron; ferritin; mortality; critically ill; meta analysis

**Core Tip:** This systematic review presents evidence of a negative correlation between serum iron levels and mortality among patients with sepsis. Furthermore, it reveals a minor yet adverse impact of serum ferritin on mortality among the US population.

**INTRODUCTION**

Iron is an essential nutritional element of the human body with many important biological functions (1). With the varying cellular environment, the interconversion between the two oxidized states of iron (Fe^{2+} and Fe^{3+}) keeps iron relevant to a variety of important biochemical reactions, but also with potential hazard risks (2). Under oxygentic conditions, the Fenton/Haber-Weiss reaction of free iron catalyzes the production of harmful atomic groups, and this mechanism has been hypothesized to underlie iron toxicity in some pathological states (3).

With the progress of clinical and experimental studies, iron metabolism has been shown to play a crucial role not only in metabolic diseases, but also in monitoring disease prognosis using serum iron indicators (4-6). Changes in iron metabolism indicators occur in critically ill patients, and some of these serum iron metabolism indicators have been reported to be used to predict prognosis in these patients. In a study on multiple serum iron metabolism indicators among 51 critically ill patients after surgery, elevated serum ferritin was associated with poor clinical outcomes (7). Another study on a prospective cohort of 121 patients under critical care in an integrated ICU revealed a significant association between plasma iron levels and increased risk of inpatient 30-day mortality (8). According to another prospective study, serum iron metabolism indicators are associated with prognosis of ICU patients. In-survival analysis revealed that lower serum iron and iron utilization levels could increase short-term and long-term survival outcomes. Furthermore, after multivariate analysis
adjusting for other indicators, iron was found to be an independent predictor of short-
term and long-term survival outcomes of mortality among ICU patients (9). Currently,
no conclusions have been established as to whether serum iron metabolism indicators
can accurately predict the prognosis of critically ill patients. The relevant underlying
mechanisms are still being explored.

Therefore, a better understanding of the importance of iron metabolism among ICU
patients is urgently needed. In consequence, we analyzed the effect of iron parameters
on mortality among critically ill patients admitted to ICU.

MATERIALS AND METHODS

Search strategy

This meta-analysis study was conducted by following the Meta-analysis Of
Observational Studies in Epidemiology (MOOSE) guidelines (10). A literature search of
relevant published studies that analyzed the association between iron parameters and
mortality outcomes among critically ill patients was conducted on October 1, 2021.
Using literature searches on PubMed, Embase, Web of Science, and Cochrane Library
databases, we identified articles using the following terms: ferritin, iron, anemia,
critically ill, sepsis, sepsis shock, and mortality. Only studies published in English were
identified for the analysis in this study. By consulting the reference lists in these
research articles, we identified additional studies relevant to the subject.

Study selection criteria

Studies were included, if (a) they were cohort or case-control studies; (b) the study
evaluated the association between iron parameters and mortality among critically ill
patients admitted to ICUs; and (c) they provided sufficient data on odds ratios (OR);
and (d) the Newcastle-Ottawa Scale (NOS) score was ≥6. All studies containing
overlapping data were excluded.

The data extracted included the first author's name, year of publication, study
population and country, period, study type, age, ORs with 95% confidence intervals
(CIs), ICU type, patient types, and NOS scores (Table 1). For publications that did not
report the association between iron or ferritin and mortality among critically ill patients, we calculated the ORs, if data on these variables were available.

**Statistical analysis**

The strength of the association between iron or ferritin and mortality among critically ill patients was reported using ORs and 95% CIs. When adjusted and crude ORs were provided, the most adjusted ORs were extracted. We used the $I^2$ test and $Q$-statistic to detect any possible heterogeneity, as a quantitative measure of inconsistency among studies (11). Meta-regression analyses were used to investigate the sources of heterogeneity. Pooled ORs and 95% CIs were calculated using a random-effects model (12).

All statistical analyses in the meta-analysis were performed using STATA version 13.0. All reported $P$ values were from two-sided statistical tests. Statistical significance was set at $P \leq 0.05$. Egger’s and Begg’s regression models were used to evaluate potential publication bias (11).

**RESULTS**

The process for selecting the studies is outlined in Figure 1. After the literature search, 267 potentially relevant records were reviewed. Out of this number, 19 studies, including 125,490 patients, were included in the meta-analysis (Table 1). Subsequently, 247 studies were excluded, because they were either duplicated reports or were of relatively low quality. All 19 selected studies were cohort studies (8, 9, 13-29).

Six studies were conducted in Europe; five studies were conducted in America; and five studies were conducted in other regions (Asia, Australia). Four studies presented data on mortality and iron and ferritin separately. The NOS scores of eight, six, and two studies were 6, 7, and 8, respectively (Table 2). The data on mortality and serum iron and ferritin were extracted separately. Most of the included studies had contrasting findings. Six studies reported that high ferritin levels were associated with high mortality among critically ill patients, whereas the other 10 studies reported no association. Similarly, the studies on serum iron had contrasting findings. Four studies
reported that high serum iron levels were associated with high mortality among critically ill patients, whereas the other three studies reported no association or corresponding decrease in mortality among critically ill patients. The analysis of the studies yielded a combined risk estimate, RR of 1.00 (95% CI, 1.00–1.00; \( P = 0.001 \)) with a heterogeneity value (I²) of 84.4% for ferritin (Figure 2A), and a combined risk estimate, RR of 1.02 (95% CI, 0.99–1.05; \( P < 0.001 \)) with a heterogeneity value (I²) of 85.3% for iron (Figure 2B). We also assessed the stability and explored the sources of heterogeneity of the results using sensitivity analysis for serum ferritin and iron (Figure 3A and Figure 3B). After a meta-regulation test, geographical area was associated with 50.51% heterogeneity reduction across the studies for serum ferritin and 41.53% heterogeneity reduction across the studies for serum iron (Figure 4A and Figure 4B).

Due to the differences in geographic area (Europe, America, and others), NOS (6, 7, or 8), patient category (sepsis, other critically ill patients), and ICU type (adult ICU, PICU, or general ICU) among the studies, we further conducted subgroup analyses to determine the effect of these factors in our analyses (Table 2). We found a significant negative effect of serum ferritin on mortality in the US population (RR, 1.002; 95% CI, 1.002–1.004) and in the general ICU (RR, 1.025; 95% CI: 0.25-1.8). We obtained a statistically negative effect on patients with sepsis (RR, 1.567; 95% CI, 1.208–1.925) for serum iron.

Based on Egger’s and Begg’s regression models, evidence of publication bias (Figures 5A, B and 6A, B) were noted for iron or ferritin, in relation to mortality. Egger’s funnel plot and Begg’s linear regression test revealed \( P \) values <0.05.

**DISCUSSION**

To the best of our knowledge, this study is the first systematic review examining the role of iron parameters on mortality in critically ill patients. High iron parameters had no association with mortality among critically ill patients. Due to the heterogeneity of the meta-analysis, we performed subgroup analysis, sensitivity analysis, and regression analysis to explore the source of heterogeneity. Subgroup analyses were used to
determine the effect of geographic area (Europe, America, or others), NOS score (6, 7, or 8), patient types (sepsis, other critically ill patients), and ICU types (Adult ICU, PICU, or general ICU) in our analyses (Table 2). For iron, sepsis had a statistically negative effect (RR, 1.567; 95%CI, 1.208-1.925). Sensitivity analysis revealed stable conclusions and no apparent source of heterogeneity for serum ferritin and iron (Figure 3A, 3B). From the meta-regulation test, geographical area was associated with 50.51% heterogeneity reduction across studies on serum ferritin and 41.53% heterogeneity reduction across studies on serum iron (Figure 4A and Figure 4B). Due to publication bias, further studies of higher quality are needed to confirm our findings.

The meta-analysis concluded that serum ferritin had no association with mortality among critically ill patients. However, since few studies with high level of heterogeneity were included, exact conclusions could not be made. Ferritin is an indicator of iron level and storage in the body. However, it is also an acute phase reactive protein. A significantly increased serum ferritin level in stress conditions, such as inflammation, does not accurately reflect the body's iron storage. Pro-inflammatory cytokines can induce increased ferritin transcription and translation, resulting in elevated serum ferritin level. Inflammation is a common pathological state in critically ill patients that may likely result in multi-organ dysfunction, depending on disease severity (30, 31). According to studies on iron parameter levels in critically ill patients, serum ferritin levels in critically ill patients are significantly higher during sepsis than during the recovery stage. This implies that serum ferritin level can reflect the state and severity of infection (7). Additionally, inflammatory stimuli can upregulate the expression of ferromodulin and modulate iron metabolism by inhibiting intestinal iron absorption and limiting iron release in the mesh endothelial system, resulting in a relative iron deficiency state in the circulatory system (32-34). Currently, the nature of association between ferritin level and mortality among critically ill patients is yet to be elucidated. To remedy the situation, separate clinical studies on different diseases with varying severities in different populations should be conducted.
The meta-analysis concluded that no association existed between iron level and mortality in critically ill patients, although subgroup analysis revealed that in patients with sepsis, iron is a risk factor. Under normal physiological conditions, iron metabolism is in a balanced state, which does not only maintain the important biological function of iron but also prevents excessive iron accumulation that could result in oxidative stress due to injury to the body. Iron homeostasis ensures that changes in iron metabolism present in ICU patients are essentially a defense mechanism. From initial studies, the trend of serum iron metabolism indicators in critically ill patients was similar to that in chronic inflammation, which is a common pathological state in critically ill patients. Infectious inflammation is the most common pathological state (35, 36). One feasible mechanism underlying the high iron level is the state of histiocyte breakdown in ICU patients. The disruption of erythrocytes and other tissues gradually decreases iron consumption and increases iron release. As a result, repeated blood transfusions further increases iron level in circulation after erythrocytolysis (37-39). The increase in iron-associated mortality may be due to excess iron, which directly promotes increased infection in patients with sepsis. Furthermore, iron catalyzes the chemical production of reactive oxygen species, such as hydroxyl anions and superoxide, thereby accelerating the development of multi-organ dysfunction (40). There is a lack of definitive evidence on the effect of iron on survival and mortality in critically ill patients, except those with sepsis.

This study had few limitations. First, only studies published in English journals were included. However, a significant portion of the literature were studies conducted in Asia, where the official language is not English. Second, predicting the effect of misclassification of cohort studies on the results was challenging. Third, systematic confounding or the risk of bias in observation studies cannot be ruled out easily. Fourth, due to heterogeneity across the studies, regression analysis was used to explain the source of heterogeneity, which may be due to differences in study geographical areas. In this study, analyses of the association between concentration of ferritin and duration
of ferritin abnormality and mortality among critically ill patients were not included. The original studies lacked data on these parameters for this analysis.

CONCLUSION
In summary, this systematic review presents evidence of a negative correlation between serum iron levels and mortality among patients with sepsis. Additionally, it identifies a minor but adverse effect of serum ferritin on mortality within the US population. Further high-quality cohort studies and experimental studies on molecular mechanisms are needed to confirm our findings.

ARTICLE HIGHLIGHTS
Research background
The effect of serum iron or ferritin parameters on mortality among critically ill patients is not well characterized.

This systematic review presents evidence of a negative correlation between serum iron levels and mortality among patients with sepsis. Furthermore, it reveals a minor yet adverse impact of serum ferritin on mortality among the US population.

Research objectives

Web of Science, Embase, PubMed, and Cochrane Library databases were searched for studies on serum iron or ferritin parameters and mortality among critically ill patients.

Research motivation
To determine the association between serum iron or ferritin parameters and mortality among critically ill patients.

Research perspectives
Further high-quality cohort studies and experimental studies on molecular mechanisms are needed to confirm our findings.
**Research conclusions**

This systematic review presents evidence of a negative correlation between serum iron levels and mortality among patients with sepsis. Furthermore, it reveals a minor yet adverse impact of serum ferritin on mortality among the US population.

**Research results**

Nineteen studies comprising 125,490 patients were eligible for inclusion. We observed a slight negative effect of serum ferritin on mortality in the US population (RR, 1.002; 95% CI, 1.002 - 1.004). In patients with sepsis, serum iron had a significant negative effect on mortality (RR, 1.567; 95% CI, 1.208 - 1.925).

**Research methods**

Two reviewers independently assessed, selected, and abstracted data from studies reporting on serum iron or ferritin parameters and mortality among critically ill patients. Data on serum iron or ferritin levels, mortality, and demographics were extracted.
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