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EDITORIAL

Deciphering the iron enigma: Navigating the complexities of iron metabolism in critical illness

Anjali Mishra, Deven Juneja

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Abstract

Iron is a double-edged sword! Despite being essential for numerous physiological processes of the body, a dysregulated iron metabolism can result in tissue damage, exaggerated inflammatory response, and increased susceptibility to infection with certain pathogens that thrive in iron-rich environment. During sepsis, there is an alteration of iron metabolism, leading to increased transport and uptake into cells. This increase in labile iron may cause oxidative damage and cellular injury (ferroptosis) which progresses as the disease worsens. Critically ill patients are often complicated with systemic inflammation which may contribute to multiple organ dysfunction syndrome or sepsis, a common cause of mortality in intensive care unit. Originally, ferritin was known to play an important role in the hematopoietic system for its iron storage capacity. Recently, its role has emerged as a predictor of poor prognosis in chronic inflammation and critical illnesses. Apart from predicting the disease outcome, serum ferritin can potentially reflect disease activity as well.

Key Words: Critical illness; Ferritin; Inflammation; Iron; Mortality; Sepsis

Core Tip: Traditionally serum iron parameters including ferritin have served as biomarkers for assessing the iron status. Recently, the spectrum of utility for these markers has widened as tools for assessing inflammation and predicting outcomes in critically ill patients. These markers have been associated with high mortality and poor clinical outcomes in various critical illnesses. Serial measurement of iron parameters, especially in patients admitted to intensive care units, may be used as potential tools to determine worsening and progression towards multiorgan failure. However, their interpretation must be in accordance with the patient's clinical condition and other biochemical parameters, for guiding further treatment to optimize clinical care and prognosis.

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INTRODUCTION

Iron plays an important role in crucial biological processes and biochemical functions, including oxygen signalling, adenosine triphosphate production, deoxyribonucleic acid synthesis and repair, erythropoiesis, inflammation regulation and supporting immune function[1]. Despite this, excess iron can injure cells and tissues, by inducing oxidative stress and mitochondrial dysfunction and triggering inflammation resulting in cell death[2]. The imbalance in iron-metabolism is complex but common in critically ill patients and the change in iron indices may provide an opportunity to conceive valuable biomarkers to study disease progression and devising therapeutic strategies.

IRON INDICES IN CRITICAL ILLNESS

Anaemia is one of the most common nutritional deficiencies witnessed worldwide, more so in developing countries, and has been associated with poor outcomes in critically ill patients. Anaemia in intensive care unit (ICU) patients can be broadly classified into two categories: One with absolute iron deficiency (IDA), characterised by total depletion of iron stores and the anaemia of inflammation (AI), marked by functional iron deficiency with low serum iron levels (normal iron stores) and normal or high ferritin levels[3,4].

Compared to IDA, inflammation results in the dysfunction of iron distribution and transportation, causing its storage within iron-cycling macrophages. Critically ill patients, often victims of high inflammation, develop AI because of circulating pro-inflammatory cytokines, impaired red blood cell proliferation related to reduced iron metabolism and a dysregulated erythropoietin response[5]. Biochemically, AI is marked by low levels of erythropoietin and transferrin and high levels of ferritin, hepcidin and interleukin-6. Serum ferritin concentration is related to the leakage of tissue ferritin, which serves the purpose of storing iron intracellularly[6]. While tissue ferritin manages intracellular iron stores, serum ferritin is believed to play a role of inflammatory mediator and an acute phase reactant. The plasma ferritin levels indicate a fine balance between its secretion and clearance through the liver. In a state of inflammation, this balance of synthesis and clearance is affected, causing increased serum ferritin levels[6,7].

Serum ferritin levels

The role of serum ferritin as a marker for inflammation and infection has been evaluated relentlessly in both, adult and paediatric populations. Elevated levels may occur in iron overload, inflammatory diseases, chronic alcoholism, liver/renal disease, metabolic syndrome and even in malignancies[8]. A cohort study that evaluated serum ferritin levels in children (aged 1 month to 16 years) with severe sepsis and septic shock concluded that ferritin > 500 ng/mL was associated with a significantly higher relative risk (RR) of death [RR 3.2 (1.3-7.9), (P = 0.01)][9]. In another study, ferritin (> 4420 ng/mL) was found to be diagnostic of macrophage activation-like syndrome and predictive of mortality in septic patients[10]. In a similar research conducted in critically ill septic patients, serum ferritin was found to accurately predict in-hospital mortality and organ failure, with an area under the curve (AUC) of 0.655 and 0.646, respectively. The identified cut-off values for ferritin were 411 ng/mL for predicting in-hospital mortality and 581 ng/mL for predicting organ failure[11].

In a large retrospective study involving 2451 patients, serum ferritin levels (> 591.5 ng/mL) was found to be an independent predictor of hospital mortality in septic patients with an AUC of 0.651[12]. Another recent single-center study conducted by He *et al*[13], on a large public database, exhibited a significant relationship between ferritin levels and outcomes in sepsis, including mortality at day 28, 90, 180 and 1-year. Further, they reported that for every 1000 ng/mL increase in ferritin levels, the risk of mortality increased by 13% to 17%.

Studies have also shown the outcome predictive accuracy of ferritin to be similar to more commonly used clinical scores like sequential organ failure assessment (SOFA) score[7,14]. In a study by Rusu *et al*[7], serum ferritin was found to have similar predictive accuracy and a statistically significant positive correlation with SOFA score [r = 0.7, 95% confidence interval (CI) for r = 0.64 to 0.76, P < 0.01] in patients with prolonged ICU stay. Although serum ferritin levels

at the time of admission to the ICU did not show any significant difference between survivors and non-survivors, as the duration of stay advanced, non-survivors displayed higher SOFA scores and ferritin levels compared to survivors. The results of these studies, along with ongoing research in this area, suggests that serum ferritin levels are more linearly indicative of progression of inflammation and organ dysfunctions, with higher values being associated with worst outcomes, although the exact cut-offs still need to be determined.

Serum iron levels

Disrupted iron metabolism leads to impaired aerobic metabolism which has been associated with a reduction in maximal oxygen consumption, and diminished muscle endurance and cognitive performance[15-17]. Several studies have assessed the impact of serum iron levels on the outcomes of critically ill patients. In a retrospective study, Shu *et al*[18] extensively studied serum iron parameters in patients admitted to ICU with acute kidney injury. They found higher serum iron levels (> 60 μg/dL) to be associated with increased short-term [28-day, hazard ratio (HR) 1.832; $P < 0.001$] and long-term (90-day, HR 1.741; $P < 0.001$) mortality. Study by Zhao *et al*[19] inferred a higher 60-day mortality with higher concentrations of serum iron and urinary neutrophil gelatinase-associated lipocalin levels. Additionally, when combined with SOFA score, these markers significantly enhanced the accuracy of prognosis prediction.

Furthermore, elevated levels of other iron parameters such as transferrin saturation (TSAT) and non-transferrin bound iron (NTBI) have been associated with worse clinical outcomes in ICU[14,20]. Studies have highlighted the association of lower TSAT values with better long and short-term outcomes[21]. As suggested by these studies, iron overload is now emerging as a valuable predictor of in-hospital mortality in critically ill patients, pressing the urgent need for therapeutic interventions that can potentially neutralize the culprit parameters such as NTBI[22].

The correlation between iron indices and clinical outcomes has largely been evaluated in single-center trials. In the recent issue of Yang *et al*[23] and colleagues published an interesting meta-analysis addressing a relevant concern in clinical practice that can potentially guide clinicians about prognostic indicators and outcome predictors in critically ill patients. The study aimed to determine the association between iron parameters and mortality among critically ill patients. This review analyzed data from nineteen cohort studies conducted at various geographical locations including six in Europe, five in the United States, and five in other regions, with a total of 125490 patients. Overall, they concluded that serum iron and ferritin levels had no association with mortality among critically ill patients.

The authors noted that most of the included studies had contrasting findings and there was high heterogeneity across studies, as indicated by the I^2 values of 84.4% for ferritin and 85.3% for iron. Hence, they conducted subgroup and meta-regression analyses based on the geographic area, Newcastle-Ottawa scale, patient category, and ICU type to explore the potential sources of heterogeneity. Significant differences were observed based on the geographical regions from where the studies were originating. On sub-group analysis, a significant correlation was found between serum ferritin and mortality in the American patient population (RR = 1.002; 95%CI: 1.002-1.004) and in the general ICU patients (RR = 1.025; 95%CI: 0.25-1.8). Similarly, high serum iron levels correlated with higher mortality in patients with sepsis (RR = 1.567; 95%CI: 1.208-1.925). This meta-analysis demonstrates the necessity for large-scale trials to be conducted in varied geographical regions and in different patient populations assessing the efficacy of serum iron and ferritin levels to predict outcomes in critically ill patients. However, the authors acknowledged the fact that they had included studies published in English, potentially excluding data from many studies published in their native regional languages, which could have affected their results[23].

There is a constant need to find an ideal biomarker to aid in early diagnosis and prognostication of life-threatening conditions like sepsis and septic shock. Over the years, hundreds of biomarkers have been evaluated and compared for their efficacy in the management of sepsis. In resource-limited settings, an ideal biomarker should not only be accurate and effective, but also cheap and readily available[24]. Iron indices have been in routine clinical use for decades and hence, they provide a unique opportunity to become a vital tool in sepsis management.

FUTURE PROSPECTS AND ADVANCES

The future role of serum ferritin and iron markers as predictors of mortality in sepsis and critically ill patients is likely to evolve rapidly as research continues in this territory. Large-scale randomised trials in different patient populations may help in further determining their accuracy and efficacy. Combining these markers with other inflammatory and sepsis-related biomarkers (like procalcitonin, C-reactive protein, and lactate) and utilizing machine learning models to analyze patterns and combinations of these markers can enhance predictive accuracy and help in devising early intervention strategies. These machine learning models (Random Forest and eXtreme Gradient Boosting) could also provide a robust method for stratifying patients upon ICU admission and guide further treatment based on that stratification[25,26].

CONCLUSION

The simplified understanding of serum ferritin levels and the theory that low ferritin levels indicate iron deficiency and high levels can only suggest hemochromatosis is now obsolete. It has been increasingly reported that the presence of inflammation alters the direct linear relationship between serum ferritin levels with iron stores. While the role of certain cytokines (pro-inflammatory and anti-inflammatory) have been reviewed extensively, further research and evidence is required to better understand the role of other key molecules in persistent inflammation. Among these molecules are the

serum iron and ferritin levels.

FOOTNOTES

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