Association between serum ferritin and outcomes in critically ill patients: a retrospective analysis of a large intensive care unit database

Linli Sang, Weiyun Teng, Mengmeng Zhao, Ping Ding, Xinxiang Xu, Yuxiu Wang, Liuzhao Cao

Department of Pulmonary and Critical Care Medicine, Northern Jiangsu People's Hospital Affiliated to Yangzhou University, Yangzhou, Jiangsu 225001, China.

To the Editor: Critically ill patients are always complicated with systematic inflammation causing organ dysfunction, even multiple organ dysfunction syndrome (MODS) or sepsis, which commonly contributes to mortality in intensive care unit (ICU). It was originally thought that ferritin plays an important role in the hematopoietic system for its iron storage capacity. Recently, it was reported that the raised plasma ferritin is correlated with a poor prognosis of diseases. The level of ferritin could not only reflect disease activity, but also may predict the outcomes.[1] The relationship between plasma ferritin and clinical outcomes of critically ill or sepsis patients remained controversial.[2,3] We hypothesized that among critically ill patients especially sepsis, measuring plasma ferritin levels may help identify the severe cases with unfavorable outcomes (hospital mortality or organ failure). In this study, we obtained a large quantity of patients' data from the Medical Information Mart for Intensive Care-III (MIMIC-III) database. The data may help to analyze whether ferritin could be a reliable predictor of the outcomes in adult critically ill patients.

We extracted data from MIMIC-III (version 1.4) database[4] which is a large, single-center database containing critically ill patients admitted to Beth Israel Deaconess Medical Center (BIDMC) from 2001 to 2012. Access to the database for research was approved by the Institutional Review Boards of the Massachusetts Institute of Technology (Cambridge, MA, USA) and the BIDMC after completion of the National Institutes of Health web-based course named "Protecting Human Research Participants" (Record ID: 39075197). Since all patients were de-identified, informed consent was waived by the ethical committee of BIDMC. The patients were divided into four groups according the quartiles of ferritin level (<102 ng/mL [IQR1], > 102 and ≤264 ng/mL [IQR2], >265 and ≤645 ng/mL [IQR3], and >645 ng/mL [IQR4]). The association between ferritin level quartiles and mortality or MODS was assessed by Kaplan–Meier curves. Receiver operator characteristic curves and area under the curve (AUC) were calculated to evaluate the accuracy. Wilcoxon rank sum test was conducted to compare ferritin level between survivors and non-survivors. Kruskal-Wallis test was conducted to evaluate the difference in the duration of ICU stay and ventilation between quartiles of ferritin. A multivariable logistic regression model was constructed to determine the independent effects of ferritin on hospital mortality and MODS. Variables with $P < 0.05$ in the univariate analysis were further incorporated into multivariable logistic regression models. The results were expressed as odds ratio (ORs) with 95% confidence intervals (CIs). Comparison of baseline characteristics between quartiles was provided as Supplementary Table 1, http://links.lww.com/CM9/A956. For all tests, a two-sided $P < 0.05$ was considered statistically significant. All statistical analysis was performed using STATA software (v14.0, StataCorp, College Station, TX, USA) and GraphPad Prism 6 (v 6.02 GraphPad Software Inc, San Diego, CA, USA).

A total of 5159 patients with the result of ferritin available after ICU admission were included in this study. The median age of the entire cohort was 65 (Q_1–Q_3: 52–79) years. Totally, 2625 (50.9%) patients involved were men. Overall ICU mortality was 14.0% (722/5159). A total of 2188 (42.4%) patients involved were diagnosed as sepsis during the ICU stay.

The median ferritin values of survivors and non-survivors were 241 (Q_1–Q_3: 90–574) ng/mL and 511.5 (Q_1–Q_3: 193–1199) ng/mL, respectively ($Z = -13.40$, $P < 0.001$). Among patients with sepsis, the median ferritin values were 331 (Q_1–Q_3: 131–770) ng/mL and 584 (Q_1–Q_3: 213–1343) ng/mL for survivors and non-survivors,

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002019

Correspondence to: Liuzhao Cao, Department of Pulmonary and Critical Care Medicine, Northern Jiangsu People's Hospital Affiliated to Yangzhou University, #98 Nantong Xi Road, Yangzhou, Jiangsu 225001, China
E-Mail: lzcao1992@163.com

Copyright © 2022 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2022;135(21)

Received: 22-07-2021; **Online:** 16-02-2022 **Edited by:** Peifang Wei

respectively ($Z = -6.07$, $P < 0.001$). Totally, 3712 (72.0%) patients were complicated with at least one organ failure and 2020 (39.2%) patients progressed to MODS. MODS was observed in 33.2% (1474/4437) of survivors and in 75.6% (546/722) of non-survivors ($\chi^2 = 468.635$, $P < 0.001$).

One thousand five hundred and fifty-three (35.0%) survivors and 471 (65.2%) non-survivors needed mechanical ventilation ($\chi^2 = 238.092$, $P < 0.001$). Durations of ICU stay (median 2.0, 2.1, 2.3, 2.8 days, $H = 112.43$, $P < 0.001$) and ventilation (median 0.9, 1.1, 1.8, 2.9 days, $H = 86.19$, $P < 0.001$) grouped according to ferritin quartiles were significantly different. Duration of ICU stay and ventilation showed a tendency of increasing with the ferritin quartiles [Supplementary Figure 1A and 1B, http://links.lww.com/CM9/B33].

Vital signs, age, body mass index, Sequential Organ Failure Assessment scores, Simplified Acute Physiology Score II, ethnicity, comorbidities (heart failure, chronic obstructive pulmonary disease, liver disease, metastatic cancer, depression, and deficiency anemia), lab results (international normalized ratio, white blood cell count, platelets, lactate, ferritin, blood urea nitrogen, and potassium), use of norepinephrine and mechanical ventilation were incorporated into the multivariable logistic regression model. Logistic regression analysis demonstrated that ferritin was independently associated with MODS (OR = 1.000, 95% CI: 1.000–1.001, $P = 0.001$) or sepsis among the whole population (OR = 1.001, 95% CI: 1.001–1.002, $P < 0.001$). The hospital mortality rate was 7.1%, 11.3%, 13.4%, and 24.1% for the IQR1, IQR2, IQR3, and IQR4 groups, respectively ($\chi^2 = 168.93$, $P < 0.001$). The association between ferritin quartiles and hospital mortality among the whole cohort and septic patients was shown through Kaplan-Meier curves [Supplementary Figure 1C and 1D, http://links.lww.com/CM9/B33]. The fourth quartile of ferritin increased the risk of hospital mortality (hazard ratio [HR]: 2.02, 95% CI: 1.60–2.56, $P < 0.001$). Among septic patients, the fourth quartile of ferritin had an increased hospital mortality as well (HR: 1.55, 95% CI: 1.21–2.00, $P = 0.001$).

The AUC for ferritin in predicting hospital mortality was 0.655 (95% CI: 0.633–0.677; Supplementary Figure 1E, http://links.lww.com/CM9/B33). The AUC in predicting MODS was 0.646 (95% CI: 0.631–0.662; Supplementary Figure 1F, http://links.lww.com/CM9/B33). Among patients with sepsis, the AUC for ferritin in predicting hospital mortality was 0.628 (95% CI: 0.580–0.636; Supplementary Figure 1G, http://links.lww.com/CM9/B33) and in predicting MODS was 0.608 (95% CI: 0.605–0.653; Supplementary Figure 1H, http://links.lww.com/CM9/B33). Cutoff values for mortality were 411 ng/mL with a sensitivity of 56.51% and a specificity of 66.64% among the whole cohorts and 581 ng/mL with a sensitivity of 50.49% and a specificity of 68.14% among the septic patients.

Serious inflammation and organ dysfunction were common in the critically ill patients admitted to ICU, and there was lack of reliable biomarkers to predict clinical outcomes. Sepsis is a common risk factor predisposing to MODS, which determines the clinical course in ICU patients. A reliable biomarker can help diagnosis, describe progression, and assess prognosis. Currently, studies found that the expression of ferritin was involved in systematic inflammation and organ dysfunction. Therefore, we explored the critical association between ferritin and unfavorable outcomes. In our study, we found that serum ferritin level was positively correlated with the duration of ICU stay and ventilation. High ferritin in the fourth quartile (>645 ng/mL) measured after admission to ICU was significantly associated with higher hospital mortality compared with the first quartile of ferritin (ferritin ≤102 ng/mL). Additionally, the AUCs for ferritin in predicting hospital mortality and MODS were 0.655 and 0.646, respectively.

However, the role of ferritin in predicting the prognosis of sepsis still remained controversial. Based on the large database from MIMIC-III, our study also discussed the definite value of ferritin in predicting the prognosis of sepsis. Our findings, consistent with the previous study among children, indicated that increased ferritin might be the independent risk factor contributing to the progression of MODS as well, whereas the association between ferritin and hospital mortality might be affected by other potential factors.[5] Although ferritin is not magnificently and highly specific according to our results, it still has a certain hint for the clinical prognosis as well. As shown in the results, K-M curves of the second quartile (>102 and ≤264 ng/mL) crossed the third quartile (>265 and ≤ 645 ng/mL). The Chi-squared test of hospital mortality showed no significant difference between the second and third quartile, which means that mildly elevated ferritin might have positive impacts systematically. Bennett *et al*'s[3] study also suggested that ferritin might play a protective role in inflammation in pediatric patients and very high levels of ferritin were related to a high risk of critical illness or death. Consistent with their results, the fourth quartile of ferritin (>645 ng/mL) increased the risk of mortality (HR: 2.02, 95% CI: 1.60–2.56, $P < 0.001$) in our study. Therefore, we proposed that a high level of ferritin could alert the clinicians that the prognosis could be poor and more approaches should be taken to treat primary disease.

Hyperferritinemia is frequently seen in critically ill patients. Considering the contribution of systemic inflammation to MODS and sepsis and the definite correlation between ferritin and inflammation, the level of ferritin played a potential role in demonstrating the unfavorable clinical condition. It was reported that over 1980 ng/ml of ferritin suggested poor outcome in children with severe sepsis.[1] Plasma ferritin value was significantly associated with unfavorable outcomes in septic pediatric patients.[3] Controversially, Williams *et al*[2] proposed that serial ferritin estimation predicted neither organ dysfunction nor mortality in pediatric sepsis. However, subjects involved in recent studies were almost children. Besides, we proposed that another limitation was lack of large-scale studies.

There are still some limitations in our study. The selection bias could not be inevitable because the data of MIMIC-III

were from a single medical center. As a retrospective study, some clinical indicators were missing, which might affect the comparison. This study was a retrospective research, so some basic variables were uncontrollable. More prospective randomized controlled trials are required to be implemented to explore the role of ferritin and treatments for hyperferritinemia.

In conclusion, we explored the important and reliable role of ferritin in predicting the prognosis of critically ill adults in ICU based on a large and publicly available database-MIMIC-III. Clinicians should raise attention when encountering patients with hyperferritinemia. The level of ferritin is an easily accessible and practical parameter, so it could serve as a supporter to other parameters or clinical scores to improve the prognostic prediction. However, clinicians should not rely on a single parameter when coming to a complicated situation. Only comprehensive consideration can help solve clinical problems.

Funding

This work was supported by grants from the Northern Jiangsu People's Hospital Foundation (Nos. yzucms 201919 and yzucms202001).

Conflicts of interest

None.

References

1. Carcillo JA, Sward K, Halstead ES, Telford R, Jimenez-Bacardi A, Shakoory B, *et al*. A Systemic Inflammation Mortality Risk Assessment Contingency Table for Severe Sepsis. Pediatr Crit Care Med 2017;18:143–150. doi: 10.1097/PCC.0000000000001029.
2. Williams V, Menon N, Bhatia P, Biswal M, Sreedharanunni S, Rawat A, *et al*. Serum ferritin predicts neither organ dysfunction nor mortality in pediatric sepsis due to tropical infections. Front Pediatr 2020;8:607673. doi: 10.3389/fped.2020.607673.
3. Bennett TD, Hayward KN, Farris RWD, Ringold S, Wallace CA, Brogan TV. Very high serum ferritin levels are associated with increased mortality and critical care in pediatric patients. Pediatr Crit Care Med 2011;12:e233–e236. doi: 10.1097/PCC.0b013e31820abca8.
4. Johnson AEW, Pollard TJ, Shen L, Lehman LWH, Feng M, Ghassemi M, *et al*. MIMIC-III, a freely accessible critical care database. Sci Data 2016;3:160035. doi: 10.1038/sdata.2016.35.
5. Horvat CM, Bell J, Kantawala S, Au AK, Clark RSB, Carcillo JA. C-reactive protein and ferritin are associated with organ dysfunction and mortality in hospitalized children. Clin Pediatr (Phila) 2019;58:752–760. doi: 10.1177/0009922819837352.

How to cite this article: Sang L, Teng W, Zhao M, Ding P, Xu X, Wang Y, Cao L. Association between serum ferritin and outcomes in critically ill patients: a retrospective analysis of a large intensive care unit database. Chin Med J 2022;135:2634–2636. doi: 10.1097/CM9.0000000000002019