

Hyperferritinemia is Associated with Thrombocytopenia and Increased Mortality Risk in Adult Sepsis Patients: A Retrospective Study of Two Observational Cohorts

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Abstract

Objective: Markedly elevated serum ferritin serves as a laboratory marker of macrophage activation syndrome and is associated with increased mortality in sepsis, where hyperinflammation, coagulopathy, and immune dysregulation interplay. Although laboratory studies suggest a relationship between hyperferritinemia and coagulopathy in sepsis, clinical evidence remains limited. This study aims to assess mortality risk and the interplay between hyperferritinemia (ferritin ≥ 500 ng/mL) and thrombocytopenia in two sequential cohorts of adult patients with sepsis. **Patients:** Patients with sepsis (≥ 18 years old) admitted to adult ICUs at Beth Israel Deaconess Medical Center between 2001 and 2008, and 2008 to 2019, with at least one ferritin value recorded within a 48-h window preceding or following the initial ICU admission. **Results:** Among 2339 eligible patients with hyperferritinemic sepsis, 921 (39.4%) were categorized into the high ferritin (HF) group (ferritin ≥ 500 ng/mL). Multivariate logistic regression analysis revealed a significant association between the HF group and increased in-hospital mortality ($p < .01$). Survival analysis revealed significantly lower survival probabilities at 28 and 90 days in the HF group compared to the low ferritin group. The interaction between the HF group and thrombocytopenia revealed a statistically significant association with in-hospital mortality. Furthermore, causal mediation analysis showed that platelet count mediated 12.6% (95% CI: 0.063-0.27; $p < .001$) of the effect of elevated ferritin levels on in-hospital mortality. **Conclusions:** Hyperferritinemia is associated with an increased mortality risk in adult septic patients. Thrombocytopenia not only interacts with hyperferritinemia but also serves as a mediating factor in its impact on mortality.

Keywords

sepsis, ferritin, hyperferritinemia, thrombocytopenia, macrophage activation syndrome

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Introduction

The intricate interplay between hyper-inflammation, dysregulated immunity, and coagulopathy in sepsis has long captivated the interest of both scientists and clinical practitioners. Given its heterogeneous clinical nature encompassing various phenotypes, optimizing treatment efficacy in sepsis hinges upon identifying distinct subtypes and promptly addressing treatable conditions through early interventions.¹ Serum ferritin, traditionally requested in laboratory test as a key marker for iron storage and homeostasis, is now recognized for its additional roles as an acute phase reactant and immunomodulator,

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supported by growing evidence.²⁻⁴ It also emerges as a potential indicator for distinguishing sepsis subtypes, proposing a practical addition to the sepsis laboratory panel.⁵ Ferritin is primarily secreted by macrophages in the liver, kidneys, spleen, and heart. *In vitro* studies² have revealed a ferritin-mediated positive feedback loop of inflammatory signals upon macrophage stimulation, potentially leading to cytokine storm in extreme cases. Clinical observations have indicated cytokine storm as the hallmark of severe sepsis, posing a significant risk of rapid mortality if not appropriately managed.⁶ The correlation between hyperferritinemia and disease severity, as well as increased mortality, was initially established in children,⁷⁻⁹ and later corroborated in adults.^{5,10,11} Research conducted in a pediatric intensive care unit (ICU) in 2007 was the first to report that patients with ferritin levels exceeding 500 ng/mL exhibited the highest mortality rates.⁹ In their study on adults, Schuster et al¹¹ also utilized a threshold of 500 ng/mL to delineate hyperferritinemia and identify sepsis or septic shock, liver disease, and hematological malignancy as crucial differential diagnoses for patients with non-hemophagocytic lymphohistiocytosis (HLH) hyperferritinemia. Lachmann et al⁵ conducted an analysis of 2623 critically ill adults with hyperferritinemia over a 12-year period, revealing a frequent occurrence of hyperferritinemia associated with a heightened risk of in-hospital mortality. Notably, extreme ferritin levels have been observed in patients with HLH, sepsis, and septic shock.

Considering the association between hyperferritinemia and hyperinflammation, coupled with established researches linking inflammatory responses to coagulopathy,^{2,12,13} alongside autopsy findings in hyperferritinemic patients with sepsis diagnosed with conditions such as macrophage activation syndrome (MAS),¹⁴ HLH¹⁵ or COVID-19¹⁶ revealing disseminated microvascular thromboses, question emerges regarding the potential interaction between hyperferritinemia and coagulopathy in septic patients. To answer this question, Bashir et al¹⁷ conducted an *in vitro* study by stimulating human umbilical vein endothelial cells (HUVEC) with a high concentration of ferritin, resulting in increased von Willebrand factor (vWF) secretion from HUVEC and a moderate suppression of ADAMTS-13 cleavage of vWF, which theoretically leads to a pro-coagulative state. These findings suggest that hyperferritinemia may play an active role in thrombosis by stimulating endothelial vWF secretion and reducing ADAMTS-13 activity. Informed by the preceding studies, we postulate that hyperferritinemia interacts with coagulopathy to influence mortality risk among adult patients with sepsis and verified this through exploration of the extensive Medical Information Mart for Intensive Care (MIMIC)-IV and MIMIC-III datasets, providing evidence from a clinical perspective.

Methods

Study Population

This retrospective observational cohort study included data from the Medical Information Mart for Intensive Care III

CareVue subset (originally 2001-2012; to avoid patient overlap with the following version, limited to 2001-2008, MIMIC-III_cv)¹⁸ and MIMIC-IV (2008-2019).¹⁹ These open online datasets comprise hospitalization information of approximately 30 000 and 310 000 patients admitted to the ICU of Beth Israel Deaconess Medical Center (BIDMC). The Institutional Review Board of the Beth Israel Deaconess Medical Center (2001-P-001699/14, Boston, MA) and Massachusetts Institute of Technology (No. 0403000206, Cambridge, MA) approved the data sharing initiative as all data were observational and de-identified and informed consent was waived. Author DZL obtained the requisite certification (certification number 11301870) and conducted data extraction. The inclusion criteria were as follows: (A) age $\geq$ 18 years; (B) patients meeting the Sepsis 3.0 criteria²⁰ in MIMIC-IV and the criteria outlined by Angus et al²¹ in MIMIC-III; (C) serum ferritin testing performed on the day of ICU admission or within one day before or after admission; and (D) for patients with multiple ICU admissions, only data from the initial admission were included in the analysis. The exclusion criteria were as follows: (A) age $<$ 18 years; (B) multiple ICU admissions for sepsis, with only data from the first admission included; (C) insufficient data, such as missing height measurements or respiration scores required for the Sequential Organ Failure Assessment (SOFA) score; and (D) a diagnosis of HLH, hemochromatosis, or malignancies, identified based on ICD-9 or ICD-10 codes in both datasets.

Clinical Variables and Outcomes

We stratified the study cohort into two distinct groups based on ferritin concentrations, employing a threshold of 500 ng/mL: a low-ferritin group (ferritin $<$ 500 ng/mL) and a high-ferritin group (ferritin $\geq$ 500 ng/mL), which is consistent with established practices.^{9,11} Additional variables included in our analysis comprised age, sex, race, weight, Acute Physiology Score (APSI), SOFA score, Model for End-stage Liver Disease (MELD) initial score, Elixhauser comorbidity score (in MIMIC-III_cv), Charlson comorbidity index (in MIMIC-IV), implementation of renal replacement therapy (RRT), and the status of sepsis-induced coagulopathy (SIC) and MAS. The SIC status was calculated according to the revised sepsis definition, incorporating the sum of four SOFA score components (respiratory, cardiovascular, hepatic, renal) alongside the stratified scoring for prothrombin time (PT) expressed as International Normalized Ratio (INR) and platelet count. A total score of 4 or more, with the additional scores of PT-INR and platelet exceeding 2, indicates SIC.²² The diagnosis of MAS was defined by platelet count $<$ 100 k/uL + INR $>$ 1.5 + ALT $>$ 100 u/L + bilirubin $>$ 1 mg/dL.^{3,14,23} Laboratory findings entailed ferritin levels, anion gap, hematocrit, hemoglobin, white blood cell (WBC), INR, PT, partial thromboplastin time (PTT), and platelet count (PLT). The primary outcome was in-hospital all-cause mortality, the secondary outcomes including 28-day mortality and 90-day mortality.

Statistical Analysis

Non-normally distributed variables were reported as medians with interquartile ranges (IQR) and compared using the Kruskal-Wallis rank-sum test. Categorical variables were presented as proportions (total number and percentage) and analyzed using either the χ^2 test or Fisher's exact test. Missing data, assumed to be randomly distributed, were imputed using multiple imputation with the mice package in R. To minimize covariate imbalances between groups, propensity score matching (PSM), a statistical technique used to reduce bias from confounding variables, was performed using 1:1 nearest neighbor matching with a caliper width of 0.05, implemented via the MatchIt package in R. Risk associations and interactions between ferritin levels, coagulation scores, and outcomes were assessed through multivariate logistic regression analysis across three models. Overall survival was estimated using the Kaplan-Meier method, with differences in survival curves assessed via the log-rank test. Subgroup analyses were visualized using the ggplot2 package in R. Causal mediation analysis (CMA) is a method for separating the total effect of a treatment into direct and indirect effects. The analysis reports consist of the average causal mediation effect (ACME), average direct effect (ADE), and total effect, which was performed using the mediation package in R. This study adheres to the STROBE guidelines. All statistical analyses were two-sided and performed using R software (version 4.3.3.) A p-value of <.05 was considered statistically significant.

Results

Study Enrollment and Baseline Characteristics

We analyzed data from 2339 septic patients with available ferritin records comprising 681 patients from MIMIC-III_cv and 1658 from MIMIC-IV. A detailed flowchart outlining the study's inclusion and exclusion criteria is presented in Figure 1. The baseline characteristics and outcomes of patients from both datasets are summarized in Table 1. Based on prior research,^{9,11} patients were stratified into a low ferritin (LF, ferritin levels <500 ng/mL) group and a high ferritin (HF, ferritin levels $\geq$ 500 ng/mL) group. Age was categorized as <65 or $\geq$ 65 years, with the distributions of ferritin levels and age illustrated in eFigures 1 and 2. Missing data are detailed in eTable 1. In both cohorts, patients under 65 years of age were more common in the HF group, whereas those aged $\geq$ 65 years were more prevalent in the LF group. Male patients slightly outnumbered females in both cohorts, with males predominating in the HF group. The median ferritin levels were 173 ng/mL and 161 ng/mL in the LF group and 1001 ng/mL and 1255 ng/mL in the HF group for MIMIC-III_cv and MIMIC-IV, respectively. Significant differences were observed between the HF and LF groups across key parameters, including APACHE II score, SOFA score, MELD initial score, Charlson comorbidity index, proportion of patients receiving RRT, maximum anion gap, and WBC levels on the first ICU Day. Among hyperferritinemic septic patients, 258 (37.9%) in MIMIC-III_cv and 663 (40.0%) in MIMIC-IV, a significantly higher proportion of the

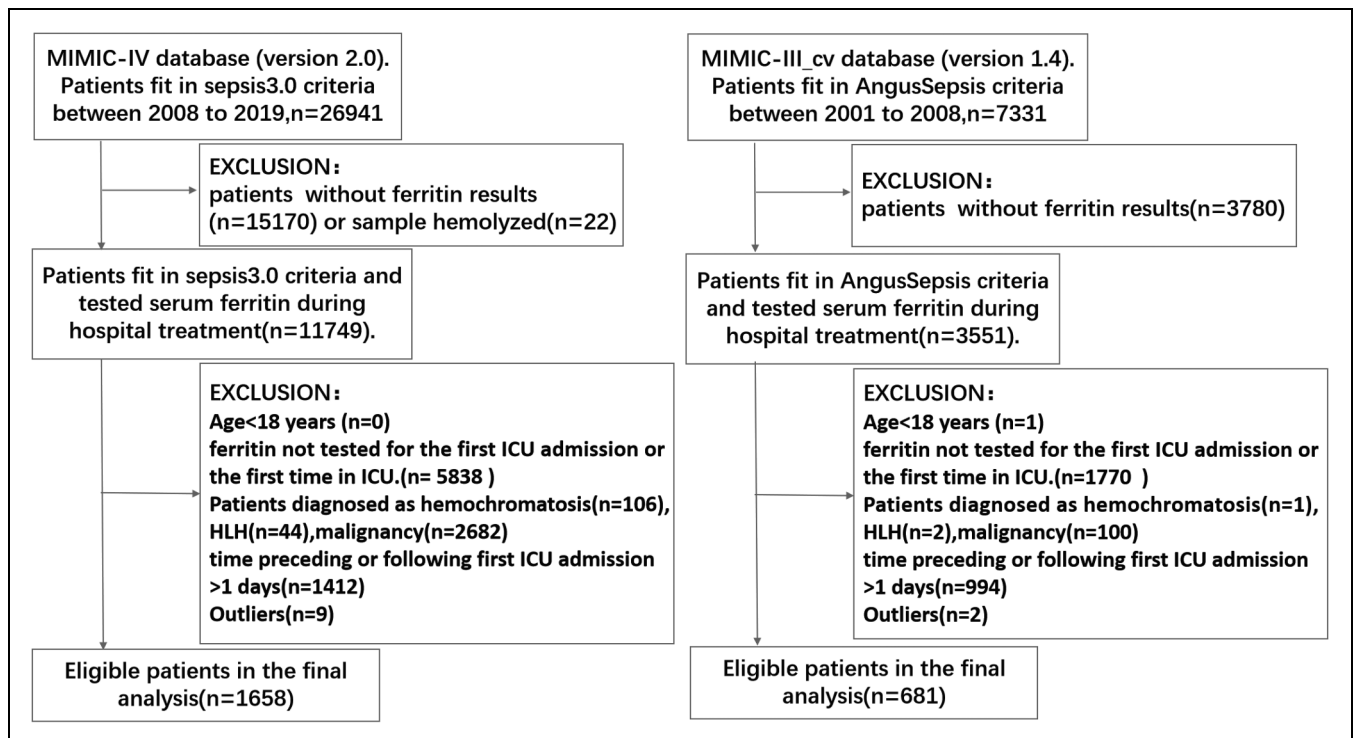


Figure 1. Inclusion and exclusion flowchart of the study. Abbreviations: MIMIC-III_cv, Medical Information Mart for Intensive Care III CareVue subset; MIMIC-IV, Medical Information Mart for Intensive Care IV; HLH, hemophagocytic lymphohistiocytosis.

Table 1. Baseline Characteristics and Outcomes of Patients from the MIMIC-III_cv and MIMIC-IV Datasets.

Characteristic	MIMIC-III_cv		p-value ^b	MIMIC-IV		p-value ^b
	LF ^a , N = 423	HF ^a , N = 258		LF ^a , N = 995	HF ^a , N = 663	
Age(year)			.027			<.001
<65	178 (42.1%)	131 (50.8%)		463 (46.5%)	377 (56.9%)	
≥65	245 (57.9%)	127 (49.2%)		532 (53.5%)	286 (43.1%)	
Gender			<.001			.001
Male	195 (46.1%)	154 (59.7%)		479 (48.1%)	372 (56.1%)	
Female	228 (53.9%)	104 (40.3%)		516 (51.9%)	291 (43.9%)	
Race			.025			.058
White	315 (74.5%)	172 (66.7%)		639 (64.2%)	400 (60.3%)	
Black	55 (13.0%)	38 (14.7%)		123 (12.4%)	70 (10.6%)	
Asian	5 (1.2%)	11 (4.3%)		26 (2.6%)	18 (2.7%)	
Others	48 (11.3%)	37 (14.3%)		207 (20.8%)	175 (26.4%)	
Weight (kg)	77 (64, 90)	77 (63, 92)	.716	76 (64, 92)	80 (68, 95)	<.001
APSIII	46 (36, 58)	55 (42, 67)	<.001	48 (38, 63)	60 (45, 87)	<.001
SOFA	4.0 (2.0, 6.0)	6.0 (3.0, 8.0)	<.001	5.0 (3.0, 8.0)	7.0 (5.0, 12.0)	<.001
CNS	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	.418	1.0 (0.0, 2.0)	1.0 (0.0, 3.0)	.006
Cardiovascular	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	.608	1.0 (1.0, 2.0)	1.0 (1.0, 3.0)	<.001
Liver	0.0 (0.0, 0.0)	0.0 (0.0, 2.0)	<.001	0.0 (0.0, 0.0)	0.0 (0.0, 2.0)	<.001
Renal	1.0 (0.0, 2.0)	1.0 (0.0, 3.0)	<.001	1.0 (0.0, 2.0)	1.0 (0.0, 3.0)	<.001
Coagulation	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	.001	0.0 (0.0, 1.0)	1.0 (0.0, 2.0)	<.001
MELD initial	10 (10, 20)	20 (10, 20)	<.001	14 (9, 22)	21 (13, 28)	<.001
RRT	21 (5.0%)	41 (15.9%)	<.001	48 (4.8%)	109 (16.4%)	<.001
CCI				6.0 (4.0, 8.0)	5.0 (3.0, 7.0)	<.001
ECS	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	.109			
Chronic pulmonary disease	6 (1.4%)	0 (0.0%)		319 (32.1%)	159 (24.0%)	<.001
Congestive heart failure	3 (0.7%)	1 (0.4%)		436 (43.8%)	196 (29.6%)	<.001
Liver disease	5 (1.2%)	0 (0.0%)		227 (22.8%)	259 (39.1%)	<.001
Renal disease				282 (28.3%)	171 (25.8%)	.254
Peripheral vascular disease	1 (0.2%)	0 (0.0%)		111 (11.2%)	73 (11.0%)	.927
Rheumatic disease				33 (3.3%)	34 (5.1%)	.066
Diabetes	1 (0.2%)	2 (0.8%)		342 (34.4%)	168 (25.3%)	<.001
Paraplegia				30 (3.0%)	15 (2.3%)	.356
Ferritin (ng/mL)	173 (92, 293)	1001 (698, 1673)	<.001	161 (69, 281)	1255 (750, 2262)	<.001
Aniongap (mEq/L)	16.0 (13.0, 19.0)	17.0 (14.0, 21.0)	<.001	16.0 (14.0, 20.0)	19.0 (15.0, 23.0)	<.001
Hematocrit (%)	31.5 (28.8, 35.0)	30.2 (28.2, 33.9)	.002	30.5 (27.1, 35.1)	30.3 (26.7, 35.4)	.338
Hemoglobin (g/dl)	9.30 (8.25, 10.40)	9.10 (8.00, 9.80)	.008	8.60 (7.35, 10.20)	8.70 (7.40, 10.30)	.522
WBC (k/uL)	11 (8, 16)	13 (9, 20)	<.001	12 (8, 16)	13 (9, 18)	.007
Platelets (k/uL)	201 (143, 277)	195 (105, 300)	.287	182 (118, 254)	144 (79, 218)	<.001
INR (iu)	1.40 (1.20, 1.89)	1.50 (1.20, 1.89)	.141	1.40 (1.20, 2.00)	1.60 (1.20, 2.30)	<.001
PT (s)	15 (14, 18)	16 (14, 18)	.088	15 (13, 22)	17 (14, 25)	<.001
PTT (s)	35 (29, 45)	36 (30, 45)	.343	34 (29, 46)	37 (30, 51)	.003
SIC	191 (50.7%)	146 (56.6%)	.011	446 (44.8%)	405 (61.1%)	<.001
MAS	3 (0.7%)	19 (7.4%)	<.001	18 (1.8%)	71 (10.7%)	<.001
LOS hospital (day)	8 (5, 16)	9 (6, 18)	.014	8 (5, 14)	10 (5, 18)	<.001
LOS ICU (day)	3 (2, 7)	3 (2, 7)	.268	2.5 (1.5, 4.9)	3.4 (1.7, 7.1)	<.001
In-hospital mortality	51 (12.1%)	56 (21.7%)	<.001	109 (11.0%)	171 (25.8%)	<.001
28-day mortality	67 (15.8%)	64 (24.8%)	.004	138 (13.9%)	183 (27.6%)	<.001
90-day mortality	108 (25.5%)	87 (33.7%)	.022	214 (21.5%)	239 (36.0%)	<.001

Abbreviations: MIMIC-III_cv, Medical Information Mart for Intensive Care III CareVue subset; MIMIC-IV, Medical Information Mart for Intensive Care IV; LF, low ferritin group; HF, high ferritin group; APSIII, Acute Physiology Score III; SOFA, Sequential Organ Failure Assessment; MELD, model for end-stage liver disease; RRT, renal replacement therapy; CCI, Charlson comorbidity index; ECS, Elixhauser comorbidity score; WBC, white blood cell; INR, international normalised ratio; PT, prothrombin time; PTT, partial thromboplastin time; SIC, sepsis induced coagulopathy; MAS, macrophage activation syndrome; LOS, length of stay.

^an (%).

^bPearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test.

HF group in both cohorts met the diagnostic criteria for SIC and MAS (7.4% in MIMIC-III_cv vs 10.7% in MIMIC-IV, p <.05). In terms of outcomes, patients in the HF group in

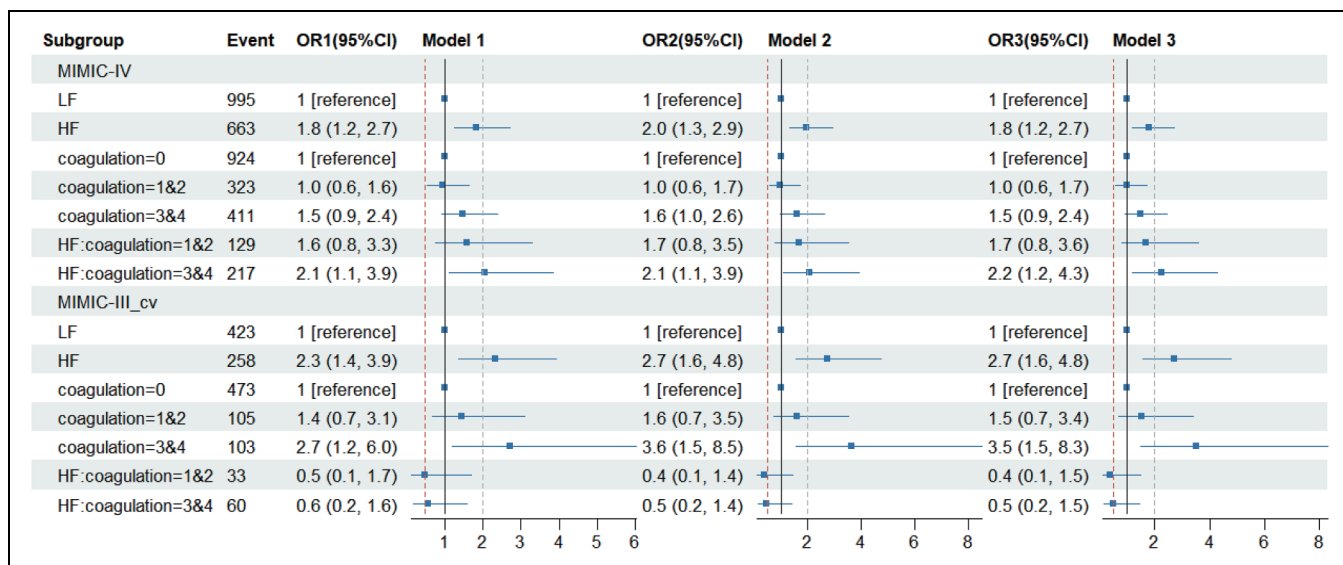


Figure 2. Associations and interacting effects of ferritin group and coagulation score with in-hospital mortality. Model 1: Unadjusted; Model 2: Adjusted for age (age group in MIMIC-III_cv), sex, weight, race; Model 3: Adjusted for Model 2 plus Charlson comorbidity index (MIMIC-IV) or Elixhauser vanwalraven score (MIMIC-III_cv), RRT; LF: low ferritin group; HF: high ferritin group.

MIMIC-IV experienced longer hospital stays (10 vs 8 days, $p < .001$), longer ICU stays (3.4 vs 2.5 days, $p < .001$), and higher in-hospital mortality (171 [25.8%] vs 109 [11%], $p < .001$), 28-day mortality (183 [27.6%] vs 138 [13.9%], $p < .001$), and 90-day mortality (239 [36.0%] vs 214 [21.5%], $p < .001$). These findings were consistent after PSM (eTable 2). Similarly, in MIMIC-III_cv, the HF group demonstrated worse major outcomes after PSM (eTable 2).

Risk Association and Interaction Analysis of Ferritin Levels and Thrombocytopenia with Outcome

To explore the association between ferritin levels and clinical outcomes, as well as the interaction between ferritin levels and thrombocytopenia, we performed multivariate logistic regression analysis on stratified groups of ferritin levels (LF and HF) and coagulation scores. The coagulation score, a subset of the SOFA score,²⁴ was based on platelet count and categorized into three groups: 0 (PLT ≥ 150 k/uL), 1 and 2 (50 k/uL $<$ PLT < 150 k/uL), and 3 and 4 (PLT ≤ 50 k/uL). We employed three analytical models, incorporating variables identified through univariate logistic regression analysis (eTable 3) and clinically significant factors. Model 1 included ferritin and coagulation group variables without adjustment. Model 2 adjusted for age, sex, weight, and race. Model 3 further adjusted for comorbidity scores (Elixhauser comorbidity score in MIMIC-III_cv and Charlson comorbidity index in MIMIC-IV) and RRT use. Hyperferritinemia (HF group) was significantly associated with higher in-hospital mortality rates across all models in both datasets ($p < .01$; Figure 2 and eTable 4). Similar associations were observed for 28-day and 90-day mortality rates in MIMIC-IV ($p < .05$; eTable 5). To investigate the interaction between hyperferritinemia and

thrombocytopenia, the same three models were evaluated. Across all models in MIMIC-IV, there was a statistically significant multiplicative interaction between the HF group and the coagulation score 3 and 4 group, with odds ratios (95% CI) of 2.068 (1.109-3.857), $p = .022$; 2.075 (1.100-3.917), $p = .024$; and 2.243 (1.178-4.271), $p = .014$, respectively. (Figure 2 and eTable 4). Additionally, Model 3 demonstrated a statistically significant interaction effect between hyperferritinemia and coagulation groups 1 and 2 on 28-day and 90-day mortality among septic patients in the MIMIC-IV dataset (eTable 5). However, data from the MIMIC-III_cv dataset did not yield statistically significant results.

Survival and Subgroup Analysis

The Kaplan-Meier (KM) survival curves revealed significantly lower survival probabilities at 28 and 90 days in the HF group compared to the LF group in both MIMIC-III_cv and MIMIC-IV cohorts. The log-rank test further confirmed more pronounced differences in survival in MIMIC-IV (Figure 3). Additionally, Figure 4 presents a detailed analysis of the stratified and interaction effects of variables with the ferritin groups, identifying significant associations between in-hospital mortality and factors such as age, sex, PLT, INR, SIC, RRT, chronic pulmonary disease, congestive heart disease, liver disease, renal disease, peripheral vascular disease, diabetes, and paraplegia. Notably, significant interactions were observed between the HF group and younger age ($p = .031$), liver disease ($p = .017$), renal disease ($p = .025$), and PLT < 100 k/uL ($p = .044$).

Causal Mediation Analysis

To further elucidate the relationship between ferritin and thrombocytopenia, we conducted Causal Mediation Analysis (CMA),

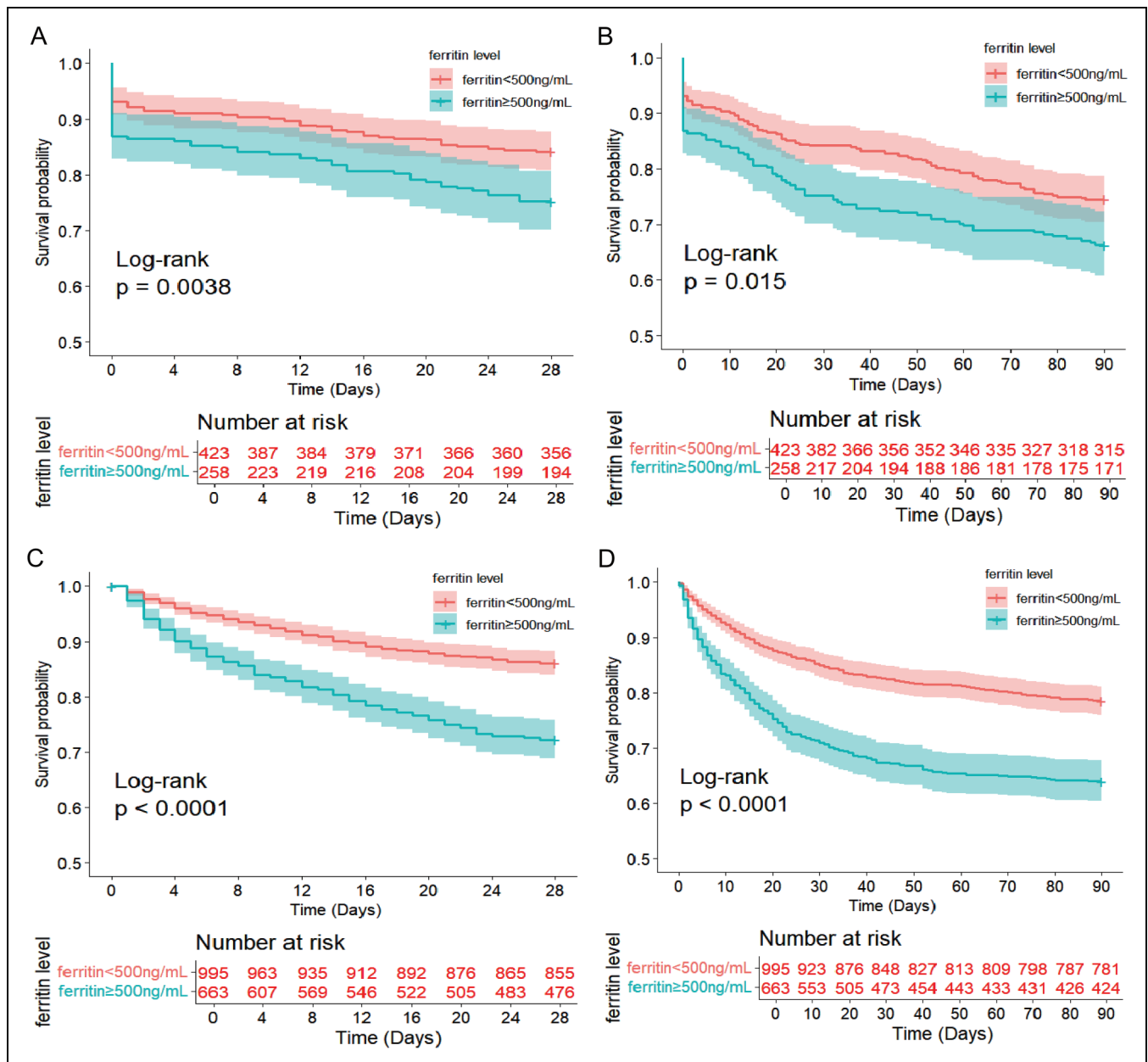


Figure 3. Survival analysis of ferritin group on 28 days and 90 days mortality risk in the MIMIC-III_cv and MIMIC-IV datasets. A: Survival analysis of ferritin group on 28 days mortality risk in the MIMIC-III_cv dataset. B: Survival analysis of ferritin group on 90 days mortality risk in the MIMIC-III_cv dataset. C: Survival analysis of ferritin group on 28 days mortality risk in the MIMIC-IV dataset. D: Survival analysis of ferritin group on 90 days mortality risk in the MIMIC-IV dataset.

as illustrated in Figure 5 and eTable 6. In MIMIC-IV, PLT was found to play a mediating role in the risk associated with ferritin levels in in-hospital mortality. Two models were examined: Model 1, without adjustment, revealed that the association between elevated serum ferritin and in-hospital mortality risk mediated by PLT was 15.6% (95% CI: 0.079-0.300, $p < .001$), with the average causal mediation effect (ACME) also significant ($p < .001$) (Figures 5A and B). Model 2 adjusted for age, sex, race, weight, Charlson comorbidity index, and RRT usage, showed that PLT mediated 12.6% (95% CI: 0.063-0.270; $p < .001$) of the association between elevated

serum ferritin and in-hospital mortality risk, with the ACME remaining significant ($p < .001$) (Figure 5C and D). However, in MIMIC-III_cv, no statistically significant results were observed.

Discussion

Despite advances in understanding the intertwined relationship between hyperinflammation, coagulopathy, and immune dysregulation in sepsis, overall mortality rates have not significantly improved. One notable breakthrough, derived from a post hoc

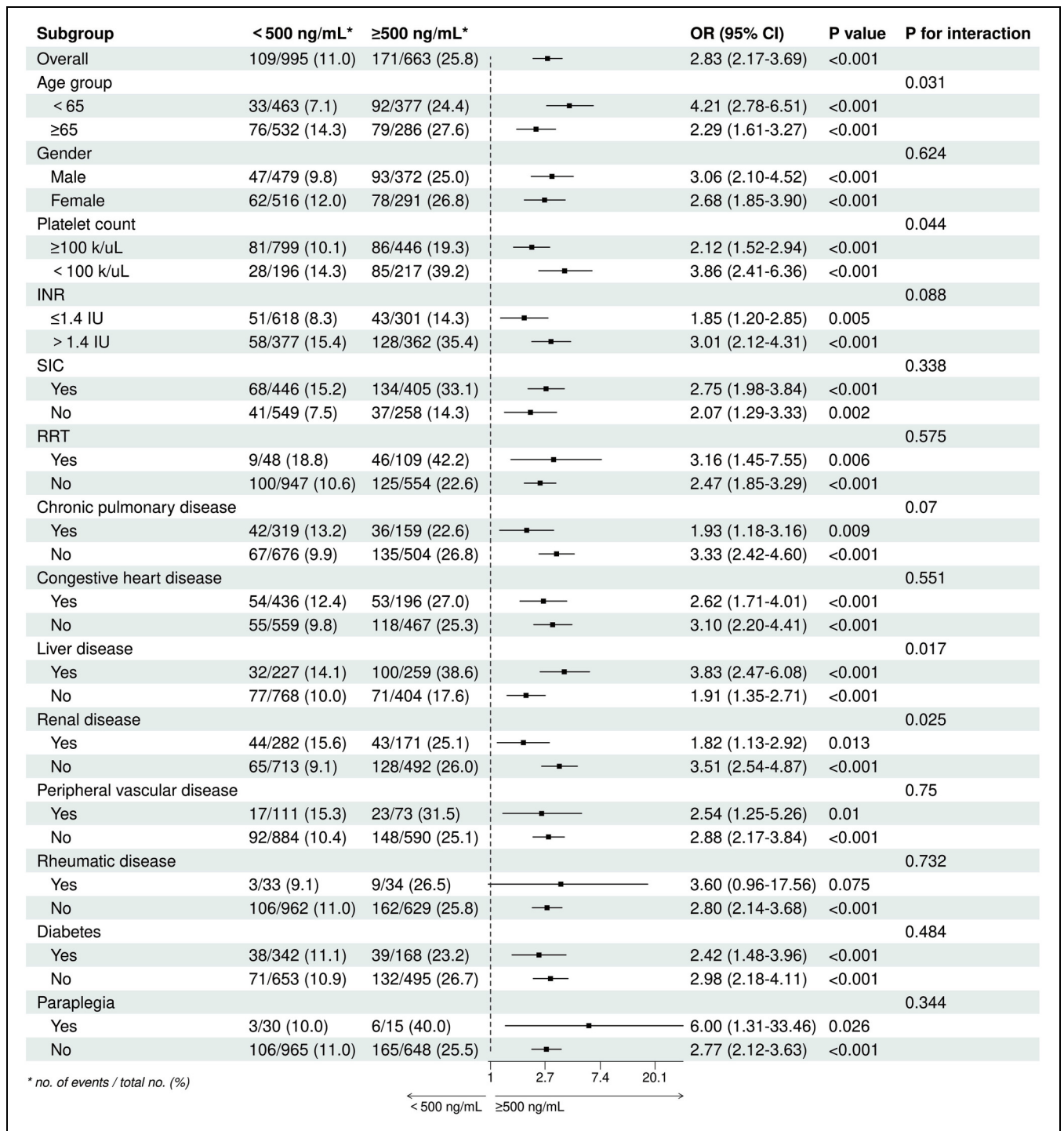


Figure 4. Subgroup analysis of ferritin group with different variables. Abbreviations: INR, international normalised ratio; SIC, sepsis induced coagulopathy; RRT, renal replacement therapy.

analysis, is the identification of the interleukin-1 receptor antagonist anakinra, which has demonstrated substantial benefits in septic patients with macrophage activation-like syndrome (MALS).²³ MALS is a clinically pragmatic alternative to MAS, which is also known as hemophagocytic lymphohistiocytosis (HLH), manifested with extreme elevation of serum ferritin, along with comprehensive evaluation of clinical,

laboratory, and histological findings that facilitated rapid progression to death in septic patients.²⁵ However, timely initiation of therapy is often delayed due to challenges in establishing a diagnosis of MAS in the ICU. Bone marrow biopsy as the gold-standard diagnostic procedure, is difficult to perform at the bedside in every critically ill patients, and specialized tests, such as soluble IL-2R α levels and NK cell functional assays,

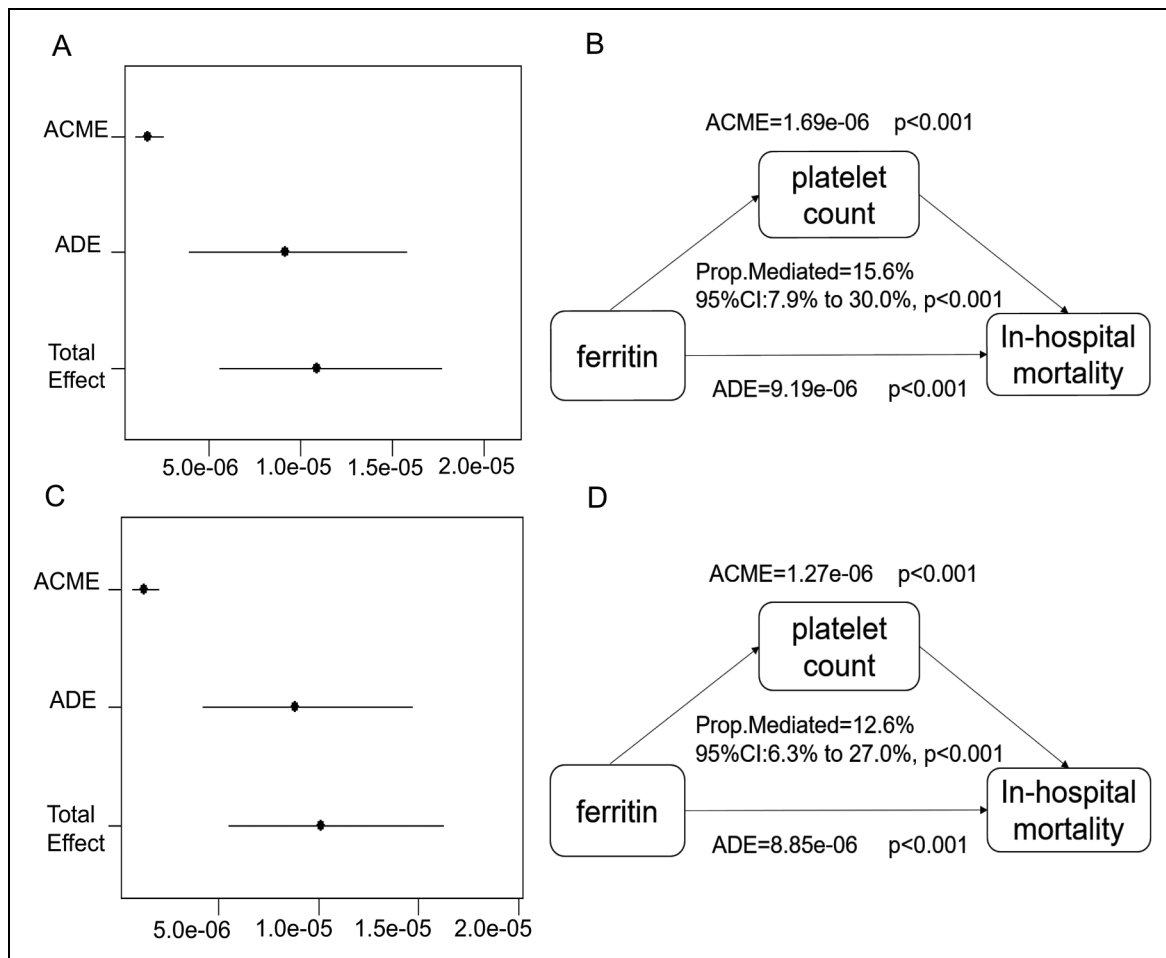


Figure 5. The causal mediation analysis of ferritin and platelet on in-hospital mortality in the MIMIC-IV dataset. A and B: model1 without adjustment; C and D: model2 incorporated adjustments for age, sex, weight, and race.

may not be readily available. Thus, serum ferritin level as a timely and practical diagnostic and monitoring tool is of crucial help in stratification of septic patients with MALS for targeted management. Kyriazopoulou et al¹⁴ reported a 3%-4% prevalence of MALS in septic patients, with a high early mortality rate. Our analysis of hyperferritinemic septic patients in the MIMIC-III and MIMIC-IV databases demonstrated a higher prevalence of MALS (7.4% and 10.7%, respectively). Multivariate logistic regression and survival analyses revealed significant associations between hyperferritinemia and increased in-hospital, 28-day, and 90-day mortality. In our study, patients diagnosed with HLH, hemochromatosis, or malignancies were excluded, as malignancy accounts for approximately 50% of HLH/MAS cases in adults,²⁶ and hemochromatosis has distinct mechanisms regarding hyperferritinemia. We focused on adult septic patients with serum ferritin measurements but no HLH diagnosis, aiming to explore the unique characteristics of this subset of septic patients that seldomly targeted before.

Coagulopathy is a recognized feature of MALS and is part of its diagnostic criteria, yet its etiology remains poorly understood.²⁷ In septic patients with MALS phenotypes, mechanisms

of coagulopathy maybe even more complicated. One *in vitro* study¹⁷ demonstrated that a high concentration of ferritin promotes thrombosis by facilitating von Willebrand factor (vWF) secretion and decreasing ADAMTS-13 activity. This observation and other previous studies inspired our investigation into the clinical associations between hyperferritinemia and coagulopathy. Since platelet count (PLT) is crucial in the pathology of sepsis²⁸ and plays an important part in coagulopathy, therefore, we specifically investigated the associations between hyperferritinemia and thrombocytopenia, and utilized PLT as a continuous variable and the coagulation score, which is based on PLT, as categorical variable in the mediation and interaction analyses, respectively, employing the MIMIC-III_cv and MIMIC-IV datasets. The results demonstrated a 12.6% mediation effect in the adjusted model for MIMIC-IV, and a positive multiplicative interaction effect, highlighting the increased mortality risk of hyperferritinemia attributable to decreased PLT. Previous cellular studies have shown that extreme hyperferritinemia results from macrophage overactivation and reduced apoptosis, leading to a pro-inflammatory cytokine storm. Cytokines such as interleukin(IL)-1- β , IL-6, IL-18, and interferon- γ exacerbate endothelial injury and contribute to

coagulopathy.^{2,14,29,30} Brands et al³¹ demonstrated that not only strongly elevated ferritin levels (>4420 ng/ml) as seen in MAS, but also mildly elevated ferritin levels (>250 ng/ml) were associated with endothelial injury and glycocalyx disruption in critically ill patients with community-acquired pneumonia. Additionally, this study demonstrated a link between hyperferritinemia and decreased PLT as well as increased D-dimer levels. Consistent with this, we observed decreased PLT alongside increased INR, PT, and PTT in septic patients with hyperferritinemia. However, D-dimer was not analyzed due to excessive missing data. Given the multifaceted nature of coagulopathy and the lack of consensus on the associations between ferritin levels, sepsis severity, and progression, further meticulously designed prospective studies are warranted. Our subgroup analysis identified statistically significant interactions between hyperferritinemia and underlying liver or renal disease, suggesting potential avenues for further investigation. Additionally, evaluating whether serum ferritin levels can serve as markers for treatment response to anakinra is an area of interest.

The rationale for treating MIMIC-III_cv and MIMIC-IV as distinct cohorts stems from differences in the definition of sepsis between the two datasets, which reflect the evolving understanding of sepsis. Additionally, the recording of ferritin levels at extreme values was more precise in MIMIC-IV (eg, ferritin levels above 1000 ng/mL were recorded as '>1000 ng/mL' in MIMIC-III_cv, but as exact measurements in MIMIC-IV), providing more detailed data for analysis. Combined with the larger sample size in MIMIC-IV, these factors help explain the positive interaction and mediation effects observed in the MIMIC-IV cohort, as well as the inconsistent findings in the MIMIC-III_cv cohort. Additionally, these results underscore the importance of accurately measuring serum ferritin, particularly at extreme values, to better illuminate underlying pathologies and enhance statistical power in data analysis. Unfortunately, due to resource limitations, many hospitals, including ours, do not provide precise measurements at these extreme levels, which may partially explain the under recognized diagnostic potential of hyperferritinemia in septic patients.

Limitations

As it is beyond the scope of retrospective observational studies to illustrate the causality of associations, our study provides evidence suggesting an increased risk of mortality of early hyperferritinemia and potential association between hyperferritinemia and coagulopathy in adult patients with sepsis, leveraging the largest and meticulously designed ICU database known to us. The available data fall short in providing closely related variables, such as D-dimer, C-reactive protein, transferrin, fibrinogen, IL-6, soluble CD163, ADAMTS-13 and so on, limits the comprehensiveness of our analysis. We also did not evaluate the influence of transfusions, hemodialysis, or extracorporeal life support, although a prior study suggested these

interventions minimally affect ferritin levels over an interval exceeding 14 days between two ICU ferritin measurements.³²

Conclusions

Hyperferritinemia correlates with an increased mortality risk among adult patients with sepsis and is associated with thrombocytopenia. It is practical and necessary to integrate serum ferritin levels into the routine monitoring panel for sepsis. Additionally, a more proactive approach to managing thrombocytopenia in patients with hyperferritinemic sepsis is needed.

List of abbreviations

HF	group high ferritin group
PSM	propensity score matching
MIMIC	Medical Information Mart for Intensive Care
MAS	macrophage activation syndrome
ICU	intensive care unit
HLH	hemophagocytic lymphohistiocytosis
HUVEC	human umbilical vein endothelial cells
vWF	von Willebrand factor
BIDMC	Beth Israel Deaconess Medical Center
SOFA	Sequential Organ Failure Assessment
APSIII	Acute Physiology Score
MELD	Model for End-stage Liver Disease
RRT	renal replacement therapy
SIC	sepsis-induced coagulopathy
INR	international normalization ratio
WBC	white blood cell
PT	prothrombin time
PTT	partial thromboplastin time
PLT	platelet count
LOS-ICU	length of ICU stay
LOS-hospital	length of hospital stay
LF	low ferritin
HF	high ferritin

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available in the PhysioNet repository, <https://physionet.org/content/mimiciv/2.0/>.

Credit Authorship Contribution Statement

All authors contributed to writing and editing the manuscript. DZL, XQL, and BW collaborated on the data extraction, visualization, and analysis. DZL wrote the first draft. DZL, XQL, BW, BLL and WY interpreted and validated results. DZL, YZ and JL designed the study. YZ and JL supervised this work.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The MIMIC dataset is publicly available and open access to all researchers with acquisition licenses. The Institutional Review Board of the Beth Israel Deaconess Medical Center (2001-P-001699/14, Boston, MA) and Massachusetts Institute of Technology (No. 0403000206, Cambridge, MA) approved the data sharing initiative as all data were observational and de-identified and informed consent was waived.

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Supplemental Material

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