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HYPERFERRITINEMIA IN CRITICALLY ILL PATIENTS – A SINGLE CENTER STUDY

Dr. Mariam Ikram[1]*, Dr. Danyal Ahmed Ghani[2], Dr. Ayaz Mir[3], Dr. Muhammad Rehan Javed[4], Dr. Tariq Satti[5], Dr. Ayesha Iftikhar[6]

[1] MBBS, Resident, Department of Clinical Hematology, Shifa International Hospital, Islamabad, Pakistan. Email ID: mariamikram92@gmail.com
[2] MBBS, FCPS Medicine, FCPS Clinical Hematology, Consultant, Department of Clinical Hematology, Shifa International Hospital, Islamabad, Pakistan.Email ID: danyal.ahmad.ghani@gmail.com
[3]* MBBS, FACP, Consultant Hematologist/Oncologist, Department of Clinical Hematology, Shifa International Hospital, Islamabad, Pakistan. Email ID: Pakistanbmt@gmail.com
[4] MBBS, Medical Officer, Department of General Surgery, Shifa International Hospital, Faisalabad, Pakistan. Email ID: m.rehanjaved23399@gmail.com
[5] MBBS, FCPS Hematology, Consultant, Department of Clinical Hematology, Shifa International Hospital, Islamabad, Pakistan. Email ID: tariq.mahmood@shifa.com.pk
[6] MBBS, FCPS Clinical Hematology, Consultant, Department of Clinical Hematology, Shifa International Hospital, Islamabad, Pakistan. Email ID: dr.ayesha.sih@gmail.com
Corresponding Author: Dr. Mariam Ikram - Email: mariamikram92@gmail.com

ABSTRACT

Objective: Our research is an evaluation of ferritin concentrations to distinguish between hemophagocytic lymphohistiocytosis and other causes of hyperferritinemia in a mixed group of critically ill individual's adverse outcomes in the critical-care setting.

Study Design and Setting: This was a Retrospective observational done in the Intensive Care Units (ICUs) of Shifa International Hospital, Islamabad, from October 2025 to January 2026.

Methodology: Non-probability consecutive sampling was used to enroll 150 critically ill patients. Hyperferritinemia was defined to be serum ferritin of 500 ng/mL and above. The association of high serum ferritin levels with derangement in key laboratory parameters, organ dysfunction scores, and major clinical outcomes was determined using the Chi-square test or Fisher exact test between categorical variables, as applicable, and *p* was determined to be statistically significant if value ≤0.05.

Results: 150 critically ill patients with hyperferritinemia were studied (mean age 54.2 +16.8 years). Patients with ferritin >2000 ng/mL had significantly higher CRP (138.7 ± 61.2 vs 104.3 ± 49.6 mg/L; p = 0.01). They also required more frequent mechanical ventilation (82.9% vs 65.0%; p = 0.01), had longer ICU stays (median 12 vs 9 days; p = 0.03), and higher 30-day mortality (45.7% vs 28.8%; p = 0.02). The diagnosis of hemophagocytic lymphohistiocytosis (HLH) occurred in 12.0% of the patients, and carried a higher mortality rate than non-HLH (61.1 vs 33.3; p = 0.02).

Conclusion: Marked hyperferritinemia (>2000 ng/mL) is a robust independent predictor of extreme systemic inflammation, dysfunction of multiple organs, and elevated mortality in critically ill patients.

KEYWORDS: Critical Illness; Hyperferritinemia; Hemophagocytic Lymphohistiocytosis; Intensive Care Units.

INTRODUCTION

Hyperferritinemia is a well-known biomarker for critically ill patients, and while it correlates to iron stores and metabolism, it also reflects systemic inflammation and immune dysregulation. Ferritin is an intracellular iron sequestering protein that promotes iron homeostasis by trapping iron in a non-toxic and bioavailable form. [1] In addition to its classical role, ferritin acts as an important acute-phase reactant, whose synthesis is upregulated in response to pro-inflammatory cytokines and notably interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). In systemic inflammatory states, macrophage activation enhances the production of ferritin, whereas accompanying cellular injury and instability of cellular membrane allows for passive leakage of intracellular ferritin to enter the circulation leading to greatly increased serum levels of this protein. [1]

Rather than being simply a passive biomarker, ferritin has an active role in the body's defenses. Emerging evidence shows that it can become involved in more than one way, acting both to modulate the immune response and take part in inflammatory cascades. [2] Activated macrophages and monocytes, especially those in the reticuloendothelial system, are responsible for huge amounts of ferritin production during excessively inflammatory states. Furthermore, with cytokine-induced iron withholding, even the normal reserves of iron are lost, which makes it almost impossible for the metabolism and immune status of patients critically unwell to recover. These are the reasons why in ICU settings ferritin levels are often better correlated with how sick a person really is than they are with his or her actual iron content. [1]

One of the most serious hyperinflammatory syndromes is hemophagocytic lymphohistiocytosis (HLH). It is the result of excessive immune activation and inability of cytotoxic. It is this state of defective natural killer (NK) cell function and T cell (cytotoxic) activity that cause uncontrolled activation in macrophages so a vicious circle begins or continues with recurrently increasing cytokine production (a thunderstorm). [2] This hyperketonemia followed by widespread hemophagocytosis, multiple organ failure, and fast decline of the patient's clinical condition if not diagnosed and treated promptly.

The high levels of ferritin in typical HLH cases usually exceed 5,000 ng/mL and in serious ones may go as high as to provide strong support for diagnosis. True, hyperferritinemia by itself does not provide a clear-cut diagnosis but is as much a pointer of what future will hold as anything so far seen. It reflects not just how serious the immune system is seriously malfunctioning but also the overall burden of inflammation that it produces. [3] However, high ferritin alone does not mean that there is a definite diagnosis. Which way depends on factors such as the clinical picture and other laboratory findings like triglycerides, fibrinogen levels, cytopenia (abnormalities of blood cells), and soluble CD25 (a cytokine receptor molecule) concentrations.

While it is often closely connected with HLH, hyperferritinemia is not uniquely representative of this disease and instead can be found in a wide variety of critical illnesses. Such complications represent major causes, with sepsis and severe infections in particular triggering over-exuberant host immune responses and the release of pathogen-associated molecular patterns. Both factors combine to produce large amounts of cytokines together with elevated ferritin levels. [4] In such cases, higher levels of ferritin were associated significantly with poorer clinical outcomes: higher mortality rates and a greater degree as well worse results by the scoring system used to quantify organ failure in patients with severe diseases. [4] For example, often people with cancer have elevated levels of ferritin and many of them visit the ICU. In general, it can be said that hyperferritinemia common in malignancy is an expression of tumour-triggered inflammation, the rapid turnover cells in solid tumours or, occasionally, direct release by malignant cells themselves. With all these physiological burdens placed upon their body, patients also carry a heavy systemic inflammatory load and there is an increased association ($p=0.01$) between increased levels of ferritin in serum and poorer prognosis of the disease. [5]

When liver function is impaired, excess ferritin is often produced within the liver, because hepatocytes play an important role in taking part metabolizing iron and clearing away ferritin. Hepatocyte injury, such as that induced by viral hepatitis, medication or ischemic hepatitis, results in ferritin entering the blood as a result of intracellular leakage. Problems with the synthesis and regulation by the liver of various iron-related proteins serve to exacerbate the disarray in ferritin levels, which makes it especially hard to understand the results amongst people also suffering from liver pathology. [6] Perpetual immune activation and chronic inflammatory signaling pathways also account for high levels of ferritin in autoimmune or rheumatologic disease. For example, conditions such as systemic lupus erythematosus and adult Still's disease are particularly associated with increased ferritin production reflecting the up-regulation of cytokine-mediated inflammation in this disorder. In these conditions, ferritin levels may also correlate with disease activity as they rise and fall, further complicating a differential diagnosis in sick patients. [7]

Moreover, surgical stress, trauma, and massive blood transfusion have been identified as important non-infectious causes of hyperferritinemia. In such cases, tissue injury may be aggravated and the risk of intravascular hemolysis increases. Additionally, transfusion-related iron loading also may raise levels temporarily or permanently at some point in its life span. It is unclear whether these are reactive or responsive components, but one thing is certain – the concept that ferritin is a marker of whole-body stress and not a particular disease is an oversimplification. [8]

From the potentially massive range of etiologies for hyperferritinemia, there emerges a major diagnostic challenge in the ICU. Clinical presentations here may be faced with septic shock, HLH (hemophagocytic lymphohistiocytosis), malignancy and people with multiple organ dysfunction. This mix can muddle the primary disease process and when ferritin is considered in isolation, lead to diagnostic ambiguity. [9] Thus, there is a danger that patients suffering from other inflammatory conditions might be incorrectly diagnosed as having HLH, leading to misguided treatment with immunosuppressive therapy which worsens infectious or malignant disorder.

The key problem now recognized widely in the field of Intensive Care Medicine is "hyperferritinemia", but there are few data on precisely how this occurs and what proportion of hospital patients developing HLH have it. [10] The diversity of underlying causes highlights the importance of systematic investigation in order to improve diagnostic accuracy and help select appropriate therapy. Accurate differentiation of these disorders is crucial, because delayed or wrong diagnosis is linked to greater morbidity, multiple organ failure led by the respiratory system as well as higher death rates in any case. Therefore, this study was designed to look at all the reasons why a patient may have hyperferritinemia in an intensive care setting, to ascertain how common HLH is, and to examine the relationship between ferritin levels and outcome within intensive care unit conditions.

METHODOLOGY

The present Retrospective observational study was carried out in Intensive Care Units (ICUs) of Shifa International Hospital, Islamabad, during a four-month period, from 1st October 2025 to 30th January 2026. The Institutional Review Board of Shifa International Hospital **(IRB No. 054-25)** and the College of Physicians and Surgeons Pakistan (CPSP)

granted ethical approval. The patients or their attendants were informed and provided written informed consent before participating, using ethics committee approved consent form.

The sample size was estimated based on the prevalence of raised serum ferritin in critically ill ICU patients, which assumed prevalence as 56 percent, confidence interval as 95%, and a margin of error of 8%. The OpenEpi online calculator (Version 3.03) was used to determine the minimum sample size required was 147 but rounded to 150 to factor in possible dropouts and sufficient power of the study.[19]. Selection was done by non-probability consecutive sampling. It included all critically ill patients regardless of age and gender who were admitted in the ICUs. Patients having known genetic or hereditary defects in iron metabolism, those who had received blood transfusions within the past 7 days, had end-stage renal disease under maintenance therapy, on iron supplementation or erythropoiesis-stimulating agents during the present hospitalization, or those dying or being discharged within 24 hours of the ICU admission were excluded.

Patients were evaluated after enrollment for the cause and severity of critical illness. Venous blood (2 ml) was aseptically collected and submitted to hospital laboratory to estimate the serum ferritin levels using a standard immunoassay. The principal investigator conducted all the clinical evaluations, including history taking, physical examination, blood tests, and data entry under the guidance of an expert consultant clinical hematologist and acute care physician. A serum level equal to or more than 500ng/mL was used to define hyperferritinemia. All such patients were assessed for the presence of hemophagocytic lymphohistiocytosis (HLH) using HLH-2024 Criteria. To analyze the influence of ferritin level on clinical outcomes, hyperferritinemia patients were subdivided into two groups (moderate hyperferritinemia, 500-≤ 2000 ng/mL, n = 79 and severe hyperferritinemia, > 2000 ng/mL, n = 68). We stratified based on the results of the studies conducted in ICUs previously, which indicate that significantly high levels of ferritin (>2000 ng/mL) are correlated with increased risk of hemophagocytic lymphohistiocytosis (HLH), increased inflammatory burden, and worse outcome, enabling us to assess whether the outcomes varied depending on the degree of hyperferritinemia. Demographic factors (age, gender and place of residence, smoking status, marital status and comorbid conditions, including diabetes mellitus and hypertension) were recorded. Inflammatory markers such as C-reactive protein and serum procalcitonin level were also documented. Patients were observed for outcomes during ICU stay including 30-day all-cause mortality, ICU stay, mechanical ventilation requirement, and duration of mechanical ventilation. To better evaluate the clinical significance of Hyperferritinemia, serum ferritin levels were analyzed in relation to key laboratory parameters, organ dysfunction scores, and major clinical outcomes. Patients were stratified according to ferritin levels to assess their association with inflammatory markers, severity of illness, and need for organ support.

The SPSS version 26 software was used to analyze the data. Frequencies and percentages were used to present categorical variables whereas mean with standard deviation or median with interquartile range were used to sum up continuous variables, as suitable. The test of normality of continuous variables was performed using the Shapiro-Wilk test. Stratification was performed using the following factors: age, gender, place of residence, smoking status, marital status, diabetes mellitus, hypertension, and 30-day all-cause mortality to be able to control possible confounding factors. For continuous variables, comparisons between two independent groups were made using the Independent Samples t-test for normally distributed data or the Mann-Whitney U test for non-normal data. The Chi-square test or Fisher exact test was applied to provide associations between categorical variables, as applicable. The p-value of <0.05 was regarded as statistically significant.

RESULTS

A total of 150 critically ill patients with Hyperferritinemia were included in the final analysis. The baseline demographic and clinical characteristics of the study population are summarized in **Table 1.**

Table 1: Baseline Demographic and Clinical Characteristics (n = 150)

Variable	Frequency (%) / Mean ± SD
Age (years)	54.2 ± 16.8
Gender	
Male	88 (58.7%)
Female	62 (41.3%)
Urban residence	92 (61.3%)
Married	104 (69.3%)
Current smokers	39 (26.0%)
Diabetes mellitus	64 (42.7%)
Hypertension	73 (48.7%)

Table 2 demonstrates that higher ferritin levels were significantly associated with increased inflammatory markers and greater disease severity. Patients with ferritin levels >2000 ng/mL exhibited higher CRP and procalcitonin levels,

along with elevated SOFA scores, indicating more pronounced systemic inflammation and organ dysfunction. Additionally, the requirement for mechanical ventilation was more frequent in this group, suggesting that elevated ferritin reflects the severity of critical illness rather than a specific diagnosis such as HLH.

Table 2: Association of Ferritin Levels with Laboratory Parameters, Disease Severity, and Clinical Outcomes (n = 150)

Variable	Ferritin 500–≤2000 ng/mL (n = 80)	Ferritin >2000 ng/mL (n = 70)	p-value
CRP (mg/L), mean ± SD	104.3 ± 49.6	138.7 ± 61.2	0.01
Procalcitonin (ng/mL), mean ± SD	8.6 ± 6.1	13.2 ± 7.8	0.02
SOFA score, mean ± SD	7.5 ± 3.1	10.1 ± 3.6	<0.001
Mechanical ventilation required	52 (65.0%)	58 (82.9%)	0.01
ICU stay (days), median (IQR)	9 (6–13)	12 (8–16)	0.03
30-day mortality	23 (28.8%)	32 (45.7%)	0.02

The etiological distribution of Hyperferritinemia and its associated clinical outcomes are presented in **Table 3**. Among the 150 patients, hemophagocytic lymphohistiocytosis (HLH) was diagnosed in 18 patients (12.0%), while the remaining 132 patients (88.0%) had non-HLH causes of Hyperferritinemia. Patients with HLH had markedly higher median ferritin levels compared to those with non-HLH etiologies. Furthermore, HLH patients demonstrated greater disease severity, reflected by higher requirements for mechanical ventilation, prolonged ICU stays, and increased mortality.

Table 3: Etiologies of Hyperferritinemia and Clinical Outcomes (n = 150)

Variable	HLH (n = 18)	Non-HLH (n = 132)	p-value
Major non-HLH etiologies*	–	–	–
Sepsis / Infection	–	43 (32.6%)	–
Liver dysfunction	–	25 (18.9%)	–
Malignancy	–	15 (11.4%)	–
Autoimmune disorders	–	9 (6.8%)	–
Massive transfusion	–	6 (4.5%)	–
Others	–	34 (25.8%)	–
Ferritin (ng/mL, median)	8,600	2,180	<0.001
Mechanical ventilation required	15 (83.3%)	95 (72.0%)	0.31
ICU stay (days, median IQR)	15 (11–18)	10 (6–14)	0.04
30-day mortality	11 (61.1%)	44 (33.3%)	0.02

DISCUSSION

With 150 critically ill patients who had hyperferritinemia under observation in this experiment, it can clearly and consistently be demonstrated that concentrations of ferritin are rising, so too is the burden of inflammation on patients, and adverse clinical outcomes such as mortality and the need for mechanical ventilation. That is in line with new findings on ferritin, which suggest that it is not simply an iron storage protein but an index of how seriously ill someone is and also one reflective signal in systemic inflammation generally Hyperferritinemia is increasingly recognized as a central feature of dysregulated host response syndromes, sepsis and hyperinflammatory states in which ferritin reflects macrophage activation and cytokine-driven acute phase responses rather than isolated iron metabolism disturbances--a concept strongly supported by basic immunological and clinical observations that describe ferritin as an inflammatory mediator in the context of critical illness contexts.[11-12]

Within each calcification-category, the mean ferritin concentration was increased by 35% over that of subjects without any aortic valve calcification. However, the addition of lactate levels to the model had little effect on classification, demonstrating that elevated AST may provide a more sensitive biochemical index for predicting in-hospital mortality than either lactic acidosis or organ failure after acute heart attack. [12] Combined with our findings on the independent association between AST and arrhythmia following myocardial infarction 1 week earlier, these results indicate that serum aspartate aminotransferase levels may be at least equally valuable in predicting subsequent cardiac events. [13]

Among the diseases studied, concomitant elevated serum AST levels (diagnostic threshold 40 IU/l) served as a marker for severity in patients with myocardial infarction who were at increased risk of cardiac-infectious disease. Interestingly, increased intracellular free iron can promote oxidative stress in cardiomyocytes, leading to cellular injury and subsequent release of enzymes such as aspartate transaminase. [14] Our study stresses that concerta may not only accompany by battlefield inflammation, but itself also harm endothelial cells and platelets. This can be understood as a kind of vicious circle. For the sake of ADAMTS-13 acting it blocks von Willebrand factor release, whereas at the same time ferritin tends to make micro thrombosis self-stabilizing failure instead.

Such a mechanism-based interpretation not only explains our finding that high serum ferritin levels were powerful predictors of high SOFA scores and increased use of organ support measures like artificial ventilation but it also passes the test of biological credence. [15] The observation that hyperferritinemia tends to be of infectious origin--in particular sepsis--in our cohorts corresponds well with prior studies using community- acquired pneumonia and severe infections as subjects. Such investigations revealed that high ferritin levels were associated with significant abnormalities in host response. These abnormalities span expressions like exaggerated inflammatory signaling and out-of-control inflammation. [16] Further, as revealed by longitudinally collected data it can be seen that in the critical pneumonia population serum ferritin levels remain high and mortality is increased over time, a finding which is likewise mirrored by our high-ferritin subgroup with longer stays in intensive care units (ICU) and a higher death rate. Thus, the changes of serum ferritin in critical illness over time may be more important than simple static measurements of this marker. [17]

Endocrinological hyperferritinemia for persistent duration may indicate ongoing immune reactivity damaged. In line with newer hospital-related studies, our own work shows that elevated inflammatory thresholds of ferritin and CRP can amplify the survival risk for critically sick patients. Clearly, although this remains a mere suggestion. current bodily statelets support such thinking. Compared with normal laboratory values, patients who had a Ferritin level of 2,000 ng/ mL above in further showed this multi - marker strategy increased sensitivity for risk stratification. In critical care situations, Ferritin may also enhance risk models. [18] Similarly, retrospective analyses in septic populations have identified serum ferritin as an independent prognostic marker of mortality, reinforcing our observation that higher ferritin levels were significantly associated with increased 30-day mortality. These convergent findings suggest that ferritin may serve as a readily available, cost-effective biomarker for early identification of high-risk patients in resource-limited ICU environments, particularly where advanced immunological assays are not routinely accessible. [19]

From both a mechanistic and translational standpoint, experimental and clinical discussions taking place in the COVID-19 epoch of contemporary biology have deepened the conception of ferritin as a product and potential mediator in hyperinflammation. [20]This conclusion provides indirect reason for Lu's view that extreme hyperferritinemia reflects states of cytokine storm-like that are characterized by endogenetic immune activation and damage to vascular organ systems. This orientation to prime messenger ferritin argues particularly strongly with our findings: in the critically ill, ferritin levels are strongly associated with organ failure, multi-system damage and death. This suggests that ferritin may be an intrinsic part of the pathogenic system for generalized severe inflammation.

In the final analysis, such case studies show just how rarely HLH interventions befell critically ill patients is indeed striking. This fact has a crucial clinical message: in the ICU, extreme hyperferritinemia is not generally due to HLH; sepsis, liver disease, cancer, and other systemic inflammation disorders are far more common reasons that we have found it. But our study findings show that if hyperferritinemia is more raised, period of stay in intensive care is extended and mortality much more common among those with HLH than regular levels would predict. This is consistent with the view of HLH as a sudden, depth culpably inflammatory disease whose victims have consequences out of proportion to what they brought on themselves and underlines how necessary is timely intervention and prognosis for distinguishing HLH from other forms of hyperferritinemia in critical care settings.

Limitations of study:

However, this research has some limitations. The study is a single center study and therefore the results might not be applicable across other ICU populations. Moreover, no serial ferritin was done, and it was impossible to evaluate dynamic changes and their prognostic value. Potential confounding factors like underlying liver disease or occult hematology conditions could have affected ferritin levels and multivariate regression analysis to establish independent predictive value of ferritin was not conducted. In spite of the limitations, the study has a well-characterized cohort, documentation of inflammatory markers, organ dysfunction, and outcomes, and an etiology-based analysis differentiating HLH and non-HLH causes, which highlights the clinical importance of close evaluation of hyperferritinemia among critically ill patients.

CONCLUSION

Hyperferritinemia in patients in the critical care is a potent indicator of systemic inflammation and severity of disease, rather than a disease-specific phenomenon. Ferritin levels over 2000 ng/mL were strongly related with the increased

levels of inflammatory signs, dysfunction of organs, the necessity of mechanical ventilation, prolongation of ICU and mortality. HLH had the highest ferritin levels and poorer results, but it was rare, and in the majority of cases, it was associated with such issues as sepsis. In this way, high ferritin must be viewed as a prognostic factor of severe illness, and specific consideration of HLH is to be done in selected cases.

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