



The Role of Ferritin as an Inflammation and Prognostic Marker in Systemic Infectious Diseases: A Litterature Review

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Abstract

Systemic infectious diseases, including sepsis, COVID-19, and tuberculosis, remain major causes of morbidity and mortality worldwide and require reliable biomarkers for early risk stratification and prognosis. This literature review aims to evaluate the role of serum ferritin as an inflammatory and prognostic marker in systemic infectious diseases. This study used a systematic literature review design guided by the PICOS framework. Articles were identified through electronic databases, including PubMed, Google Scholar, ScienceDirect, ResearchGate, and other relevant sources, focusing on studies published between 2020 and 2026. The review included peer-reviewed full-text studies that measured serum ferritin levels and reported relevant clinical outcomes, such as disease severity, mortality, length of hospitalization, intensive care requirement, or inflammatory parameters. A total of 15 eligible studies were included in the synthesis. The findings showed that elevated serum ferritin is closely associated with systemic inflammation through cytokine-mediated pathways, macrophage activation, and neutrophil extracellular trap formation. In sepsis, high ferritin levels were consistently associated with increased mortality, longer intensive care stay, and multiorgan dysfunction. In COVID-19, ferritin was higher in severe cases and was related to ICU admission and mortality. In tuberculosis, ferritin was more relevant for monitoring treatment response and persistent infection. Overall, serum ferritin has important clinical value as an accessible and affordable biomarker for assessing inflammation, disease severity, and prognosis in systemic infectious diseases, although standardized cut-off values remain necessary for broader clinical application.

Introduction

Systemic infections continue to be a leading cause of morbidity and mortality globally, with sepsis being the most severe manifestation, affecting approximately 49 million individuals and causing over 11 million deaths annually, often progressing to Multiple Organ Dysfunction Syndrome (MODS) in intensive care units. In addition to sepsis, other infections such as tuberculosis (TB), COVID-19, and typhoid fever continue to burden global health systems. In fact, according to the WHO, TB will again be the deadliest infectious disease in 2023, with 1.25 million deaths and approximately 10.8 million new cases. This situation underscores the urgency of developing more effective diagnostic and prognostic tools for the management of systemic infections (Tiewsoh et al., 2025; Kumar, 2025).

Ferritin acts as the primary iron storage protein within cells and is also used as a marker of the body's iron reserves. However, its role extends beyond iron storage, as ferritin is also an acute-

phase protein whose levels increase with inflammation, whether in infections, autoimmune diseases, hematological disorders, or malignancies. Elevated ferritin levels (above 400 ng/mL) often indicate severe inflammation and are closely associated with hyperferritinemia syndromes, such as MAS, AOSD, CAPS, and septic shock. The mechanism of this increase involves the body's production of hepcidin during inflammation, which is triggered by cytokines such as IL-6; this inhibits iron efflux from cells, resulting in elevated serum ferritin levels even though systemic iron stores are not always excessive (Noviana, 2025; Liao et al., 2025).

Numerous studies have highlighted ferritin's role as a crucial biomarker of inflammation in systemic infections. Specifically in COVID-19, hyperferritinemia elevated ferritin levels is closely associated with disease severity and a higher risk of mortality. This phenomenon is triggered by a cytokine storm, including IL-1 β , IL-6, and IFN- γ , which triggers ferritin secretion from cells. Ferritin also serves as an indicator of the immune response in bacterial infections such as sepsis, both as an acute-phase reactant and as a marker of immune system dysregulation. Furthermore, ferritin elevation often accompanies elevations in other inflammatory biomarkers, such as procalcitonin (PCT). Therefore, ferritin can be used as an essential parameter to evaluate the severity, prognosis, and dynamics of the inflammatory response in patients with systemic infections (Jacob et al., 2023; Sari et al., 2022; He et al., 2023).

Other studies have confirmed the prognostic value of serum ferritin levels in severe systemic infections. Analysis of the MIMIC-IV database, for example, revealed a linear correlation between ferritin elevation and mortality in sepsis patients, with a cutoff of approximately 591.5 ng/mL significantly increasing the risk of death. These results remained consistent across various follow-up intervals, from 28 days to 1 year, with higher ferritin levels consistently associated with increased mortality. In children, hyperferritinemia (ferritin >500 ng/mL) was found to increase the risk of death by nearly five times compared to cases without the condition. In the ICU setting, high ferritin levels have been repeatedly associated with adverse outcomes, including higher mortality, longer hospital stays, and increased morbidity. Similarly, in COVID-19, extreme ferritin levels (>3000 ng/mL) are associated with greater ICU admission requirements and increased mortality, reinforcing ferritin's position as a key biomarker for disease severity and immune dysregulation (Fang et al., 2022; Fan et al., 2023; Dhondge et al., 2024; Para et al., 2021).

Given the ever-evolving nature of scientific evidence, and the large number of studies with varying designs, populations, infection types, and measurement methods, a systematic review integrating all of this evidence is needed. This literature review aims to summarize, evaluate, and synthesize the role of serum ferritin as an inflammatory and prognostic marker in various systemic infectious diseases, including sepsis, COVID-19, tuberculosis, and other systemic infections, to provide evidence-based recommendations for optimal clinical application.

Methods

Research Design

This study employed a literature review design that systematically analyzed previous research findings using the PICOS Framework. Primary studies were represented by individual studies, while the literature review was secondary research. The approach applied combined quantitative and qualitative methods, including randomized controlled trials (RCTs), cohort studies, case-control studies, and prevalence studies.

The data selected and used were primary and secondary data obtained from observational studies and various online sources, such as theses, journals, textbooks, and e-books. The search process was conducted through PubMed, Google Scholar, ScienceDirect, ResearchGate, and

others, as well as manual searches of various Indonesian journals published between 2020 and 2026, written in both Indonesian and English.

Research Location and Time

This research was conducted online using several scientific databases such as Google Scholar, PubMed, ResearchGate, ScienceDirect, and others. The study was conducted between March and April 2026.

Inclusion and Exclusion Criteria

Inclusion criteria for this review included articles published in peer-reviewed scientific journals with accessible, full-text versions; measuring and reporting serum ferritin levels as the primary variable or a meaningful variable studied in the context of systemic infection; reporting at least one relevant clinical outcome, such as mortality, length of stay, disease severity score, or response to antibiotic therapy; using a cohort study design, either prospective or retrospective, case-control, cross-sectional with complete clinical data, or controlled clinical trials; and published within the last six years, i.e., 2020–2026, to ensure the relevance of the evidence to current clinical practice. Exclusion criteria included case reports and case series with fewer than five subjects due to limited generalizability; studies that did not measure serum ferritin as a specific and meaningful variable studied in the context of systemic infection; and in vitro studies and studies using animal models because they cannot be directly generalized to the human population.

Identification of Variables

The independent variables in this study consisted of two main components: serum ferritin levels and characteristics of systemic infectious diseases. Serum ferritin levels represent the concentration of ferritin in blood serum as measured in a laboratory. This variable is the primary exposure variable focused on and serves as an indicator of the acute inflammatory response and a clinical prognostic marker. Meanwhile, the characteristics of systemic infectious diseases include the type of infection, the source of infection, and the etiology of the causative microorganism. These variables serve as the clinical context that determines the relevance of interpreting serum ferritin levels. The dependent variables in this study include inflammatory parameters, such as CRP, IL-6, and leukocytes, as well as clinical outcomes as prognostic factors, such as disease severity, mortality, length of hospitalization, and the need for intensive care.

Operational Definition

Table 1. Operational Definitions

Variable	Variable Types	Operational Definition	Methods & Measuring Tools	Measurement Results and Data Scale
Serum Ferritin Levels	Independent Variable	Serum ferritin protein concentration, measured through standard laboratory tests, is expressed in ng/mL. It reflects the body's iron stores and is an acute-phase inflammatory reactant, which	Immunoassay (ELISA, ECLIA, or CMIA) on venous serum samples; results derived from data reported in the primary study	Continuous numeric value (ng/mL); can be categorized as: Normal <300, High 300-1000, Very High >1000 ng/mL. Scale: Ratio / Ordinal (if categorized)

		increases in conditions of infection and inflammation.		
Systemic Infectious Diseases	Independent Variable	A pathological condition resulting from the invasion of microorganisms (bacteria, viruses, fungi) that triggers a systemic inflammatory response. Includes: (1) Sepsis: life-threatening organ dysfunction due to dysregulation of the host response to infection; (2) Septic shock: a subset of sepsis with vasopressor requirements and lactate levels >2 mmol/L; (3) Bacteremia: culture-confirmed bacteria in the bloodstream; based on the Sepsis-3 criteria (Singer et al., 2016).	Clinical diagnosis and/or microbiological confirmation (blood culture, PCR) included in the primary study	Categories: Sepsis / Septic Shock / Bacteremia / Other Severe Infections. Scale: Nominal
Mortality	Dependent Variable - Primary	Patient death occurring during hospitalization (in-hospital mortality) or within 28 or 90 days of the diagnosis of systemic infection, as reported by primary studies.	Medical record/clinical report data recorded in the primary study	Dead / Alive (dichotomous). Scale: Nominal
Disease Severity Score	Dependent Variable - Secondary	Clinical severity is assessed using: (1) SOFA score (0-24): assesses dysfunction of 6 organ systems; (2) APACHE II (0-71): assesses the severity of acute	SOFA, APACHE II, and qSOFA clinical scoring instruments reported in the primary study	Numerical value of each instrument's score. Scale: Ratio / Interval

		illness; (3) qSOFA (0-3): rapid screening for sepsis outside the ICU; as reported by the primary studies analyzed.		
Hospitalization & ICU Stay	Dependent Variable - Secondary	Total length of hospital stay and/or intensive care unit stay (length of ICU stay) from admission to discharge or death, expressed in days, as reported in the primary studies.	Inpatient administrative data recorded in the primary study	Number of days (continuous numeric value). Scale: Ratio
Prognostic Value of Ferritin (AUC-ROC & Cut-off)	Dependent Variable - Secondary	The discriminatory ability of serum ferritin in predicting adverse outcomes (mortality, disease severity) was measured by: (1) Area Under the ROC Curve (AUC-ROC): a value of 0.5-1.0, the closer to 1.0 the better; (2) Optimal cut-off value determined by the Youden Index method or equivalent; along with its sensitivity and specificity.	ROC statistical analysis reported in the primary study (AUC, sensitivity, specificity, positive and negative predictive values)	AUC (0-1); Cut-off in ng/mL; Sensitivity and Specificity in %. Scale: Ratio

Data Collection Techniques

Data collection was conducted through a systematic literature search of relevant scientific sources, with a focus on the Role of Serum Ferritin as an Inflammatory and Prognostic Marker in Systemic Infectious Diseases. Data collection in this study was conducted through a systematic search of scientific literature in electronic databases such as Google Scholar, PubMed, ScienceDirect, ResearchGate and ProQuest

The literature search used a combination of keywords designed based on the main research concepts, both in Indonesian and English. Examples of keywords used include: "serum ferritin" / "ferritin levels" / "hyperferritinemia" / "ferritin concentration"; "sepsis" / "septic shock" / "bacteremia" / "severe infection" / "systemic infection" / "bloodstream infection; "inflammation marker" / "prognostic marker" / "biomarker" / "mortality" / "clinical outcome" / "prognosis"

Data Management and Analysis

Data analysis in this study was conducted using the PICOS approach, namely Population, Intervention, Comparison, Outcome, and Study Design, to ensure the literature synthesis process runs systematically and purposefully. Population refers to the population and sample as research subjects that are the target of the study. Intervention refers to the influence or benefit to be assessed on a specific group. Comparison is a group with a specific application that serves as a comparison to the intervention group. Outcome refers to the analytical results obtained from the study, while Study Design refers to the research design used, whether observational or analytical, such as cross-sectional, case-control, cohort, descriptive studies, or surveys.

Research Flow

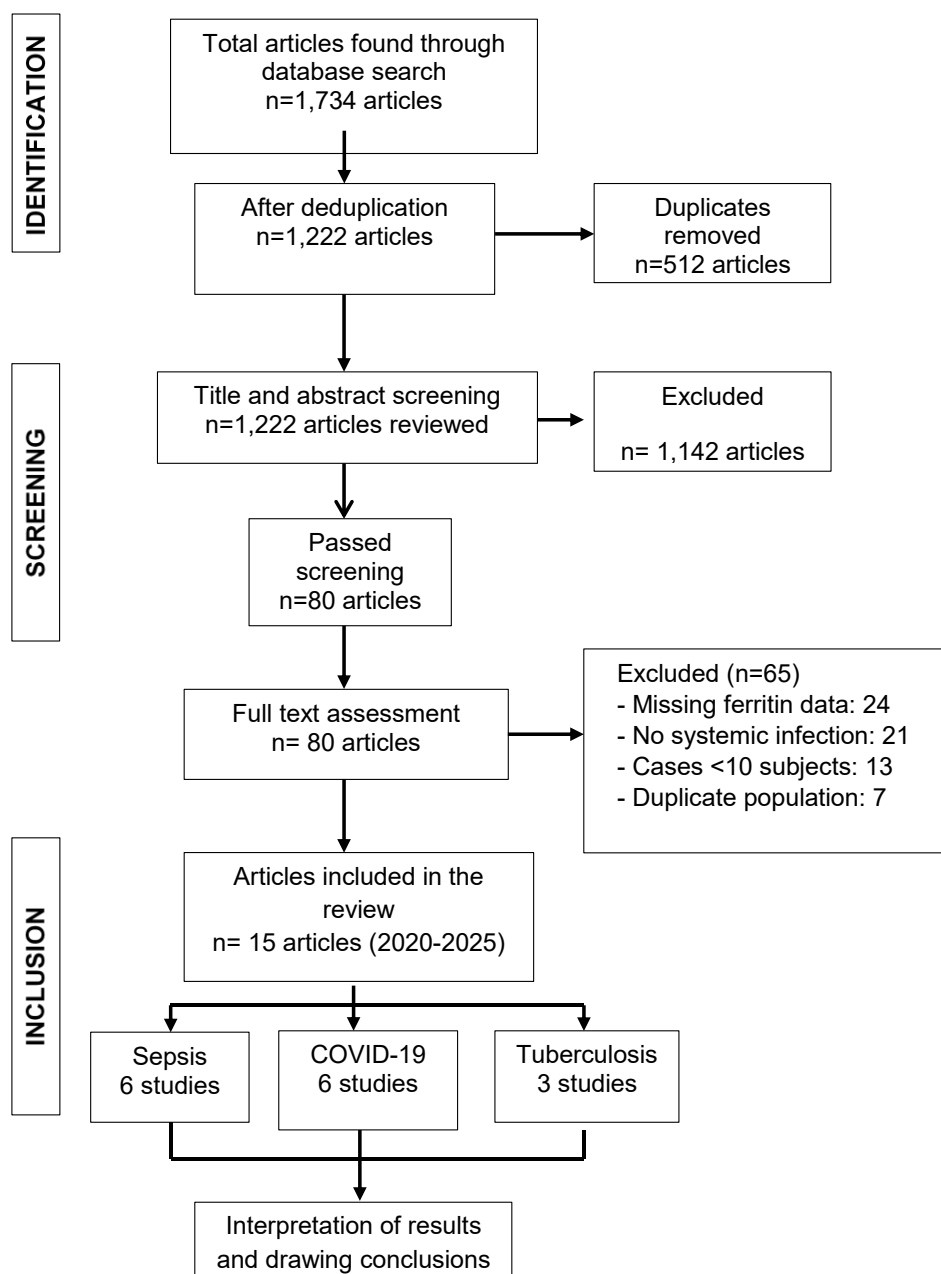


Figure 1. Research Flow

Result and Discussion

Literature Selection Results

A systematic literature search was conducted across six electronic databases: PubMed/MEDLINE, Scopus, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and Google Scholar, covering publications from January 2020 to April 2025. All selection stages adhered to the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

The initial search identified 1,734 articles from all database sources. After deduplication, 512 articles were eliminated as duplicates, leaving 1,222 articles to proceed to the title and abstract screening stage. During this screening stage, 1,142 articles were excluded for not meeting the inclusion criteria. Of the 80 articles that passed the screening, a full-text assessment was conducted, with 65 articles excluded for predetermined reasons. Based on all stages of selection, 15 articles met all inclusion criteria and were included in this systematic review. Each article was thoroughly reviewed using the PICOS Framework, with the following components:

Population: The population in this study were patients with systemic infections, including sepsis, systemic bacterial infections, severe viral infections, and conditions with a systemic inflammatory response, without age or gender restrictions.

Intervention/Exposure: The exposure analyzed was serum ferritin levels, a biomarker reflecting the inflammatory response and potentially acting as a prognostic indicator.

Comparison: Comparisons were made between high and normal ferritin levels, as well as between groups with different clinical outcomes. Comparisons were also made with other inflammatory biomarkers such as CRP, IL-6, and procalcitonin.

Outcome: Outcomes included the relationship between ferritin levels and inflammatory parameters (CRP, IL-6, and leukocytes) and prognostic indicators such as disease severity, mortality, length of hospitalization, and need for intensive care.

Study Design: Most of the studies in this study used a cohort design (80%), which is good for examining associations but cannot yet confirm cause and effect. There are two systematic reviews with mixed results, and there are no randomized clinical trials (RCTs) on ferritin, so there is still a lack of evidence.

Article Description

Table 2. Article Description

Authors	Year	Source
Liudang He et al. ⁷	2023	ResearchGate
Yi-Peng Fang et al. ⁸	2022	Pubmed
Zhenziang Fan et al. ⁹	2023	Pubmed
Yang Deng Chan et al. ³⁹	2024	Pubmed
Laura evan et al. ⁴⁰	2021	Pubmed
Yingying liao et al. ⁴¹	2025	Pubmed
Karanvir Kaushal. ⁴²	2020	Pubmed
Shila Jacob et al. ⁵	2023	Pubmed
Hulkoti et al. ⁴³	2022	ResearchGate
Ombretta para et al. ¹¹	2021	Pubmed
Bianconi et al. ⁴⁴	2022	Pubmed
Mahroum et al. ¹²	2022	Pubmed
Miranda et al. ⁴⁵	2021	Pubmed

Rodriguez et al. ⁴⁶	2022	pubmed
Jinchao Jia et al. ⁴⁷	2022	ResearchGate

Table 3. Research Results

Research Title	Population (P)	Intervention (I)	Comparison (C)	Outcome (O)	Study Design (S)
He et al. (2023) – The Relationship Between Serum Ferritin Level and Clinical Outcomes in Sepsis Based on a Large Public Database	Adult ICU patients with sepsis (n=1,947)	Serum ferritin measurement (CLIA) on ICU admission	High vs. low ferritin levels	High ferritin independently predicted increased 28-day, 90-day, 180-day, and 1-year mortality. The ferritin–mortality relationship was U-shaped with significant ROC performance.	Retrospective cohort
Fang et al. (2022) – Effect of Serum Ferritin on the Prognosis of Patients with Sepsis: Data from the MIMIC-IV Database	Adult ICU patients with sepsis (n=289)	Serum ferritin measurement (CLIA)	High vs. low ferritin levels	High ferritin was associated with increased in-hospital mortality, longer ICU stay, higher SOFA score, and greater AKI incidence.	Retrospective cohort
Fan et al. (2023) – Hyperferritinemic Sepsis, Macrophage Activation Syndrome, and Mortality in a Pediatric Research Network	Pediatric patients with sepsis (n=397)	Ferritin measurement (ELISA)	Hyperferritinemia (>500 µg/L) vs. normal ferritin	Hyperferritinemia significantly increased mortality and macrophage activation syndrome (MAS).	Prospective cohort
Yang Dengchan et al. (2024) – Iron and Ferritin Effects on Intensive Care Unit Mortality: A Meta-analysis	Sepsis patients from multiple studies (n=125,490)	Measurement of serum ferritin and iron	High vs. low ferritin/iron	Higher ferritin and iron levels significantly increased mortality risk across studies.	Systematic review & meta-analysis
Evans et al. (2021) – Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and	Patients with sepsis and septic shock	Ferritin used as an additional biomarker	Ferritin-guided vs. standard management	Ferritin is recommended as an adjunct biomarker for identifying hyperinflammation and risk stratification.	Clinical guideline

Septic Shock 2021					
Liao et al. (2025) – Ferritin's Role in Infectious Diseases: Exploring Pathogenic Mechanisms and Clinical Implications	Patients with sepsis and inflammatory diseases	Analysis of ferritin- mediated Msr1- NETs pathway	Severe vs. mild inflammation	Ferritin promotes NET formation through Msr1, worsening cytokine storm and organ damage.	Systematic review
Kaushal et al. (2022) – Serum Ferritin as a Predictive Biomarker in COVID-19	Patients with COVID-19 from multiple studies	Serum ferritin measurement	Severe vs. mild/moderate COVID-19	Ferritin was significantly higher in severe COVID-19 and associated with mortality, mechanical ventilation, and ICU admission.	Systematic review & meta- analysis
Jacob et al. (2023) – Association of Serum Ferritin with Severity and Clinical Outcome in COVID-19 Patients	COVID-19 patients (n=244)	Serum ferritin measurement	Severe vs. mild COVID-19	Ferritin predicted disease severity with an AUC of 0.776 and cutoff value of 287.4 µg/L.	Prospective observational
Hulkoti et al. (2022) – Association of Serum Ferritin with COVID-19 in ICU Patients	ICU patients with severe COVID-19 (n=200)	Ferritin measurement (ELISA)	Survivors vs. non-survivors	Ferritin was significantly higher in non- survivors and correlated with HRCT score and neutrophil- lymphocyte ratio.	Cross- sectional
Para et al. (2022) – Ferritin as Prognostic Marker in COVID-19: The FerVid Study	Patients with severe COVID-19	Ferritin measurement	Survivors vs. non-survivors	Elevated ferritin was associated with ARDS, MAS, coagulopathy, and mortality.	Prospective cohort
Bianconi et al. (2022) – The Detrimental Impact of Elevated Ferritin-to-Iron Ratio on In- hospital Prognosis of Patients with COVID-19	Severe COVID-19 patients (n=362)	Ferritin-to- Inflammatory Ratio (FIR)	FIR ≥ 29 vs. FIR <29	FIR ≥ 29 predicted ICU admission and in- hospital mortality better than ferritin alone.	Prospective cohort

Mahroum et al. (2022) – Ferritin – From Iron, Through Inflammation and Autoimmunity, to COVID-19	Patients with severe COVID-19 from multiple studies	Hyperferritinemia analysis	COVID-19 vs. other hyperferritinemic syndromes	Ferritin contributes to macrophage activation and cytokine storm; IL-1 and IL-6 inhibitors may be therapeutic.	Review
Miranda et al. (2021) – Sustained Elevated Levels of C-Reactive Protein and Ferritin in Pulmonary Tuberculosis Patients	Pulmonary tuberculosis patients (n=165)	Ferritin measurement (ELISA)	Culture-positive vs. culture-negative TB	Ferritin correlated with bacterial burden and delayed sputum conversion during treatment.	Prospective cohort
Rodriguez et al. (2022) – The Iron Response of Mycobacterium tuberculosis and Its Implications for Tuberculosis Pathogenesis and Novel Therapeutics	Experimental models of Mycobacterium tuberculosis	Analysis of iron/ferritin metabolism	High vs. low iron availability	Ferritin supports bacterial persistence; iron depletion may improve TB treatment.	Mechanistic review
Jia et al. (2022) – Ferritin Triggers Neutrophil Extracellular Trap-Mediated Cytokine Storm Through Msr1	Patients with severe infection/sepsis and experimental models	Analysis of ferritin-induced Msr1-NET pathway	Msr1 pathway activation vs. inhibition	Ferritin induces NET formation and cytokine storm; Msr1 blockade reduced mortality in experimental sepsis.	Prospective + experimental cohort

Biological Mechanisms of Hyperferritinemia in Systemic Infection

Elevated serum ferritin levels in systemic infections are part of the acute phase response triggered by proinflammatory cytokines such as IL-1 β , TNF- α , IL-6, and IFN- γ through activation of the NF- κ B pathway in hepatocytes and macrophages. This process increases ferritin production, which binds and stores iron intracellularly, thereby reducing iron availability in the circulation and limiting its utilization by invading pathogens for growth and replication. This host defense mechanism is known as nutritional immunity. Ferritin not only acts as an inflammatory marker but also as an active mediator that can amplify the inflammatory response. Excessive ferritin can interact with immune cells through specific receptor pathways, promoting the formation of neutrophil extracellular traps (NETs) via activation of peptidylarginine deiminase 4 (PAD4), neutrophil elastase, and reactive oxygen species (ROS). Although NET formation initially serves to trap and eliminate pathogens, excessive NET production contributes to endothelial injury, microvascular thrombosis, and dysregulated immune activation. These NETs can subsequently trigger a cytokine storm, further exacerbating systemic inflammation and leading to progressive organ damage (Liao et al., 2025; Jia et al., 2022).

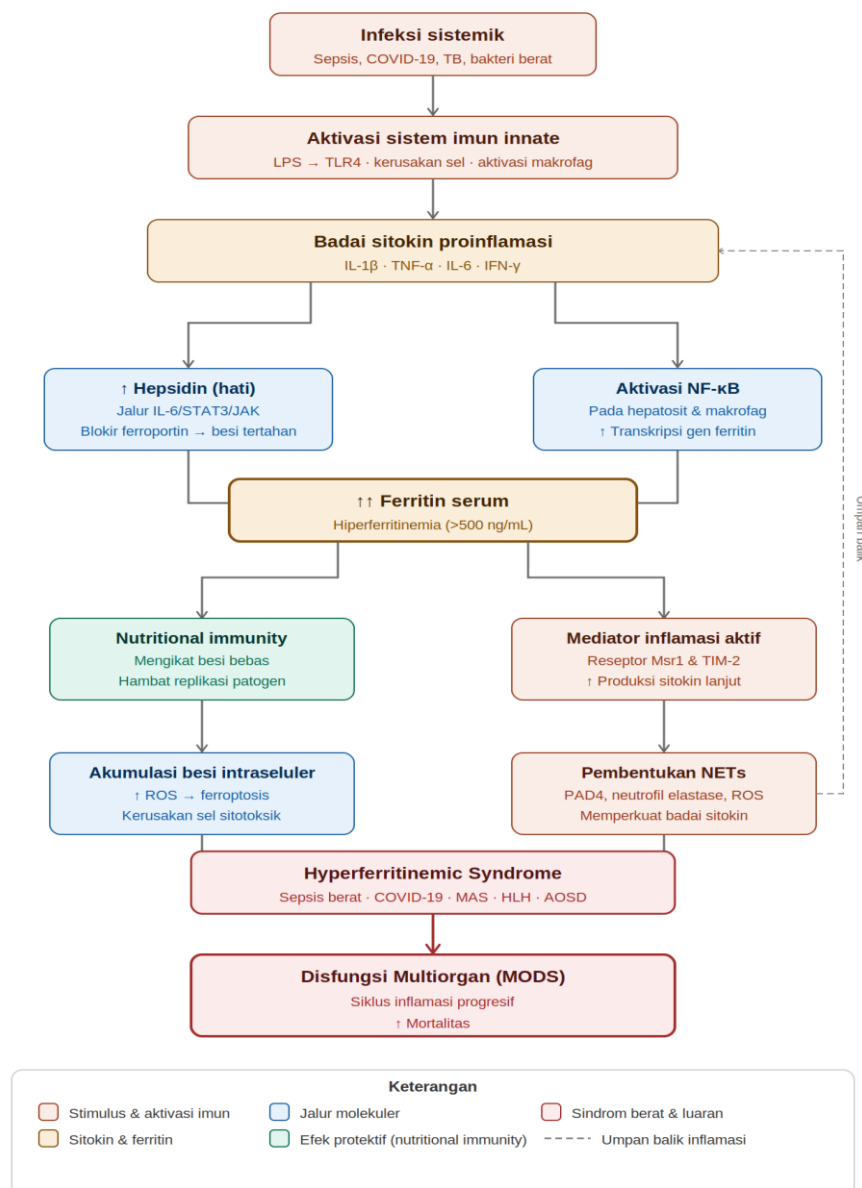


Figure 2. Pathomechanism of Hyperferritinemia in Systemic Infection

In sepsis, ferritin has been shown to be directly associated with increased risk of death, not solely through cytokines. This is consistent with the concept of hyperferritinemic syndrome, which encompasses conditions such as severe sepsis, COVID-19, and other inflammatory diseases with similar mechanisms (Fan et al., 2023; Mahroum et al., 2021).

Prognostic Value of Ferritin: Comparison across Conditions

Comparative analysis of ferritin's prognostic value shows that its predictive power varies across clinical conditions. In sepsis, the association between ferritin and mortality has the strongest evidence, with AUC values of around 0.75–0.85 and significant OR/HR across various studies. This reflects the highly inflammatory response and rapid cell damage in sepsis, resulting in significant release of ferritin into the circulation (He et al., 2023; Fang et al., 2022; Fan et al., 2023).

In COVID-19, ferritin also has good predictive value, but results are more variable. This variation is due to differences in patient clinical conditions, ranging from severe to mild inflammation. Several studies have shown that the ferritin ratio (FIR) is more accurate than ferritin alone in predicting patient outcomes (Kaushal et al., 2020; Bianconi et al., 2022).

In tuberculosis, ferritin plays a more important role in monitoring therapy response than in predicting mortality. Persistently high ferritin levels after 60 days of treatment can be a sign of therapy failure, providing additional clinical value compared to other inflammatory biomarkers (Miranda et al., 2021).

Clinical Implications

Based on the results of 15 studies, there are three main clinical implications. First, serum ferritin testing upon admission to patients with systemic infection can provide important information regarding prognosis and can be used in clinical risk stratification. The 2021 SSC Guidelines also recommend the use of biomarkers in the management of sepsis, making ferritin a practical and affordable additional option (Evans et al., 2021).

Second, studies have shown that ferritin levels $>4,500 \mu\text{g/L}$ have a high specificity (98.0%) for MALS, and anakinra therapy can improve clinical outcomes within 7 days. This suggests that ferritin is not only a biomarker but can also aid in the selection of more appropriate therapies (precision medicine) (Liao et al., 2025).

Third, the use of ferritin is particularly relevant in developing countries like Indonesia. Compared with other biomarkers such as procalcitonin and IL-6, which require specialized equipment, ferritin is easier to measure because it is readily available in many hospitals. In cases of tuberculosis, ferritin testing during treatment can also help detect the risk of therapy failure early (Miranda et al., 2021; Rodriguez et al., 2022).

Data Limitations

This systematic review has several limitations. First, the absence of randomized controlled trials (RCTs) directly using ferritin levels as the basis for interventions means that a causal relationship between ferritin and clinical outcomes cannot be firmly established. Although some studies have used causal analysis, most are observational, thus limiting the strength of the evidence (Fan et al., 2023).

Second, there are differences in ferritin cut-off values between studies, ranging from <500 to $>4,500 \mu\text{g/L}$. These differences are influenced by variations in population, type of infection, and research methods, so a single, universally accepted cut-off value cannot be determined. Third, the possibility of publication bias remains, as most published studies tend to report significant results (Yang et al., 2024).

Conclusion

Based on the results of the systematic review, the following conclusions can be drawn: 1) Increased serum ferritin in systemic infections occurs through activation of the NF- κ B pathway by pro-inflammatory cytokines (IL-1 β , TNF- α , IL-6, IFN- γ), which stimulates ferritin production in hepatocytes and macrophages. Ferritin not only functions as a passive marker but also acts as an active mediator of inflammation through activation of the Msr1 receptor, which triggers the formation of Neutrophil Extracellular Traps (NETs), thereby amplifying the cytokine storm and exacerbating organ damage; 2) Sepsis: Ferritin levels directly correlate with mortality risk. A cut-off of $\geq 591.5 \text{ ng/mL}$ has been shown to significantly increase the risk of death. In children, levels $>500 \text{ ng/mL}$ are associated with a risk of death of up to 58%; 3) COVID-19: Ferritin levels are significantly higher in severe cases than in mild cases (SMD 0.882). Values $>400 \text{ ng/mL}$ indicate severe disease, while $>3,000 \text{ ng/mL}$ are associated with a higher risk of death; 4) Tuberculosis: Ferritin levels are elevated in patients with positive *Mycobacterium tuberculosis* cultures and correlate with mycobacterial burden.

Serum ferritin has been shown to have significant prognostic value for three key clinical outcomes: 1) Mortality: AUC 0.75–0.85 in sepsis; ferritin is an independent predictor of mortality at 28, 90, 180 days, and 1 year; 2) ICU length of stay: High ferritin correlates with

longer ICU stays, particularly in sepsis and severe COVID-19; 3) Multiorgan dysfunction (MODS): Hyperferritinemia triggers a progressive inflammatory cycle through excessive macrophage activation, leading to multiorgan damage.

Serum ferritin has important diagnostic and prognostic value in various infectious diseases, but the optimal cut-off value varies according to the type of infection, patient population, and clinical characteristics. Elevated ferritin levels are consistently associated with disease severity, mortality risk, and hyperinflammatory conditions, thus offering potential use as a biomarker in risk stratification and clinical decision-making. However, heterogeneity in cut-off values across studies suggests that a universal cut-off value is not yet available. Therefore, more standardized prospective studies are needed to determine specific and relevant cut-off values for each population, including in Indonesia.

Comparison with Other Inflammatory Biomarkers

CRP: Ferritin has superior prognostic ability for predicting 28-day mortality in severe community-acquired pneumonia and COVID-19. The combination of the two improves the accuracy of clinical prediction.

PCT: PCT is more accurate for bacterial infections (high specificity), but insensitive for viral infections. Ferritin excels in viral infections and has the strongest correlation with viral load.

IL-6: IL-6 increases more rapidly and reflects acute inflammation at the time, while ferritin is more stable and reflects the long-term inflammatory process. The two complement each other in clinical assessment.

Advantages of ferritin: More affordable, widely available in healthcare facilities, including in developing countries like Indonesia.

Based on a synthesis of 15 studies (2020–2026), the following recommendations are recommended:

Ferritin testing on admission in patients with suspected systemic infection for initial risk stratification.

Serial ferritin monitoring during hospitalization provides greater accuracy than a single test.

Combining ferritin with clinical scores (SOFA, APACHE II) and other biomarkers (CRP, PCT) to improve the accuracy of prognostic prediction.

Using the Ferritin-to-Albumin Ratio (FAR) as an independent predictor of 28-day mortality in sepsis.

Ferritin is worthy of inclusion in systemic infection management protocols, especially in healthcare facilities with limited resources.

Further research needs to be directed at ferritin-based RCTs and the establishment of specific cut-offs for the Indonesian population.

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