THE ASSOCIATION BETWEEN FERRITIN LEVELS AND INFECTION IN PATIENTS WITH β-THALASSEMIA : A LITERATURE REVIEW

Dini Amelia Rahmawati Prasetya[1*], Budiono Raharjo[2]
Medical Education Program, Faculty of Medicine, University of Wijaya Kusuma Surabaya[1], *Department of Clinical Pathology, Faculty of Medicine, University of Wijaya Kusuma Surabaya*[2]
**Corresponding Author :* diniamelia78@gmail.com

ABSTRAK
Transfusi darah kronis pada pasien β-thalassemia sering kali menyebabkan penumpukan zat besi (*iron overload*) yang secara klinis umumnya tercermin dari meningkatnya ferritin serum sebagai penanda cadangan besi tubuh. Selain merefleksikan beban besi, peningkatan ferritin juga dapat mencerminkan proses patologis yang berkontribusi terhadap peningkatan kerentanan terhadap infeksi. Tinjauan literatur naratif ini bertujuan untuk menganalisis bukti ilmiah terkini (2020–2025) mengenai hubungan kadar ferritin tinggi/*iron overload* dengan kerentanan risiko infeksi pada pasien β-thalassemia serta mekanisme yang mendasarinya. Pencarian dilakukan melalui PubMed (via NCBI) dan Google Scholar, lalu disintesis secara naratif berdasarkan relevansi dan kualitas temuan. Hasil kajian menunjukkan bahwa ferritin tinggi berasosiasi dengan peningkatan kejadian dan kerentanan infeksi, terutama pada *iron overload* berat, berasosiasi dengan peningkatan kejadian infeksi seperti pneumonia, infeksi bakteri Gram-negatif, dan sepsis. Temuan mekanistik mengindikasikan disfungsi imun bawaan dan adaptif (gangguan neutrofil, perubahan subset monosit, serta perubahan profil sel NK pada kondisi tertentu seperti pasca splenektomi), disbiosis mikrobiota usus dan perubahan metabolit, serta disfungsi organ seperti gangguan hati, gangguan jantung dan disfungsi tubulus ginjal. Secara keseluruhan, kadar ferritin tinggi berpotensi meningkatkan risiko infeksi pada pasien β-thalassemia melalui kombinasi multifaktorial seperti ketersediaan besi bagi bakteri siderofilik, disbiosis mikrobiota, gangguan respons imun, dan disfungsi organ, namun interpretasinya perlu mempertimbangkan status inflamasi dan komorbid.

Kata kunci : β-thalassemia, disfungsi imun, ferritin, infeksi, penumpukan zat besi

ABSTRACT
Chronic blood transfusions in β-thalassemia commonly lead to iron overload, often reflected by elevated serum ferritin. This narrative review summarizes 2020–2025 evidence on the association between ferritin/iron overload and infection susceptibility in β-thalassemia, including underlying mechanisms. Literature was searched in PubMed (via NCBI) and Google Scholar and synthesized narratively. Overall, higher ferritin levels were consistently associated with greater infection burden and susceptibility, particularly in severe iron overload. Mechanistic findings indicate immune impairment affecting innate and adaptive responses (neutrophil dysfunction, shifts in monocyte subsets with reduced pro-inflammatory signaling, and altered NK cell profiles in specific contexts such as splenectomy), gut microbiota dysregulation with related metabolites, and organ involvement including hepatic injury and markers of renal tubular dysfunction. Thus, elevated ferritin may increase infection risk via siderophilic bacterial advantage, microbiota dysbiosis, immune dysfunction, and iron-related organ injury, while interpretation should consider inflammatory status and other clinical factors influencing ferritin.

Keywords *: β-thalassemia, ferritin, immune dysregulation, infection, iron overload*

INTRODUCTION

Thalassemia is one of the most prevalent hereditary hematologic disorders worldwide, particularly in regions such as the Mediterranean, the Middle East, Southeast Asia (Tuo et al. 2024). This disease is characterized by impaired synthesis of globin chains, resulting in suboptimal hemoglobin production and chronic anemia of varying severity (Zhang et al. 2025).

Its estimated prevalence in Indonesia ranges from 3% to 10%, underscoring its significance as a major public health concern (Hernaningsih et al. 2022). Patients with thalassemia major often require regular blood transfusions to maintain adequate hemoglobin levels, support normal growth and development, and prevent complications related to tissue hypoxia (Sadiq et al. 2024). However, long-term transfusion therapy carries serious consequences, most notably iron overload. The human body lacks a physiological mechanism for actively excreting excess iron, leading to accumulation from transfused blood and increased gastrointestinal absorption secondary to chronic hypoxic anemia (Saliba and Taher 2015; Taher and Saliba 2017). This excess iron deposits in vital organs such as the liver, heart, pancreas, and endocrine glands. Iron overload has long been associated with increased infection risk (Taher and Saliba 2017). Several pathogens, including *Escherichia coli*, *Klebsiella*, and *Yersinia* species, are classified as siderophilic bacteria because they flourish in iron-rich environments (Kramer, Ozkaya, and Kümmerli 2019). Additionally, excessive iron disrupts immune function through oxidative stress, neutrophil dysfunction, impaired antibody formation, and reduced CD4 lymphocyte counts (Ni et al. 2022).

Serum ferritin is widely used because it is low-cost and minimally invasive, requiring only a blood sample. Ferritin reflects body iron stores, although its levels may be influenced by inflammatory or infectious states (Islam et al. 2024; Liao et al. 2025). In transfusion-dependent thalassemia, ferritin is commonly used to determine the initiation of iron chelation therapy, evaluate treatment effectiveness, and adjust chelation dosage with agents such as deferasirox or deferoxamine (James and Prakash 2025; Premawardhena et al. 2024). Nevertheless, the relationship between serum ferritin and total body iron burden is not always straightforward. Several studies indicate that ferritin levels may fail to accurately reflect whole-body iron stores in certain patients, particularly those with chronic inflammation, liver disease, malnutrition, or recurrent infections (Islam et al. 2024; Powell, Halliday, and Cowlishaw 1978; Rusch et al. 2023). Understanding the relationship between ferritin levels and infection risk is therefore critical for optimizing clinical management in β-thalassemia. This review aims to examine clinical and mechanistic evidence regarding the correlation between ferritin levels and infection in patients with β-thalassemia.

METHOD

This article employed a narrative literature review approach. Articles were retrieved from PubMed (via NCBI) and Google Scholar. Inclusion criteria were original research articles published between 2020 and 2025, written in Indonesian or English, and relevant to the topic based on title, abstract, and full-text screening. Eligible studies included clinical observational studies, clinical trials, and relevant animal/in vivo studies that reported ferritin levels and/or iron overload in β-thalassemia and examined infection outcomes and/or pathways related to infection susceptibility, including immunological alterations, microbiota dysregulation, or organ dysfunction associated with iron overload. Exclusion criteria were review articles and publications that did not discuss ferritin levels or iron overload in β-thalassemia patients or did not report infection outcomes or related mechanistic findings (immune, microbiota, or organ dysfunction). The data used were research articles published in national and international journals).

RESULTS

The analysis of the included studies indicates that elevated ferritin levels and iron overload in β-thalassemia are consistently associated with immune dysregulation and a higher susceptibility to infections, as listed in the table 1.

Table 1. Summary of Included Studies on Ferritin/Iron Overload and Infection Susceptibility in β-Thalassemia

Title	Author	Method	Result
Predisposing Factors to Infections in Thalassemia Syndrome Patients	(Mansory et al. 2025)	A retrospective analysis was conducted on 303 patients with thalassemia at a tertiary care center from 2007 to 2022.	A retrospective analysis of 303 patients demonstrated that markedly elevated ferritin levels—particularly values exceeding 2,500 ng/mL—were strongly associated with an increased incidence of infections, including pneumonia, Gram-negative bacterial infections, and sepsis
Differential gut microbiota composition in β-Thalassemia patients and its correlation with iron overload	(Nonejuie et al. 2024)	A cross-sectional analysis of fecal microbiota of 70 non-transfusion-dependent β-thalassemia/HbE patients and 30 healthy controls.	A cross-sectional microbiota study revealed that β-thalassemia patients with iron overload exhibited significant gut dysbiosis, characterized by an overrepresentation of *Enterobacteriaceae* and heightened intestinal inflammation, thereby increasing susceptibility to infection
Iron Status in Newly Diagnosed *β*-Thalassemia Major: High Rate of Iron Status due to Erythropoiesis Drive	(Susanah et al. 2021)	A case-control study which included 41 children with *β*-thalassemia major.	Among newly diagnosed β-thalassemia major patients, ferritin levels were elevated even prior to substantial transfusion exposure, likely driven by erythropoietic activity and inflammation. This early ferritin elevation may contribute to increased infection risk from the onset of disease
Ferritin thresholds for cardiac and liver hemosiderosis in β-thalassemia patients: a diagnostic accuracy study	(Darvishi-Khezri et al. 2022)	T2*-weighted magnetic resonance imaging (T2*-weighted MRI) was applied to determine cardiac and liver hemosiderosis on 1959 β-thalassemia patients in Iran	In a large MRI-based diagnostic accuracy study involving 1,959 patients, higher ferritin levels correlated with cardiac and hepatic hemosiderosis. Resultant organ dysfunction may further predispose patients to infection through impaired immune and metabolic regulation.
Iron overload and liver function in patients with beta thalassemia major: A cross sectional study	(Faruqi et al. 2024)	A cross-sectional study on 135 patients of beta thalassemia major receiving transfusions at Islamabad Medical and Dental College	A cross-sectional study of 135 patients found that elevated ferritin levels were accompanied by increased AST/ALT and hepatic inflammation, indicating iron overload that may augment vulnerability to infectious complications.
Neutrophil Diversity (Immature, Aged, and Low-Density Neutrophils) and Functional Plasticity: Possible Impacts of Iron Overload in β-Thalassemia	(Sae-Khow, Charoensappakit, and Leelahavanichkul 2024)	Blood samples from β-thalassemia patients and healthy controls were analyzed via flow cytometry and functional assays to assess neutrophil subtypes and functions	Patients showed increased immature and low-density neutrophils with impaired chemotaxis, phagocytosis, ROS production, and NET formation, indicating iron-overload–induced neutrophil dysfunction
Effects of Splenectomy on Natural Killer Cell Levels in β-	(Kurtoğlu et al. 2024)	Case control study comparing splenectomized and non-splenectomized β-thalassemia major patients	The study reported differences in immune-cell profiles between groups, with NK cell levels notably lower in the splenectomized group

Thalassemia Major Patients		with a healthy control group. Serum ferritin was measured, and immune profiles were evaluated using flow cytometry, including T-lymphocyte markers (CD3+, CD4+, CD8+) and natural killer (NK) cells (CD3−/CD16+CD56+).	compared with controls, indicating that splenectomy may further modify immune status in β-thalassemia major.
Exploring alterations of gut/blood microbes in addressing iron overload-induced gut dysbiosis and cognitive impairment in thalassemia patients	(Suparan et al. 2024)	A cross-sectional study recruiting 60 participants (healthy controls, transfusion-dependent thalassemia, and non-transfusion-dependent thalassemia) to evaluate iron overload (serum ferritin), cognition, and gut and blood microbiome profiles.	Most thalassemia patients exhibited gut dysbiosis and around 25% developed minor cognitive impairment; serum ferritin levels were negatively correlated with cognitive scores, suggesting iron overload is associated with microbiota imbalance and systemic effects that may contribute to clinical vulnerability.
The gut microbiota metabolite trimethylamine-N-oxide in children with β-thalassemia: potential implication for iron-induced renal tubular dysfunction	(Ghalwash et al. 2025)	A case-control study enrolling 40 children with transfusion-dependent β-thalassemia major and 40 healthy controls. Biomarkers assessed included serum TMAO, fecal short-chain fatty acids, oxidative stress and inflammatory biomarkers, TMAO-regulated proteins (SIRT1 and HMGB1), and renal tubular dysfunction biomarkers; correlation and regression analyses were performed.	Patients showed iron overload with elevated renal tubular dysfunction biomarkers and higher serum TMAO, alongside lower fecal SCFAs. Correlation analysis supported a close relationship between circulating ferritin, TMAO, and renal dysfunction, indicating iron overload may contribute to organ dysfunction and increased clinical vulnerability.
Alteration of monocyte subsets and their functions in thalassemia patients	(Piyajaroenkij et al. 2023)	A case-control study including 78 thalassemia patients and 26 controls. Monocyte subsets were analyzed by flow cytometry, while monocyte-derived TNF-α expression was measured using qRT-PCR and ELISA (with subgroup comparisons, including splenectomy status).	Thalassemia groups showed significantly reduced monocyte-derived TNF-α and a decreased proportion of non-classical monocytes compared to controls, indicating impaired innate immune function that may weaken host defense against infections.

Across the reviewed evidence, iron overload is linked to altered lymphocyte profiles and impaired innate immune responses, including changes in neutrophil and monocyte function, which may weaken host defense. In addition, emerging evidence suggests that iron overload may also contribute to microbiota dysregulation and related metabolic changes, which can further influence systemic inflammation and infection susceptibility. Studies comparing splenectomized and non-splenectomized patients highlight differences in immune cell distributions, suggesting that splenectomy may further modify immune status in β-thalassemia patients. Moreover, organ dysfunction associated with iron burden has been reported as a

potential downstream effect that may aggravate clinical vulnerability in this population. Overall, the findings support ferritin as a clinically relevant marker in this population; however, its interpretation should consider inflammatory status and other clinical factors that may influence ferritin levels.

DISCUSSION

Iron overload is a hallmark complication of transfusion-dependent β-thalassemia and is routinely monitored in clinical practice by measuring serum ferritin. While ferritin is widely recognized as an indicator of total body iron stores an accumulating body of evidence suggests that its elevation is not merely a static marker of iron burden but also reflects pathological processes that may predispose patients to increased risk of infection (Mishra and Tiwari 2013; Saliba and Taher 2015; Taher and Saliba 2017). Taken together, the included studies highlight a multifaceted interplay between iron homeostasis and host immune defense, with ferritin serving as a central reference point in describing these interactions (Obeagu 2025).

From a clinical standpoint, multiple observational studies reinforce the association between elevated ferritin and infection burden in β-thalassemia. Mansory et al. observed that transfusion-dependent β-thalassemia patients with ferritin levels above 2,500 ng/mL experienced a significantly higher incidence of infectious complications compared to those with lower ferritin levels (Mansory et al. 2025). The infections encountered in this cohort were predominantly pulmonary and systemic, which is consistent with the tendency of several Gram-negative pathogens to thrive in iron-rich environments (Fokam et al. 2020; Kramer, Ozkaya, and Kümmerli 2019). The retrospective nature of this analysis spanning fifteen years enhances its generalizability, highlighting that infection risk is not an episodic phenomenon but a persistent concern across the disease continuum. This supports the view that infection risk in β-thalassemia may persist across the disease course rather than occurring as isolated episodes.

While observational studies establish associations, mechanistic investigations provide insights into the biological underpinnings of these clinical outcomes. Nonejuie et al. demonstrated that iron overload is associated with significant alterations in gut microbiota composition. Specifically, they reported an overrepresentation of *Enterobacteriaceae* and other pro-inflammatory taxa in β-thalassemia patients with elevated ferritin. Such dysbiosis is implicated in compromised intestinal barrier integrity, favouring the translocation of bacterial endotoxins into systemic circulation (Nonejuie et al. 2024). This may contribute to chronic inflammation and immune dysregulation, which can paradoxically increase susceptibility to infections rather than providing protection (Liao et al. 2025). Consistent with this, Suparan et al. also reported gut and blood microbiome alterations in transfusion-dependent and non-transfusion-dependent thalassemia patients and observed that higher serum ferritin was associated with adverse systemic outcomes, supporting the possibility that iron overload-related dysbiosis may contribute to downstream inflammation and clinical vulnerability (Suparan et al. 2024).

Experimental models further extend our understanding of how iron overload translates into infectious vulnerability. Sae-Khow et al. showed that β-thalassemia patients have increased immature and low-density neutrophils alongside significant impairments in chemotaxis, phagocytosis, ROS production, and NET formation. In-vitro iron exposure reproduced these defects in healthy neutrophils, indicating that iron overload directly contributes to neutrophil dysfunction and heightened infection susceptibility (Sae-Khow, Charoensappakit, and Leelahavanichkul 2024). In addition, Kurtoğlu et al. (2024) reported differences in immune-cell profiles between splenectomized and non-splenectomized β-thalassemia major patients, with NK cell levels notably lower in the splenectomized group compared with controls, suggesting that splenectomy may further modify immune status and potentially weaken

immune surveillance (Kurtoğlu et al. 2024). This is consistent with broader evidence that splenectomy can be associated with clinically relevant immune alterations in thalassemia, particularly in the setting of iron overload and chronic inflammation (Asadov and Aliyeva 2025). Beyond neutrophil impairment, Piyajaroenkij et al. identified alterations in monocyte subsets and reduced monocyte-derived TNF-α in thalassemia patients, indicating impaired innate immune function that may weaken host defense and reduce pathogen clearance capacity (Piyajaroenkij et al. 2023).

Beyond immunological mechanisms, organ dysfunction plays a pivotal role in modulating infection susceptibility. Darvishi-Khezri et al. conducted a large T2*-weighted MRI study involving 1,959 β-thalassemia patients to delineate the relationship between ferritin and organ-specific iron deposition. Elevated ferritin strongly correlated with cardiac and hepatic hemosiderosis, conditions closely associated with cardiac arrhythmias, congestive heart failure, and hepatic fibrosis (Darvishi-Khezri et al. 2022). Faruqi et al. supported these conclusions, where ferritin elevation paralleled increased transaminases and markers of hepatic inflammation. Chronic hepatic stress may reduce metabolic and immunological reserve, creating a more permissive environment for infections (Faruqi et al. 2024). Susanah et al. observed that even newly diagnosed β-thalassemia major patients, before considerable transfusional iron loading, manifested elevated ferritin levels. This aligns with the intrinsic pathophysiology of thalassemia, where ineffective erythropoiesis and marrow expansion can drive increased intestinal iron absorption (Susanah et al. 2021). Importantly, organ involvement may extend beyond the heart and liver: Ghalwash et al. described renal tubular dysfunction in children with transfusion-dependent β-thalassemia and reported close relationships between circulating ferritin, microbiota-derived metabolites, and renal dysfunction biomarkers, suggesting kidney injury as an additional pathway that may aggravate overall clinical vulnerability (Ghalwash et al. 2025).

Taken together, these findings paint a cohesive narrative: iron overload, reflected by elevated ferritin, is not merely a static indicator of iron burden but may contribute to immune dysfunction and increased infection susceptibility (Liao et al. 2025). Several interrelated mechanisms likely contribute to this phenomenon. First, iron serves as a critical nutrient for many pathogenic bacteria; increased extracellular iron may directly enhance microbial proliferation and virulence (Kramer, Ozkaya, and Kümmerli 2019; Nairz and Weiss 2020). Second, iron overload perturbs mucosal barriers and microbiota composition, facilitating microbial translocation and systemic inflammation (Chen et al. 2025; Nonejuie et al. 2024). Third, iron-induced oxidative stress impairs critical immune cell functions and may diminish antigen-specific responses, thereby reducing pathogen clearance capacity (Asadov and Aliyeva 2025; Sae-Khow, Charoensappakit, and Leelahavanichkul 2024). Fourth, organ dysfunction, particularly hepatic and cardiac, can attenuate systemic defenses and disrupt metabolic processes essential for effective immunity (Faruqi et al. 2024; Liu et al. 2023).

In addition, studies comparing splenectomized and non-splenectomized patients highlight differences in immune cell distributions, suggesting that splenectomy may further modify immune status in β-thalassemia. Overall, the findings support ferritin as a clinically relevant marker in this population; however, its interpretation should consider inflammatory status and other clinical factors that may influence ferritin levels. Recent evidence strengthens the mechanistic links outlined above by demonstrating (i) microbiota dysregulation associated with ferritin elevation (Suparan et al. 2024), (ii) broader innate immune impairment beyond neutrophils, including monocyte functional alterations (Piyajaroenkij et al. 2023), and (iii) renal tubular dysfunction as a potential downstream consequence of iron overload (Ghalwash et al. 2025).

CONCLUSION

Elevated ferritin levels in β-thalassemia are associated with a higher susceptibility to infections. The reviewed evidence suggests that iron overload may contribute to infection risk through multiple pathways, including impaired immune defenses (e.g., altered neutrophil function and immune-cell profiles), enhanced iron availability for siderophilic bacteria, gut microbiota dysregulation, and iron-related organ dysfunction. These findings also highlight the limitation of using ferritin as the sole indicator of iron burden, since ferritin can be influenced by concurrent inflammation, hepatic injury, and other metabolic disturbances. Therefore, ferritin should be interpreted alongside clinical assessment and complementary markers of inflammation, immune status, and organ involvement to better identify vulnerable patients. Optimizing iron chelation remains a cornerstone of management and may help reduce iron deposition while potentially improving downstream immune and microbiota-related disturbances. Future prospective and interventional studies are needed to clarify causality and to evaluate whether adjunct strategies such as gut microbiome modulation can provide additional clinical benefit.

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