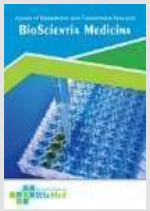
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Iron Deficiency and Anemia of Inflammation in Tuberculosis: A Systematic Review of the Evidence

Deddy Herman[1*], Rizanda Machmud[2], Nur Indrawaty Lipoeto[2]

[1]Department of Pulmonology and Respiratory Medicine, Doctoral Programme in Public Health, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

[2]Department of Public Health and Community Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

ARTICLE INFO

Keywords:
Anemia
Anemia of inflammation
Iron deficiency
Systematic review
Tuberculosis

***Corresponding author:**
Deddy Herman

E-mail address:
deddykaterine@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v9i2.1207

A B S T R A C T

Background: Tuberculosis (TB) remains a major global health problem, with anemia being a frequent comorbidity. Anemia in TB is multifaceted, with iron deficiency and anemia of inflammation (AI) being the most common types. This systematic review aims to synthesize the evidence on iron deficiency and AI in TB, their prevalence, impact on outcomes, and management strategies. **Methods**: A systematic search of PubMed and ScienceDirect databases was conducted for articles published in the last 10 years. Observational studies examining the prevalence, types, and impact of anemia on TB outcomes were included. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. **Results**: The review included 7 studies involving 1,133 participants. Anemia prevalence ranged from 61% to 89% in TB patients. AI was the predominant type, with iron deficiency also prevalent. Anemia was associated with increased mortality, delayed sputum culture conversion, and impaired TB treatment response. **Conclusion**: Anemia, primarily AI and iron deficiency, is highly prevalent in TB and negatively impacts treatment outcomes and survival. Effective management of anemia is crucial for improving TB outcomes. Further research is needed to optimize diagnostic and treatment strategies for iron deficiency and AI in TB.

1. Introduction

Tuberculosis (TB), an infectious disease primarily caused by Mycobacterium tuberculosis, continues to pose a significant global health challenge. The World Health Organization (WHO) estimates that approximately 10.6 million people contracted TB in 2021, leading to 1.6 million deaths. This persistent prevalence underscores the urgent need for comprehensive strategies to control and manage TB effectively. Anemia, a prevalent comorbidity in TB patients, further complicates the disease's trajectory and prognosis. Characterized by a reduction in red blood cells or hemoglobin levels, anemia compromises the body's capacity to transport oxygen, resulting in fatigue, weakness, and shortness of breath. The presence of anemia in TB patients is notably higher than in healthy individuals or those infected with M.tb but without active disease. This disparity points to the complex interplay between TB and anemia, warranting in-depth investigation. Anemia in TB is not a monolithic entity; it encompasses various types, each with unique etiologies and implications. Among these, iron deficiency anemia (IDA) and anemia of inflammation (AI) are the most prevalent.[1-4]

IDA arises from insufficient iron stores to support red blood cell production. Iron is a critical component

of hemoglobin, the protein responsible for oxygen transport. When iron stores are depleted, hemoglobin production falters, leading to reduced oxygen-carrying capacity and the onset of anemia. In TB patients, iron deficiency can stem from several factors, including malnutrition, malabsorption, and the inflammatory response to the infection. AI, also known as anemia of chronic disease, is a complex form of anemia that develops in the presence of chronic inflammation, a hallmark of TB. The inflammatory response disrupts iron metabolism, hindering iron utilization for red blood cell production. Additionally, inflammation can suppress erythropoietin production, a hormone that stimulates red blood cell formation. This intricate interplay between inflammation and iron regulation contributes to the development of AI in TB patients.[5-7]

The presence of anemia, particularly IDA and AI, in TB patients carries significant clinical implications. It can impair treatment response, increasing the risk of treatment failure and prolonged treatment duration. Moreover, anemia is associated with a higher risk of mortality and a diminished quality of life in TB patients. The fatigue, weakness, and decreased physical performance associated with anemia can significantly impede daily activities and overall well-being. Given the substantial prevalence and detrimental effects of anemia in TB, a comprehensive understanding of its various facets is crucial.[8-10] This systematic review focuses specifically on IDA and AI in TB, aiming to provide a thorough analysis of their prevalence, impact on TB outcomes, and current management strategies.

2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring a rigorous and transparent approach to literature synthesis. A comprehensive search strategy was implemented to identify relevant studies investigating iron deficiency anemia (IDA) and anemia of inflammation (AI) in tuberculosis (TB) patients. Two prominent electronic databases, PubMed and ScienceDirect, were systematically searched to capture a broad range of published literature. These databases were selected for their extensive coverage of biomedical and scientific research, ensuring the inclusion of diverse studies relevant to the review's objectives. The search strategy employed a combination of keywords and Medical Subject Headings (MeSH) terms to maximize the retrieval of pertinent articles. The following search terms were utilized: "tuberculosis," "TB," "anemia," "iron deficiency anemia," "IDA," "anemia of inflammation," "AI," "anemia of chronic disease," "ACD," and their various combinations. This comprehensive search string aimed to capture all studies examining the interplay between TB and anemia, specifically focusing on IDA and AI. The search was limited to articles published in the last 10 years (2014-2024), ensuring the inclusion of recent and up-to-date evidence. This timeframe was chosen to reflect the contemporary understanding and management of anemia in TB, considering the evolving landscape of medical research and clinical practice.

The study selection process followed a two-stage approach: title/abstract screening and full-text review. Initially, all identified articles from the database searches were screened based on their titles and abstracts. This preliminary screening aimed to exclude studies that were clearly irrelevant to the review's objectives, such as those focusing on other types of anemia or those not related to TB. Following the initial screening, full-text articles of the remaining potentially relevant studies were retrieved and assessed for eligibility. The inclusion criteria were as follows; Study design: Observational studies, including cross-sectional, case-control, and cohort studies, were considered. These study designs are suitable for investigating the prevalence and impact of anemia in TB patients; Population: Studies involving human subjects diagnosed with TB were included; Intervention/Exposure: The presence of anemia, specifically IDA and/or AI, was considered as the exposure or intervention of interest; Outcomes: Studies reporting on the prevalence of IDA and/or AI

in TB patients, the impact of anemia on TB treatment outcomes (e.g., treatment response, mortality), and/or the management strategies for anemia in TB were included. Studies that did not meet the inclusion criteria were excluded from the review. The exclusion criteria included; Study design: Reviews, editorials, case reports, and studies with insufficient data were excluded; Population: Studies not involving TB patients or those focusing on other types of anemia were excluded; Outcomes: Studies not reporting on the prevalence, impact, or management of IDA and/or AI in TB were excluded.

Data extraction was performed using a standardized data extraction form. This form was developed to ensure consistency and completeness in data collection across all included studies. The following information was extracted from each study; Study characteristics: Author(s), year of publication, study design, study setting, sample size, and participant characteristics (e.g., age, sex, TB type); Anemia assessment: Methods used to diagnose anemia and classify anemia types (IDA, AI); Prevalence of anemia: The proportion of TB patients with anemia, IDA, and AI; Impact of anemia: The association between anemia (IDA, AI) and TB treatment outcomes, including treatment response, mortality, and quality of life; Management strategies: Interventions used to manage anemia in TB patients, including iron supplementation, erythropoiesis-stimulating agents, and blood transfusion.

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies. The NOS is a widely used tool to evaluate the risk of bias in observational studies, considering factors such as selection of study groups, comparability of groups, and ascertainment of outcomes. Each study was assessed on three domains: selection, comparability, and outcome. Studies were assigned a star rating for each item within the domains, with a higher score indicating better quality.

A narrative synthesis approach was employed to synthesize the findings of the included studies. This approach involves summarizing and interpreting the results of individual studies in a descriptive manner, considering the heterogeneity in study designs, populations, and outcomes. The narrative synthesis focused on describing the overall prevalence of IDA and AI in TB patients, their impact on TB treatment outcomes, and the current management strategies.

3. Results

Figure 1 visually represents the process of identifying and selecting studies for inclusion in the systematic review on iron deficiency anemia (IDA) and anemia of inflammation (AI) in tuberculosis (TB). The initial search across PubMed and ScienceDirect databases yielded a substantial pool of 1,490 records. This highlights the extensive literature search conducted to capture a wide range of potentially relevant studies. After removing duplicates, 1,135 records remained. Titles and abstracts of these records were screened for relevance to the review's focus on IDA and AI in TB, resulting in 66 records being excluded. This step ensured that only studies with a clear focus on the topic were considered further. Full-text articles of the remaining 13 records were assessed for eligibility based on pre-defined inclusion and exclusion criteria. This rigorous evaluation considered factors such as study design, population, and reported outcomes. 6 articles were excluded at this stage for various reasons, such as not meeting the study design criteria (e.g., reviews, case reports) or not focusing on the relevant types of anemia. Ultimately, 7 studies met all the inclusion criteria and were included in the systematic review. These studies formed the basis for the analysis and synthesis of evidence on the prevalence, impact, and management of IDA and AI in TB.

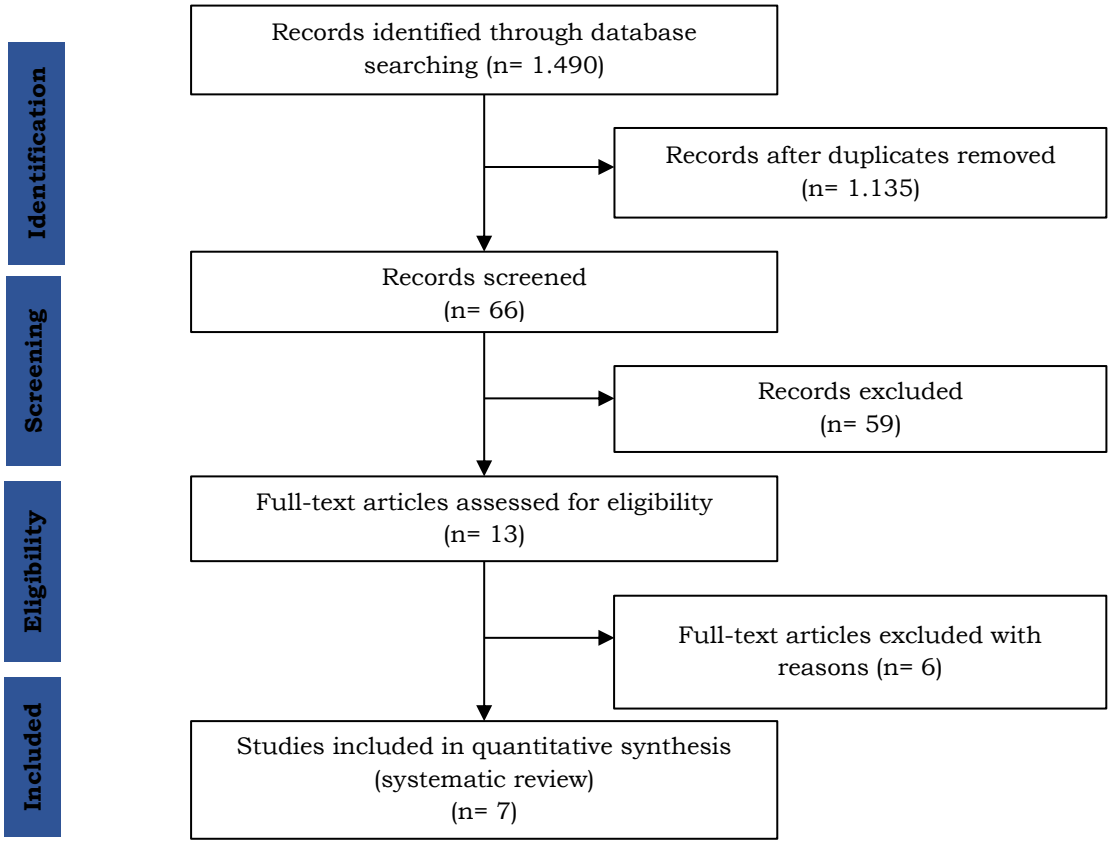


Figure 1. PRISMA flow diagram.

Table 1 provides a concise summary of the key characteristics of the seven studies included in the systematic review on iron deficiency anemia (IDA) and anemia of inflammation (AI) in tuberculosis (TB). The studies span a diverse geographical range, including Brazil (two studies), Gambia, India, China, and Pakistan. This diversity enhances the generalizability of the findings and provides insights into potential regional variations in the prevalence and management of anemia in TB. The majority of the studies employed a retrospective design (4 out of 7), with two studies using a prospective cross-sectional design and one a case-control design. This mix of study designs allows for a comprehensive understanding of the research question, with each design offering unique strengths and limitations. The sample sizes vary across the studies, ranging from 109 to 258 participants. While some studies have relatively small sample sizes, the overall pool of participants across all studies (1,133) provides a substantial basis for analysis. Two studies were conducted in Brazil, one prospective and one retrospective, both focusing on cross-sectional designs. This suggests a particular interest in this region regarding the topic. Three studies used this design, indicating a focus on examining the impact of anemia on TB outcomes over time. The study by Minchella et al. (2015) utilized a case-control design, which is particularly useful for investigating risk factors associated with anemia in TB.

Table 1. Study characteristics.

No.	Author (Year)	Location	Study design	Sample size
1	Oliveira MG, et al. (2014)	Rio de Janeiro, Brazil	Prospective cross-sectional	166
2	Minchella PA, et al. (2015)	Gambia	Case-contact (TB)/Case-control	131
3	Gil-Santana L, et al. (2019)	Brazil	Retrospective cohort	236 (118 cases, 118 controls)
4	Chhabra S, et al. (2021)	India	Cross-sectional	150
5	Mendonça EB d, et al. (2021)	Rio de Janeiro, Brazil	Retrospective cross-sectional	258
6	Luo M, et al. (2022)	Shanghai, China	Retrospective cohort	155
7	Ahmad S, et al. (2023)	Pakistan	Retrospective cross-sectional	109

Table 2 presents a summary of the prevalence and types of anemia observed across the seven studies included in the systematic review; Prevalence of Anemia: Anemia is highly prevalent in TB patients, with reported rates ranging from 61.2% to 89.1% across the studies. This highlights the significant burden of anemia in this population. There is some variation in prevalence rates, which could be attributed to differences in study populations, diagnostic criteria, and the severity of TB. Study 5 (Mendonça EB d, et al. (2021)) reported the lowest prevalence (61.2%), potentially due to its focus on a specific population or setting; Types of Anemia: AI appears to be the predominant type of anemia in TB patients. Studies 1, 3, and 4 specifically identify AI as the most common type, with prevalence as high as 75.9% in one study. While less prevalent than AI, IDA is also observed in TB patients. Studies 1 and 4 report IDA prevalence, although at lower rates (2.4% and 2.29%, respectively). Study 2 indicates the presence of both AI and IDA in TB patients, sometimes occurring together (AI+IDA). This highlights the complex interplay between these types of anemia in the context of TB. Studies 5 and 7 categorize anemia based on red blood cell morphology (size and color). This provides a different perspective, indicating a significant proportion of normocytic normochromic anemia (which can be associated with AI) and microcytic hypochromic anemia (often indicative of IDA).

Table 2. Prevalence and type of anemia.

No.	Author (Year)	Anemia prevalence	Type of anemia
1	Oliveira MG, et al. (2014)	89.1%	AI (75.9%), IDA (2.4%)
2	Minchella PA, et al. (2015)	67%	AI, IDA, AI+IDA
3	Gil-Santana L, et al. (2019)	88.9%	AI
4	Chhabra S, et al. (2021)	85.7% (Extrapulmonary TB), 88.5% (Pulmonary TB)	AI (97.17%), IDA (2.29%)
5	Mendonça EB d, et al. (2021)	61.2%	Normochromic normocytic (60.8%), Microcytic hypochromic (27.8%)
6	Luo M, et al. (2022)	-	-
7	Ahmad S, et al. (2023)	82.56%	Microcytic (83.20%), Normocytic (11.20%), Macrocytic (5.60%)

Table 3 focuses on the impact of anemia on tuberculosis (TB) treatment outcomes, drawing from two of the studies included in the systematic review; Study 1 (Mendonça EB d, et al. (2021)): This study found a statistically significant association ($p = \leq 0.05$) between anemia and several adverse factors in TB patients: Anemia may contribute to or be a marker of more severe TB disease, leading to significant weight

loss. Anemia could increase the risk of complications and the need for hospitalization in TB patients. Anemia may be more prevalent in TB patients co-infected with HIV, potentially due to the combined impact on the immune system. Microcytosis refers to smaller-than-normal red blood cells, often seen in IDA, indicating a potential link between iron deficiency and worse TB outcomes. High platelet count could reflect an inflammatory response associated with both anemia and TB, potentially influencing disease progression; Study 2 (Luo M, et al. (2022)): This study compared TB patients with anemia (TB-A group) to those without anemia. The TB-A group showed poorer improvement in lung injury during TB treatment, specifically in Slower healing of cavities (air-filled spaces) in the lungs, indicating a less effective treatment response. Less reduction in lung fluid, suggesting persistent inflammation and potentially slower recovery.

Table 3. Impact of anemia on TB outcomes.

No.	Author (Year)	Impact of anemia on TB outcomes
1	Mendonça EB d, et al. (2021)	Anemia was significantly associated (p = ≤0.05) with a history of weight loss >10%, hospitalization, Human immunodeficiency virus (HIV) infection, microcytosis, and high platelet count.
2	Luo M, et al. (2022)	The TB-A group (n = 66) had worse lung injury improvement in terms of cavity closure (4.7 ± 3.59 vs 10.56 ± 7.42; p = 0.036) and fluid improvement [4 (30.77%) vs 12 (92.31%); p = 0.001] during conventional treatment.

4. Discussion

The high prevalence of anemia observed in this systematic review is indeed a critical finding, and it aligns with a growing body of evidence demonstrating the significant association between tuberculosis (TB) and anemia. Anemia, a condition characterized by a deficiency of red blood cells or hemoglobin, compromises the body's capacity to transport oxygen, leading to fatigue, weakness, and shortness of breath. In the context of TB, anemia is particularly concerning as it can exacerbate the already debilitating effects of the disease and hinder treatment outcomes. A meta-analysis of 36 studies, conducted to assess the global prevalence of anemia in TB patients, reported a pooled prevalence rate of 53%. However, the prevalence rates observed in this systematic review ranged from 61% to 89%, slightly higher than the pooled estimate from the meta-analysis. This discrepancy could be attributed to several factors, including differences in study selection, diagnostic criteria, and the severity of TB in the included studies. TB is characterized by chronic inflammation, which disrupts iron metabolism and erythropoiesis (red blood cell production). Inflammatory cytokines, such as interferon-gamma and tumor necrosis factor-alpha, increase the production of hepcidin, a hormone that regulates iron absorption and release. Elevated hepcidin levels lead to reduced iron availability for erythropoiesis, contributing to anemia. TB can lead to malnutrition and malabsorption, further compromising iron intake and utilization. Patients with TB often experience loss of appetite, nausea, and vomiting, which can lead to inadequate dietary iron intake. Additionally, TB can affect the gastrointestinal tract, impairing the absorption of nutrients, including iron. The body's demand for iron increases during infection to support immune function and tissue repair. In TB, the chronic inflammatory state and ongoing immune response can further increase iron requirements, potentially exceeding dietary intake and leading to iron deficiency. Some TB medications, such as isoniazid and rifampicin, can interfere with iron absorption and

utilization, further contributing to anemia. The studies included in this review were carefully selected based on specific inclusion and exclusion criteria, focusing on research conducted in the last 10 years (2014-2024). This timeframe ensured the inclusion of recent and up-to-date evidence, reflecting contemporary understanding and management of anemia in TB. The selected studies varied in terms of geographical locations, including Brazil, Gambia, India, China, and Pakistan. The prevalence of anemia can vary across different regions due to factors such as socioeconomic status, nutritional habits, and genetic predisposition. The studies employed different study designs, including prospective cross-sectional, case-control, and retrospective cohort studies. Each study design has inherent strengths and limitations that can influence the reported prevalence of anemia. The sample sizes varied across the studies, ranging from 109 to 258 participants. Larger sample sizes generally provide more accurate estimates of prevalence. The diagnostic criteria used to define anemia can also influence prevalence rates. Different studies may use varying hemoglobin threshold values to diagnose anemia, leading to variations in reported prevalence. The World Health Organization (WHO) defines anemia as hemoglobin levels below 13 g/dL in men and below 12 g/dL in women. However, some studies may use lower thresholds, particularly in populations with a high prevalence of anemia. Additionally, the severity of TB can impact the prevalence of anemia. Patients with more severe TB, such as those with extensive pulmonary involvement or extrapulmonary TB, may be more likely to develop anemia due to factors such as malnutrition, malabsorption, and the inflammatory response to the infection. The higher prevalence rates observed in this review compared to the meta-analysis could also be attributed to an increased awareness and recognition of anemia in TB patients. Healthcare professionals are becoming more vigilant in screening for anemia in TB patients, leading to earlier detection and potentially higher reported prevalence rates. This increased awareness is crucial as anemia can significantly impact TB treatment outcomes and overall prognosis. The high prevalence of anemia in TB patients underscores the urgent need to address anemia as an integral part of TB management. Anemia can impair treatment response, increase the risk of treatment failure, and prolong treatment duration. Moreover, anemia is associated with a higher risk of mortality and a diminished quality of life in TB patients. To effectively manage anemia in TB patients, a multifaceted approach is required. Healthcare professionals should be vigilant in screening for anemia in all TB patients, using appropriate diagnostic criteria and tools. Determining the specific type of anemia (iron deficiency, anemia of inflammation, or other types) is crucial for targeted management. Addressing the underlying cause of anemia, such as iron deficiency or chronic inflammation, is essential for effective management. Providing supportive care, such as nutritional counseling and lifestyle modifications, can help improve anemia symptoms and overall quality of life. By addressing anemia as an integral part of TB management, healthcare professionals can improve treatment outcomes, reduce mortality, and enhance the quality of life for TB patients. The high prevalence of anemia in TB patients highlighted in this systematic review emphasizes the need for increased awareness, early detection, and effective management strategies to combat this significant comorbidity.[11,12]

This systematic review has shed light on the prevalent types of anemia in tuberculosis (TB) patients, specifically Anemia of Inflammation (AI) and Iron Deficiency Anemia (IDA). This finding is consistent with the understanding that chronic inflammation, a hallmark of TB, disrupts iron metabolism and erythropoiesis, leading to AI. AI, also known as anemia of chronic disease, is a complex form of anemia that develops in the presence of chronic inflammation, such as that seen in TB. The inflammatory response disrupts iron homeostasis, the delicate balance of iron absorption, transport, and utilization. This disruption leads to reduced iron availability for erythropoiesis, resulting in anemia. TB

is characterized by chronic inflammation, which disrupts iron metabolism and erythropoiesis (red blood cell production). Inflammatory cytokines, such as interferon-gamma and tumor necrosis factor-alpha, increase the production of hepcidin, a hormone that regulates iron absorption and release. Elevated hepcidin levels lead to reduced iron availability for erythropoiesis, contributing to anemia. One of the key players in AI is hepcidin, a hormone that regulates iron metabolism. Hepcidin inhibits iron absorption from the gut and iron release from macrophages, the immune cells responsible for storing and recycling iron. During inflammation, hepcidin levels increase, leading to reduced iron availability for erythropoiesis. In addition to its effects on iron metabolism, inflammation can also suppress erythropoietin (EPO) production. EPO is a hormone produced by the kidneys that stimulates red blood cell production. When EPO levels are suppressed, erythropoiesis is impaired, further contributing to anemia. IDA arises from insufficient iron stores to support red blood cell production. Iron is a critical component of hemoglobin, the protein responsible for oxygen transport. When iron stores are depleted, hemoglobin production falters, leading to reduced oxygen-carrying capacity and the onset of anemia. TB can lead to malnutrition and loss of appetite, resulting in inadequate dietary iron intake. TB can affect the gastrointestinal tract, impairing the absorption of nutrients, including iron. The body's demand for iron increases during infection to support immune function and tissue repair. In TB, the chronic inflammatory state and ongoing immune response can further increase iron requirements, potentially exceeding dietary intake and leading to iron deficiency. Some TB medications, such as isoniazid and rifampicin, can interfere with iron absorption and utilization, further contributing to anemia. The complex interplay between inflammation, iron deficiency, and erythropoiesis underscores the need for a comprehensive approach to diagnose and manage anemia in TB patients. Differentiating between AI and IDA can be challenging, as they can coexist and share similar features. However, distinguishing between these types of anemia is crucial for effective management. For AI, the primary focus should be on treating the underlying inflammation driving the anemia. While iron supplementation may seem intuitive, it is often not beneficial for AI and could potentially have adverse effects. In some cases, iron supplementation may exacerbate inflammation and worsen TB outcomes. For IDA, oral iron supplementation is typically the first-line treatment. However, the absorption of oral iron can be impaired in the presence of inflammation, and some patients may experience gastrointestinal side effects. In such cases, intravenous iron administration may be considered to ensure adequate iron delivery. In addition to iron supplementation, other management strategies may include erythropoiesis-stimulating agents (ESAs) and blood transfusions. ESAs can stimulate red blood cell production, but their use in TB patients is controversial due to potential safety concerns and limited evidence of benefit. Blood transfusions may be necessary in cases of severe anemia to rapidly improve oxygen delivery and stabilize the patient.[13,14]

The detrimental effects of anemia on TB outcomes are a significant concern, and understanding these effects is crucial for effective TB management. Anemia is associated with a higher risk of death in TB patients. Anemia reduces the oxygen-carrying capacity of the blood, leading to decreased oxygen delivery to tissues. This can impair the function of vital organs and compromise the body's ability to fight infection, making TB patients more susceptible to severe disease and complications. Oxygen is crucial for the optimal functioning of immune cells, particularly those involved in combating TB infection. Anemia can impair the function of these cells, hindering the body's ability to control the infection and promote healing. TB itself can cause systemic effects such as fever, night sweats, and weight loss. Anemia can exacerbate these effects, further weakening the body and making it more difficult to recover from the disease. Anemia can delay the time it takes for a TB patient's sputum culture to

become negative, indicating persistent infection. A delayed sputum culture conversion suggests that the TB bacteria are still present and actively replicating, necessitating a longer treatment duration to ensure complete eradication of the infection. Patients with persistent positive sputum cultures are more likely to transmit TB to others, as the bacteria are still present in their respiratory secretions. Prolonged treatment duration increases the risk of the TB bacteria developing resistance to the medications used, making treatment more challenging and potentially leading to treatment failure. Anemia can impede the healing process of lung injury caused by TB. Cavities, or air-filled spaces, can form in the lungs due to TB infection. Anemia can slow down the closure of these cavities, indicating less effective treatment response and potentially leading to chronic lung problems. Anemia can hinder the clearance of fluid from the lungs, suggesting persistent inflammation and potentially slower recovery. This can lead to prolonged respiratory symptoms and decreased lung function. In some cases, persistent lung inflammation can lead to fibrosis, or scarring of the lung tissue. Anemia may increase the risk of fibrosis, further compromising lung function and overall health. Anemia's adverse effects on TB outcomes are multifaceted, stemming from a complex interplay of physiological and immunological factors. Anemia fundamentally disrupts the body's ability to transport oxygen efficiently. With fewer red blood cells or a lower hemoglobin concentration, the blood carries less oxygen, leading to decreased oxygen delivery to tissues and organs. Oxygen is vital for cellular respiration, the process by which cells generate energy. Insufficient oxygen supply compromises cellular function, affecting energy production and metabolic processes critical for overall health and immune response. Immune cells, particularly those involved in combating infections like TB, rely heavily on oxygen for optimal function. Reduced oxygen delivery can impair the activity of macrophages and lymphocytes, key players in the immune response against TB. This can hinder the body's ability to control the infection, leading to more severe disease and complications. Oxygen is crucial for the proliferation and activation of T cells, a type of white blood cell that plays a central role in cell-mediated immunity. T cells are essential for recognizing and destroying TB bacteria within infected cells. Anemia can impair T cell function, weakening the body's ability to contain the infection. Macrophages, another type of white blood cell, engulf and destroy TB bacteria through a process called phagocytosis. This process requires energy and oxygen. Anemia can reduce the efficiency of phagocytosis, allowing the bacteria to survive and multiply within macrophages. Cytokines are signaling molecules that regulate immune responses. Anemia can affect the production and balance of cytokines, potentially disrupting the coordinated immune response needed to control TB infection. Anemia-induced fatigue and weakness are not merely inconveniences, they reflect a fundamental energy deficit at the cellular level. Reduced oxygen delivery compromises energy production, leaving patients feeling tired and weak. Fatigue and weakness can limit physical activity and daily functioning. This can further contribute to a cycle of debilitation, making it challenging for patients to maintain their overall health and well-being. The fatigue and weakness associated with anemia can make it difficult for patients to adhere to their TB medication regimen. Consistent medication intake is crucial for successful TB treatment, and any disruption can lead to prolonged treatment duration, treatment failure, and the development of drug-resistant TB. Recovery from TB involves repairing damaged tissues, particularly in the lungs. This repair process requires adequate oxygen and nutrients. Anemia can hinder tissue repair by limiting oxygen supply and compromising cellular function. Anemia can prolong the overall convalescence period, or the time it takes to recover from TB. This can delay the return to normal activities and overall well-being. Delayed recovery can increase the risk of developing long-term complications from TB, such as lung fibrosis (scarring) and pulmonary hypertension (high blood pressure in the arteries of

the lungs). Addressing anemia in TB patients is crucial for improving treatment adherence, enhancing immune function, and ultimately leading to better treatment outcomes. By improving the oxygen-carrying capacity of the blood and supporting immune function, managing anemia can help TB patients better tolerate treatment, fight infection more effectively, and experience faster recovery. Anemia can cause significant fatigue and weakness, which are already common symptoms of TB. By addressing anemia and improving oxygen delivery to tissues, patients may experience less fatigue and weakness, making it easier for them to carry out daily activities and adhere to their TB medication regimen. Anemia can significantly impact a patient's quality of life, leading to decreased physical and mental well-being. Managing anemia can improve overall quality of life, making it easier for patients to cope with the challenges of TB treatment and adhere to their medications. When patients feel better and experience less fatigue, they are more likely to be motivated to complete their TB treatment course. This improved adherence can lead to better treatment outcomes and reduce the risk of treatment failure and drug resistance. Immune cells, particularly those involved in combating TB infection, require adequate oxygen supply for optimal function. Addressing anemia improves oxygen delivery to these cells, enhancing their ability to fight the infection and promote healing. Phagocytosis, the process by which macrophages engulf and destroy TB bacteria, is an energy-intensive process that requires oxygen. Managing anemia can improve oxygen supply to macrophages, increasing their efficiency in phagocytosis and bacterial clearance. T cells, a type of white blood cell that plays a central role in cell-mediated immunity against TB, also require oxygen for optimal function. Addressing anemia can improve oxygen delivery to T cells, enhancing their ability to recognize and destroy TB bacteria within infected cells. By improving treatment adherence and enhancing immune function, managing anemia can increase the likelihood of successful TB treatment outcomes. This can lead to faster sputum culture conversion, reduced treatment duration, and a lower risk of treatment failure and drug resistance. Anemia can delay recovery from TB by hindering the body's ability to repair damaged tissues and restore normal function. Addressing anemia can improve oxygen delivery and support tissue repair, leading to faster recovery and a quicker return to normal activities. Anemia can increase the risk of developing long-term complications from TB, such as lung fibrosis and pulmonary hypertension. Managing anemia can help reduce the risk of these complications by improving oxygen delivery and supporting immune function. By improving overall health and immune function, addressing anemia can contribute to reduced mortality rates in TB patients.[15-17]

Anemia of inflammation (AI), also referred to as anemia of chronic disease (ACD), is a common type of anemia observed in individuals with chronic inflammatory conditions, including tuberculosis (TB). In TB, the persistent inflammatory state triggered by the infection disrupts the intricate balance of iron metabolism and red blood cell production (erythropoiesis), leading to the development of AI. The inflammatory response associated with TB involves the release of various signaling molecules called cytokines, such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α). These cytokines play a crucial role in orchestrating the immune response against the infection. However, they also disrupt iron homeostasis, the delicate balance of iron absorption, transport, and utilization. One of the key players in AI is hepcidin, a hormone that regulates iron metabolism. Hepcidin inhibits iron absorption from the gut and iron release from macrophages, the immune cells responsible for storing and recycling iron. During inflammation, hepcidin levels increase, leading to reduced iron availability for erythropoiesis. In addition to its effects on iron metabolism, inflammation can also suppress erythropoietin (EPO) production. EPO is a hormone produced by the kidneys that stimulates red blood cell production. When EPO levels are suppressed, erythropoiesis is

impaired, further contributing to anemia. The primary focus in managing AI in TB patients is to address the underlying inflammation driving the anemia. While iron supplementation may seem intuitive, it is often not beneficial for AI and could potentially have adverse effects. In some cases, iron supplementation may exacerbate inflammation and worsen TB outcomes. The most effective way to manage AI is to treat the underlying condition causing the inflammation. In the case of TB, this involves adhering to the prescribed TB medication regimen and completing the full course of treatment. Successful treatment of TB leads to a reduction in inflammation, which in turn can improve anemia. In some cases, anti-inflammatory medication may be used to reduce inflammation and improve anemia. However, the use of anti-inflammatory medication in TB patients should be carefully considered, as it may interfere with the immune response needed to fight the infection. Iron supplementation is generally not recommended for AI, as it may worsen inflammation and TB outcomes. In AI, the body has sufficient iron stores, but the iron is not readily available for erythropoiesis due to the inflammatory response. Providing additional iron through supplementation may not improve anemia and could potentially exacerbate inflammation. Iron deficiency anemia (IDA) is a common type of anemia characterized by insufficient iron stores to support adequate red blood cell production. Iron is a critical component of hemoglobin, the protein in red blood cells responsible for transporting oxygen throughout the body. When iron stores are depleted, hemoglobin production falters, leading to a decrease in the number of red blood cells and their oxygen-carrying capacity. This results in various symptoms, including fatigue, weakness, shortness of breath, and pallor. In the context of tuberculosis (TB), IDA can arise from a combination of factors, including reduced dietary iron intake, malabsorption due to gastrointestinal TB or TB medications, and increased iron demand during infection. Addressing IDA in TB patients is crucial, as it can significantly impact treatment outcomes and overall quality of life. For iron deficiency anemia, oral iron supplementation is typically the first-line treatment. However, the absorption of oral iron can be impaired in the presence of inflammation, and some patients may experience gastrointestinal side effects. In such cases, intravenous iron administration may be considered to ensure adequate iron delivery. Oral iron supplements are widely available and generally well-tolerated. Ferrous sulfate is the most commonly used form of oral iron supplement. It is readily absorbed and relatively inexpensive. However, it can cause gastrointestinal side effects such as constipation, nausea, and abdominal discomfort. Ferrous gluconate form of iron is generally better tolerated than ferrous sulfate, with fewer gastrointestinal side effects. However, it contains a lower amount of elemental iron, requiring a higher dosage to achieve the same effect. Ferrous fumarate form of iron is also well-tolerated and has a higher amount of elemental iron compared to ferrous gluconate. However, it may be more expensive than ferrous sulfate. The choice of supplement and dosage will depend on the severity of iron deficiency, patient tolerance, and cost considerations. It is important to note that oral iron absorption can be affected by various factors, including the presence of inflammation, dietary factors, and other medications. Intravenous iron administration may be necessary in cases of severe iron deficiency, malabsorption, or intolerance to oral iron. Intravenous iron can rapidly replenish iron stores and improve anemia. Several intravenous iron preparations are available, each with its own advantages and disadvantages. Iron Dextran is one of the oldest intravenous iron preparations. It is effective in replenishing iron stores but can cause allergic reactions in some patients. Iron sucrose preparation is generally well-tolerated and has a lower risk of allergic reactions compared to iron dextran. However, it requires multiple administrations to achieve the desired effect. Ferric carboxymaltose is a newer intravenous iron preparation that can be administered in larger doses, requiring fewer administrations. It is generally well-tolerated and has a low risk of allergic reactions. The choice of intravenous iron preparation

will depend on the patient's individual needs and the availability of different preparations. In addition to iron supplementation, encouraging patients to consume iron-rich foods can help improve iron deficiency. Red meat is a good source of heme iron, which is more readily absorbed than non-heme iron found in plant-based foods. Poultry, such as chicken and turkey, also contains heme iron. Fish is a good source of iron, particularly oily fish like salmon and tuna. Beans and lentils are excellent sources of non-heme iron. Leafy green vegetables, such as spinach and kale, are good sources of non-heme iron. It is important to note that the absorption of non-heme iron can be enhanced by consuming it with vitamin C-rich foods, such as citrus fruits and tomatoes.[18-20]

5. Conclusion

Effective management of anemia is critical for improving TB outcomes. Further research is needed to optimize diagnostic and treatment strategies for iron deficiency and AI in TB. The high prevalence of anemia in TB patients underscores the urgent need to address anemia as an integral part of TB management. Anemia can impair treatment response, increase the risk of treatment failure, and prolong treatment duration. Moreover, anemia is associated with a higher risk of mortality and a diminished quality of life in TB patients. To effectively manage anemia in TB patients, a multifaceted approach is required. Healthcare professionals should be vigilant in screening for anemia in all TB patients, using appropriate diagnostic criteria and tools. Determining the specific type of anemia (iron deficiency, anemia of inflammation, or other types) is crucial for targeted management. Addressing the underlying cause of anemia, such as iron deficiency or chronic inflammation, is essential for effective management. Providing supportive care, such as nutritional counseling and lifestyle modifications, can help improve anemia symptoms and overall quality of life. By addressing anemia as an integral part of TB management, healthcare professionals can improve treatment outcomes, reduce mortality, and enhance the quality of life for TB patients. The high prevalence of anemia in TB patients highlighted in this systematic review emphasizes the need for increased awareness, early detection, and effective management strategies to combat this significant comorbidity.

6. References

1. Oliveira MG, Delogo KN, de Oliveira HM de MG, Ruffino-Netto A, Kritski AL, Oliveira MM. Anemia in hospitalized patients with pulmonary tuberculosis. J Bras Pneumol. 2014; 40(4): 403–10.
2. Minchella PA, Donkor S, Owolabi O, Sutherland JS, McDermid JM. Complex anemia in tuberculosis: the need to consider causes and timing when designing interventions. Clin Infect Dis. 2015; 60(5): 764–72.
3. Gil-Santana L, Cruz LAB, Arriaga MB, Miranda PFC, Fukutani KF, Silveira-Mattos PS, et al. Tuberculosis-associated anemia is linked to a distinct inflammatory profile that persists after initiation of antitubercular therapy. Sci Rep. 2019; 9(1): 1–8.
4. Chhabra S, Kashyap A, Bhagat M, Mahajan R, Sethi S. Anemia and nutritional status in tuberculosis patients. Int J Appl Basic Med Res. 2021; 11(4): 226–30.
5. de Mendonça EB, Schmaltz CAS, Sant'Anna FM, Vizzoni AG, Mendes-De-Almeida DP, de Vasconcellos Carvalhaes de Oliveira R, et al. Anemia in tuberculosis cases: a biomarker of severity? PLoS One. 2021; 16(2): 1–12.
6. Luo M, Liu M, Wu X, Wu Y, Yang H, Qin L, et al. Impact of anemia on prognosis in tuberculosis patients. Ann Transl Med. 2022; 10(6): 329–329.
7. Ahmad S, Rehman S, Ikramullah Q, Ahmad I. Frequency of anemia in patients with pulmonary tuberculosis. Int J Endorsing Heal Sci Res. 2023; 11(4): 171–8.
8. Sharma G, Rani D, Verma A, Chakrabarti SS. Abdominal tuberculosis presenting as anemia

refractory to standard therapy in an elderly male. J Indian Acad Geriatr. 2023; 19(4): 287–9.

9. Ashenafi S, Loreti MG, Bekele A, Aseffa G, Amogne W, Kassa E, et al. Inflammatory immune profiles associated with disease severity in pulmonary tuberculosis patients with moderate to severe clinical TB or anemia. Front Immunol. 2023; 14: 1296501.
10. Alebbi SM, Kambal A, Abo Samra H, Sharaf Eldean MZ, Mohamed SF, Al-Shokri SD. Case report: Tuberculosis-induced autoimmune hemolytic anemia. Am J Trop Med Hyg. 2023; 108(2): 313–6.
11. Hithaish Kumar RN, Rao CR, Maradi R, Umakanth S, Chidananda Sanju SV, Sreenivasa Rao BP. Impact of anemia on sputum smear conversion and treatment outcomes among newly diagnosed tuberculosis patients in Southern India. Int J Mycobacteriol. 2023; 12(2): 117–21.
12. Abaynew Y, Ali A, Taye G, Shenkut M. Prevalence and types of anemia among people with tuberculosis in Africa: a systematic review and meta-analysis. Sci Rep. 2023; 13(1): 5385.
13. Gao Z, Liu Q, Deng Q, Kong L, Liu Y. Growth and anemia among children with tuberculosis infection at different sites in Southwest China. Front Pediatr. 2023; 11: 1188704.
14. Luo M, Zou X, Zeng Q, Wu Y, Yang H, Qin L, et al. Monocyte at diagnosis as a prognosis biomarker in tuberculosis patients with anemia. Front Med (Lausanne). 2023; 10: 1141949.
15. Srinivas J, Arul J, Nasrin T. M. A, Jayaraman D, Palraj KK, Murali A, et al. Tuberculosis presenting with multiple osteolytic lesions in an adolescent boy with Fanconi anemia. Int J Contemp Pediatr. 2024; 11(12): 1844–6.
16. Tabares B, Sarmiento-Suárez AD, Gil Ó, Hernández-Pabón JC, Firacative C. Fatal co-infection by multiple pathogens in an indigenous woman with autoimmune hemolytic anemia and tuberculosis: a case report. BMC Infect Dis. 2024; 24(1): 645.
17. Biswal S, Chatterjee P. Tuberculosis-induced autoimmune hemolytic anemia. J Indian Acad Geriatr. 2024; 20(3): 154–6.
18. Ahmed MA, Diriye AS, Ali MA, Yusuf BJ. Magnitude of anemia and associated factors among adults with tuberculosis in Galkaio Public Health Facilities Puntland, Somalia 2024: a cross-sectional study design. J Drug Deliv Ther. 2024; 14(8): 73–83.
19. Han C, Fang Y, Dong L, Guo D, Lei M, Guo W, et al. Correlation of tuberculosis-related anemia severity with tuberculosis-induced inflammation in children: a six-year retrospective study. Ital J Pediatr. 2024; 50(1): 116.
20. Park JW, Chung CU, Shin JY, Jung SY, Yoo SJ, Lee JE, et al. Erdheim-Chester disease with hepatitis, glomerulonephritis, aplastic anemia and lung involvement. Tuberc Respir Dis (Seoul). 2009; 67(4): 345.