

ISSN (E): 2708-2601

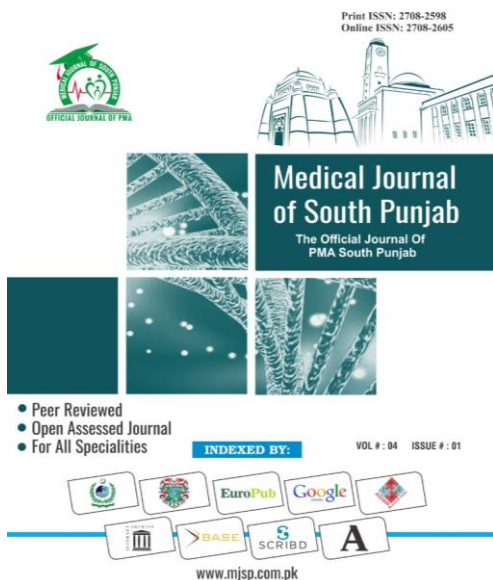
ISSN (P): 2708-2598

## Medical Journal of South Punjab

Article DOI:

<https://doi.org/10.61581/mjosp.v4i01.99>

Volume 4, Issue 1, 2023



## Frequency of Anemia in Patients with Pulmonary Tuberculosis Presenting at Nishtar Hospital Multan

### Publication History

Received: May 01, 2023 Revised: May 10, 2023

Published: June 03, 2023 Accepted: May 29, 2023

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### Conflict of Interest:

Author(s) declared no conflict of interest.

### Acknowledgment:

No Funding received.

**Citation:** Khan SA, Ramzan F, Javed N, Arshad H, Hussain S, Zaffar MU. Frequency of Anemia in Patients with Pulmonary Tuberculosis Presenting at Nishtar Hospital Multan. Medical Journal of South Punjab. 2023 June 3; 4(1):1-9.

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**Medteach Private Limited, Multan, Pakistan.**

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## Frequency of Anemia in Patients with Pulmonary Tuberculosis Presenting at Nishtar Hospital Multan

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### ABSTRACT

**Objective:** The present study aimed to determine the frequency of anemia in patients with pulmonary TB presenting at Nishtar Hospital Multan and its classification as per the severity and morphological characteristics.

**Methods:** This retrospective cross-sectional study was conducted at Nishtar Hospital Multan. A total of 109 TB patients were enrolled and underwent physical and systemic examination. Blood samples were collected to estimate complete blood counts (CBC), liver and renal function tests (LFT; RFT), serum albumin, and C - reactive protein (CRP) levels. Abdominal ultrasound was performed when suspected of any organomegaly. Hemoglobin was estimated using an automated analyzer (SYSMEX-SP100) and repeated manually among doubted cases. Before inclusion, written informed consent was obtained from all patients before inclusion.

**Results:** The female majority (54%) in the studied sample, with a mean age of  $38 \pm 15.3$  years, and most belonged to low socioeconomic status (80%). Moreover, 43% were from Multan, 30% from D.G. Khan, and the remaining were from Khanewal, Layyah, and Vehari districts. Anemia was found in 82.56% of the enrolled TB patients. Most patients were moderately weak ( $Hb < 10 \text{ g/dl} > 7 \text{ g/dl}$ ), and microcytic anemia was found in more than 80% of the anemic patients.

**Conclusion:** In our study, anemia was prevalent in TB patients, specifically microcytic anemia. Hence, TB patients must be monitored for dietary deficiencies and inflammatory modulators to avoid such complications.

**Keywords:** Tuberculosis, Anemia, Iron Deficiency Anemia, Anemia of Inflammation

## 1. INTRODUCTION

Tuberculosis is a potentially severe infection caused by *Mycobacterium tuberculosis*. TB has been known to infect humans and affects millions of people. With increased efforts to enhance TB care and management, significant progress has been made in reducing the global burden of TB, yet this disease remains a primary global health concern. According to a Global Tuberculosis report published by World Health Organization (WHO), around 10 million people developed TB in 2017<sup>1</sup>. TB remained one of the top 10 diseases causing death and the most infection-causing death<sup>1</sup>. The report also states that almost one-third population of the world is infected by *Mycobacterium tuberculosis*, with approximately 8.8 million new cases annually<sup>1</sup>.

It is recognized as a disease of resource-poor countries<sup>2-4</sup>. Although the actual statistics of TB in Pakistan are difficult to state due to underreporting of cases, in 2011, the approximate incidence and prevalence rates of TB in Pakistan were reported to be 231 and 364 per 100,000 population, respectively<sup>3,4</sup>. According to WHO, Pakistan stands fifth among countries with the highest burden of TB worldwide, accounting for 61% of the total burden of WHO Eastern Mediterranean Region<sup>5</sup>. We encounter an estimated 510,000 new cases of TB each year, and approximately 15,000 develop drug resistant TB<sup>5,6</sup>. The leading primary causes for the severity of TB, as declared by WHO, are social inequality, aging, and

a large flow of migration.

Along with this, the risk factors associated with TB include smoking, diabetes mellitus, alcoholism, malnutrition, any previous history of TB, and low socioeconomic status<sup>6,7</sup>. People with poor immunity are at the highest risk of developing TB. Chronic inflammation in pulmonary TB is mainly reflected by the increased circulating C-reactive protein (CRP) and other inflammatory cytokines<sup>7</sup>. Two interactions have also been identified within the association between TB and malnutrition. These include the effect of TB on the status of nutrition and the effect of malnutrition on the clinical manifestation of TB. Both these interactions result due to immunological impairment in TB<sup>7</sup>.

Studies suggest that iron homeostasis disturbance may also be developed when there is an increase in the uptake and retention of iron in the reticuloendothelial system that gets altered or damaged due to chronic infections like TB<sup>8</sup>. Because iron is a crucial growth factor for *Mycobacterium TB*, iron retention in the reticuloendothelial system is regarded as one of the host's defense systems, and numerous treatment studies have been conducted<sup>8</sup>.

Anemia, a common diagnosis among TB patients, results from iron deficiency anemia (IDA) or inflammation; the reported prevalence in TB ranges between 32%-86%<sup>8</sup>. Anemia can be defined as the concentration of hemoglobin that is less than 13g/dl in males and 12g/dl in females, as recommended by WHO<sup>8</sup>. At the same

time, the resolution of anemia is defined as the concentration of hemoglobin more significant than 13 g/dl in males and 12 g/dl in females, with follow-up of two tests being done more than a month apart<sup>9</sup>. One of the most common micronutrient deficiencies in the world is iron deficiency. Many studies have been conducted to evaluate the association between serum iron levels and IDA<sup>8</sup>. IDA is associated with serum ferritin levels of < 30 ng/ml<sup>9</sup>, while in certain malignancies, chronic infections, and autoimmune diseases, serum ferritin levels also increases<sup>10</sup>. However, serum transferrin saturation values drop in these two types of anemia<sup>11</sup>. Anemia increases lethality among TB patients<sup>12</sup> and is associated with unfavorable outcomes<sup>14</sup>. Furthermore, it is more frequent among patients with HIV-TB than those without HIV.

IDA and anemia due to chronic disease are considered the most common type of anemia, characterized by distorted metabolism of iron<sup>13</sup>. Studies also suggest that IDA can result due to chronic blood or urinary losses, poor intake or absorption of iron, and elevated blood volume<sup>8</sup>. Patients with IDA have decreased iron plasma levels, ultimately limiting erythropoiesis. Studies suggest that infants and women of childbearing age have a high risk of developing IDA<sup>13</sup>. Studies suggest that with anti-TB therapy, the inflammation reduces along with the burden of the organism, iron retention, erythropoietin response, nutritional status, and improvement in malabsorption. This may explain why a positive treatment response

indicated a proclivity for anemia remission<sup>13</sup>.

Just as IDA, anemia of chronic disease or inflammation is a clinical syndrome characterized by anemia due to fungal, bacterial, or viral infectious diseases. These autoimmune diseases include tuberculosis, inflammatory, autoimmune, and neoplastic diseases<sup>12</sup>. Anemia of chronic disease or inflammation is characterized by the association of decreased levels of serum iron and its binding capacity, along with elevated levels of ferritin<sup>12</sup>.

To date, few studies have identified the association of anemia with a deficiency of iron or chronic disease or inflammation in patients with active TB. The present study aimed to determine the frequency of anemia in patients with pulmonary TB and its classification per severity and morphological characteristics.

## 2. METHODOLOGY

The hospital ethical review committee granted the ethical approval for the study [R.No.7313 dated 25/03/2019], and written informed consent was obtained from all patients before inclusion.

This retrospective cross-sectional study was conducted in the Department of Medicine presenting at Nishtar Hospital, Multan. Of the TB patients presenting at the study site, 127 were enrolled. All TB patients aged 18 to 70 years were eligible, while patients with autoimmune diseases, hematological and other malignancies were excluded from the study.

A physical and systemic examination was carried out, a respiratory system examination was done thoroughly, and the abdomen was palpated for organomegaly. The precordium examination was carried out for any murmurs, added sounds, etc. Blood samples were collected to estimate complete blood counts (CBC), liver and renal function tests (LFT; RFT), serum albumin, and CRP level. In case of any organomegaly, abdominal ultrasound was performed. An automated analyzer (SYSMEX-SP100) was used for hemoglobin estimation, and in doubted cases, Hemoglobin (Hb) was repeated via manual method.

Statistical analysis was performed on SPSS version 22.0, and frequency and percentages were calculated for categorical variables. Mean and standard deviation was used for presenting continuous variables.

### 3. RESULTS

Out of 109 TB patients, 59(54%) patients were females, and 50(46%) were males. The mean age was  $38 \pm 15.3$  years, and most patients had low socioeconomic status (80%).

Furthermore, 27% were ex-smokers, and 24% were current smokers. Based on the geographical distribution, 43% of the patients belonged to Multan, 30% from D.G. Khan, 18% from Khanewal, 6% from Layyah, and 3% from Vehari districts.

Among the total anemic patients, 29(32.3%) were classified as mild anemic, 48(53.3%) were moderately anemic, and 13(14.4%) were severely anemic.

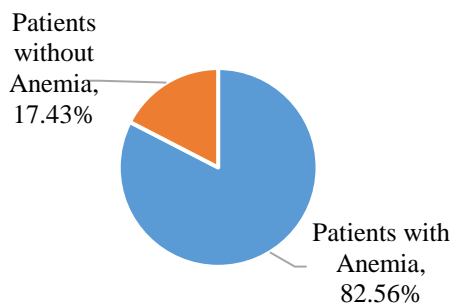
Stratification of anemic patients with respect to gender is shown in table 1.

**Table 1:** Classification and gender-wise distribution of the patients with respect to anemia (in %)

Variables	Total	Males	Females
Mild anemia	29(32.3)	15(37.5)	14(28)
Moderate anemia	48(53.3)	19(47.5)	29(58)
Severe anemia	13(14.4)	06(15)	07(14)

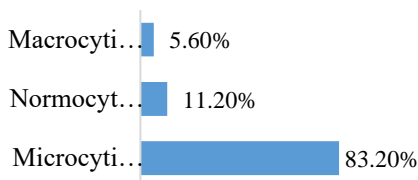
**Source:** Author's Own Calculation

Of the total, 90 (82.56%) patients were found anemic. Furthermore, more female patients had hemoglobin levels below 11.5 g/dl (84.74%) than males (80%) (Figure 1).



**Figure 1:** Frequency of anemia among enrolled TB patients

Most of these anemic patients had microcytic anemia (83.20%), followed by normocytic and macrocytic anemia (Figure2).



**Figure2:** Anemia based on Mean corpuscular volume (MCV)

We observed raised CRP in 70% of these patients, and 80% had low serum albumin, reflecting malnutrition. Moreover, the platelet count was normal in 75% of patients, 15% had thrombocytopenia, and 10% were observed with thrombocytosis.

The white cell counts were normal in 78% of the enrolled cases. At the same time, 13% and 9% developed leukocytosis and leucopenia, respectively. Only two patients presented with hemolytic anemia.

#### 4. DISCUSSION

In this study, we found anemia in 82.56% of the total pulmonary TB patients, which is comparatively higher than that reported in studies from South Korea (32%) and Indonesia (63%)<sup>14,15</sup>. At the same time, studies from Tanzania and Malawi reported a higher prevalence of anemia than in the present study, i.e., 96% and 88%, respectively<sup>12,16</sup>.

Furthermore, we found it more frequent among women than men. Similar studies suggest that 80% of their TB-

affected females were anemic<sup>17</sup>. A study by Oliveria et al.<sup>18</sup> also suggests that pulmonary TB is most common in young adult males, with associated factors of alcoholism, smoking, drug intake, and HIV. TB is considered the most devastating disease in the elderly, with atypical, nonspecific, or confused clinical features and already existing diseases<sup>17</sup>. Studies suggest that in such elderly patients of TB, antitubercular chemotherapy is mainly associated with adverse effects<sup>15,16</sup>. Results evaluated from different studies suggest that the iron-retention effect might also be exaggerated in females with TB. This happens because women are more likely to be iron deficient as compared to men, also defined by existing literature<sup>17</sup>.

Characterizing TB-associated anemia factors is essential for clinical decision-making and therapeutic recommendations. Iron deficiency causes most anemia worldwide. Several causes often coexist. Suppose iron deficiency is a major cause of TB-related anemia. In that case, supplemental iron may be administered to TB patients on a case-by-case basis to increase hemoglobin levels and improve clinical outcomes. Iron deficiency without anemia can impair immune function and infection regulation, which may accelerate tuberculosis disease progression<sup>15,16</sup>. Anemia without iron shortage has been linked to TB recurrence, mortality, and HIV disease progression, suggesting that factors other than iron deficiency contribute to poor clinical outcomes.<sup>19</sup>

In this study, nearly 80% of

participants came from low-income families, supporting the link between TB and poverty. Most patients' hypoalbuminemia strengthens TB's association with poverty and malnutrition. These patients had ordinary white cell counts, although 13% had leukocytosis and 9% had leucopenia. 15% had thrombocytopenia, and 10% had thrombocytosis.

Banerjee et al. found leukocytosis in 28.63% of TB patients, leucopenia in 2.20%, neutrophilia (66.15%), lymphocytosis (21.53%), thrombocytosis (17.62%), and thrombocytopenia in 5.28%<sup>9</sup>. Anemia-related TB patients had changed LFT and RFT values as well as CBC. Most subjects had elevated CRP and low serum albumin. Similar investigations found hypoalbuminemia<sup>19,20</sup>, higher CRP<sup>21</sup>, and lower BMI in TB patients with anemia compared to non-anemic<sup>21,22</sup>. CRP may indicate therapy efficacy and inflammation remission.

With antituberculosis treatment, CRP levels return to normal<sup>19</sup>. Most proteins are also higher in TB patients. These proteins include transferrin and hemoglobin<sup>20</sup> concentrations. In anemic TB patients, transferrin decreases and ferritin increases<sup>21</sup>. Protein concentration is crucial as ferritin is the most sensitive in non-inflammatory situations. It is essential for diagnosing iron deficiency<sup>22</sup>. In patients with TB, ferritin levels can indicate both iron deficiency and increased ferritin<sup>23</sup>, so they should be used cautiously. The decreased MCV and high prevalence of

microcytic anemia (83.20%) among recruited TB cases suggest that dietary iron shortage or inflammatory metabolic changes may cause anemia in TB patients. Due to lower bone marrow iron availability, anemic patients produce more megakaryocytes with higher ploidy, which release more platelets than lower-ploidy ones<sup>23</sup>.

While the study was retrospective, we could not analyze certain more precise factors for studying the etiologies of anemia, i.e., the present data needs to be more sufficient to separate IDA or anemia owing to inflammation or other probable causes. Although TB/HIV co-existence is crucial, patients were not checked for HIV. We couldn't use all required indicators to distinguish IDA from chronic illness or inflammation-related anemia.

## 5. CONCLUSION

In conclusion, most TB patients have primarily microcytic anemia, which must be treated immediately. All anemic TB patients must be tested for total iron-binding capacity, serum ferritin, transferrin saturation, folate, and vitamin B12. TB patients must be checked for HIV; however, this study did not investigate this. A peripheral smear of anemic patients could provide crucial prognostic information. More extensive studies with more parameters for a precise diagnosis are recommended.

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