

**Prevalence and Predictors of Anemia Among Drug Resistant Tuberculosis Patients in King Abdulaziz University Hospital, Jeddah.**

**Abstract**

**Introduction:** Among multiple hematological changes, anemia is one of the most common hematological problems in patients with tuberculosis (TB). [1] Many studies were conducted in different countries and reported various results. [1][2]

**Methods:** A retrospective cohort study was conducted on all TB-positive cases reported to the King Abdulaziz University Hospital between January 2012 and January 2021. Detailed demographic and biomedical data were collected from the hospital record section. All culture-confirmed and PCR-positive TB cases were included in this study. Categorical baseline characteristics of TB patient has been compared with the anemic status by Fisher's exact and Pearson's chi-square test. Continuous variables like hematological parameters compared with anemia by t-test. The univariable and multivariable logistic regression analyses were done to estimate the association between TB positive cases and the anemic status of the patient.

**Result:** Out of 695 TB-positive cases, 443 (63.74%) are anemic. Among these anemic patients, most are less than 39 years old; 228 (51.47%), clearly males outnumbered the number females. Approximately 289 (65.24%) are non-Saudi. A majority of the patient, 163(54.40%), had a BMI range of 18.5 – 24.9. A significant difference had been noticed in the anemic and non-anemic patients in variables like gender, BMI, nationality, and site of TB. In the case of anti-TB drug-resistant cases, the percentages of mild, moderate, and severe anemia are 12.21%, 12.20%, and 13.64%. This study did not find any significant association between DR-TB and anemia.

**Conclusion:** The prevalence of anemia among TB patients was high. Thus, it warrants frequent screening for anemia in all TB-positive cases to improve mortality and morbidity in these patients.

Keywords: Anemia, tuberculosis.

**1. Introductions**

Anemia is a global concern affecting approximately 1-8 % of the world's population.[3][4] Different types of hematological problems have been identified in the case of TB-positive patients, but the major hematological problem with a TB-positive patient is anemia. [2][3] According to the studies conducted in many other countries, anemia has been noted among 32%

to 94% of these patients.[3][4][5][6] Previous evidence showed that TB patients with anemia have a higher risk of mortality and poor response to treatment. [6]

There is a proven interaction between TB and nutrition that indicates the influence of TB on the nutritional status of the patient and the impact of nutrition on the clinical symptoms of TB. [5] Instead of a strong association between anemia and TB, no exact mechanism has been found that explains anemia among TB patients. As reported, anemia is caused by inflammation and iron deficiency, both of which are more common in developing countries. [2][7] Studies conducted in India and Tanzania reveal a prevalence of anemia in TB patients at 72.2% and 86% respectively.[2][4]

Some underlying pathogenesis of Anemia in TB patients is suppression of erythropoiesis by inflammation markers, nutritional deficiency, and malabsorption syndrome.[8][9] Furthermore, it has been found that TB-associated anemia has decreased bone marrow iron. Iron deficiency is probably a possible cause of anemia in TB cases. It has been observed that anti-TB drug therapy resolves anemia in TB-positive cases. [9][10] Most studies have discussed the association of TB with anemia but this is the first study that explores the association between drug-resistant tuberculosis (DR-TB) and anemia. As the information about anemia in TB cases is controversial, some studies say that anti-TB treatment improves anemia, and some studies reveal that anti-TB medications (isoniazid, pyrazinamide) cause anemia. [11] The first objective of this study is to explore the prevalence and predictors of anemia in drug-sensitive and drug resistant tuberculosis (DR-TB) patients; the secondary objective is to find whether there is any association between anemia and drug-resistant TB.

## **2. Methods**

### **2.1 Setting and Participants**

All TB-positive patients treated in King Abdulaziz University Hospital between 1<sup>st</sup> January 2012 to 31<sup>st</sup> January 2021 were included in this study. King Abdulaziz University Hospital (KAUH) is one of the largest tertiary hospitals in the western region. KAUH is well equipped with the most advanced technology. [12] This study includes all TB-positive patients over 17 years old. Diagnosis of TB is confirmed by culture or positive PCR outcome, with drug susceptibility test. We extracted a total of 695 TB positive patients with information of anemia. Moreover, socio-demographic data, including age, gender, nationality, body mass index (BMI), smoking habits (smokers vs. non-smokers), and site of TB (either pulmonary or extrapulmonary TB), were collected by medical record review.

### **2.2 Data from laboratory diagnosis and others:**

The socio-demographic data, including age, sex, marital status, smoking habit, and previous history of TB, was collected from the history taking part by the electronic record review. The diagnosis of TB was made by reviewing the test report of blood culture for TB and the PCR test.

A drug susceptibility test was also reviewed with this test result to find whether the patient is resistant to any 1st line anti TB drug or not. Furthermore, the diagnosis of anemia was made by reviewing the test reports of hemoglobin (g/dl) from electronic medical records. WHO categorized anemia according to the severity into 3 groups mild anemia (10 – 11.9 g/dl), moderate anemia (8 – 9.9 g/dl), and severe anemia (< 8 g/dl). Backward elimination of logistic regression analysis was done to find out the confounder in this study. We found that age, BMI, site of TB, hematocrit, and prothrombin time were a confounder. Our model has been adjusted for the confounders (table number 4)

## **2.3 Statistical analysis**

Categorical baseline characteristics of TB cases include age (18-39, 40- 60, >60), gender (male or female), nationality (Saudi or non-Saudi), marital status (single, married, other), BMI (<18.5, 18.5 – <25, 25 - <30, 30 – <=39, >=40 ), smoking habit (smoker, non-smoker, unknown), site of TB (pulmonary or extrapulmonary), history of previous TB (yes or no), were compared by the anemic status of the patient by Pearson chi-square test. The continuous variables include all the hematological parameters of the patients (Hemoglobin, red blood cell count, white blood cell count, platelet count, neutrophil count, lymphocyte count, hematocrit, prothrombin time, APTT, INR, ESR, CRP random blood sugar, HbA1c) compared with anemia by t-test. To estimate the association between anemia and DR-TB and drug-sensitive TB, univariable and multivariable logistic regression analyses were done. All statistical analyses of these studies were performed by using Stata version 13.0 (Stata Corp, College Station, Texas, USA)

## **2.4 Ethics statement**

Ethical approvals of our study were attained from the Bio-medical Ethical Committee of King Abdulaziz University Hospital, Jeddah.

The patient's informed consent was not required as the study was limited to reviewing existing electronic medical records.

## **3. Result**

The baseline characteristic of TB-positive cases with or without anemia is enlisted in table 1. The maximum number of patients with anemia is 228 (51.47%) observed in the younger patients (18 – 39 years old). Males commonly have anemia with TB 222 (50.11%) compared to females 22 (49.89%). Also, anemia is more seen in non-Saudi 289 (65.24%) compared to Saudi TB cases 154 (34.56%). In the case of BMI, the majority of anemic patients with TB are found in patients with an average body mass index (BMI: (>=18.5 - <25)). Furthermore, anemic cases are more common in pulmonary TB 349 (78.78%) than in extrapulmonary TB patients 94 (21.22%). (Table 1)

**Table 1: Baseline characteristics of the tuberculosis patients with and without anemia in King Abdul Aziz University Hospital from 2012 to 2021. (n = 695)**

Characteristics	Anemic (n = 443)		Non - anemic (n = 252)		P value
	N	%	N	%	
<b>Age (years)</b>					
Young age (18 – 39)	228	51.47	113	44.84	0.21
Middle age (40 – 60)	116	26.19	71	28.17	
Older age (>60)	99	22.35	68	26.98	
<b>Gender</b>					
Male	222	50.11	167	66.27	0.00
Female	221	49.89	85	33.73	
<b>Nationality</b>					
Saudi	154	34.76	111	44.05	0.01
Non-Saudi	289	65.24	141	55.95	
<b>Marital status</b>					
Single	163	36.79	77	30.56	0.22
Married	264	59.59	167	66.27	
Divorced	16	3.61	8	3.17	
<b>BMI (Kg/m<sup>2</sup>)</b>					
Under weight (<18.5)	90	20.32	33	13.10	0.00
Normal weight (≥18.5 - <25)	241	54.40	115	45.63	
Overweight (≥25 - <30)	70	15.80	62	24.60	
Obese (≥30 - <=39)	24	5.42	24	9.52	
Morbid obese (≥40)	18	4.06	18	7.14	
<b>Site of TB</b>					
Pulmonary	349	78.78	173	68.65	0.00
Extrapulmonary	94	21.22	79	31.35	
<b>History of the previous TB</b>					
Yes	32	7.22	411	92.78	0.81
No	17	6.75	235	93.25	
<b>Smoking status</b>					
Non- smoker	269	60.72	135	53.57	0.09
Smoker	64	14.45	51	20.24	
Unknown	110	24.83	66	26.19	

<b>Drug sensitivity of TB</b>					
Not resistant TB	388	87.58	215	85.32	0.38
Resistant TB	88	12.42	37	14.68	

**Table 2: Association between Anemia and different hematological parameter (n= 695)**

<b>Characteristics</b>	<b>Anemic (n = 443)</b>		<b>Non - anemic (n = 252)</b>		<b>P value</b>
	<b>Mean</b>	<b>S.D</b>	<b>Mean</b>	<b>S.D</b>	
<b>Hemoglobin (g/dl)</b>	9.6	1.64	13.44	1.59	<b>0.00</b>
<b>Red blood cell (million/cumm)</b>	4.09	4.01	4.89	4.81	<b>0.00</b>
<b>White blood cell (thousand/cumm)</b>	9.66	7.37	8.64	3.75	<b>0.04</b>
<b>Platelet (thousand/cumm)</b>	342.8	168.8	304.2	109.3	<b>0.00</b>
<b>Lymphocyte (cells/microliter)</b>	1.62	2.58	1.96	2.46	0.10
<b>Neutrophil (cells/microliter)</b>	8.98	11.86	7.77	11.75	0.21
<b>Hematocrit (L/L)</b>	30.35	5.10	41.72	25.43	<b>0.00</b>
<b>RBS (mg/dl)</b>	8.12	9.89	9.65	7.16	0.05
<b>HbA1c</b>	4.97	12.59	5.20	4.03	0.78
<b>PT (Seconds)</b>	13.96	3.97	12.51	1.51	<b>0.00</b>
<b>APTT (Seconds)</b>	37.81	19.45	32.71	5.96	<b>0.00</b>
<b>INR</b>	1.25	0.66	1.12	0.31	<b>0.01</b>
<b>ESR (ml/hour)</b>	67.49	35.18	42.04	28.09	<b>0.00</b>
<b>CRP (mg/dl)</b>	84.56	72.82	55.83	59.77	<b>0.00</b>

In the case of patients with TB associated with anemia, the mean hemoglobin (g/dl) is  $9.6 \pm 1.64$ , Red blood cell ( $4.09 \pm 4.01$ million/cumm), White blood cell ( $9.66 \pm 7.37$  thousand/cumm), Platelet ( $342.8 \pm 168.8$  thousand/cumm), Lymphocyte ( $1.62 \pm 2.58$  cells/microliter), Neutrophil ( $8.98 \pm 11.86$  cells/microliter), Hematocrit ( $30.35 \pm 5.10$  L/L). Furthermore, the mean value of prothrombin time, APTT, INR, ESR and CRP are ( $13.96 \pm 3.97$  seconds), ( $37.81 \pm 19.45$  Seconds), ( $1.25 \pm 0.66$ ), ( $67.49 \pm 35.18$  ml/hour), ( $84.56 \pm 72.82$  mg/dl) respectively. (Table 2)

Variables of blood parameters like hemoglobin, red blood cell, white blood cell, platelet count, hematocrit, PT, APTT, INR, ESR, and CRP show a significant difference between an anemic and non-anemic group of patients with TB. (P value <0.05) (Table 2)

The percentage of mild, moderate, and severe anemia in 1<sup>st</sup> line anti TB DR-TB patients is 26 (12.21%), 20 (12.20%), and 9 (13.64%). (Table 3)

**Table 3: Percentage of types of anemia (according to the severity) in King Abdulaziz University hospital tuberculosis patients. (n = 443)**

Severity of anemia	Resistant TB (n = 55)	Non-resistant TB (n = 388)
Mild anemia (10 – 11.9 g/dl)	26 (12.21%)	187 (87.79%)
Moderate anemia (8 – 9.9 g/dl)	20 (12.20%)	144 (87.80%)
Severe anemia (< 8 g/dl)	9 (13.64%)	57 (86.36%)

**Table 4: The anemic and non-anemic profile in anti-TB drug-resistant and sensitive patients in King Abdul Aziz University Hospital from 2012 to 2021. (n = 695)**

Total TB patients (n=695)	Anemic (n = 443)		Non - anemic (n = 252)		Univariable analysis		Multivariable analysis	
	No.	%	No.	%	OR (95% C.I)	P value	a OR ** (95% C.I)	P value
Drug sensitive (n = 603)	388	87.5	215	85.3	1.21 (0.77 – 1.90)	0.39	0.32 (0.07 -1.39)	0.13
Drug Resistant (n = 92)	55	12.4	37	14.6				

\*\*Adjusted for age, BMI, site of TB, ESR, hematocrit level, and Prothrombin time.

Table 4 illustrates the association between anemia and DR-TB. In the univariable analysis, anemia was not significantly associated with DR-TB (OR: 1.21, 95% C.I, 0.77 – 1.90). Similarly, In the multivariable analysis, anemia does not show any significant association with DR-TB. (aOR: 0.32, 95% CI, 0.07 – 1.39).

#### 4. Discussion

Among TB-positive patients, anemia is the most common hematological complication. The proposed mechanism of anemia in TB patients is inflammation and iron deficiency anemia. [13] The reported prevalence of anemia in TB patients ranges from 20% to 94%. [2] In our study, more than half (63.74%) of TB patients are anemic. A similar study done by Marina *Oliveria et al.* (2014) found that 89.2% of TB patients were associated with anemia, [5] and another study done by *Hussain et al.* (2004) observed that 62% of miliary TB cases had anemia. [14]

The majority of these anemic patients with TB belong to the young age group, which is not similar to the study results done in India by *Anirudh Mukherjee et al.* (2018), which reveals that the older age group of TB patient have a higher risk of developing anemia as they are associated with chronic diseases, poor nutrition, decreased bone marrow cellularity, and reduced vitamin B12 levels in the blood. [15] Another important reason for TB patients suffering from anemia is anti-tubercular drugs, such as isoniazid, pyrazinamide, and cycloserine. These drugs are known to cause sideroblastic anemia by interfering with the conversion of vitamin B6 to its active coenzyme, which inhibits the activity of 5-aminolevulinic acid synthesis. [11]

As shown in table number 1, males are more common (50.11%) to have anemia with TB compared to females (49.89%); our result is similar to the study done previously by *Oliveria et al.* [5]. On the other hand, a study done by *Khurram et al.* did not find any statistical difference between males and females.[16] Furthermore, a study by *lee et al.* reveals a higher number of female TB patients with anemia than males.[17]

Our study reveals that patients with average body weight (BMI 18 to <24.9) are at a higher risk of anemia than other TB patients. Our outcome differs from the previous studies; those studies highlighted that malnourished TB patients have a higher risk of developing anemia. [18][19][20] This study also reveals that anemia is more common in pulmonary TB (78.78%) compared to extrapulmonary TB. A similar result is also seen in other studies where anemia is more common in pulmonary TB cases. [2][5][7][8]

Table number 2 illustrates the association between anemia and different hematological parameters. In our study among multiple hematological parameters, we found hemoglobin, red blood cell, white blood cell, platelet count, hematocrit, PT, APTT, INR, ESR, and CRP have a significant association with anemia (P value <0.05)

As shown in table 3, the majority of TB cases had mild anemia (48.08%); a similar outcome was also seen in a study done by *lee et al.* [17]

In table 4, the percentage of anemic cases in DR-TB is 12.42%. Unexpectedly, we did not find a significant association between DR-TB and anemia in univariable and multivariable analyses. It is possibly due to the limited number of DR-TB patients in KAUH from January 2012 to January 2021. Although, previously done studies showed that TB has a significant association with anemia. [2][5] Unfortunately, no study has been done till now to find that either anemia is more common in DR-TB or drug-sensitive TB patients.

## **Conclusion**

In conclusion, anemia is a common hematological abnormality in TB cases. Frequent anemia in TB patients demands routine screening for anemia in all cases of TB. The health care provider has a crucial role to investigating, diagnosing, and treating anemia in patients who are TB positive. This will not only improve the patient's overall health condition but also reduce the rate of mortality and morbidity.

The strength of our study is that this is the first study that tries to explain the association between anemia and DR-TB cases. DR-TB is much more complicated and life-threatening. Drug-sensitive TB has a cure rate of 96% compared to only 54% for DR-TB. The treatment for patients infected with DR-TB strains is exceptionally challenging due to the complexity and increasing treatment duration of the chemotherapy regimen and the associated side effects of the alternative drugs, which also increase the cost of the treatment. [21]

The limitation of our study is the limited number of DR-TB patients in KAUH in the selected study duration period.

We recommend that more studies focusing on bacteriologically confirmed TB cases that objectively diagnose anemia with clearly defined types of TB and anemia (mild, moderate, and severe) coupled with solid controls for potential confounding should be done with larger sample size.

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