Prevalence, characteristics, and predictors of tuberculosis associated anemia

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Abstract

Tuberculosis is an infectious disease caused by mycobacterium tuberculosis. It is one of the deadliest disease and a major burden on the healthcare system in India. India, a second most populous country in the world, has a very high global annual incidence of tuberculosis. Multiple hematological changes have been reported in patients with tuberculosis such as iron deficiency anemia, folate deficiency, and sideroblastic anemia. **Aims and Objectives:** The present study was planned to find the prevalence and characteristics of anemia in the new cases of pulmonary tuberculosis. The secondary objective was to assess the predictors of anemia in new cases of pulmonary tuberculosis. **Methods:** The retrospective study was carried out at a tertiary care hospital of Uttarakhand and included all the new cases of tuberculosis aged more than 18 years attending medicine outpatient and inpatient departments over a period of 1 year. Detailed demographic, clinical, and biochemical data were obtained from the hospital record section and tabulated. **Results:** Most patients with tuberculosis and anemia were more than 50 years of age. Clearly, males outnumbered females. Approximately, 80% patients were illiterates. A majority (71, 39.2%) of the patients had BMI within the range of 18.5 to 24.9 kg/m^2. The most common symptoms of tubercular patients with and without anemia were cough, fever, breathlessness, and hemoptysis. However, pallor was the most common sign. Clearly, hematological indices were lower in patients with anemia. In total, 112 (60%) patients had mild anemia and 103 (56.9%) patients had normocytic normochromic anemia. Significant association was found between Body Mass Index (BMI) and anemia in patients with pulmonary tuberculosis. Similarly, severity of anemia co-related significantly with BMI of patients with pulmonary tuberculosis. BMI showed a significant correlation with hemoglobin, packed cell volume, mean corpuscular cell volume, and red cell distribution width (RDW). In addition, age showed a significant correlation with hemoglobin and RDW. **Conclusion:** Normocytic normochromic anemia is a common hematological abnormality in patients with pulmonary tuberculosis. Thus, it warrants frequent screening for anemia in all the cases of pulmonary tuberculosis to improve morbidity and mortality in these patients.

Keywords: Folate deficiency, mycobacterium tuberculosis, normocytic normochromic anemia

Introduction

Tuberculosis is caused Mycobacterium tuberculosis. The cardinal features of the disease are cough with or without expectoration, intermittent fever, weight loss, decrease appetite, and hemoptysis.[1] It has been observed that around one-third of the world's population is infected with pulmonary tuberculosis.[2] The major hematological abnormality seen in patients with tuberculosis is anemia. The underlying pathogenesis of anemia in patients with tuberculosis is suppression of erythropoiesis by inflammatory markers, nutritional deficiency, and malabsorption syndrome.[3,4] It has been observed that patients with tuberculosis associated anemia have reduced bone marrow iron. Thus, iron deficiency is a possible cause of anemia in these patients. It has been observed that anemia resolves with anti-tubercular therapy in patients.[4,5] This study was done to study the prevalence and characteristics of anemia in newer cases of pulmonary tuberculosis.

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Materials and Methods

The retrospective study was carried out at a tertiary care hospital of Uttarakhand. It included all the new cases of pulmonary tuberculosis aged more than 18 years of age attending medicine OPD or medical ward over a period of 1 year from May 2017 to May 2018. Ethical clearance was sought from the ethics committee. A new case of pulmonary tuberculosis was defined as a patient who has never received treatment for tuberculosis or who had taken antitubercular therapy (ATT) for less than 1 month.[6] A sputum positive pulmonary tuberculosis was defined as a patient with one or more initial sputum smears examination (direct smear microscopy) acid-fast bacilli (AFB) positive or one sputum examination AFB positive and radiographic abnormalities consistent with active tuberculosis. All the cases of pulmonary tuberculosis categorized as relapse, treatment failure, and defaulters and chronic cases were excluded from the study. The detailed demographic and clinical data were obtained from the hospital record section and tabulated. Results of investigations such as complete hemogram, reticulocyte count, stool examination, serum iron, vitamin B12 and folic acid levels, general blood picture, and bone marrow examination (if done) were noted from the patient record files. The new cases of pulmonary tuberculosis were categorized as with and without anemia. Anemia was defined as per WHO guidelines, which are hemoglobin levels less than 12 gm/dl. Anemia was further subdivided as mild (11.9–10 gm/dl), moderate (9.9–8 gm/dl), and severe (<8 gm/dl) as per severity.[7] Microcytic anemia was defined as MCV (<80 fl), normocytic (MCV = 80–95 fl), and macrocytic (MCY > 95 fl).[8] The results were analyzed as SPSS (version 17.0). A significance of difference between proportions was tested using Chi-square test. Comparison of continuous data was done using student unpaired t test. Pearson's product moment correlation coefficient was used to determine the correlation between different variables. A "*P*" value of < 0.05 was considered to be significant.

Results

The baseline characteristics of patients with pulmonary tuberculosis with anemia are enlisted in Table 1. Maximum (87, 48%) number of patients with anemia were more than 50 years of age. As evident, males outnumber female patients. More than 60% of the patients with pulmonary tuberculosis with and without anemia belonged to lower socio-economic status. Approximately, 80% of patients with pulmonary tuberculosis were illiterates. The other risk factors were alcoholism (44, 25.3%) and smoking (58,32.0%). Tubercular patients with anemia (107, 59.1%) had lower BMI as compared to patients without anemia (3, 4.2%). Cough followed by fever, palpitation, and breathlessness were common symptoms in patients with tuberculosis with and without anemia. Clearly, pallor (96, 53%) was more common in patients with anemia. The mean respiratory rate (22.6 ± 2.8) and mean heart rate (82.3 ± 11.7) were more in patients with tuberculosis with anemia. Table 2 demonstrates a comparison of laboratory parameters in patients with pulmonary tuberculosis with and without anemia. The mean hemoglobin (9.65 ± 1.32),

Table 1: Demographic and clinical profile of patients of pulmonary tuberculosis with anemia and without anemia

Parameters		No. of patients (%) *n*=252	
		Anemic (*n*=181)	Non-anemic (n-=71)
Age	18-30 years	36 (19.8%)	15 (21.1%)
	31-50 years	61 (33.7%)	12 (16.9%)
	>50 years	87 (48%)	41 (57.7%)
Gender	Males	135 (74.5%)	49 (69%)
	Females	46 (25.4%)	22 (30.9%)
Socio-economic status	Middle	59 (32.5%)	26 (36.6%)
	Lower	123 (67.9%)	44 (61.9%)
Literacy	Illiterate	145 (80.1%)	56 (78.8%)
Diet	Non-vegetarian	95 (52.4%)	37 (52.1%)
Risk factor	Alcoholic	44 (24.3%)	18 (25.3%)
	Smoker	58 (32.04%)	32 (45%)
BMI	<18.5	107 (59.1%)	3 (4.2%)
	18.5-24.9	71 (39.2%)	47 (66.1%)
	25-29.9	3 (1.6%)	19 (26.7%)
	≥30	0 (0)	2 (0.7%)
Fever		88 (48.6%)	37 (52.1%)
Cough		135 (74.5%)	64 (90.1%)
Palpitations		29 (16%)	12 (16.9%)
Breathlessness		32 (17.6%)	13 (18.3%)
Hemoptysis		102 (56.3%)	28 (39.4%)
Pallor		96 (53%)	0 (0)
Cyanosis		5 (2.7%)	2 (2.8%)
Clubbing		6 (3.3%)	1 (1.4%)
Weight loss		13 (40.3%)	14 (19.7%)
Pedal edema		7 (3.8%)	2 (2.8%)
Respiratory rate		22.6±2.8	19.9±2.2
Pulse rate		82.3±11.7	76.2±15.1

Table 2: Comparison of laboratory parameters of patients of pulmonary tuberculosis with and without anemia

Parameters	Anemic patients	Non-anemic patients	*P*
Hemoglobin (g/dl)	9.65±1.32	12.5±1.4	<0.001
Total leucocyte count (thousand/cumm)	13150.26±5237.74	11653±4758	0.002
RBC (million/cumm)	3.32±0.63	4.75±0.81	0.001
PCV (%)	25.02±3.13	31±5.78	<0.001
MCV (fl)	81.11±10.66	88.73±5.12	0.04
MCH (pg)	26.77±3.18	25.73±2.17	0.27
MCHC (%)	32.52±6.54	32.331±0.78	0.21
Platelet count (thousand/cumm)	293.75±111.23	299.67±125.4	0.65
RDW (%)	17.25±2.9	16.23±3.19	0.002
Serum creatinine (mg/dl)	0.83±0.56	0.92±0.36	0.36
RBS (mg/dl)	116.47±23.05	119.031±33.4	0.45
Serum iron (μg/dl)	18.17±17.22		
TIBC (μg/dl)	232.72±67.42		
Serum ferritin (μg/dl)	95.54±116.93		
Serum folate (μg/dl)	11.32±5.84		
Serum B12 (pg/ml)	366.98±212.3		
Sputum for AFB+			

red blood cell count (3.32 ± 0.63 million/cumm), packed cell volume (PCV) (25.02 ± 3.13%), mean corpuscular cell

Table 3: Types and morphological variants of anemia in patients with pulmonary tuberculosis

Type of anemia	No. of patients (%)
Mild (Hb 10-11.9 g/dl)	112 (61.8)
Moderate (Hb 8-9.9 g/dl)	46 (25.4)
Severe (Hb <8 g/dl)	23 (12.7)
Microcytic hypochromic	52 (28.7)
Normocytic normochromic	103 (56.9)
Macrocytic	22 (12.1)
Dimorphic	4 (2.2)

Table 4: Correlation of various predictor variables and hematological parameters

Predictor parameters	Dependent variables									
	Hb (g/dl)		PCV (%)		MCV (fl)		MCH (pg)		RDW (%)	
	R	P	R	P	r	P	r	P	r	P
BMI	0.706	0.0001	0.228	0.0001	−0.192	0.00135	−0.045	0.232	−0.347	0.0001
Age	0.129	0.018	0.23	0.318	0.005	0.476	0.012	0.37	−0.142	0.011
Duration of disease	−0.023	0.352	0.064	0.156	0.0062	0.48	0.64	0.153	−0.122	0.024

Table 5: Correlation of severity of anemia with various social and demographic parameters

(n=181)		Mild	Moderate	Severe	P
Age	18-30 years	22	6	9	
	31-50 years	36	17	7	0.151
	>50 years	52	25	7	
Gender	Males	86	34	19	0.319
	Females	24	14	4	
Socio-economic status	Middle	36	17	5	
	Lower	75	29	18	0.460
Literacy	Illiterate	23	7	5	0.81
Diet	Non-vegetarian	88	39	19	
Risk factor	Alcoholic	62	30	15	
	Smoker	38	20	16	0.336
BMI	<18.5	38	45	23	<0.0001
	18.5-24.9	70	1	0	
	>24.9	4	0	0	

volume (MCV) (81.11 ± 10.66 fl), and red cell distribution width (RDW) (17.25 ± 2.9) were lower in patients with tuberculosis with anemia. There were no significant sputum positivity rates of tuberculosis patients with and without anemia. Table 3 depicts the severity of anemia in patients with tuberculosis. In total, 112 (61.8%) patients presented with mild anemia and maximum 103 (56.9%) patients had normocytic normochromic anemia. Table 4 shows correlation of various predictor variables and hematological parameters. There was a significant correlation between BMI and hemoglobin, PCV, MCV, and RDW. Age showed a significant correlation with hemoglobin and RDW. Duration of disease correlated significantly with only RDW. Table 5 shows correlation of severity of anemia with social and demographic parameters. Age, gender, socio-economic status, literacy, and duration of disease did not show significant correlation with BMI and severity of anemia. Table 6 shows that age and BMI had significant correlation with hemoglobin levels on univariate analysis, but by multivariate analysis, only BMI was found to be an independent predictor for hemoglobin.

Discussion

Anemia is a known complication of pulmonary tuberculosis. Both inflammation and iron deficiency anemia are proposed mechanisms of anemia in patients with pulmonary tuberculosis.[9] The reported prevalence of anemia in patients with pulmonary tuberculosis ranges from 20 to 94%.[10] In our study, around half of the tubercular patients with anemia were more than 50 years of age. Previous studies have also reported age as a significant risk factor of anemia in patients with pulmonary tuberculosis. Aging has been associated with increased duration of chronic disease, poor nutrition, reduced marrow cellularity, and decreased vitamin B12 levels.[11] Another important cause of anemia in patients with pulmonary tuberculosis is drug induced. The anti-tubercular drugs such as isoniazid, cycloserine, and pyrazinamide have been found to cause sideroblastic anemia. These drugs interfere with the conversion of vitamin B6 to its active coenzyme, thus inhibiting the 5-aminolevulinic acid synthase activity.[12] Although folate deficiency has also been reported in many of the tubercular patients, the incidence of megaloblastic anemia is low in these patients.[13] Rare cases of myelofibrosis associated with disseminated tuberculosis have been described in the past.[14] In our study, 181 (71.8%) cases of pulmonary tuberculosis with anemia were studied out of 252 cases. In a similar study by oliveria *et al.*, 104 (89.2%) of pulmonary tuberculosis had anemia were observed and Hussain *et al.* observed 62% cases of miliary tuberculosis had anemia.[15,16] In our study, anemia was more common in male (74.5%) patients with pulmonary tuberculosis as compared to the females (25.4%). Similar results were reported by a study conducted by oliveria *et al.*[15] However, Khurram *et al.* did not find a statistical difference between gender and prevalence of anemia.[17] In our study, maximum number of patients [61.8%] had mild anemia. A similar result was observed by lee *et al.*[18] In our study, 103 (56.9%) patients had normocytic normochromic anemia; Lee *et al.* described 72% patients had normocytic normochromic anemia and was the most common type of anemia in patients with pulmonary tuberculosis.[18]

Table 6: Predictors of hemoglobin levels by multiple linear regression analysis						
Predictor variables	Unstandardized Coefficients		Standardized Coefficients	t	P	95.0% Confidence Interval for B
	B	Std. Error	Beta			Lower	Upper
Constant	3.023	0.543		5.67	0.0001	1.89	4.19
BMI	0.479	0.035	0.689	15.13	0.0001	0.339	0.468
Age	0.007	0.0006	0.045	1.039	0.234	−.004	0.017

Similarly, Bashir *et al.* observed that most of the patients with pulmonary tuberculosis had anemia of chronic disease (15,34%) followed by iron deficiency (12,27%), macrocytic anemia (2,5%), and normocytic normochromic anemia (8,18%).[19] In our study, 107 (59.1%) patients of pulmonary tuberculosis with anemia were malnourished (BMI < 18.5 kg/m²). Malhotra *et al.* described a similar result, showing lower BMI in anemic patients of pulmonary tuberculosis.[20] Previous studies have highlighted that malnourished tubercular patients have reduced levels of iron and zinc as compared to healthy patients.[21] Iron deficiency has been found to impair T-cell immunity by interfering with the effector cell activity.[22] Past studies have also reported a possible correlation between prediction of treatment failure with low ferritin levels.[23] In our study, smoking has been found to be an independent risk factor of anemia in patients with pulmonary tuberculosis. Smoking causes virulent changes in the respiratory tree. This facilitates adherence of Mycobacterium to the airway epithelial cells, leading to TB infection.[24] In our study, cough was the most common symptom in patients with pulmonary tuberculosis, with and without anemia. However, there was no significant difference between the two groups of patients with and without anemia. In a study conducted by Sahirat madja *et al.*, anemia was most common in patients with longer duration of cough.[21] Our study did not show a significant association between age of the patient and presence of anemia. Similar results were observed by a study conducted by Majur *et al.*[25] In the current study, anemia was more common in patients belonging to lower socio-economic background. This result was confirmed by the study conducted by Malhotra *et al.*[26] In our study, significant correlation was observed between BMI and hemoglobin, PCV, MCV, and RDW. Age showed a significant association with hemoglobin and RDW. In a similar study conducted by Oliveria *et al.*, anemia has significant association with BMI, MCV, RDW, and ESR.[15] Tuberculosis is a chronic infectious disease and is affected by multiple demographic and socio-economic parameters. It leads to multiple complications. Anemia is one of them. Taking into consideration, the large burden of anemia in our study population, categorization of severity, and treatment of anemia deserves a priority setting. Dual burden of HIV infection and tuberculosis is on the rise. Anemia has been found to delay the sputum conversion in patients with pulmonary tuberculosis in a dose-dependent manner.[27] This underscores the role of primary care physician in these patients. Further studies are needed to assess the effect of treatment of anemia on final clinical outcomes of these patients.

The prompt recognition and treatment of anemia in these patients can improve their overall well-being significantly. Thus, the treatment of tuberculosis involves a combined role of a medical physician, family physician, and chest physician.

Conclusion

Anemia is a common hematological abnormality in new patients of pulmonary tuberculosis. Mild anemia and normocchromic normocytic anemia is the most common type of anemia. Severity of anemia has significant association with nutritional status of the patients assessed by BMI. BMI is an independent predictor of anemia in patients of pulmonary tuberculosis. Thus, frequent occurrence of anemia in new cases of pulmonary tuberculosis demands routine screening for anemia in all the cases of pulmonary tuberculosis. Thus, the role of family physician is of paramount importance who can identify, investigate, and treat anemia in patients of pulmonary tuberculosis. This will not only improve the overall wellness of these patients but also improve mortality and morbidity in these patients.

Conflicts of interest

There are no conflicts of interest.

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