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Correlation of Clinical Symptoms with Hematological and Biochemical Abnormalities Among Tuberculosis Patients.

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ABSTRACT

Objective: Tuberculosis (TB) is a key health issue and is characterized by a wide variety of clinical symptoms which can be affected by the underlying biochemical and hematological status of the patients. Therefore, this study assessed the association of clinical symptoms with biochemical and hematological findings among patients with tuberculosis.

Methodology: This cross-sectional experimental study was conducted in institute of Basic Medical Sciences (IBMS), Khyber Medical University. A total of 103 patients aged ≥15 years suspected with pulmonary tuberculosis, were included in the study. A chi-square test and Fisher's exact test was used to observe the association between clinical symptoms and demographics, hematological, and biochemical findings. Additionally, a Mann Whitney test was employed to analyze the relationship between the means of demographic variables.

Results: The study findings showed that all patients reported cough, and 100 (97.1%) had fever, with no significant association between symptoms and demographics, comorbidities, medication use, or hematological markers such as TLC and ESR ($p>0.05$). Significant associations were found with diabetes, where weight loss 48 (55.2%) ($p=0.032$) and reduced appetite ($p=0.002$) were more common among diabetics. Reduced appetite was also significantly linked to fasting blood sugar levels ($p=0.017$) and chronic illness ($p=0.020$), while all other variables showed no significant associations.

Conclusion: This study concluded that comorbid diabetes and chronic illnesses were significantly associated with main clinical symptoms, such as weight loss and reduced appetite. A significant association was identified between fasting blood sugar levels and reduced appetite. In contrast, hematological parameters including Total Leukocyte Count (TLC) and Erythrocyte Sedimentation Rate (ESR), showed no significant association with clinical symptoms.

Keywords: *Pulmonary Tuberculosis, clinical symptoms, reduced apatite, weight loss, hematological parameters*

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1. INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains a major global health concern and continues to be one of the leading causes of infectious disease-related morbidity and mortality. According to the World Health Organization (WHO), approximately 8.3 million new TB cases were reported worldwide in 2024, with pulmonary TB accounting for the majority of notified cases [1]. Pakistan remains among the high-burden countries, contributing substantially to the global TB burden and facing increasing challenges related to drug-resistant disease [2]. The coexistence of TB with chronic conditions such as diabetes further complicates disease management and outcomes [3].Tuberculosis exists in latent and active forms. While latent infection is asymptomatic, active disease may involve pulmonary or extrapulmonary manifestations and can be either drug-susceptible or drug-resistant [1,5]. Pulmonary TB commonly presents with chronic cough, sputum production, chest pain, fever, night sweats, weight loss, and fatigue, whereas

extrapulmonary TB produces symptoms depending on the affected organ system [6].Recent advances in TB diagnostics, including molecular assays such as Xpert MTB/RIF Ultra, Truenat, line-probe assays, and TB-LAMP, have improved the accuracy and speed of disease detection [7]. Similarly, treatment outcomes have improved with standardized first-line regimens for drug-susceptible TB and newer all-oral treatment strategies for multidrug-resistant tuberculosis [8]. Despite these developments, delayed diagnosis and limited access to healthcare resources remain important barriers in many low-resource settings.In addition to microbiological confirmation, laboratory abnormalities are frequently observed in patients with active TB. Hematological and biochemical alterations, including anemia, elevated erythrocyte sedimentation rate (ESR), leukocytosis, thrombocytosis, lymphopenia, and increased inflammatory markers, have been reported among newly diagnosed patients [9]. These abnormalities may reflect disease severity, systemic inflammation, and host immune responses to infection [10].Understanding the relationship between clinical manifestations and laboratory findings may provide valuable insights for early disease recognition and assessment of disease burden, particularly in resource-constrained settings where advanced diagnostic facilities are not always readily available [11]. Identification of readily available hematological and biochemical markers could support clinical decision-making and improve patient management [12].Therefore, this study aimed to evaluate the association between clinical symptoms and biochemical as well as hematological findings among patients with active tuberculosis and to determine whether specific laboratory abnormalities correlate with particular clinical presentations.

2. METHODOLOGY

This cross-sectional study was performed in institute of Basic Medical Sciences (IBMS), Khyber Medical University, Khyber Teaching Hospital, Lady Reading Hospital Peshawar and Rehman Medical Complex, Peshawar and conducted from June 2024 to Dec 2024. A total of 103 patients aged ≥15 years suspected with pulmonary tuberculosis based on clinical features, biochemical, and hematological parameters; and willingness to participate in the study were included. While, patients with extrapulmonary TB only, incomplete medical records, previous anti-TB treatment in the last six months, concomitant immunocompromised conditions excluding diabetes (e.g., HIV), and those with severe systemic disorders preventing reliable data collection were excluded from the study.Demographic variables assessed included age group, gender, height, and weight, while additional clinical history variables captured comorbid conditions such as diabetes mellitus, history of prior tuberculosis infection, presence of any chronic illness, current use of medications, and the presence or absence of a BCG vaccination scar. Hematological and biochemical parameters consisted of Total Leukocyte Count (TLC), Erythrocyte Sedimentation Rate (ESR) and Fasting Blood Sugar (FBS), all classified according to the determined normalized values from clinical references to ensure the standardization of the results. Clinical symptoms were evaluated through a structured clinical assessment conducted by trained healthcare professionals. Each participant was examined to document the presence or absence, of key symptoms for instance cough, fever, weight loss, and reduced appetite.Data was analyzed using SSPS version 23.0. The demographic details and signs and symptoms were reported in frequencies and percentages. Quantitative variables were reported as means with standard deviations. A chi-square test was used to observe the association between clinical symptoms and hematological and biochemical findings. Additionally, a Mann Whitney test was employed to analyze the relationship between the means of demographic variables. Categorical variables were compared between symptoms with hematological and biochemical findings using the Fisher's exact test, due to small cell counts. A p-value of < 0.05 was reflected as statistically significant.

3. RESULTS

A total of 103 patients with suspected of pulmonary tuberculosis were included in the study, all participants reported cough, and almost all 100(97.1%) presented with fever. Demographic factors, including age group and gender, showed no statistically significant association with either cough or fever ($p>0.05$). Most patients with fever were above 51 years of age 55(55.0%), while males 54(54.0%) and females 46(46.0%) were similarly represented. Mean weight and height did not differ significantly between febrile and afebrile patients ($p>0.05$). Use of medications, presence of diabetes, previous history of tuberculosis, chronic illnesses, and BCG vaccination status also showed no significant association with fever ($p>0.05$). Hematological findings revealed that the majority of patients had normal TLC levels 82(82.0%) and normal ESR values 57(57.0%), with no significant association between variations in TLC or ESR and the presence of fever ($p>0.05$). Fasting blood sugar levels were also insignificantly associated with fever status ($p>0.05$), as most patients with fever had normal glycemic levels 58(58.0%), as depicted in Table I.Regarding other symptoms, weight loss was reported in 87(84.5%) patients, while reduced appetite was present in 80(77.7%) patients. Age and gender distributions did not show statistically significant associations with either weight loss or reduced appetite ($p>0.05$). Similarly, mean weight and height were insignificantly associated with weight loss or reduced appetite ($p>0.05$). Significant associations were observed for comorbid diabetes and clinical symptoms. Patients with diabetes were more likely to report weight loss 48(55.2%) compared to non-diabetic patients 39(44.8%) with ($p=0.032$), and reduced appetite with ($p=0.002$). Presence of chronic illness was also significantly associated with reduced appetite 16(100%) compared to patients without chronic illness 64(80%), ($p=0.020$). Fasting blood sugar levels were significantly associated with reduced appetite ($p=0.017$), with

42(52.5%) of patients with reduced appetite having normal FBS, 13(16.3%) in the diabetic range, and 25(31.3%) with high uncontrolled levels. Hematological parameters, including Total Leukocyte Count and ESR, did not show significant associations with either weight loss or reduced appetite ($p>0.05$). Other variables such as history of TB, BCG scar, and medication use were also not significantly associated with these clinical symptoms, as depicted in Table II.

Table 1. Association of Demographic, Biochemical, and Hematological Characteristics with Cough and Fever Among Tuberculosis Patients (N = 103)

Variable	*Category*	*Cough, n (%)*	*p-value*	*Fever, n (%)*	*p-value*
Age (years)	15–30	12 (11.7)		12 (12.0)	0.692
	31–50	33 (32.0)		33 (33.0)	
	>50	58 (56.3)	NA*	55 (55.0)	
Gender	Male	55 (53.4)	NA*	54 (54.0)	0.478
	Female	48 (46.6)		46 (46.0)	
Weight (kg)	Mean ± SD	58.93 ± 11.77	NA*	58.74 ± 11.80	0.231
Height (ft)	Mean ± SD	5.43 ± 0.26	NA*	5.43 ± 0.26	0.968
Diabetes	Yes	52 (50.5)	NA*	52 (52.0)	0.118
	No	51 (49.5)		48 (48.0)	
Previous TB History	Yes	23 (22.3)	NA*	23 (23.0)	1.000
	No	80 (77.7)		77 (77.0)	
Chronic Illness	Yes	16 (15.5)	NA*	16 (16.0)	1.000
	No	87 (84.5)		84 (84.0)	
BCG Scar	Yes	64 (62.1)	NA*	63 (63.0)	0.555
	No	39 (37.9)		37 (37.0)	
TLC	Normal	83 (80.6)	NA*	82 (82.0)	0.072
	Mild elevation	14 (13.6)		13 (13.0)	
	Moderate elevation	5 (4.9)		4 (4.0)	
	Severe elevation	1 (1.0)		1 (1.0)	
ESR	Normal	58 (56.3)	NA*	57 (57.0)	0.246
	Mild elevation	12 (11.7)		11 (11.0)	
	Moderate elevation	15 (14.6)		14 (14.0)	
	High elevation	18 (17.5)		18 (18.0)	
Fasting Blood Sugar	Normal	61 (59.2)	NA*	58 (58.0)	0.700
	Diabetic range	13 (12.6)		13 (13.0)	
	Uncontrolled diabetes	29 (28.2)		29 (29.0)	

Table 1. Association of demographic characteristics, biochemical parameters, and hematological findings with cough and fever among patients with tuberculosis (N = 103). Most participants presented with cough (100%) and fever (97.1%). No statistically significant associations were observed between fever and demographic characteristics, comorbid conditions, hematological parameters, or fasting blood glucose levels (all p > 0.05). Statistical analysis was performed using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables.

Table 2. Association of Demographic, Biochemical, and Hematological Characteristics with Weight Loss and Reduced Appetite Among Tuberculosis Patients (N = 103)

Variable	*Category*	*Weight Loss n (%)*	*p-value*	*Reduced Appetite n (%)*	*p-value*
Age (years)	15–30	12 (13.8)	0.330	11 (13.8)	0.171
	31–50	27 (31.0)		28 (35.0)	
	>50	48 (55.2)		41 (51.3)	
Gender	Male	45 (51.7)	0.427	45 (56.3)	0.279
	Female	42 (48.3)		35 (43.8)	
Weight (kg)	Mean ± SD	58.68 ± 12.31	0.760	58.78 ± 12.01	0.978
Height (ft)	Mean ± SD	5.42 ± 0.27	0.271	5.43 ± 0.26	0.854
Diabetes	Yes	48 (55.2)	**0.032**	47 (58.8)	**0.002**
	No	39 (44.8)		33 (41.3)	
Previous TB History	Yes	18 (20.7)	0.351	19 (23.8)	0.777
	No	69 (79.3)		61 (76.3)	

Chronic Illness	Yes	15 (17.2)	0.456	16 (20.0)	**0.020**
	No	72 (82.8)		64 (80.0)	
BCG Scar	Yes	52 (59.8)	0.279	50 (62.5)	0.887
	No	35 (40.2)		30 (37.5)	
TLC	Normal	71 (81.6)	0.064	65 (81.3)	0.718
	Mild elevation	13 (14.9)		11 (13.8)	
	Moderate elevation	3 (3.4)		3 (3.8)	
	Severe elevation	0 (0.0)		1 (1.3)	
ESR	Normal	48 (55.2)	0.624	46 (57.5)	0.243
	Mild elevation	10 (11.5)		7 (8.8)	
	Moderate elevation	12 (13.8)		11 (13.8)	
	High elevation	17 (19.5)		16 (20.0)	
Fasting Blood Sugar	Normal	48 (55.2)	0.107	42 (52.5)	**0.017**
	Diabetic range	13 (14.9)		13 (16.3)	
	Uncontrolled diabetes	26 (29.9)		25 (31.3)	

Table 2. Association of demographic characteristics, biochemical parameters, and hematological findings with weight loss and reduced appetite among patients with tuberculosis (N = 103). Weight loss was significantly associated with diabetes mellitus (p = 0.032). Reduced appetite showed significant associations with diabetes mellitus (p = 0.002), chronic illness (p = 0.020), and fasting blood glucose level (p = 0.017). No significant associations were observed for age, gender, hematological parameters, or BCG vaccination status (all p > 0.05). Statistical analysis was performed using the Mann–Whitney U test, Chi-square test, and Fisher's exact test as appropriate.

4. DISCUSSION

This study evaluated the association between clinical symptoms and biochemical and hematological findings among patients with tuberculosis. Cough and fever were the most frequently reported symptoms; however, they showed no significant association with age, sex, comorbidities, total leukocyte count, or ESR. In contrast, diabetes mellitus was significantly associated with weight loss and reduced appetite, suggesting that metabolic disturbances may contribute to symptom severity in tuberculosis patients [13].Previous studies have consistently reported hematological abnormalities among patients with active tuberculosis. A recent meta-analysis demonstrated high frequencies of anemia, leukocytosis, thrombocytosis, lymphopenia, and elevated ESR, highlighting their potential role as supportive diagnostic markers [14]. Similar findings have been reported from studies conducted in India, Pakistan, and other developing countries, where anemia and elevated inflammatory markers were common among newly diagnosed tuberculosis patients [15–18].In the present study, anemia and elevated ESR were also frequently observed. However, unlike earlier reports, no significant association was found between major clinical symptoms and hematological parameters such as hemoglobin level, total leukocyte count, or ESR. These findings suggest that while laboratory abnormalities are common in tuberculosis, they may not directly reflect the severity or pattern of clinical manifestations in all patient populations [19].The observed hematological changes may result from chronic inflammation, nutritional deficiencies, bone marrow suppression, and altered immune responses associated with tuberculosis infection [20]. Previous investigations have demonstrated reduced hemoglobin levels alongside increased ESR, leukocyte counts, and platelet counts, supporting the presence of an ongoing inflammatory process in affected individuals [21].Although significant correlations between laboratory parameters and symptom profiles were limited, routine hematological and biochemical investigations remain valuable in the evaluation and monitoring of tuberculosis patients. These inexpensive and readily available tests may provide supportive information regarding disease burden and systemic inflammation, particularly in resource-constrained settings [22].Several limitations should be acknowledged. The cross-sectional design prevents causal interpretation, while the single-center setting and relatively small sample size may limit the generalizability of the findings. Future multicenter prospective studies involving larger populations are needed to further clarify the relationship between clinical presentation and laboratory abnormalities in tuberculosis.

Limitations

This study has several limitations. Its cross-sectional design limits the ability to establish causal relationships between clinical symptoms and laboratory findings. The study was conducted at a single center with a relatively small sample size, which may affect generalizability. Additionally, potential confounding factors, including nutritional status and coexisting infections, were not fully evaluated.

5. CONCLUSION

This research concluded that diabetes and chronic illnesses were observed to be significantly associated with symptoms of the clinical condition such as weight loss, decreased appetite. In contrast, hematological parameters of Total Leukocyte Count and erythrocyte sedimentation rate did not show significant association with clinical symptoms. However, a significant association was found between fasting blood sugar levels and reduction in appetite. These findings recommend that the severity of clinical manifestations and the presence of symptoms in patients with TB may be influenced by metabolic and chronic health conditions, but routine hematological and biochemical parameters may not predict the presence of symptoms.

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Conflict of Interest: Nil

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Authors Contribution

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Final Approval of version: All Authors Approved .

REFERENCES

[1] Al-Hazmi WA. Tuberculosis of the Malar and Zygomatic bone: A case report". International journal of health sciences. 2011;5(2):197-200:https://doi.org/[10.1038/s41598-022-16915-8]
[2] Aref ZF, Bazeed S, Hassan MH, Hassan AS, Rashad A, Hassan RG, et al. Clinical, Biochemical and Molecular Evaluations of Ivermectin Mucoadhesive Nanosuspension Nasal Spray in Reducing Upper Respiratory Symptoms of Mild COVID-19. International journal of nanomedicine. 2021;16:4063-72.10.2147/ijn.s313093: https://doi.org/[10.2147/ijn.s313093]
[3] Barreda NN, Arriaga MB, Aliaga JG, Lopez K, Sanabria OM, Carmo TA, et al. Severe pulmonary radiological manifestations are associated with a distinct biochemical profile in blood of tuberculosis patients with dysglycemia. BMC Infect Dis. 2020;20(1):139.10.1186/s12879-020-4843-0: https://doi.org/[10.1186/s12879-020-4843-0]
[4] Boisson-Dupuis S, Ramirez-Alejo N, Li Z, Patin E, Rao G, Kerner G, et al. Tuberculosis and impaired IL-23-dependent IFN-γ immunity in humans homozygous for a common TYK2 missense variant. Science immunology. 2018;3(30).10.1126/sciimmunol.aau8714: https://doi.org/[10.1126/sciimmunol.aau8714]
[5] Brat K, Merta Z, Čundrle I. Is it intestinal tuberculosis again? Case report. Vnitr Lek. 2017;63(5):354-60
[6] Brookes RH, Hill PC, Owiafe PK, Ibanga HB, Jeffries DJ, Donkor SA, et al. Safety and immunogenicity of the candidate tuberculosis vaccine MVA85A in West Africa. PLoS One. 2008;3(8):e2921.10.1371/journal.pone.0002921: https://doi.org/[10.1371/journal.pone.0002921]
[7] Dawra S, Mandavdhare HS, Singh H, Prasad KK, Dutta U, Sharma V. Extra-abdominal involvement is associated with antitubercular therapy-related hepatitis in patients treated for abdominal tuberculosis. Clinical and experimental hepatology. 2019;5(1):60-4.10.5114/ceh.2019.83158: https://doi.org/[10.5114/ceh.2019.83158]
[8] Dong Z, Shi J, Dorhoi A, Zhang J, Soodeen-Lalloo AK, Tan W, et al. Hemostasis and Lipoprotein Indices Signify Exacerbated Lung Injury in TB With Diabetes Comorbidity. Chest. 2018;153(5):1187-200.10.1016/j.chest.2017.11.029: https://doi.org/[10.1016/j.chest.2017.11.029]
[9] Esmaeel HM, Ahmed HA, Elbadry MI, Khalaf AR, Mohammed NA, Mahmoud HA, et al. Coagulation parameters abnormalities and their relation to clinical outcomes in hospitalized and severe COVID-19 patients: prospective study. Sci Rep. 2022;12(1):13155.10.1038/s41598-022-16915-8: https://doi.org/[10.1038/s41598-022-16915-8]
[10] Khan FY. Review of literature on disseminated tuberculosis with emphasis on the focused diagnostic workup. J Family Community Med. 2019;26(2):83-91.10.4103/jfcm.JFCM_106_18: https://doi.org/[10.4103/jfcm.JFCM_106_18]
[11] Kiliç A, Gül U, Soylu S, Kaya I, Albayrak L. Scrofuloderma: a forgotten disease? Skinmed. 2007;6(6):303-4.10.1111/j.1540-9740.2007.06607.x: https://doi.org/[10.1111/j.1540-9740.2007.06607.x]
[12] Kumar T, Nigam JS, Jamal I, Jha VC. Primary pituitary tuberculosis. Autopsy & case reports. 2021;11:e2020228.10.4322/acr.2020.228: https://doi.org/[10.4322/acr.2020.228]
[13] Kurup R, Flemming K, Daniram S, Marks-James S, Roberts Martin R. Hematological and Biochemistry Profile and Risk Factors Associated with Pulmonary Tuberculosis Patients in Guyana. Tuberculosis research and

treatment. 2016;2016:6983747.10.1155/2016/6983747: https://doi.org/[10.1155/2016/6983747]
[14] Mirlohi MS, Ekrami A, Shirali S, Ghobeishavi M, Pourmotahari F. Hematological and liver toxicity of anti-tuberculosis drugs. Electronic physician. 2016;8(9):3005-10.10.19082/3010: https://doi.org/[10.19082/3010]
[15] Mukherjee A, Kaeley N, Dhar M, Kumar S, Bhushan B. Prevalence, characteristics, and predictors of tuberculosis associated anemia. Journal of family medicine and primary care. 2019;8(7):2445-9.10.4103/jfmpc.jfmpc_311_19: https://doi.org/[10.4103/jfmpc.jfmpc_311_19]
[16] Munivenkatappa A, Sahay RR, Yadav PD, Viswanathan R, Mourya DT. Clinical & epidemiological significance of Kyasanur forest disease. Indian J Med Res. 2018;148(2):145-50.10.4103/ijmr.IJMR_688_17: https://doi.org/[10.4103/ijmr.IJMR_688_17]
[17] Rasool M, Malik A, Manan A, Aziz K, Mahmood A, Zaheer S, et al. Determination of potential role of antioxidative status and circulating biochemical markers in the pathogenesis of ethambutol induced toxic optic neuropathy among diabetic and non-diabetic patients. Saudi J Biol Sci. 2015;22(6):739-43.10.1016/j.sjbs.2014.09.019: https://doi.org/[10.1016/j.sjbs.2014.09.019]
[18] Sharma V, Bhatia A, Malik S, Singh N, Rana SS. Visceral scalloping on abdominal computed tomography due to abdominal tuberculosis. Therapeutic advances in infectious disease. 2017;4(1):3-9.10.1177/2049936116685262: https://doi.org/[10.1177/2049936116685262]
[19] Shiraishi W, Tateishi T, Sonoda K, Yamasaki R, Kira JI. [A case of brain tuberculoma resembling a malignant tumor]. Rinsho Shinkeigaku. 2021;61(4):253-7.10.5692/clinicalneurol.cn-001557: https://doi.org/[10.5692/clinicalneurol.cn-001557]
[20] Siddiqi Z, Siddiqi MS, Fatma J, Karoli R, Singhal V, Gupta M. Cerebrospinal Fluid Lactate in Tubercular Meningitis: Diagnostic or Prognostic Marker? J Assoc Physicians India. 2018;66(5):18-21
[21] Singal A, Kaur I, Jakhar D, Pandhi D, Grover C, Gandhi V. Clinicoepidemiological characteristics of cutaneous tuberculosis in 1458 Indian patients: a retrospective analytical study from a tertiary care center. Int J Dermatol. 2022;61(8):1012-22.10.1111/ijd.16267: https://doi.org/[10.1111/ijd.16267]
[22] Toscano-Guerra E, Martínez-Gallo M, Arrese-Muñoz I, Giné A, Díaz-Troyano N, Gabriel-Medina P, et al. Recovery of serum testosterone levels is an accurate predictor of survival from COVID-19 in male patients. BMC Med. 2022;20(1):129.10.1186/s12916-022-02345-w: https://doi.org/[10.1186/s12916-022-02345-w]