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Relationship Between Clinical, Laboratory, and Radiological Symptoms with The Incidence of Active Pulmonary Tuberculosis in People with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Type 2 diabetes mellitus (DM) is an independent risk factor for TB that increases the risk of morbidity and mortality. ***Method:*** This research is an observational analytical study using a cross-sectional design, which was conducted at Prof. Ngoerah General Hospital Denpasar, Bali over a 3-year period (January 2019-March 2023). ***Results:*** There were 106 samples that met the inclusion criteria consisting of 53 DM-TB subjects and 53 non-TB DM subjects. The results of bivariate analysis showed that there was a significant relationship between cough (PR= 13.67, p= <0.001), weight loss (PR= 3.18, p= <0.001), night sweats (PR= 2.02, p= 0.001), NLR≥ 4.76 (PR= 2.53, p= <0.001), MLR≥ 0.44 (PR= 2.58, p= <0.001), anemia (PR= 2.26, p= <0.001), uncontrolled HbA1c (PR= 1.65, p= 0.042) with the incidence of active pulmonary TB in people with type 2 DM. The results of multivariate analysis showed that the independent variables consisted of cough (OR= 91.90, p= < 0.001), weight loss (OR= 11.32, p= < 0.001), night sweats (OR= 24.27, p = 0.008), atypical lesions (OR= 2183.74 p= 0.002), typical lesions (OR= 12273.19, p=0.033) affect the incidence of active pulmonary TB in people with type 2 DM. TB scoring results were obtained in people with type 2 DM if suggestive of pulmonary TB if major criteria by adding one or more minor criteria and non-suggestive TB if one or more minor criteria without major criteria. ***Conclusion:*** There is a relationship between coughing, night sweats, weight loss, increased NLR, MLR, HbA1c, anemia, typical lesions and atypical lesions with the incidence of active pulmonary TB in people with type 2 DM. TB scoring results were obtained in people with type 2 DM if suggestive of pulmonary TB if major criteria by adding one or more minor criteria and non-suggestive TB if one or more minor criteria without major criteria.

Keywords: DM-TB; clinical symptoms; NLR; MLR; Anemia; HbA1c; Typical lesions; Atypical lesions.

INTRODUCTION

Type 2 diabetes mellitus (DM) is one of the risk factors for TB. DM is a chronic non-communicable disease that occurs due to increased blood glucose levels because the body cannot produce the hormone insulin. This causes a decrease in the immune system so that sufferers are easily infected [1].

Several studies have shown that type 2 DM and TB are interrelated chronic diseases and therefore type 2 DM is an independent risk factor for TB infection. This strong correlation is a major epidemiologic health problem with a global impact and high mortality rate. Many studies have shown that the incidence of TB is two to five times higher in people with type 2 DM compared to non-DM, which can double to triple the risk of TB infection, double the risk of death during TB treatment, quadruple the risk of recurrence of TB after completion of treatment and double the risk of Multidrug-Resistant TB (MDR-TB) [2].

Poor glycemic control in type 2 DM patients also affects the radiological picture. People with type 2 DM with poor glycemic control show a radiologic picture with atypical lesions that are generally found at the apex of the lower lobe of the lung [3]. This is in line with research conducted by Soerono and Soewondo from 50 patients found 84% of thoracic X-ray images on the apex of the lower lobe of the lung [4].

Many inflammatory cells play a role in fighting M.tb bacilli including macrophages, monocytes, neutrophils, Natur Killer (NK), T cells and B cells. Monocytes and lymphocytes are the most important part of the immune response to M.tb infection. Monocytes are the target cells of M.tb bacteria and lymphocytes are the main cells in the immune system against M.tb. Studies show that there is an increase in monocytes, neutrophils and a decrease in serum lymphocytes in type 2 DM patients with active pulmonary TB infection [5]. Studies also show that pulmonary TB infection in people with type 2 diabetes can affect immune system disorders, especially the cellular components, namely Neutrophil Lymphocyte Ratio (NLR) and Monocyte Lymphocyte Ratio (MLR) which are used as markers of pulmonary TB infection (Yu et al., 2022) [6].

Hemoglobin (Hb) is one indicator that plays a significant role. Anemia is the most common complication observed in hematological parameters in TB patients [7]. Anemia in TB is most often caused by malnutrition. In addition, increased release of cytokines such as Tumor necrosis Factor-α (TNF-α), Interferon-gamma (IFN-γ), Interleukin-1 (IL-1) and Interleukin-6 (IL-6) causes a reduction in erythropoietin formation, which results in bone marrow depression along with changes in ferritin metabolism leading to anemia [8].

This decade standardized the diagnosis of pulmonary TB infection using the Xpert/MTB RIF test. However, often people with type 2 DM and HIV co-infection have negative sputum results. Another challenge is the limited Xpert/MTB RIF facilities, especially at health service centers in private hospitals and peripheral areas, which is certainly a challenge for clinicians in confirming the diagnosis of pulmonary TB in people with type 2 DM [9].

The association of these two diseases creates a global health burden and increases morbidity and mortality, especially in Indonesia with its high burden of TB and DM. WHO and The Union Against Tuberculosis and Lung Disease (The Union) have issued a "collaborative framework" for the management and control of TB-DM. One of these recommendations is to implement TB screening in people with DM if the prevalence of TB in the country is above 100 per 100,000 population, this is very necessary in Indonesia given the high prevalence of TB. According to Putra et al., (2017) screening assessment is carried out every 3 months including clinical and radiology [10].

Until now, no routine screening has been conducted to detect TB in people with DM, although several studies of TB screening in people with DM have been conducted in various countries including Indonesia.

Therefore, the researchers wanted to assess the association of clinical (cough, weight loss, night sweats, malaise), laboratory (elevated NLR and MLR, anemia, HbA1c) and radiological (atypical lesions) symptoms with the incidence of active pulmonary TB in people with type 2 DM and the relationship between some of these parameters can be made into a scoring system to be used for screening active pulmonary TB in people with type 2 DM.

METHOD

This study was an observational analytic study using a cross-sectional study design. The research was conducted at the Prof. Dr. I.G.N.G Ngoerah Central General Hospital from November 2022 to October 2023. Samples were taken using non-probability sampling techniques, namely sample withdrawal by quota sampling. The inclusion criteria in this study are: 1) People with type 2 DM who have been screened for pulmonary TB aged≥ 20 years; 2) People with type 2 DM who have been screened for pulmonary TB with data on clinical symptoms, complete blood test results, HbA1c and complete thoracic X-rays. The exclusion criteria in this study are: 1) Patients with HIV/AIDS diagnosis; 2) Patients with stage 5 CKD diagnosis; 3) Patients with pregnancy; 4) Patients with malignancy; 5) Patients with pneumonia; 6) Patients with diabetic foot; 7) Patients diagnosed with pulmonary TB before being diagnosed with type 2 DM. Data analysis in this study consisted of descriptive statistical analysis, Receiver Operating Characteristics (ROC) analysis, proportion comparison analysis, multiple logistic regression test and validity test.

RESULT

In this study, the mean age of type 2 DM subjects with active pulmonary TB was 58.55± 12.334 years and without pulmonary TB was 60.43± 11.292. Based on the age category in this study, it is dominated by the age of ≥ 45 years in type 2 DM subjects with and without active pulmonary TB. Male gender was found to be more in subjects of type 2 DM with active pulmonary TB and female gender was found to be more in subjects of type 2 DM without pulmonary TB. Male gender was found to be 39 people (73.6%) in type 2 DM subjects with active pulmonary TB. Female gender was found to be 27 people (50.9%) in type 2 DM subjects without pulmonary TB. The highest level of education in type 2 DM subjects with and without active pulmonary TB was high school (50.9%) followed by elementary / junior high school as many as 37 people. The majority of subjects in this study had working status as much as 79.2% in type 2 DM subjects with active pulmonary TB and 56.6% in type 2 DM without TB.

Fisher's Exact test results showed no significant association of age with the incidence of active pulmonary TB in people with type 2 DM ($p > 0.05$). The results of the chi square test with continuity correction showed a significant relationship between gender and work with the incidence of active pulmonary TB in people with type 2 diabetes ($p < 0.05$). The results of the chi square test showed no significant relationship between education and the incidence of active pulmonary TB in people with type 2 diabetes ($p > 0.05$). Details are listed in Table 1.

TABLE 1: Demographic characteristics of study subjects.

Characteristics	Group		P-value[a]
	Pulmonary TB (n = 53)	No TB (n = 53)	
Mean± SD	58.55± 12,334	60.43± 11,292	
Age (th)			
< 45 years	6 (11,3%)	3 (5,7%)	0,488
≥ 45 years old	47 (88,7%)	50 (94,3%)	
Gender			
Male	39 (73,6%)	26 (49,1%)	0,017*
Female	14 (26,4%)	27 (50,9%)	
Education			
Elementary/Middle School	22 (41,5%)	15 (28,3%)	
High School	27 (50,9%)	27 (50,9%)	0,101
D3 / S1 / S3	4 (7,5%)	11 (20,8%)	
Jobs			
Work	42 (79,2%)	30 (56,6%)	0,022*
Not Working	11 (20,8%)	23 (43,4%)	

[a]: Analysis using Chi-square test.

The most common clinical symptom in this study was cough 65.1% followed by weight loss as much as 44.3%. In laboratory results, the mean absolute neutrophils were 9.27, absolute lymphocytes 1.70 and absolute monocytes 0.99. The NLR value obtained a mean of 7.71 and MLR 0.71. Anemia was found to be 19.8% and uncontrolled HbA1c was 65.1%. In radiology results, typical lesions (33.9%), atypical lesions (17%) and normal radiology images (49.1) were obtained. Details can be seen in Table 2.

TABLE 2: Clinical Symptoms, Laboratory and Radiology Results in Type 2 DM Subjects.

	N (%) Mean± standard deviation
Clinical symptoms	
Cough	69 (65,1)
Weight Loss	47 (44,3)
Night sweats	26 (24,5)
Malaise	46 (43,4)
Fever	44 (41,5)
Coughing up blood	5 (4,7)
Shortness of breath	20 (18,9%)
Laboratory	
Absolute neutrophils (x10^3 /L)	9.27± 6.266
Absolute lymphocytes (x10^3 /L)	1.70± 0.861
Absolute monocytes (x10^3 /L)	0.99± 1.547
NLR	7.71± 7.574
MLR	0.71± 0.889
Hemoglobin (g/dl)	
< 10	21 (19,8)
> 10	85 (80,2)
HbA1c (%)	
> 7,5	69 (65,1)
≤ 7,5	37 (34,9)
Radiology	
Normal	52 (49,1)
Typical	36 (33,9)
Atypical	18 (17)

The results of the Chi Square test with continuity correction showed that there was a significant relationship between cough, weight loss and night sweats with the incidence of active pulmonary TB in people with type 2 diabetes ($p < 0.05$), and there was no significant relationship between malaise and the incidence of active pulmonary TB in people with type 2 diabetes ($p > 0.05$) (Table 3).

TABLE 3: Relationship between clinical symptoms and incidence of active pulmonary tuberculosis in people with type 2 DM.

Clinical symptoms	Active Pulmonary TB		P-value[a]	PR (95%CI)
	Yes	No		
Cough				
Yes	51 (73,9%)	18 (26,1%)	< 0,001*	13,67 (3,53 - 53,02)
No	2 (5,4%)	35 (94,6%)		
Weight loss				
Yes	38 (80,9%)	9 (19,1%)	< 0,001*	3,18 (2,01 - 5,03)
No	15 (25,4%)	44 (74,6%)		
Night Sweats				
Yes	21 (80,8%)	5 (19,2%)	0,001*	2,02 (1,46 - 2,80)
No	32 (40,0%)	48 (60,0%)		
Malaise				
Yes	28 (60,9%)	18 (39,1%)	0,078	1,46 (1,00 - 2,13)
No	25 (41,7%)	35 (58,3%)		

[a]: Analysis using Chi-square test.

NLR and MLR data in the type 2 DM group with and without active pulmonary TB were not normally distributed so that differences in NLR and MLR were analyzed using the Mann Whitney test. The results of the Mann Whitney test showed that there were significant differences in NLR and MLR between subjects with type 2 DM with active pulmonary TB and type 2 DM without TB ($p < 0.05$) (Table 4).

TABLE 4: Differences in NLR and MLR of people with type 2 DM with and without active pulmonary TB.

	Active Pulmonary TB		P-value[a]
	Yes	No	
NLR			
Median (min - max)	7,70 (0,81 - 35,45)	3,01 (1,15 - 19,68)	< 0,001
MLR			
Median (min - max)	0,68 (0,18 - 5,03)	0,28 (0,06 - 6,83)	< 0,001

[a]: Analysis using Mann Whitney

Determination of NLR and MLR cut offs for people with type 2 DM with active pulmonary TB used ROC curve analysis. The results of the ROC curve are presented in Figure 1.

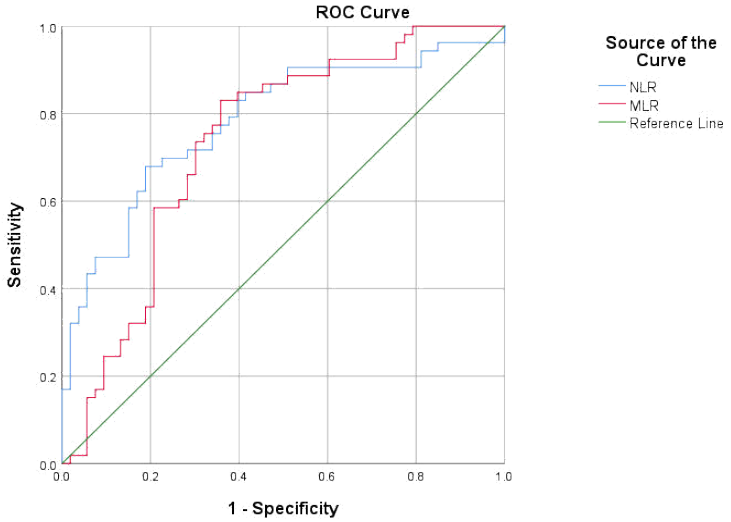

FIGURE 1: ROC curves of NLR and MLR.

The results of ROC analysis obtained AUC values for NLR and MLR of 0.783 and 0.736, respectively ($p < 0.05$) with sensitivity of 71.70%: 73.58%; specificity of 71.70%: 69.81%; NPP of 71.70: 70.91%; NPN of 71.70%: 72.55% and accuracy of 71.70%: 71,70%. With the results of specificity, sensitivity, NPP and NPN, it means that the strength of the NLR and MLR values can be used to distinguish cases of DM-TB and DM without TB so that the ROC curve coordinate analysis is carried out by looking for values that have the best sensitivity compared to specificity with the best cut off being 4.76 for NLR and 0.44 for MLR. The table of ROC NLR and MLR results, presented in Table 5.

TABLE 5: ROC analysis results for NLR and MLR.

	AUC	95%CI	P-value	Cut off
NLR	0,783	0,694 - 0,872	< 0,001	4,76
MLR	0,736	0,638 - 0,834	< 0,001	0,44

Cut off NLR≥ 4.76 to determine active pulmonary TB has a sensitivity value of 71.7% and specificity of 71.7%. Cut off MLR≥ 0.44 to determine active pulmonary TB has a sensitivity value of 73.6% and specificity of 69.8%. The diagnostic value of NLR and MLR on the incidence of active pulmonary TB in people with type 2 DM is presented in Table 6.

TABLE 6: Diagnostic cut off values of NLR and MLR on the incidence of active pulmonary TB in people with type 2 DM.

Diagnostic Value	NLR≥ 4.76	MLR≥ 0.44
Sensitivity	71,7%	73,6%
Specificity	71,7%	69,8%
Positive Prediction Value	71,7%	70,9%
Negative Prediction Value	71,7%	72,6%
Positive Likelihood Ratio	2,53	2,44
Negative Likelihood Ratio	0,39	0,38
Accuracy	71,7%	71,7%

The Chi Square test results with continuity correction showed a significant association of NLR, MLR, anemia and HbA1c with the incidence of active pulmonary TB in people with type 2 DM ($p < 0.05$). The complete results are presented in table 7.

TABLE 7: Relationship between laboratory and incidence of active pulmonary tuberculosis in people with type 2 DM.

Laboratory Results	Active Pulmonary TB		P-value[a]	PR (95%CI)
	Yes	No		
NLR				
≥ 4,76	38 (71,7%)	15 (28,3%)	< 0,001*	2,53 (1,60 - 4,02)
< 4,76	15 (28,3%)	38 (71,7%)		
MLR				
≥ 0,44	39 (70,9%)	16 (29,1%)	< 0,001*	2,58 (1,60 - 4,16)
< 0,44	14 (27,5%)	37 (72,5%)		
Anemia				
Yes	19 (90,5%)	2 (9,5%)	< 0,001*	2,26 (1,68 - 3,04)
No	34 (40%)	51 (60%)		
HbA1c				
Uncontrolled	40 (58%)	29 (42%)	0,042*	1,65 (1,02 - 2,67)
Controlled	13 (35,1%)	24 (64,9%)		

[a]: Analysis using Chi-square test.

Subjects with typical and atypical radiologic lesions experienced active pulmonary TB, while subjects with normal radiologic lesions showed no active pulmonary TB. The Chi Square test results prove that there is a significant relationship between typical and atypical lesions and the incidence of active pulmonary tuberculosis in people with type 2 diabetes ($p < 0.05$) (Table 8).

TABLE 8: Relationship between radiology and incidence of active pulmonary TB in people with type 2 DM.

Radiologic Lesions	Active Pulmonary TB		P-value
	Yes	No	
Typical	35 (97,2%)	1 (2,8%)	
Atypical	17 (94,4%)	1 (5,6%)	< 0,001
Normal	1(1,9%)	51 (98,1%)	

The results of the logistic regression analysis of clinical, laboratory and radiological symptoms of active pulmonary TB in people with type 2 diabetes showed that no variables were included in the model, therefore multivariate analysis was carried out separately.

The results of logistic regression of clinical symptoms on the incidence of active pulmonary TB in type 2 DM show that cough symptoms, weight loss and night sweats affect the incidence of active pulmonary TB in type 2 DM.

The coefficient of determination (R^2) obtained was 0.721, indicating the ability of cough, weight loss and night sweats to explain active pulmonary TB by 72.1%, the rest (27.9%) was influenced by other factors. The complete results are presented in Table 9.

TABLE 9: Multivariate results of clinical symptoms on active pulmonary TB.

Variables	β	p	OR (95% CI)	R^2
Cough	4,521	< 0,001	91,90 (9,96 - 848,03)	0,721
Weight loss	2,427	< 0,001	11,32 (3,01 - 42,66)	
Night sweats	3,189	0,008	24,27 (2,26 - 261,03)	
Constant	-4,961	< 0,001		

From the results of logistic regression, a scoring of clinical symptoms of active pulmonary TB in type 2 DM was made. The step of making the score by dividing the regression coefficient with the standard error of each independent variable, then the result is divided by the smallest value of β /SE. The result of the division is the score value of each clinical symptom.

TABLE 10: Clinical symptom scoring steps for active pulmonary TB.

Variables	β	SE	β/SE	(β /SE) / 2,631	Score	
					Yes	No
Cough	4,521	1,134	3,987	1,515	2	0
Weight loss	2,427	0,677	3,585	1,363	1	0
Night sweats	3,189	1,212	2,631	1	1	0
Total clinical symptom score					**4**	

The cut off results of the clinical symptom scoring system for active pulmonary TB were obtained≥ 3 which indicates active pulmonary TB. The cut off results have a sensitivity value of 77.4%; specificity of 92.5%; NPP of 91.1%; NPN of 80.3% and accuracy of 84.9%.

The results of laboratory logistic regression on the incidence of active pulmonary TB in type 2 DM show that NLR, anemia and HbA1c affect the incidence of active pulmonary TB in type 2 DM. The coefficient of determination (R^2) obtained was 0.453, indicating the ability of NLR, anemia and HbA1c to explain active pulmonary TB by 45.3%, the rest (54.7%) was influenced by other factors. The full results are presented in Table 11.

TABLE 11: Laboratory multivariate results on active pulmonary TB.

Variables	β	p	OR (95% CI)	R^2
NLR	1,875	< 0,001	6,52 (2,47 - 17,20)	0,453
Anemia	2,904	0,001	18,24 (3,35 - 99,24)	
HbA1c	1,562	0,006	4,77 (1,57 - 14,48)	
Constant	-2,432	< 0,001		

From the logistic regression results, laboratory scoring of active pulmonary TB in type 2 DM was made. The results are presented in table 12.

TABLE 12: Laboratory scoring steps for active pulmonary TB.

Variables	β	SE	β/SE	(β /SE) / 2,755	Score	
					Yes	No
NLR	1,875	0,495	3,788	1,375	1	
Anemia	2,904	0,864	3,361	1,220	1	
HbA1c	1,562	0,567	2,755	1	1	
Total laboratory score					**3**	

The cut off results of the laboratory scoring system for active pulmonary TB were found to be≥ 2 indicating active pulmonary TB. The cut off results have a sensitivity value of 69.8%; specificity of 83%; NPP of 80.4%; NPN of 73.3% and accuracy of 76.4%.

The total score of clinical and laboratory symptoms was carried out logistic regression on active pulmonary TB with a coefficient of determination of 0.803, which means that the total score of clinical and laboratory symptoms can explain active pulmonary TB by 80.3% and the remaining 19.7% is influenced by other factors. The full results are presented in Table 13.

TABLE 13: Multivariate results of total clinical, gender and laboratory symptom scores for active pulmonary TB.

Variables	β	p	OR (95% CI)	R^2
Total score of clinical symptoms	2,450	< 0,001	11,58 (3,8-35,31	
Total laboratory score	1,844	0,001	6,32 (2,11-18,89	0,803
Constant	-7,885	< 0,001		

The cut off results from the total score of clinical and laboratory symptoms of active pulmonary TB were obtained≥ 4 which indicates active pulmonary TB. The cut off results have a sensitivity value of 92.5%; specificity of 86.8%; NPP of 87.5%; NPN of 92% and accuracy of 89.6%.

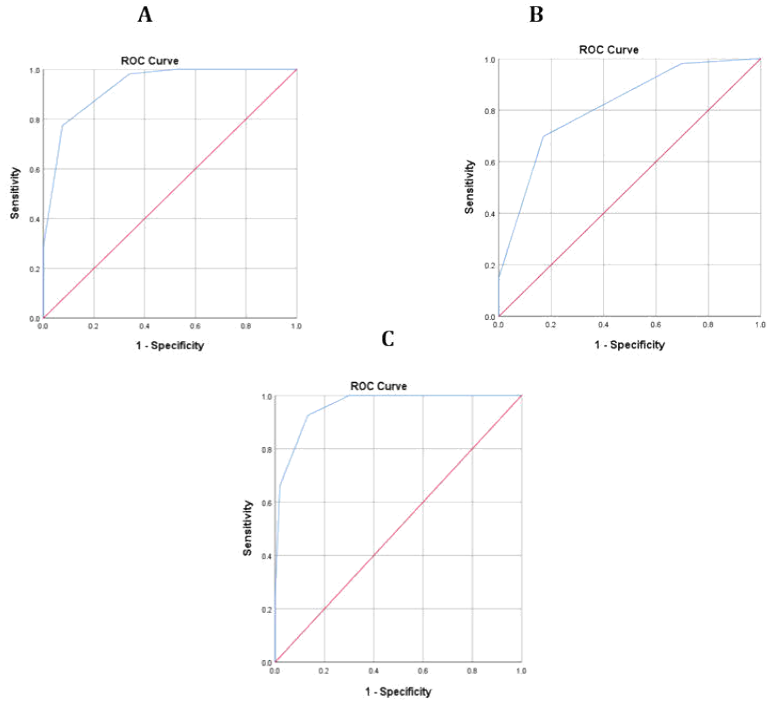

FIGURE 2: ROC curve results of total clinical, laboratory and radiology symptom scores.
Description: A. Total clinical symptom score, B. Total laboratory score, C. Total clinical and laboratory symptom score.

The results of pulmonary TB scores in people with type 2 DM based on clinical and laboratory symptoms are presented in Table 14.

TABLE 14: Pulmonary TB Scoring System in people with type 2 DM based on clinical and laboratory symptoms.

Variables	Score
Cough	2
Weight loss	1
Night sweats	1
NLR (≥ 4.76)	1
Anemia (Hb < 10 g/dl)	1
HbA1c (>7.5%)	1
Total	7

The cut off results were cross tabulated against active pulmonary TB and the chi square test results showed there was an association between total score and active pulmonary TB. Details are presented in Table 15.

TABLE 15: Cross tabulation of cut off total score of clinical and laboratory symptoms against Active pulmonary TB.

	Active Pulmonary TB		P-value	PR (95%CI)
	Yes	No		
Total score				
≥ 4	49 (87,5%)	7 (12,5%)	< 0,001	10,94 (4,25-28,15)
< 4	4 (8%)	46 (92%)		

The results of logistic regression of radiologic lesions and total clinical and laboratory symptom scores on active pulmonary TB are presented in Table 16.

TABLE 16: Results of logistic regression of radiology and total score of clinical and laboratory symptoms on active pulmonary TB.

Variables	β	p	OR (95% CI)	R^2
Radiologic lesions and total clinical and laboratory symptom scores	3,834	< 0,001	46,249 (6,706-318,947)	0,949
Constant	-10,253	< 0,001		

The Nagelkerke R Square value of 0.949 indicates the ability of radiologic lesions and the total score of clinical and laboratory symptoms to explain active pulmonary TB by 94.9%, while the rest (5.1%) is influenced by other factors outside the model. The equation model that can be formed is as follows y = -10.253 + 3.834 radiological lesions and the total score of clinical and laboratory symptoms. The calculation of the probability of active pulmonary TB based on the model is calculated by:

$$\text{Probability of pulmonary tuberculosis (+)} = \frac{1}{1 + \exp^{(-y)}}$$

TABLE 17: Calculation of the probability of active pulmonary TB based on the model.

lesion+scores of clinical and laboratory symptoms		y	-y	exp(-y)	1+exp(-y)	1/(1+exp(-y))	
-10,253							
3,834	1	-6,419	6,419	613,389	614,389	0,002	0,162763
	2	-2,585	2,585	13,263	14,263	0,070	7,011006
	3	1,249	-1,249	0,287	1,287	0,777	77,71267
	4	5,083	-5,083	0,006	1,006	0,994	99,38369

Description:
1= normal lesions and total clinical and laboratory symptom score < 4
2= normal lesions and total clinical and laboratory symptom scores≥ 4
3= atypical/typical lesions and total clinical and laboratory symptom score < 4
4= atypical/typical lesions and total score of clinical and laboratory symptoms≥ 4

Table 17 shows that if the radiologic lesion is normal and the total score is < 4, the chance of active pulmonary TB is 0.16%. If a normal lesion is obtained and the total score of clinical and laboratory symptoms is≥ 4, the chance of active pulmonary TB is 7.01%. If typical/atypical lesions are present and the total clinical and laboratory symptom score is < 4, the chance of active pulmonary TB is 77.7%. If typical/atypical lesions are found and the total score of clinical and laboratory symptoms≥ 4, the chance of active pulmonary TB is 99.38%. From table 5.17, the major criteria are typical/atypical radiologic lesions and the minor criteria are clinical and laboratory symptom scores.

TABLE 18: Cross-tabulation of radiology and total clinical and laboratory symptom scores for active pulmonary TB.

Radiologic lesions and total clinical and laboratory symptom scores	Active Pulmonary TB	
	Yes	No
Normal; score <4	0 (0%)	44 (100%)
Normal; score≥ 4	1 (12,5%)	7 (87,5%)
Typical/atypical lesion; score < 4	1 (66,7%)	1 (33,3%)
Typical/atypical lesions; score≥ 4	48 (100%)	0 (0%)

TABLE 19: Cross tabulation as major criteria in the scoring system.

The tabulation results above have a sensitivity value of 98.1%; specificity of 96.2%; NPP of 96.3%; NPN of 98.1% and accuracy of 97.2%.

Radiologic lesions and total clinical and laboratory symptom scores	Active Pulmonary TB		P-value	PR (95%CI)
	Yes	No		
Typical/Atypical; score < 4 or score≥ 4	52 (96,3%)	2 (3,7%)	< 0,001	50,07 (7,2-349)
Normal; score < 4 or score≥ 4	1 (1,9%)	51 (98,1%)		

DISCUSSION

TB can affect anyone regardless of age and gender. Various studies on the characteristics of patients with DM-TB have been conducted. Most of these studies have similar characteristics to this study.

A total of 106 people with type 2 DM who screened for TB in this study met the inclusion criteria. Research conducted by Yong et al. (2020) in Malaysia has age characteristics that tend to be similar to this study with the average age in the study in DM-TB subjects 56± 12.4 years and 62.9± 10.9 years in DM subjects without TB [11].

Research by Wahiduddin et al., (2019) in Surabaya obtained an average age in DM-TB subjects of 51.91± 7.93 and 55.78± 7.36 in DM subjects without TB. The results of this study indicate that most of the subjects were aged≥ 45 years in both DM-TB and DM without TB[12].

Other research by Putra et al., (2018) in Bali, has the same age characteristics, namely out of 365 subjects of type 2 DM who screened as many as 335 aged> 45 years [13]. Research by Das et al., (2017) in Bhubaneswar, Odisha screened for type 2 DM in subjects with pulmonary TB, out of 350 samples as many as 236 were aged≥ 45 [14] . Research by Yong (2020) also found that the total age of response of DM-TB subjects was 45-66 years. Based on the results of bivariate analysis, age is not associated with the incidence of active pulmonary TB in people with type 2 DM (p = 0.488)[11] . The same thing was found in research by Hartita Syahputri, (2023), that age is one of the factors that is not associated with the incidence of active pulmonary TB in people with type 2 DM (p = 0.877) [15].

The results of statistical analysis that are not related between these two studies can be caused by first the number of age samples in DM-TB and DM subjects without TB is the same, second≥ 45 years of age is one of the risk factors for type 2 DM, third≥ 45 years of age is a productive age with high activity and mobility so that it has a high probability of contact with other people. A systematic review shows that age is a risk factor for the development of TB disease in people with type 2 DM, as increasing age can reduce the immune system so that it is vulnerable to the development of TB, it is also said that age over 40 years has an increased risk of DM, because at that age there begins to increase glucose intolerance [16]. Another study from India, revealed that DM at an older age causes a decrease in IFN-γ resulting in susceptibility to TB infection. DM at an older age can alter Protein-Energy Malnutrition (PEM) which results in decreased T cell function thus increasing the risk of TB infection [17,18]. A study in the United States explained that the higher the age group of DM, the higher the likelihood of TB infection [19].

Most of the subjects with type 2 DM in this study were male, totaling 65 (61.3%). Based on gender characteristics, DM-TB subjects were dominated by men (73.6%) and DM without TB by women (50.9%). However, different results were found in research by Khalil and Ramadan, (2016) which has gender characteristics that are dominated by men, both in DM-TB and DM without TB subjects (70% and 68.75%) [20]. Another study by Yong (2020) had similar subject characteristics to the study by Khalil and Ramadan. Other Indonesian studies have also found a higher proportion of men than women, namely in Padang (58.62%) in DM-TB subjects[11] According to WHO data in 2022, the prevalence of TB was found in adult males, accounting for 56.5% of all cases in 2021 and women accounted for 32.5% (World Health Organization, 2022) [21].

Based on the results of bivariate analysis in this study, it is known that there is a significant relationship between gender and the incidence of active pulmonary TB in people with type 2 DM (p=0.017). Due to the higher proportion of males in this study, male subjects with type 2 DM are more at risk of TB infection. The same results were found in a study by Karminingsih (2016) that there is a significant relationship between gender and the incidence of active pulmonary TB in people with DM with men at a risk of 2.65 times compared to women (OR = 2.65: 95%CI: 1.215-5.669)[22]. In line with research Workneh et al., (2017) male gender was identified as being associated with the incidence of pulmonary TB in DM [16]. Several studies have shown that the incidence of DM-TB is more common in the male gender because men have risk factors for smoking. A study in Taiwan explained that smoking contributes highly to TB infection in men [23]. Workneh et al., (2017) revealed that smoking causes inflammation and oxidative stress in body cells, increasing the risk of DM [16]. According to Cooke et al., (2015) cigarette smoke can reduce the level of phagosity of alveolar macrophages so that they are vulnerable to the growth of M.tb germs, besides that cigarette smoke also disrupts the function of mucociliary clearance, decreased lymphocyte cell function and activation of dentritic cells [24]. Based on RISKESDAS, (2018) that the prevalence of DM is increasing in women and in the last five years has increased, an invitro study revealed that estrogen hormones can increase IFN-γ secretion and increase macrophage activation, but testosterone inhibits the immune response [23]. This may explain why in this study DM subjects without TB were found to be more female.

Subjects in this study had a secondary education background, namely high school at 50.9% each as the largest percentage of all levels of education, this is due to most of the research subjects living in the Denpasar area which is an urban area with good educational facilities, besides that health facilities in Denpasar city are easy to reach. In research by Hendra Sihombing, (2012) also obtained the characteristics of research subjects with high school graduates were the most with a proportion of 49.41%. Different things were found in research by Lamria with the majority of research subjects with elementary / junior high school education [25]. Based on the results of bivariate analysis, education is not associated with the incidence of active pulmonary TB in people with type 2 DM (p=0.101). The results of this unrelated statistical analysis are due to the first subject of DM-TB and DM without TB having the same proportion of education levels, both subjects with secondary education levels already understand the importance of health. The above is in accordance with research by Prananda et al., (2018) that there is no relationship between education and the incidence of MDR-TB [26]. According to Idowu et al., (2021) educational status plays an important role in the process of receiving various information, including health information. The existence of a high level of education causes individuals to understand the disease process, including the treatment that must be undertaken. The higher the level of education, the higher the individual's ability to receive and understand the health information received [27].

In addition to education, occupation is also a factor in the development of DM-TB disease. In line with this study based on the results of bivariate analysis that work is associated with the incidence of active pulmonary TB in people with type 2 DM (p = 0.02). The results of research by Hapsari and Isfandiari, (2017) on DM patients seeking treatment at all health centers in the Tambaksari District area in 2016 showed similar results, where there was a significant relationship between employment status and the incidence of pulmonary TB [28]. Different things were found in a study by Yosephine et al., (2021) on factors influencing the incidence of pulmonary TB in patients with DM that there was no significant relationship between employment status and the incidence of active pulmonary TB in people with DM (OR=0.802; 95%CI: 0.377-1.703) [29]. In a study by Berkowitz et al. (2018) conducted on Diabetes Mellitus patients in Cape Town, South Africa also stated that there was no significant relationship between the employment status of Diabetes Mellitus patients and the incidence of pulmonary TB [30].

People with type 2 DM who are infected with TB generally have classic symptoms of TB, namely coughing for more

than 2 weeks plus other complaints such as fever, night sweats, weight loss, malaise, shortness of breath, coughing up blood and chest pain. In this study, classic TB symptoms in all subjects were dominated by coughing as many as 69 people (65.1%) followed by weight loss as many as 47 people (44.3%), malaise as many as 46 people (43.4%), fever as many as 44 (41.5%), shortness of breath as many as 20 people (18.9%) and coughing up blood as many as 5 people (4.7%).

Based on the results of TB screening in people with type 2 DM in Sri Lanka by Hewage et al., (2021) out of 4548 study subjects a quarter of the subjects had at least classic symptoms of TB, with the most common symptom being cough 746 people, followed by shortness of breath 514 people, decreased appetite as many as 456 and night sweats as many as 393 people [31]. Another study in southern Africa reported that TB screening in patients with DM found cough, fever and weight loss to be the most common clinical symptoms [30].

Coughing for more than 2 weeks is the main symptom of pulmonary TB. Coughing for 2 weeks is the most common time criterion to consider the possibility of TB infection. There is currently no strong evidence for a minimum duration of cough when screening is required, but countries with a high prevalence of TB are advised to initiate TB evaluation regardless of cough duration.

The above statement is in accordance with the results of the Chi Square test with continuity correction bivariate analysis in this study found that subjects with TB infection experienced more cough complaints. This shows that there is a relationship between coughing and the incidence of active pulmonary TB in people with type 2 DM. Research on pulmonary TB in people with DM by (Makuka et al., 2022) in Tanzania obtained similar results, namely most of the subjects infected with TB had complaints of coughing at 54.5% [32]. In line with Berkowitz et al., (2018) in their research in South Africa on the prevalence and determinants of active TB in people with DM, as many as 440 DM subjects who screened for TB found 46.6% (95% CI 41.98-51.29) had clinical complaints of TB and cough (23.1%) was the most common complaint reported [30]

Although the exact mechanism of coughing in TB is not yet known, Cohn et al studied the involvement of lymphocytes and inflammatory cytokines to cause caseous necrosis in granulomas to produce sputum, and the body's response to expel the sputum through the coughing mechanism [33]. The cough response begins due to stimulation of cough receptors, this stimulus is then forwarded by afferent nerves through the vagus nerve to the cough center in the medulla oblongata, from the medulla oblongata the impulse is forwarded by efferent nerves through the vagus nerve, phrenic nerve and motor nerve to trigger the expiratory muscles to produce a cough [34].

TB infection may progress more rapidly in people with type 2 DM, resulting in more clinical symptoms. In addition to coughing, weight loss is a common symptom. Weight loss occurs due to hypercatabolism due to an immune response that induces an increase in pro-inflammatory cytokines such as IL-1 and TNF-α resulting in protein degradation, muscle wasting and anorexia which has an effect on weight loss [2]. In addition to the involvement of IL-1 and TNF-α in the weight loss process, the hormone leptin is thought to play a role in TB-related malnutrition, the main effects of which are associated with decreased appetite, anorexia and weight loss [33].

Based on the results in this study, it is evident that weight loss is associated with the incidence of active pulmonary TB in people with type 2 DM with the results.

This study is in line with research by Solanki et al., (2023) of 64 patients with DM-TB 58 subjects (90.6%) had complaints of weight loss [35]. A cross sectional study by Makuka et al., (2022) in Tanzania regarding active pulmonary TB in people with DM found 72.7% (n=11) of DM-TB subjects had complaints of weight loss.

It is theorized that leptin concentrations in TB are affected by two opposing mechanisms, namely, chronic inflammation that causes loss of body fat mass thereby reducing leptin production and an acute inflammatory response that increases leptin levels which theoretically causes appetite suppression, anorexia and decreased body mass [36]. Lacerda (2017) also said that the inflammatory response in TB suppresses leptin production directly through loss of body fat mass and decreased energy intake, decreased leptin leads to decreased cellular immunity [36].. According to Yu et al., (2022) leptin is a pro-inflammatory hormone found to be significantly increased in DM and TB patients [6].

There are indications that the clinical presentation of TB infection in people with type 2 DM may be exacerbated by poor glycemic control. In accordance with several studies and this study found that, people with type 2 DM with TB infection also showed one of the classic symptoms of TB, namely night sweats. This study found night sweats to be associated with the incidence of active pulmonary TB in people with type 2 DM. Similar results were obtained by Makuka et al., (2022) in Tanzania as many as 45.5% (n=11) of DM-TB subjects had complaints of night sweats [32]. Berkowitz et al., (2018) of the 46.6% of study subjects who had clinical symptoms of TB, 16.6% had this complaint. A study in Iran on TB-DM subjects found 55.5% (n = 36) of subjects had similar complaints [30].

"Night sweats", this event is associated with the body circadian rhythm that is lower body temperature in the early morning (36.1 ° C) and rises during the day (37.4 ° C), this event begins with the infection of M.tb responded with the activation of phagocytic cells (macrophages) that stimulate increased secretion of proinflammatory causes an increase in proinflammatory cytokines IL-1, IL-6 and TNF-α . IL-1 into the circulation and interacts with cytokine receptors and TLRs in the hypothalamic endothelium to produce prostaglandins (PGE2), the release of PGE2 affects the work of the hypothalamic thermostat to increase the thermostat set point The hypothalamus stimulates heat retention through vasoconstriction of cutaneous blood vessels and triggers the body to shiver in order to increase heat production immediately, hemostasis between heat production and heat loss is achieved, shivering stops, set points return to normal and skin vasodilatation occurs in releasing heat with sweating In addition, the activation of the hormone cortisol, a glucocorticoid/steroid hormone that modulates the innate and adaptive immune system, which decreases at night, may be a source of TB-related night sweats [33].

Malaise occurs due to the process of hypercatabolism due to increased proinflammatory cytokines caused by TB infection, increased proinflammatory cytokines also cause metabolic dysregulation, especially in people with type 2 DM [28]. This statement is supported by research conducted by Tong et al., (2021) out of 312 TB-DM subjects, 182 people or 58.3% had complaints of malaise (p = 0.001). A study in Semarang by Rahayu et al., (2017) stated that malaise was the second complaint found in TB suspected subjects with a proportion of 51%. Different things were found in this study, that there was no relationship between malaise and the incidence of active pulmonary TB in people with type 2 DM [37].

The results of this unrelated statistical analysis may be influenced by several things, including the main population in this study were people with type 2 DM, where malaise is one of the typical symptoms often complained of by people with type 2 DM, this can be seen from the similarity of results between DM-TB and DM without TB which can affect the significance of bivariate analysis data. Malaise in people with type 2 DM generally occurs due to acute and chronic conditions of hyperglycemia. This is because in people with type 2 DM the pancreas does not produce enough insulin or the body cannot use insulin effectively so that the body's cells do not get enough glucose to be used as energy [38].

In addition to clinical symptoms, the laboratory is one of the parameters in determining the relationship between the incidence of active pulmonary TB in people with type 2 DM in this study. The laboratory parameters studied were NLR, MLR, Hemoglobulin and HbA1c. The results in this study showed that the mean absolute neutrophils were 9.27, absolute lymphocytes were 1.70 and absolute monocytes were 0.99. The NLR value obtained a mean of 7.71 and MLR 0.71. Anemia was found to be 19.8% in the study subjects and most of the study subjects with poor glycemic control.

This study shows that there is a significant difference in NLR between DM-TB subjects and DM without TB. In bivariate analysis, it was found that an increase in NLR increased the risk of TB infection in people with type 2 DM with a cutoff of 4.76. A study by Zhang regarding the relationship between NLR with TB disease and DM also obtained similar results, namely a higher NLR (≥ 2.9) indicates the activity of TB infection in DM. This study obtained higher cut off, AUC, sensitivity and specificity values than the results of the study by Kamelia et at., (2018) which were 2.9, 0.726, 67% and 66% respectively [39].

Research by Karthik et al. (2013) proposed a new concept stating that neutrophils are the most commonly influential phagocytic cells and contribute to controlling TB infection in the blood and have an important role in the early phase of TB infection. The increase occurs on the first day of infection, then decreases, increases again after 8-15 days and persists until the end of infection. These results suggest that neutrophils play an important role in the early phase of TB infection [40]

NLR is defined as the number of neutrophils in whole blood divided by the number of lymphocytes in whole blood. An increase in NLR indicates a relative increase of neutrophils and a relative decrease of lymphocytes. NLR is considered to have a better ability to predict bacteremia than neurophils or lymphocytes [41]

In this study, the median MLR value in DM-TB subjects was 0.68 (0.18 - 5.03) while the median MLR in DM subjects without pulmonary TB was 0.28 (0.06-6.83) with a p value <0.001. This shows that there is a significant difference in MLR between DM-TB subjects and DM without TB. In bivariate analysis, it was found that an increase in MLR increased the risk of TB infection in people with type 2 DM with a cutoff of 0.44. The results of this study differ from research by Yustin et al., (2021) which obtained a cut off MLR≥ of 0.35 with a sensitivity of 90.91% and specificity of 39.58% [42]. The differences seen in these two studies were due to differences in research subjects, Yustin compared MLR in HIV-TB subjects while this study compared MLR in DM-TB subjects. Systematic review and meta-analysis by Adane et al. (2022) showed that increased MLR was associated with an increased risk of TB infection with an OR of 3.11 (95% CI: 1.40-6.93) [43].

This suggests that MLR is involved in the development of TB infection in people with type 2 DM.

Monocytes are a component of innate immunity derived from hematopoietic stem cells in the bone marrow, circulate in the bloodstream, migrate to tissues to become macrophage cells, lymphocytes are an important component of adaptive immunity as the main effector of immune cells [44]. As immune cells, monocytes and lymphocytes describe the state of a person's immunity to infection, therefore any factor that affects the function or relative amount of these two cells can potentially affect a person's response to infection [44,45].

Monocytes and lymphocytes are an important part of the immune response to TB infection, therefore MLR reflects the immune response to TB infection. An increase in MLR indicates a relative increase in monocytes and a relative decrease in lymphocytes [44]

A study explains that M.tb infection causes changes in the balance of monocyte subsets in peripheral blood resulting in the expansion of the CD16+ subset resulting in disease growth and progression, this involves the role of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 [46]. High MLR in peripheral blood due to M.tb infection causes monocytes in the blood to be activated and increased in peripheral blood circulation as a consequence of early release from the bone marrow, low lymphocyte counts in peripheral blood can be caused by lymphocyte aggregation. MLR reflects the relative frequency of monocytes as target cells for M.tb growth and lymphocytes as effector cells for M.tb clearance [43].

Anemia is a hematological disorder that often occurs in patients with TB. This study showed an association between decreased hemoglobin and pulmonary TB infection in people with type 2 DM. It is evident that DM-TB subjects are 2.26 times more likely to have anemia than DM subjects without TB. Similar research by Khalil and Ramadan, (2016) obtained lower and statistically significant hemoglobin levels in DM-TB subjects with a mean hemoglobin of 11.19 ± 1.89 mg/dl compared to 12.58 ± 2.05 mg/dl in DM subjects with a p value <0.001 [20]. Mukherjee (2019) supported the same results in his study stating that anemia was reported in 33.3% of DM-TB subjects and there was a significant association between TB, DM and anemia [7] .

Subjects with anemia in this study can be caused by suppression of erythropoesis by inflammatory mediators which is the most common pathogenesis of anemia that occurs in TB cases, this condition causes a decrease in endurance which also reduces cellular immune response [8]. Luo et al., (2022) revealed that immune factors and malnutrition are the causes of anemia and anemia usually occurs along with diseases that interfere with the immune system, one of which is DM, which is the main subject in this study is a person with type 2 DM [47].

In addition, anemia can be caused by chronic disease or an inflammatory process but can also be caused by iron deficiency [8]. Disruption of iron balance can occur due to increased uptake and retention in the reticuloendothelial system in chronic infections such as TB, disruption of iron hemostatis causes the transfer of iron from the circulation to the reticuloendothelial system storage and followed by limited iron supply for erythroid progenitor cells, this leads to limited erythrocyte formation process [48].

Based on the immunopathogenesis of anemia due to inflammation through the pathway of microorganism invasion that causes activation of T cells (CD3+) and monocytes, these cells induce immune effector mechanisms by producing cytokines such as IFN-γ from T cells, TNF-α, IL-1, IL-6 and IL-10 (from monocytes or macrophages), Excessive cytokines due to TB infection cause hematologic stress syndrome so that macrophages and iron are increasingly bound which consequently increases erythrocyte destruction in the spleen, suppresses erythropeitein production in the kidneys and causes stimulation of erythropoiesis in the bone marrow [49].

HbA1c is the gold standard and approved indicator for assessment of glycemic control status in people with DM. An elevated HbAlc level ≥ 7% is a diagnostic criterion for DM. Hyperglycemia can be caused by insulin resistance or insulin deficiency in people with DM. People with DM with hyperglycemia and high HbAlc levels cause immunosuppression conditions. In this condition, they are more susceptible to M.tb infection which causes pulmonary TB. Several studies prove that people with DM have a greater risk of being infected with pulmonary TB, poor glycemic control further exacerbates this risk [50].

After evaluating the HbA1c results in this study, it shows that there is a significant relationship between HbA1c levels of people with type 2 DM and the incidence of active pulmonary TB, which indicates that people with type 2 DM with poor glycemic control have a higher susceptibility to TB infection. Furthermore, people with type 2 diabetes with HbA1c > 7.5% have a 1.65 times increased risk of developing pulmonary TB compared to people with type 2 diabetes with good HbA1c levels. The results of this study are in line with research conducted by Khalil and Ramadan, (2016) that people with DM with high HbA1C levels (≥7%) increase susceptibility to pulmonary TB infection [20]. In line with Khalil and Ramadan, a meta-analysis concluded that poor glycemic control (HbA1c >7%) 2.05 times increased the prevalence of TB, they also observed that higher HbA1c levels were obtained in DM-TB subjects than DM-only subjects [50].

According to research by Restrepo et al., (2008) Poor glycemic control can interfere with innate immunity or adaptive immunity and trigger a hyperinflammatory state and there are significant changes in proinflammatory cytokines such as IL-2, IL-6, IL-17, TNF-α and IFN-γ, this hyperinflammatory state causes the activation of TB [51]. Poor glycemic control is associated with uncontrolled DM which can lead to a decrease in the body's immune system and cause various complications of DM so that people with DM become more susceptible to infectious diseases [19].

There have been many studies on the differences in radiologic images in DM-TB subjects and TB subjects. In general, these studies report an atypical picture in DM-TB subjects [52]. Solanki in her study found that DM-TB subjects 6.29 times had atypical lesions compared to TB without DM [35]. Research conducted by Shital and Anil, (2014) has results that support Putri's research, namely, 141 DM-TB subjects and 173 TB subjects without DM found atypical lesions as much as 24.11% in DM-TB subjects and 6.35% in TB subjects without DM[53].

Different things were found in this study, not only atypical lesions but typical lesions were found to be associated with active pulmonary TB in people with type 2 DM. This study is similar to research by Zhan et al., (2022) on the results of thoracic CT scans of DM-TB subjects with HbA1c> 9% obtained a picture of cavities and infiltrates in each lung lobe compared to subjects with normoglycemia [5].

The difference in the results of this study and Zhan with the research of Putri, Shital and Anil is because in this study and Zhan the main subjects were people with type 2 DM while the main subjects in the research of Putri, Shital and Anil were TB patients with comorbid DM. People with DM with immunocopromise status do not always find atypical radiological images, unlike HIV patients with immunocopromise status, where low CD4 + counts have atypical radiological findings [53]. This study also shows that in people with type 2 DM, the lesions found are not only atypical but can be found typical lesions and extensive lung lesions.

Regarding the typical picture in this study, it correlates with hyperglycemic conditions and impaired immunity. First, insulin resistance in people with DM leads to hyperglycemia and increased degradation of adipose tissue, which creates a good environment for the development of M.tb, second, hyperglycemia causes persistent inflammation. As a result of impaired innate immunity, hyperglycemia and oxidative stress cause an increase in pro-inflammatory cytokines such as IL-17A, IL-8 and IL-10, whereas there is a decrease in the production of TNF-α and IFN-γ due to impaired Th1 cells which causes the inability to control the growth and development of M.tb, third, hyperglycemia suppresses immune function, causing delayed antigen presentation and impaired bactericidal activity and increasing the ability of M.tb to evade the immune system. Hyperglycemia suppresses immune function, leading to delayed antigen presentation and impaired bactericidal activity and promotes immune escape by M.tb, large numbers of bacteria and excessive inflammation resulting in more extensive lung lesions, cavities, and more immune cell infiltration. Fourth, high blood sugar levels increase pathological signals associated with hypercoagulation due to TB infection and activate systemic coagulation processes, processes that lead to exacerbation of caseous necrosis in granulomas with severe fibroplasia [53].

Based on logistic regression test multivariate analysis of clinical symptoms obtained cough, weight loss and night sweats are simultaneously independently associated with the incidence of active pulmonary TB in type 2 DM. People with type 2 DM with complaints of coughing, weight loss and night sweats are 91.90 times, 11.32 times and 24.27 times respectively associated with the incidence of active pulmonary TB. The involvement of both innate and adaptive immune systems until caseous necrosis occurs and produces sputum and as compensation the body expels the sputum with a coughing mechanism. In addition to coughing, the immune system plays an important role in one of the symptoms of TB, namely weight loss. Macrophages are a component of innate immunity in addition to phagocytosing M.tb germs, macrophages also function to stimulate increased secretion of proinflammatory cytokines such as TNF-α , IL-1, IL-6. IL-6 causes increased catabolism resulting in weight loss. TNF-α , IL-1, IL-6. IL-1 if it follows the blood vessels to the brain to the hypothalamus to produce prostaglandin PGE2. The release of PGE2 affects the work of the hypothalamic thermostat, as compensation the hypothalamus will increase the set point and trigger heat conversion and production. Once the set point is reached the body will try to release excess heat by sweating [33].

Based on the logistic regression test, laboratory multivariate analysis of the incidence of active pulmonary TB in type 2 DM shows that an increase in NLR, anemia and an increase in HbA1c are simultaneously independently associated with the incidence of active pulmonary TB in type 2 DM.

Type 2 DM with increased NLR, anemia and increased HbA1c were 6.52 times, 18.24 times and 4.77 times respectively associated with the incidence of active pulmonary TB. Impaired immunity in people with DM due to hyperglycemia results in disruption of chemotaxis, granulocyte function, phagocytosis, complement and organism-killing activity in leukocytes. Neutrophils and lymphocytes are leukocyte subtypes that have an important role in TB infection. Leukocytes fight inflammatory conditions characterized by increased neutrophil counts and decreased lymphocyte counts. NLR is considered to have a stronger ability to predict bacteremia than neutrophils or lymphocytes. The physiological immune response of circulating leukocytes to various inflammatory stress conditions is characterized by an increase in neutrophil count and a decrease in lymphocyte count [51].

Impaired immunity in DM-TB is implicated in decreased hemoglobin. Chronic disease anemia is anemia that occurs in TB. In chronic disease anemia, cytokines can interfere with the body's ability to absorb and use iron. In addition, excessive production of cytokines can also interfere with the production and activity of erythropoietin, a hormone that stimulates the bone marrow to produce red blood cells, leading to anemia. Decreased Hb levels below normal values in TB infection occur due to immune system dysregulation associated with the systemic response to the disease condition. The increase in proinflammatory cytokines such as TNF-α, IL-6, IL-1β and IFN-γ affects the decrease in erythroid progenitors. This decrease in erythroid progenitors directly inhibits erythrocyte differentiation and proliferation [8]

Poor glycemic control characterized by high levels of HbA1c is associated with uncontrolled DM which can lead to a decline in the immune system which directly increases the risk of TB infection (Putra et al., 2020). DM-TB is associated with increased levels of AMP, which shows a positive relationship with HbA1c and fasting blood glucose levels. High blood glucose causes a shift in the body's condition from anti-inflammatory to pro-inflammatory conditions. This situation will induce the number of Th1 cells, Th17, Th2 cells to increase.

Increased T helper cells are followed by increased production of cytokines in the circulation such as cytokines from Th1 (TNF-α, and IFN-ɣ and IL-2), cytokines from Th2 (IL-5) and cytokines from Th17 (IL-17). CD8 T cells+ which play a protective role in the anti-tuberculosis immune response increased. Despite the increase in the levels of T helper 1 (Th1) cells, T helper type 17 (Th17) cells, T helper type 2 (Th2) cells, the body is still inadequate against M.tb bacteria because the poor activity of innate immune cells, which are the first line of defense, can weaken the body in preventing infection [54].

Based on logistic regression test multivariate analysis, typical lesions and atypical lesions are independently associated with the incidence of active pulmonary TB in type 2 DM. Decreased immune system is the cause of increased severity of TB on radiology. The increased incidence of pulmonary TB in patients with DM may also be due to defects in alveolar macrophages or T lymphocytes. Low numbers of alveolar macrophages result in greater expansion of pulmonary TB lesions and increased numbers of TB bacteria in the sputum of TB patients with DM. Pulmonary TB lesions in people with DM and old age are often located in the lower lung field due to impaired immunity. M.tb tends to reside in areas of high oxygen pressure. In DM-TB there is an increase in alveolar oxygen pressure in the lower lung lobes. This causes pulmonary TB patients with DM to have more lesions in the lower lung lobes. DM and old age increase alveolar ventilation (VA) and decrease perfusion (Q), resulting in an increased VA/Q mismatch and increased PAO2 in the lower lung field, thus affecting the lower lung field more than the upper lung field. TB lesions in DM often occur in the lower lung field due to the high VA/Q ratio and PAO2 in the lower lung field [55]. The explanation above describes the process of typical and atypical lesions obtained in this study.

Based on the results of the multivariate logistic regression test in this study, it was proven that cough, weight loss, night sweats, NLR, anemia, increased HbA1c (>7.5%), typical and atypical radiological lesions were associated with the incidence of active pulmonary TB in people with type 2 DM. From the scores listed in the Table 20 above, a flow of pulmonary TB screening management in people with type 2 DM is made in Figure 3.

TABLE 20: Pulmonary TB score in people with type 2 DM.

	Score
Major Criteria	
Radiology (typical/atypical lesions)	
Minor Criteria	
Cough	2
Weight loss	1
Night sweats	1
NLR (≥4.76) [a]	1
Anemia (Hb < 10 g/dl) [b]	1
HbA1c (> 7.5%)	1

Information:

- Suggestive of pulmonary TB: major criteria plus one or more minor criteria.
- Not suggestive of pulmonary TB: one or more minor criteria without major criteria.

[a]Not due to another infection or malignancy, [b]Not due to chemotherapy or active bleeding.

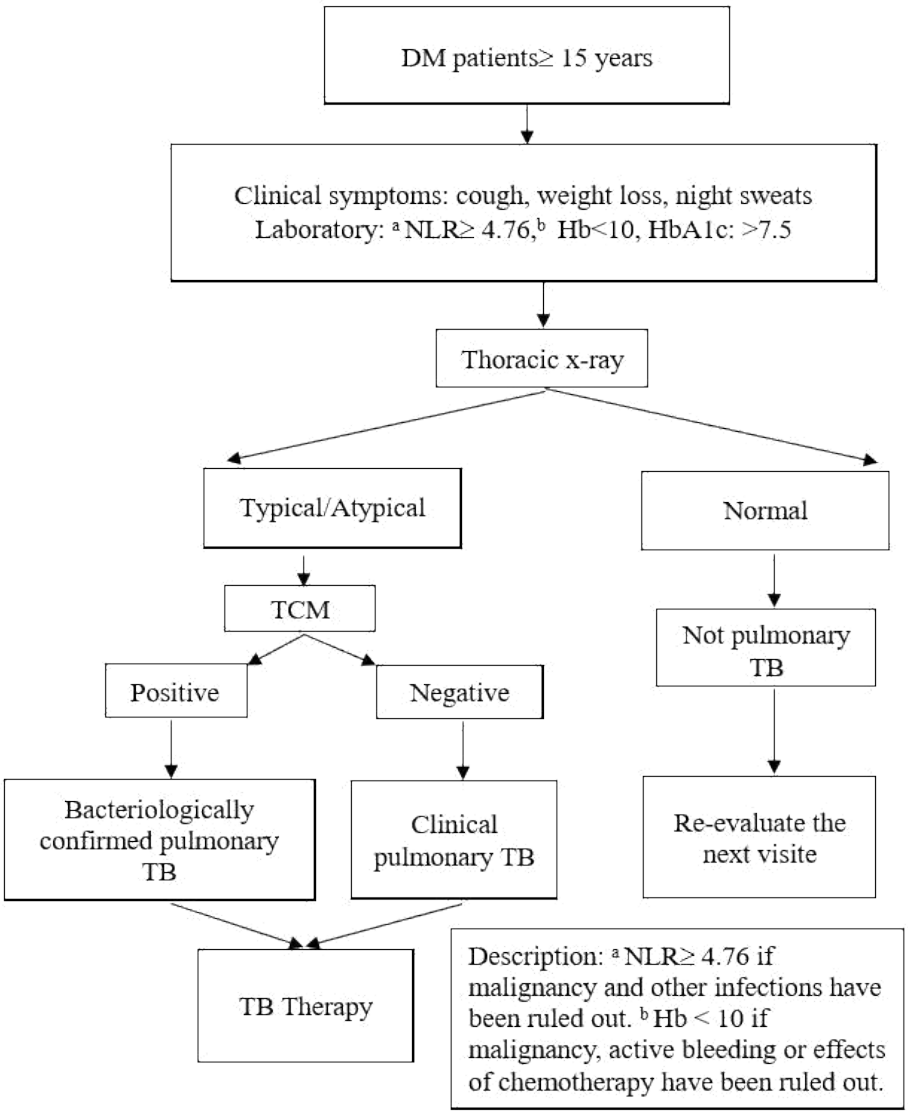

FIGURE 3: Management flow for pulmonary TB screening in people with type 2 DM.

CONCLUSION

There is a relationship between coughing, night sweats, weight loss, increased NLR, MLR, HbA1c, anemia, typical lesions and atypical lesions with the incidence of active pulmonary TB in people with type 2 DM. TB scoring results were obtained in people with type 2 DM if suggestive of pulmonary TB if major criteria by adding one or more minor criteria and non-suggestive TB if one or more minor criteria without major criteria.

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REFERENCES

[1] ReyPineda G D. Type 2 Diabetes Mellitus as a Risk Factor for Tuberculosis. Mycobacterial Diseases 2014;04. https://doi.org/10.4172/2161-1068.1000144.

[2] Zheng Y, Ma A, Wang Q, Han X, Cai J, Schouten EG, et al. Relation of Leptin, Ghrelin and Inflammatory Cytokines with Body Mass Index in Pulmonary Tuberculosis Patients with and without Type 2 Diabetes Mellitus. PLoS One 2013;8: e80122. https://doi.org/10.1371/journal.pone.0080122.

[3] Gil-Santana L, Almeida-Junior JL, Oliveira CAM, Hickson LS, Daltro C, Castro S, et al. Diabetes Is Associated with Worse Clinical Presentation in Tuberculosis Patients from Brazil: A Retrospective Cohort Study. PLoS One 2016;11: e0146876. https://doi.org/10.1371/journal.pone.0146876.

[4] Soerono LU, Soewondo W. The Correlation of Chest Radiographic Image of Pulmonary Tuberculosis in Type 2 Diabetes Mellitus Patients with HbA1C Level. KnE Life Sciences 2019; 4:45. https://doi.org/10.18502/kls.v4i12.4156.

[5] Zhan S, Juan X, Ren T, Wang Y, Fu L, Deng G, et al. Extensive Radiological Manifestation in Patients with Diabetes and Pulmonary Tuberculosis: A Cross-Sectional Study. Ther Clin Risk Manag 2022;Volume 18:595–602. https://doi.org/10.2147/TCRM.S363328.

[6] Yu Q, Weng W, Luo H, Yan J, Zhao X. The Novel Predictive Biomarkers for Type 2 Diabetes Mellitus in Active Pulmonary Tuberculosis Patients. Infect Drug Resist 2022; Volume 15:4529–39. https://doi.org/10.2147/IDR.S377465.

[7] Mukherjee A, Kaeley N, Dhar M, Kumar S, Bhushan B. Prevalence, characteristics, and predictors of tuberculosis associated anemia. J Family Med Prim Care 2019; 8:2445. https://doi.org/10.4103/jfmpc.jfmpc_311_19.

[8] Dasaradhan T, Koneti J, Kalluru R, Gadde S, Cherukuri S priya, Chikatimalla R. Tuberculosis-Associated Anemia: A Narrative Review. Cureus 2022. https://doi.org/10.7759/cureus.27746.

[9] Zuñiga J, Torres-García D, Santos-Mendoza T, Rodriguez-Reyna TS, Granados J, Yunis EJ. Cellular and Humoral Mechanisms Involved in the Control of Tuberculosis. Clin Dev Immunol 2012; 2012:1–18. https://doi.org/10.1155/2012/193923.

[10] Putra IAE, Astuti P, Duana I, Suarjana I, Mulyawan K, Kurniasari N, et al. Obstacles and Solutions for Tuberculosis Screening Among People With Diabetes Mellitus in Denpasar, Bali, Indonesia - A Need Assessment. Proceedings of the 2nd International Symposium of Public Health, SCITEPRESS - Science and Technology Publications; 2017, p. 414–8. https://doi.org/10.5220/0007515104140418.

[11] Yong KC, Muhammad NA, Lim W-Y, HSS A-S. Tuberculosis and Associated Factors among Type 2 Diabetic Patients in Perak: A Case Control Study. Sains Malays 2020;49:1081–8. https://doi.org/10.17576/jsm-2020-4905-12.

[12] Wahiduddin W, Pranoto A, Sudjarwo S. Kendali Glikemik pada Pasien Diabetes Melitus Tipe 2 dengan dan tanpa Tuberkulosis Paru. Media Kesehatan Masyarakat Indonesia 2019;15:99. https://doi.org/10.30597/mkmi.v15i1.5292.

[13] Putra IGNE, Astuti PAS, Suarjana IK, Mulyawan KH, Duana IMK, Kurniasari NMD, et al. Factors Associated with Participation in Pulmonary Tuberculosis Screening Using Chest X-Ray among Diabetes Mellitus Type II Patients in Denpasar, Bali, Indonesia. Tuberc Res Treat 2018;2018:1–7. https://doi.org/10.1155/2018/9285195.

[14] Das S, Das E, Bhuyan K, Prusty B, Barik M, Yadav VS, et al. Bi-directional screening of tuberculosis patients for type 2 diabetes mellitus and diabetes patients for tuberculosis in Bhubaneswar, Odisha. Int J Community Med Public Health 2017;4:2435. https://doi.org/10.18203/2394-6040.ijcmph20172837.

[15] Syahputri SAH, Mufida DC, Bumi C. Epidemiology of Pulmonary Tuberculosis in Diabetes Mellitus Patients. Jurnal Kesehatan 2023;14:345. https://doi.org/10.26630/jk.v14i2.3963.

[16] Workneh MH, Bjune GA, Yimer SA. Prevalence and associated factors of tuberculosis and diabetes mellitus comorbidity: A systematic review. PLoS One 2017;12:e0175925. https://doi.org/10.1371/journal.pone.0175925.

[17] Jali MV, Kavital A, Hiremath MB. Challenges of diabetes in elderly TB patients. Indian Journal of Tuberculosis 2022;69:S264–6. https://doi.org/10.1016/j.ijtb.2022.10.017.

[18] Pal R, Ansari MA, Hameed S, Fatima Z. Diabetes Mellitus as Hub for Tuberculosis Infection: A Snapshot. Int J Chronic Dis 2016;2016:1–7. https://doi.org/10.1155/2016/5981574.

[19] Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis 2009;9:737–46. https://doi.org/10.1016/S1473-3099(09)70282-8.

[20] Khalil NH, Ramadan RA. Study of risk factors for pulmonary tuberculosis among diabetes mellitus patients. Egyptian Journal of Chest Diseases and Tuberculosis 2016;65:817–23. https://doi.org/10.1016/j.ejcdt.2016.05.009.

[21] World Health Organization. Global tuberculosis report. World Health Organization, Geneva 2022.

[22] Karminiasih NLP, Putra IWGAE, Duarsa DP, Ngurah IB, Karmaya M. Faktor Risiko Kekambuhan Pasien TB Paru di Kota Denpasar : Studi Kasus Kontrol Risk Factors for Recurrences of Pulmonary TB among Patients in Denpasar : A Case-Control Study. Public Health and Preventiv Medicine Archive 2016;4:20–6.

[23] Feng J-Y, Huang S-F, Ting W-Y, Chen Y-C, Lin Y-Y, Huang R-M, et al. Gender differences in treatment outcomes of tuberculosis patients in Taiwan: a prospective observational study. Clinical Microbiology and Infection 2012;18:E331–7. https://doi.org/10.1111/j.1469-0691.2012.03931.x.

[24] Cooke A, Fergeson J, Bulkhi A, Casale TB. The Electronic Cigarette: The good, the bad, and the ugly. Journal of Allergy and Clinical Immunology: In Practice 2015;3:498–505. https://doi.org/10.1016/j.jaip.2015.05.022.

[25] Pangaribuan L, Kristina K, Perwitasari D, Tejayanti T, Lolong DB. Faktor-Faktor yang Mempengaruhi Kejadian Tuberkulosis pada Umur 15 Tahun ke Atas di Indonesia. Buletin Penelitian Sistem Kesehatan 2020;23:10–7. https://doi.org/10.22435/hsr.v23i1.2594.

[26] Prananda V, Andayani N, Inggriyani CG. Hubungan Tingkat Pendidikan Terhadap Angka Kejadian Multidrugs Resistent Tuberculosis (MDRTB) Di RSUDZA Banda Aceh. Jurnal Kedokteran Nanggroe Medika Vol 1 No 4 Banda Aceh : Universitas Syiah Kuala 2017.

[27] Idowu AA, Oluwasegun AA, Michael O, Olatunde-Aiyedun TG, Jacob ON. Prevalence and the risk factors associated with HIV-TB co-infection among clinic attendees in dots and art centres in Ibadan, Nigeria. Central Asian Journal of Medical and Natural Sciences 2021;2:73–87.

[28] Hapsari PNF, Isfandiari MA. The Association of Socioeconomic and Nutritional with Risk of Tuberculosis in DM Type 2 Patient. Jurnal Berkala Epidemiologi 2017;5:185–94.

[29] Yosephine MK, Hardy FR, Wenny DM, Nurrizka RH, Pulungan RM. Faktor yang Memengaruhi Kejadian Tuberkulosis Paru pada Penderita Diabetes Mellitus di Rumah Sakit X. Jurnal Kesehatan 2021;12:344. https://doi.org/10.26630/jk.v12i3.2542.

[30] Berkowitz N, Okorie A, Goliath R, Levitt N, Wilkinson RJ, Oni T. The prevalence and determinants of active tuberculosis among diabetes patients in Cape Town, South Africa, a high HIV/TB burden setting. Diabetes Res Clin Pract 2018;138:16–25. https://doi.org/10.1016/j.diabres.2018.01.018.

[31] Hewage S, Somasundaram N, Ratnasamy V, Ranathunga I, Fernando A, Perera I, et al. Active screening of patients with diabetes mellitus for pulmonary tuberculosis in a tertiary care hospital in Sri Lanka. PLoS One 2021;16:e0249787. https://doi.org/10.1371/journal.pone.0249787.

[32] Makuka GJ, Balandya E, Munseri P. Burden of active pulmonary tuberculosis among patients with diabetes in Dar es Salaam, Tanzania: a cross-sectional study. BMJ Open 2022;12:e065969. https://doi.org/10.1136/bmjopen-2022-065969.

[33] Luies L, du Preez I. The Echo of Pulmonary Tuberculosis: Mechanisms of Clinical Symptoms and Other Disease-Induced Systemic Complications. Clin Microbiol Rev 2020;33. https://doi.org/10.1128/CMR.00036-20.

[34] Sanjiwani MID, Setiawan NBW, Putra AIYD, Darwinata AE. Probiotic-Based Therapy for Active Tuberculosis Infection: The Role of Gut-Lung Axis and Granulocyte Macrophage-Colony Stimulating Factor. Jurnal Respirasi 2021;7:93. https://doi.org/10.20473/jr.v7-I.2.2021.93-99.

[35] Solanki H, Ranpariya P, Chudasama R. Health status and treatment outcome of tuberculosis with diabetes mellitus cases, Rajkot City, Gujarat – A longitudinal study. Indian Journal of Community Medicine 2023;48:75. https://doi.org/10.4103/ijcm.ijcm_171_22.

[36] Lacerda C, Linhas R, Duarte R. Tuberculous spondylitis: A report of different clinical scenarios and literature update. Case Rep Med 2017;2017. https://doi.org/10.1155/2017/4165301.

[37] Rahayu SR, Katsuyama H, Katsuyama M, Ota Y, Djaja Semadi NP. Tuberculosis Suspect in the Companies in Semarang District Indonesia; Case-Control Study. Jurnal Kesehatan Masyarakat 2017;12:167–76. https://doi.org/10.15294/kemas.v12i2.8657.

[38] Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D JJ eds. Harrison's Principles of Internal Medicine, 21e. McGraw Hill; Accessed April 15, 2023 Https://AccessmedicineMhmedicalCom/ContentAs px?Bookid=3095&sectionid=259856983 2022.

[39] Zhang Q. Immunology of tuberculosis. World J Exp Med 2012;2:70. https://doi.org/10.5493/wjem.v2.i4.70.

[40] Karthik K, Kesavan M, Tamilmahan P, Saravanan M, Dashprakash M. Neutrophils in Tuberculosis: will the code be unlocked. Vet World 2013;6:118. https://doi.org/10.5455/vetworld.2013.118-121.

[41] Han Y, Kim SJ, Lee SH, Sim YS, Ryu YJ, Chang JH, et al. High blood neutrophil-lymphocyte ratio associated with poor outcomes in miliary tuberculosis. J Thorac Dis 2018;10:339–46. https://doi.org/10.21037/jtd.2017.12.65.

[42] Yustin WEF, Somia IKA, Arisanti NLPE, Artana IGNBN, Kusumawardani IAJD, Candrawati NW, et al. Association between clinical parameter, laboratorium and radiology along with validation of scoring system with lung tuberculosis status in adult HIV patients. Bali Medical Journal 2021; 10:1085–92. https://doi.org/10.15562/bmj.v10i3.2787.

[43] Adane T, Melku M, Ayalew G, Bewket G, Aynalem M, Getawa S. Accuracy of monocyte to lymphocyte ratio for tuberculosis diagnosis and its role in monitoring anti-tuberculosis treatment: Systematic review and meta-analysis. Medicine 2022;101:e31539. https://doi.org/10.1097/MD.0000000000031539.

[44] Wang W, Wang L, Liu Y, Yang F, Zhu L, Zhang X. Value of the Ratio of Monocytes to Lymphocytes for Monitoring Tuberculosis Therapy. Canadian Journal of Infectious Diseases and Medical Microbiology 2019;2019:1–5. https://doi.org/10.1155/2019/3270393.

[45] Wang J, Yin Y, Wang X, Pei H, Kuai S, Gu L, et al. Ratio of monocytes to lymphocytes in peripheral blood in patients diagnosed with active tuberculosis. The Brazilian Journal of Infectious Diseases 2015;19:125–31. https://doi.org/10.1016/j.bjid.2014.10.008.

[46] Suryana K, Dharmesti NWW, Rai IN. High Pretreatment Level of Neutrophil to Lymphocyte Ratio, Monocyte to Lymphocyte Ratio and Other Factors Associated with Delayed Sputum Conversion in Patients with Pulmonary Tuberculosis. Infect Drug Resist 2022;Volume 15:5455–62. https://doi.org/10.2147/IDR.S380166.

[47] 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;10:329–329. https://doi.org/10.21037/atm-22-679.

[48] Weiss G. Iron metabolism in the anemia of chronic disease. Biochimica et Biophysica Acta (BBA)-General Subjects 2009;1790:682–93.

[49] Agyeman AA, Ofori-Asenso R. Tuberculosis—an overview. J Public Health Emerg 2017;1:7–7. https://doi.org/10.21037/jphe.2016.12.08.

[50] Chen Z, Liu Q, Song R, Zhang W, Wang T, Lian Z, et al. The association of glycemic level and prevalence of tuberculosis: a meta-analysis. BMC Endocr Disord 2021;21:123. https://doi.org/10.1186/s12902-021-00779-6.

[51] Restrepo BI, Fisher-Hoch SP, Pino PA, Salinas A, Rahbar MH, Mora F, et al. Tuberculosis in Poorly Controlled Type 2 Diabetes: Altered Cytokine Expression in Peripheral White Blood Cells. Clinical Infectious Diseases 2008;47:634–41. https://doi.org/10.1086/590565.

[52] Patel A, Rami K, Ghanchi F. Radiological presentation of patients of pulmonary tuberculosis with diabetes mellitus. Lung India 2011;28:70. https://doi.org/10.4103/0970-2113.76308.

[53] Shital P, Anil J. Tuberculosis with Diabetes Mellitus: Clinical-Radiological Overlap and Delayed Sputum Conversion Needs Cautious Evaluation-Prospective Cohort Study in Tertiary Care Hospital, India. J Pulm Respir Med 2014;04. https://doi.org/10.4172/2161-105X.1000175.

[54] Kumar Nathella P, Babu S. Influence of diabetes mellitus on immunity to human tuberculosis. Immunology 2017;152:13–24. https://doi.org/10.1111/imm.12762.

[55] PEREZ-GUZMAN C, TORRES-CRUZ A, VILLARREAL-VELARDE H, VARGAS MH. Progressive Age-related Changes in Pulmonary Tuberculosis Images and the Effect of Diabetes. Am J Respir Crit Care Med 2000;162:1738–40. https://doi.org/10.1164/ajrccm.162.5.2001040.