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ORIGINAL RESEARCH

Development and Validation of a Predictive Model Using Inflammatory Biomarkers for Active Tuberculosis Risk in Diabetic Patients

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Aim: Exploring the value of inflammatory markers in diagnosing active pulmonary tuberculosis in diabetics.

Patients and Methods: Routine clinical indicators and a range of inflammatory markers were assessed in 276 diabetic patients (DM) and 276 patients with diabetes mellitus combined with active tuberculosis (DM-PTB) from Kunming, Yunnan Province, China. Differences between indicators were compared between the two groups, and factors influencing the susceptibility of diabetic patients to active tuberculosis were analyzed. A novel predictive model was constructed by combining inflammatory and lipid markers using R-Studio in a pioneering manner, and the efficacy of the predictive model was assessed using Calibration Curve and other methods in a multifaceted manner.

Results: Univariate analysis showed that clinical markers including triglycerides, leukocytes, neutrophils, lymphocytes, monocytes, and platelets; inflammatory markers including the neutrophil-to-lymphocyte ratio (NLR), neutrophil to high-density lipoprotein ratio (NHR), platelet-to-lymphocyte ratio (PLR), platelet-to-neutrophil ratio (PNR), platelet-to-monocyte ratio (PMR), monocyte to high-density lipoprotein ratio (MHR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), aggregate inflammation systemic index (AISI), neutrophil-to-monocyte ratio (NMR), and lymphocyte-to-monocyte ratio (LMR) showed significant differences. Specifically, triglyceride, PNR, PMR, MHR, and MLR are risk factors for the development of PTB in DM patients. The model for predicting DM-PTB using a combination of indicators has a high sensitivity (75.0%) and specificity (81.9%).

Conclusion: Triglycerides, PNR, PMR, MHR, and MLR were identified as influential factors in the progression to PTB in diabetic patients. The combined application of these indicators provides an economical, convenient and direct method for early identification of diabetic patients susceptible to Mycobacterium tuberculosis infection.

Keywords: inflammatory markers, diabetes mellitus, active pulmonary tuberculosis, influencing factors, predictive modeling

Introduction

Diabetes mellitus (DM), as a chronic metabolic disease, is experiencing a year-by-year increase in its incidence globally, driven by factors such as improved living standards, lifestyle changes, and an aging population. The International Diabetes Federation (IDF) forecasts that the number of adults with diabetes will reach 784 million by 2045.[1] DM is associated with a range of acute and chronic complications that can lead to significant morbidity and mortality.[2]

Tuberculosis (TB), a chronic respiratory infectious disease caused by *Mycobacterium tuberculosis* (Mtb), remains a significant global public health challenge and poses a severe threat to human health. Despite substantial progress in TB

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control and treatment, the disease continues to exact a substantial toll on global health. According to the Global Tuberculosis Report 2024, an estimated 10.8 million incident cases of TB were reported globally in 2023, with 1.25 million individuals succumbing to the disease.[3]

DM is an established independent risk factor for pulmonary tuberculosis (PTB), with individuals with DM having a 1.5- to 2.4-fold higher risk of PTB compared to the general population.[4] It is widely acknowledged that elevated glycolipid levels in diabetic patients can impair immune function and reduce resistance to pathogenic infections, thereby increasing the risk of PTB.[5] However, there is a growing body of recent evidence linking the pro-inflammatory milieu in DM patients to the pathogenesis and clinical outcomes of PTB.[6,7] Immune cell dysfunction in diabetes leads to exaggerated inflammatory responses, which are characterized by heightened neutrophil activity, increased macrophage infiltration, and a shift towards higher levels of pro-inflammatory cytokines coupled with diminished anti-inflammatory cytokine production. Inflammatory environment facilitates the replication of mycobacterium tuberculosis and is thought to substantially augment the risk of developing active PTB.[8]

The co-morbidity of DM and PTB imposes a substantial burden on healthcare systems. According to the World Health Organization (WHO), an estimated 380,000 incident cases of tuberculosis globally in 2023 were attributable to diabetes.[3] Moreover, individuals with both DM and PTB face a significantly higher mortality risk during treatment compared to those with DM alone.[3] This highlights the critical importance of early identification and diagnosis of PTB in patients with DM.

Tuberculosis has long been diagnosed using traditional Mycobacterium tuberculosis antacid-stained smears and cultures, but the proportion of tuberculosis patients with a pathologically confirmed diagnosis will be only 62% globally in 2023, which means that more than 30% of patients will be clinically diagnosed as suspected cases.[3] This underscores the critical need for improved diagnostic tools to enhance early detection and treatment. Especially for patients with diabetes mellitus combined with pulmonary tuberculosis, the atypicality of clinical symptoms and the complexity of imaging manifestations further increase the difficulty of early diagnosis.[9]

Composite inflammatory biomarkers calculated based on complete blood count components (eg, neutrophils, lymphocytes, monocytes, and platelets) not only reflect the inflammatory state, but also synthesize the immune homeostasis of the body, and have significant predictive ability in various inflammation-related clinical conditions and prognosis.[10–12] These markers are characterized by stability and easy calculation, which makes them of high clinical value. However, research on the application of these biomarkers in the context of DM and PTB co-morbidity remains limited. Therefore, our study aims to explore the predictive value of these inflammatory biomarkers for PTB in patients with DM. We hypothesize that these biomarkers may help identify individuals at higher risk of PTB, thereby facilitating early intervention and reducing the spread of tuberculosis among susceptible populations.

Materials and Methods

Research Design

We conducted a study involving patients aged 18 years or older who were diagnosed with diabetes mellitus and admitted to the Third People's Hospital of Kunming between June 1, 2022, and May 31, 2023. The case group (DM-PTB) consisted of patients diagnosed with type 2 diabetes mellitus complicated by active primary tuberculosis, and the control group (DM) consisted of type 2 diabetes mellitus patients without active pulmonary tuberculosis. Exclusion criteria were based on several factors: a prior diagnosis of pulmonary tuberculosis before diabetes, healed tuberculosis, incomplete medical records including uncertain diabetes history or unknown medication details, concurrent malignant tumors, HIV infection, recognized primary immunodeficiency, ongoing treatment with immunosuppressive drugs, type 1 diabetes mellitus, infections of known sites, fever of unknown origin or suspected infections and critically ill patient. A total of 750 patients with DM complicated by PTB were initially identified through the hospital's electronic medical record system. According to the predefined exclusion criteria, the following patients were excluded: 409 patients with a history of PTB prior to the diagnosis of DM, 28 patients with recurrent PTB after cure, 9 patients with concomitant malignant tumors or other severe immunological diseases, 5 patients with type 1 DM, 12 patients with incomplete medical records, and 11 patients with severe infectious diseases at admission. After these exclusions, 276 patients were ultimately

included in the case group. Subsequently, 276 patients with DM but without PTB, who were treated at the same hospital during the same period, were randomly selected as the control group at a 1:1 ratio, matched by gender and age (within ±3 years). (Figure 1) The diagnosis of diabetes mellitus was established according to the Chinese Guidelines for the Prevention and Control of Type 2 Diabetes Mellitus (2020 Edition),[13] and PTB was diagnosed following the People's Republic of China Health Industry Standard for the Diagnosis of Tuberculosis (WS 288–2017).[14]

All patients provided informed consent for their clinical data to be utilized in this study. The study was conducted in accordance with the principles outlined in Declaration of Helsinki and was approved by the Ethics Committee of the Third People's Hospital of Kunming (approval number: KSLL2023032040).

Sample Size Calculation

This study employed a 1:1 matched case-control design to investigate the association between DM and PTB. The sample size was calculated based on the expected odds ratio (OR) of 2.3, which was derived from previous studies.[15] The following assumptions were made for the calculation: a two-sided significance level (α) of 0.05, a power (1-β) of 80%, and an estimated exposure rate (p0) of [0.0054] in the control group.[16]

The sample size formula for a 1:1 matched case-control study is given by:

$$M = \left(\frac{Z_{\alpha/2} + Z_{\beta}}{p(1-p)}\right)^2 \times \frac{p_0 q_1 + p_1 q_0}{(p - 1/2)^2}$$

Notes: $a = 0.05$, $Z_{\alpha} = 1.64$, $\beta = 0.20$, $Z_{\beta} = 0.84$. $P = \frac{OR}{1+OR}, p_1 = \frac{p_0 \times OR}{1+p_0(OR-1)}, q_0 = 1 - p_0, q_1 = 1 - p_1$.

Using these parameters, the calculated number of case-control pairs required was 63. To account for potential dropouts or non-response, the sample size was adjusted by an additional 10%, resulting in a final required sample size of 70 pairs.

A total of 276 patients with diabetes mellitus complicated by pulmonary tuberculosis were enrolled in the case group, fulfilling the pre-determined minimum sample size requirement. In accordance with the 1:1 matching design, 276 patients with diabetes mellitus but without pulmonary tuberculosis were enrolled as the control group. Consequently, a total of 552 participants were included in the study for analysis.

Data Collection

Upon admission, blood samples were collected by trained nurses from patients who had fasted for at least 8 hours. The total counts of white blood cells, neutrophils, monocytes, platelets, lymphocytes, and high-density lipoprotein (HDL) were determined using a hematology autoanalyzer (Sysmex XG-550). The Sysmex XG-550 automated hematology analyzer was calibrated using standardized materials and validated by assessing key performance parameters (linearity, precision, accuracy) in accordance with the manufacturer's guidelines and national standards. Regular quality control checks ensured consistent performance and result comparability. Demographic data and laboratory examination results were retrieved from the electronic medical record (EMR) system.

Statistical Analyses

Measurement data that were normally distributed are reported as mean ± standard deviation (SD), while non-normally distributed data are depicted as median (interquartile range, IQR). Wilcoxon rank-sum test or chi-square test was applied to compare measurement data between the two groups. Inflammatory markers with statistical significance ($p < 0.05$) were further analyzed using conditional logistic regression, complemented by Cox regression analysis, to identify risk indicators for tuberculosis. Receiver operating characteristic (ROC) curves were employed to assess the predictive accuracy of inflammatory indices for the risk of pulmonary tuberculosis in diabetic mellitus patients. R-Studio software (version 3.5.2) was used to draw nomograms, calibration plots, and model decision curves. Heat map was drawn using GraphPad prism. The relationship between inflammatory markers and blood glucose levels was explored using Spearman correlation analysis. Statistical analyses were conducted using SPSS software, version 29.0.1 (IBM Corporation, Armonk, New York, USA), and graphical representations were created using GraphPad Prism, version 9 (GraphPad Software, Inc., San Diego, CA, USA). Statistical significance was set at $p < 0.05$.

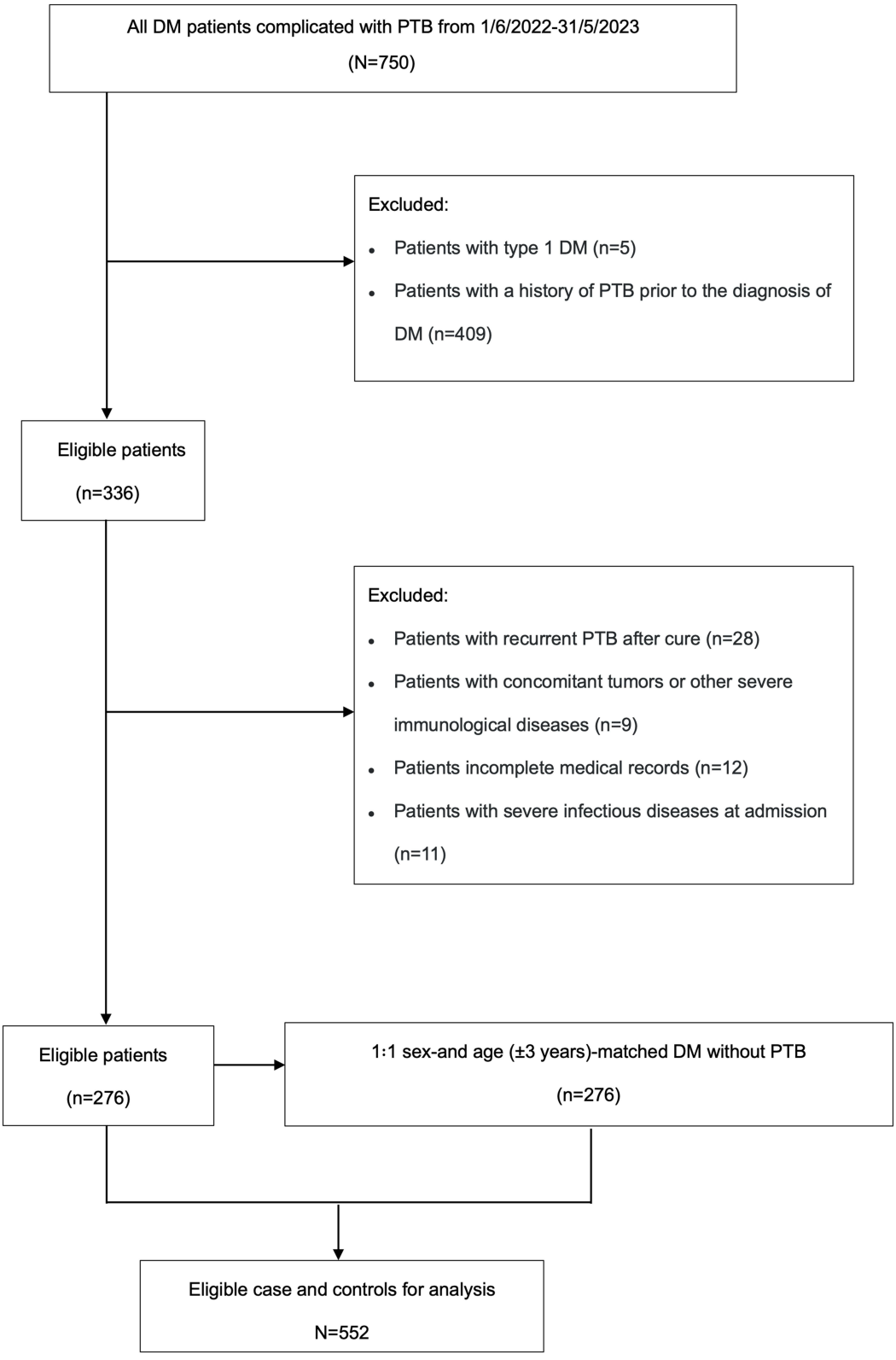

Figure 1 Study population flowchart.
Abbreviations: DM, Diabetes mellitus; PTB, pulmonary tuberculosis.

Results

Demographic and Clinical Basic Characteristics of Participants

The case and control groups comprised a total of 276 individuals, of which 209 were male and 67 were female, yielding a male-to-female ratio of approximately 3.12:1. The mean age of the case group was 59 years (interquartile range [IQR], 50 to 68 years), and the mean age of the control group was 59 years (IQR, 50 to 68 years). History of diabetes, hemoglobin A1c, fasting plasma glucose, serum creatinine, total cholesterol and high-density lipoprotein cholesterol showed no statistically significant differences between the two groups. Triglyceride, white blood cell, neutrophil lymphocyte, monocyte and platelets exhibited statistically significant differences between the two groups (Table 1).

Comparison of Two Groups of Inflammatory Indicators

We also calculated the inflammatory markers for both groups, and apart from the LHR, the rest including NLR, NHR, NMR, PLR, PNR, PMR, LMR, MHR, MLR, SII, SIRI, and AISI all showed statistically significant differences. Levels of NLR, NHR, PLR, PNR, PMR, MHR, MLR, SII, SIRI and AISI were significantly elevated in the case group compared with the control group. Conversely, the NMR and LMR were found to be lower in the case group (Figure 2).

Influence Factors for Pulmonary Tuberculosis in Diabetes Mellitus Patients

Triglycerides, PNR, PMR, MHR and MLR are risk factors for the development of tuberculosis in diabetic mellitus patients. The analysis results disclosed that levels of PNR, PMR, MHR, and MLR were markedly higher in the case group than in the control group. In contrast, the triglyceride was found to be reduced in the case group relative to the control group (Figure 3).

Predictive Capability of Inflammatory Markers for Tuberculosis in Diabetic Mellitus Patients

Based on the final multivariable results, a nomogram was generated by assigning a weighted score to each of the influence factors associated with active pulmonary tuberculosis (Figure 4A). The calibration curve tended to be ideal (Figure 4B) and the clinical net benefit of the nomogram prediction model was significant (Figure 4C). ROC curves were constructed to assess the predictive accuracy of the TG, PNR, PMR, MHR, and MLR for active pulmonary tuberculosis development (Figure 5A). The combined index demonstrated good predictive performance (Figure 5B), with an area under the curve (AUC) of 0.844, a sensitivity of 75.0%, and a specificity of 81.9%.

Correlation Analysis Between Inflammatory Indicators and Fasting Blood Glucose Levels

Further analysis was conducted to examine the relationships between fasting blood glucose, glycated hemoglobin, and PNR, PMR, MHR, MLR, and TG in both groups. Interestingly, fasting blood glucose and glycated hemoglobin showed no correlation with PNR, PMR, MHR and MLR in the diabetes group (Figure 6A), but the correlation increased in the diabetes group with tuberculosis co-infection, especially with MHR, which exhibited significant correlations with both fasting blood glucose levels and glycated hemoglobin (Figure 6B). Triglycerides are correlated with fasting blood glucose in both groups.

Discussion

In a pioneering study, we have, for the first time, delineated the clinical risk factors associated with the progression to active pulmonary tuberculosis within individuals affected by diabetes mellitus. These indicators offer an economical, accessible, and straightforward means of identification, facilitating their application in community healthcare and institutions in resource-constrained environments for the purpose of targeted screening.

Unlike traditional single-cell counts, composite inflammatory biomarkers are less susceptible to external factors such as dehydration and sampling errors, thereby enabling a more precise and sensitive reflection of the body's chronic inflammatory state. Additionally, these biomarkers have demonstrated substantial clinical value across a diverse range of

Table 1 Demographic and Clinical Basic Characteristics of Participants

Variant	DM-PTB (n = 276)	DM (n = 276)	P value
Gender (male)	209 (75.72)	209 (75.72)	
Age (years)	59 (50,68)	59 (50,68)	
18~40	21 (7.61)	21 (7.61)	
40~50	44 (15.94)	44 (15.94)	
50~60	79 (28.62)	79 (28.62)	
≥60	132 (47.83)	132 (47.83)	
History of diabetes			0.351
1~5	68 (24.6)	60 (21.7)	
5~10	71 (25.7)	69 (25.0)	
≥10	137 (49.6)	147 (53.3)	
HbA1c			0.469
<7%	95 (34.4)	87 (31.5)	
≥7%	181 (65.6)	189 (68.5)	
FPG			0.858
<7.0	85 (34.4)	97 (35.1)	
≥7.0	181 (65.6)	179 (64.9)	
Scr (umol/l)			0.537
<73	178 (64.5)	171 (62.0)	
≥73	98 (35.5)	105 (51.7)	
TG (mmol/L)			<0.001
<1.7	175 (63.4)	130 (47.1)	
≥1.7	101 (36.6)	146 (52.9)	
TC (mmol/L)			0.243
<5.2	226 (81.9)	215 (77.9)	
≥5.2	50 (18.1)	61 (22.1)	
HDL-C (mmol/L)			0.600
<1.55	260 (94.2)	257 (93.1)	
≥1.55	16 (5.8)	19 (6.9)	
WBC (×10∧9/L)			0.021
<9.5	237 (85.9)	254 (92.0)	
≥9.5	39 (14.1)	22 (9.0)	
Neutrophil (×10∧9/L)			<0.001
<6.3	222 (80.4)	251 (90.9)	
≥6.3	54 (16.9)	25 (9.1)	
Lymphocyte (×10∧9/L)			0.007
<3.2	274 (99.3)	264 (95.7)	
≥3.2	2 (0.7)	12 (4.3)	
Monocyte (×10∧9/L)			<0.001
<0.6	182 (65.9)	222 (80.4)	
≥0.6	94 (34.1)	54 (19.6)	
Platelets (×1022C09/L)			<0.001
125–350	213 (77.2)	248 (89.9)	
≤125/≥350	63 (22.8)	28 (10.1)	

Abbreviations: HbA1c, Hemoglobin A1c; FPG, fasting plasma glucose; SCr, serum creatinine; TG, Triglyceride; TC, Total Cholesterol; HDL-C, High density lipoprotein cholesterol; WBC, white blood cell.

patient populations, including those with AIDS, psoriasis, malnutrition, and cardiovascular diseases.[17–20] Regrettably, the predictive value of these biomarkers in the context of diabetes complicated by tuberculosis has not been adequately explored in previous studies. A multicenter study spanning countries such as Indonesia, Peru, Romania, and South Africa has underscored the necessity for routine tuberculosis screening among diabetic patients and emphasized the importance

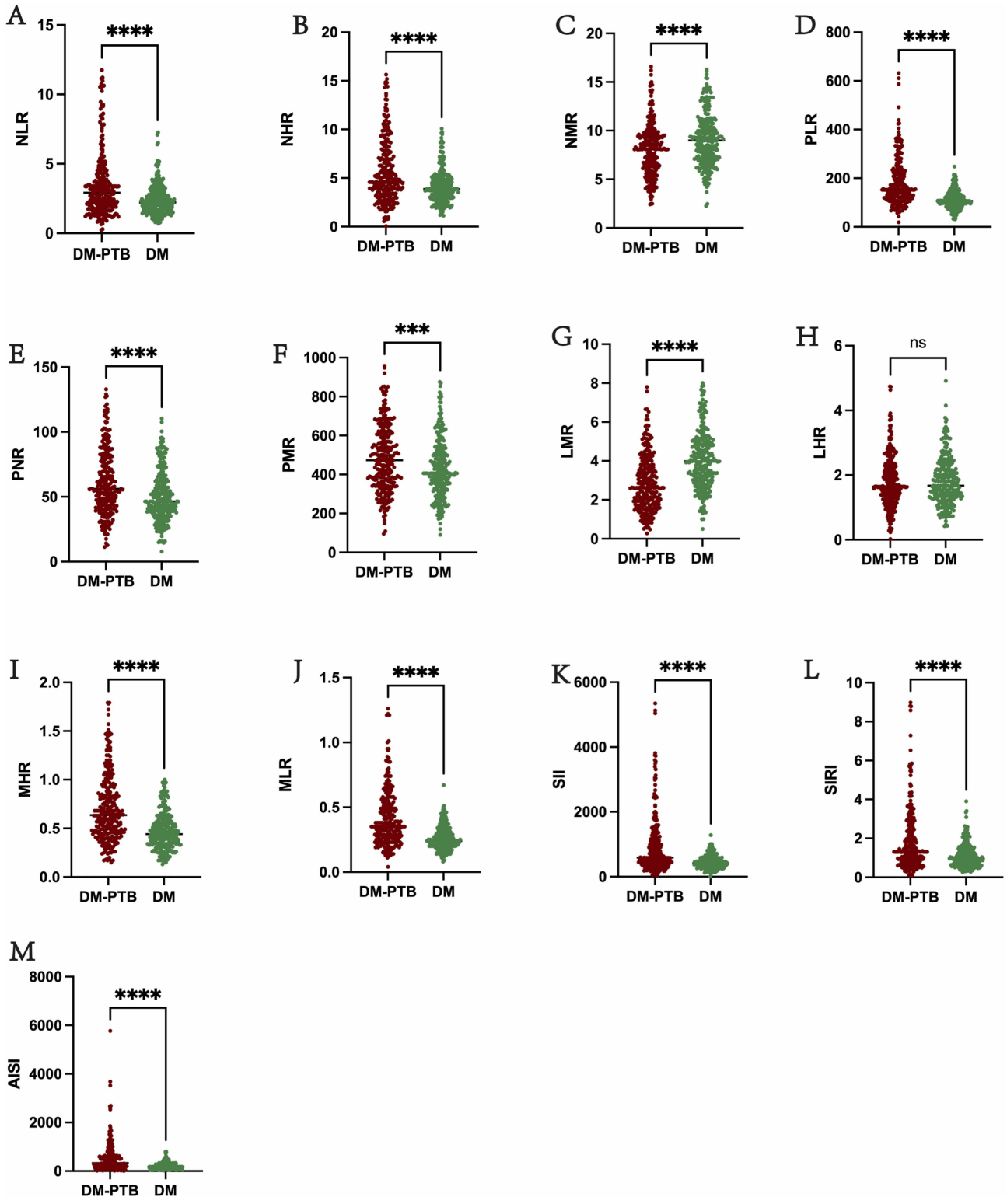

Figure 2 The differences in (**A**) NLR (**B**) NHR (**C**)NMR (**D**) PLR (**E**) PNR (**F**) PMR (**G**) LMR (**H**) LHR (**I**) MHR (**J**) MLR (**K**) SII (**L**) SIRI (**M**) AISI between the diabetes group and the diabetes-tuberculosis group. ***Means $p < 0.001$, ****Means $p < 0.0001$.

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; NHR, neutrophil to high-density lipoprotein ratio; NMR, neutrophil-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; PNR, platelet-to-neutrophil ratio; PMR, platelet-to-monocyte ratio; LMR, lymphocyte-to-monocyte ratio; LHR, lymphocyte to high-density lipoprotein; MHR, monocyte to high-density lipoprotein ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; AISI, aggregate inflammation systemic index; ns, no significance.

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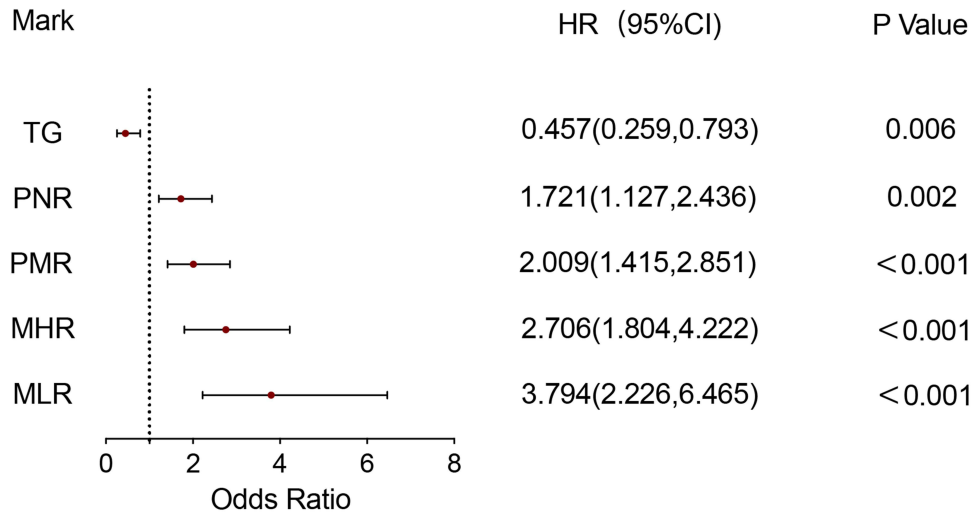

Figure 3 Results of the multifactorial analysis affecting the occurrence of pulmonary tuberculosis in diabetic patients.
Abbreviations: TG, triglyceride; PNR, platelet-to-neutrophil ratio; PMR, platelet-to-monocyte ratio; MHR, monocyte to high-density lipoprotein ratio; MLR, monocyte-to-lymphocyte ratio; PTB, pulmonary tuberculosis.

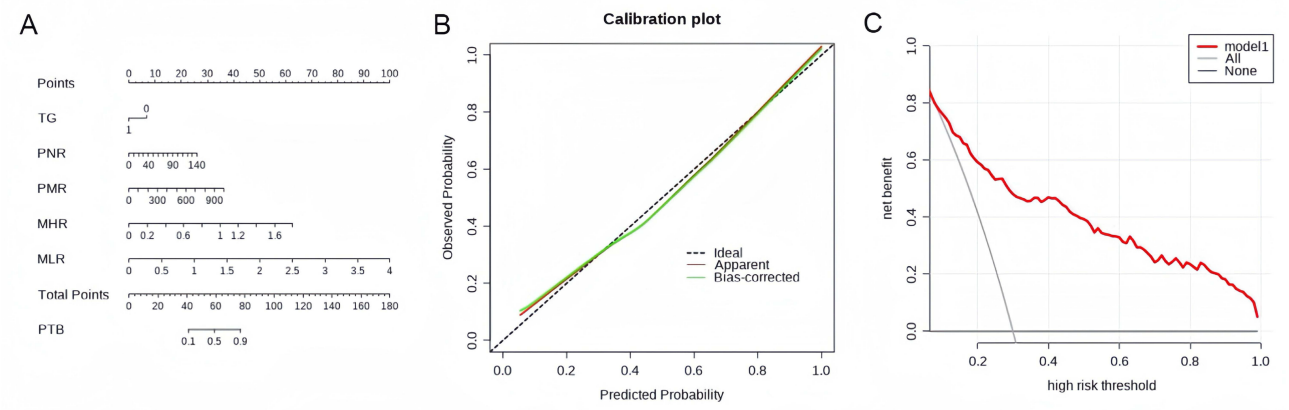

Figure 4 The occurrence of pulmonary tuberculosis in diabetic patients for (**A**) risk factors prediction nomogram (TG lower 1.7 mmol/L = 0) (**B**) predicted probability and (**C**) clinical net benefit of the nomogram prediction model.
Abbreviations: TG, triglyceride; PNR, platelet-to-neutrophil ratio; PMR, platelet-to-monocyte ratio; MHR, monocyte to high-density lipoprotein ratio; MLR, monocyte-to-lymphocyte ratio; PTB, pulmonary tuberculosis.

of making diagnostic tools more accessible.[21] Our research findings hold promise in addressing some of the challenges associated with diagnostic tools, particularly in resource-limited settings where traditional diagnostic methods may be hindered by limitations in resources. In such contexts, the application value of composite inflammatory biomarkers becomes particularly pronounced. These biomarkers, calculated based on routine blood test results, do not necessitate additional complex detection methods, thus rendering them highly valuable for clinical application in resource-constrained environments.

Research has demonstrated that patients with diabetes mellitus who also have tuberculosis exhibit elevated levels of pro-inflammatory cells, significantly higher than those observed in the general population.[6,8,22] In concordance, our study identified that, among the currently known 13 inflammatory indicators, 12 of them show significant differences in patients with comorbidities. This suggests that patients with comorbidities may exhibit a more robust inflammatory response compared to those with diabetes alone, which could be the reason why diabetic mellitus patients are more susceptible to Mycobacterium tuberculosis infection. Basic research also supports this notion, demonstrating a markedly enhanced inflammatory response in patients with diabetes complicated by tuberculosis co-morbidity. Notably, in these comorbid patients, there is a dampened Type I interferon response, coupled with an unforeseen disconnection of the

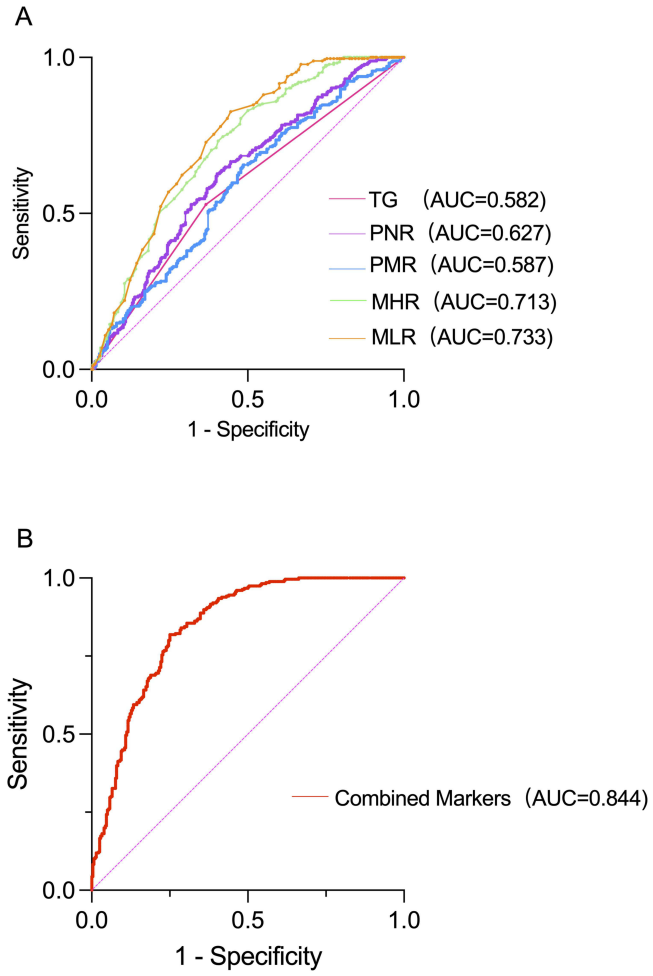

Figure 5 ROC curves for (**A**) inflammatory markers and (**B**) combined markers. Combined markers: combined TG, PNR, PMR, MHR and MLR.
Abbreviations: TG, triglyceride; PNR, platelet-to-neutrophil ratio; PMR, platelet-to-monocyte ratio; MHR, monocyte to high-density lipoprotein ratio; MLR, monocyte-to-lymphocyte ratio.

tuberculosis transcriptome signature. This highlights that, despite the utilization of advanced RNA-sequencing techniques, discerning tuberculosis infection with precision in diabetic mellitus patients continues to present a formidable challenge.[23]

Biomarkers such as PNR, PMR, MHR and MLR are indicators of the immune-inflammatory response and objectively mirror the immunological alterations induced by inflammation.[24–27] The "low-grade inflammatory" state in diabetes mellitus is thought to be one of the mechanisms leading to altered immune function, potentially augmenting the susceptibility to Mycobacterium tuberculosis infection in patients. In alignment with these studies, our research identified elevated levels of PNR, PMR, MHR and MLR, along with low levels of triglycerides, are identified as risk factors for the susceptibility of diabetic mellitus patients to active pulmonary tuberculosis.

The utility of MLR as a biomarker of inflammation in the diagnosis of tuberculosis has been thoroughly investigated in previous studies: it discerns latent tuberculosis infection from active disease and identifies active tuberculosis with specificity in HIV-positive individuals.[28,29] The chronic low-grade inflammation typical of diabetic patients is reflected in the peripheral blood by elevated monocyte counts and reduced lymphocyte counts.[30–34] Moreover, lipid level reductions have been identified as a significant risk factor for tuberculosis development.[17] Thus, elevated MLR and MHR may indicate increased susceptibility to Mycobacterium tuberculosis in diabetic patients, which emphasizes the clinical necessity of evaluating these ratios in the diabetic population.

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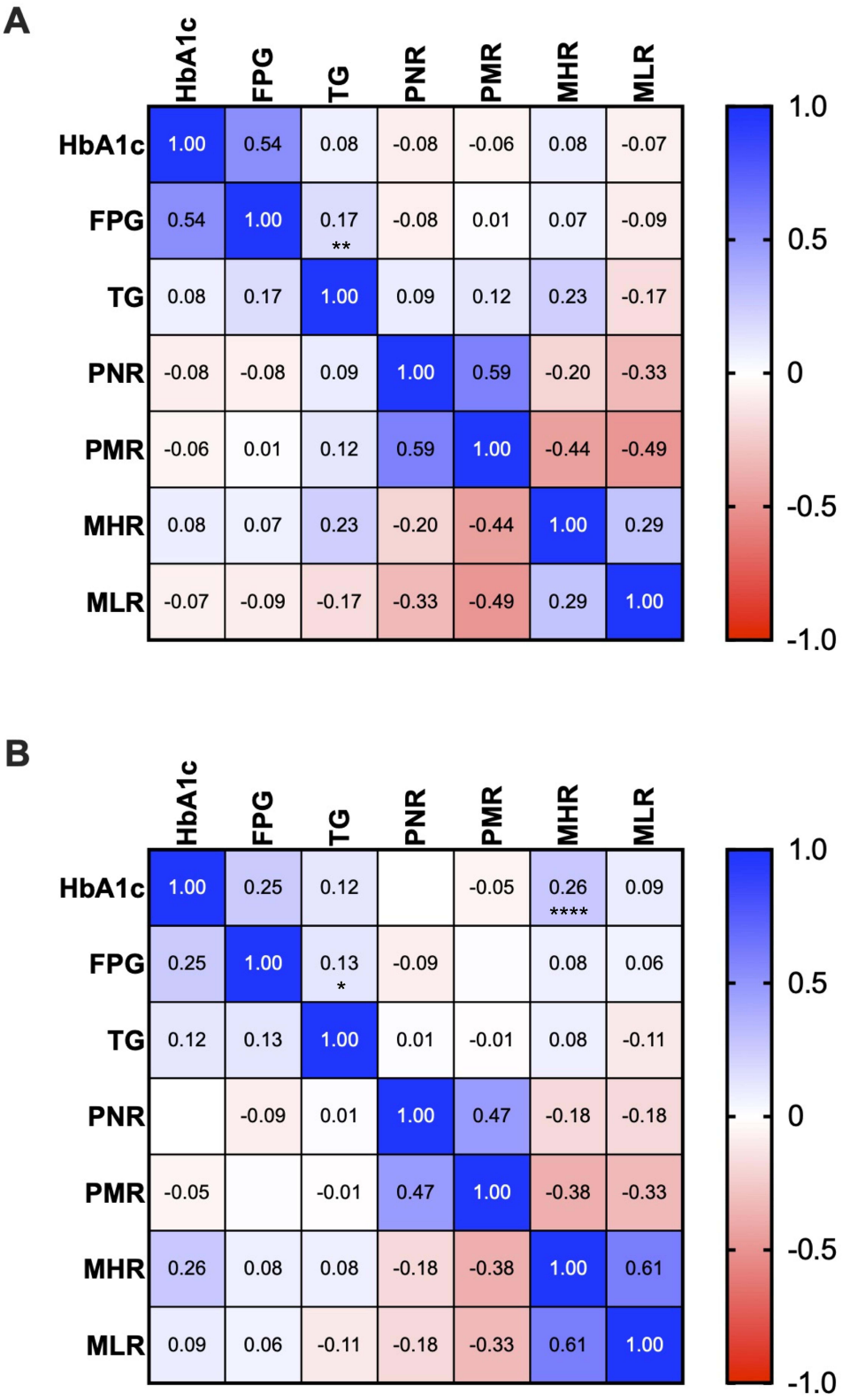

Figure 6 Correlation analysis between inflammatory indicators with blood glucose levels and glycated hemoglobin in (**A**) diabetes mellitus (DM) group and (**B**) diabetes mellitus with tuberculosis (DM-PTB) group.

Abbreviations: TG, triglyceride; PNR, platelet-to-neutrophil ratio; PMR, platelet-to-monocyte ratio; MHR, monocyte to high-density lipoprotein ratio; MLR, monocyte-to-lymphocyte ratio; PTB, pulmonary tuberculosis.

PMR and PNR are two hematologic indicators that are closely related to platelet function. Although there is no conclusive evidence directly linking the development of PTB to alterations in platelets, studies have revealed mechanisms by which platelets interact with monocytes in the lungs to modulate the immune response.[35] Specifically, in the lungs, platelets and monocytes interact to regulate the body's immunity, and it was found that intracellular survival of Mycobacterium tuberculosis increased 2.5-fold when platelets were co-cultured with monocytes, which may be related to the involvement of platelets in the polarisation of monocytes, as in the case of the M2 phenotype, which diminishes their bactericidal capacity and increases the likelihood of PTB disease.[36] In addition, the blood test results of some PTB patients frequently show thrombocytopenia and neutrophilia with a trend towards low PNR,[35] which is contrary to our results and may be due to the inflammatory environment induced by high blood glucose in diabetic mellitus patients, which leads to a significant increase in neutrophil counts with minimal accompanying changes in platelet counts. This also suggests to some extent that the changes in the body of diabetic mellitus patients infected with Mycobacterium tuberculosis may be different from those in general population.

Intriguingly, our findings reveal that elevated TG levels in diabetic patients are associated with a reduced risk of PTB, a discovery that aligns with the research by Ji et al, who posited that diabetic individuals with low TG levels are at an increased risk of developing PTB.[37] This correlation may stem from the fact that low TG levels often indicate more severe metabolic disturbances or malnutrition, conditions that can significantly impair the body's immune defenses.

In diabetic patients, the interplay between TG levels and the pathogenesis of tuberculosis appears to be multifaceted. Typically, high TG levels are linked to various complications in diabetes, most notably cardiovascular diseases.[38] However, pulmonary tuberculosis, being a consumptive disease, has a pathogenesis that is intricately connected to systemic lipid levels, particularly cholesterol. Extensive research has demonstrated that macrophages rely on lipids to maintain their phagocytic functions, and a deficiency in cholesterol can severely disrupt these essential processes.[39,40] Moreover, patients with diabetes complicated by pulmonary tuberculosis exhibit a distinctive lipid profile. In addition to the typical lipid abnormalities of diabetes, such as elevated TG and low-density lipoprotein (LDL) levels, these patients also display signs of tuberculosis-related cachexia, including reduced amino acid concentrations. This complex metabolic state suggests a dynamic interaction between the two diseases, resulting in variations in the lipid environment that may, in turn, influence the body's response to pulmonary tuberculosis infection.[38] Future studies should focus on the specific role of TG in the pathogenesis of DM and PTB, as well as how lipid metabolism regulation can improve PTB prevention and control in DM patients.

Inflammatory responses play an important role in the pathophysiology of diabetes and PTB and have provided important information for the study of related biomarkers. Nevertheless, there is a dearth of studies on the efficacy of these inflammatory biomarkers in the diagnosis of active tuberculosis in the diabetic patient population. Therefore, our study further explores and investigates this issue by pioneering the combination of PNR, PMR, MHR, MLR and triglycerides in order to construct a simpler, cost-effective and practical prediction model. Given the close association between conventional blood parameters, lipid indicators, and diabetes-related inflammation and immune function, our model encompasses not only standard hematological measures but also lipid indicators, including HDL and triglycerides. The results indicate that this model exhibits high sensitivity and specificity in diagnosing ATB in diabetic patients, with MLR demonstrating the greatest predictive value and triglycerides the least. Further analysis indicates that the model possesses an excellent calibration curve and significant net clinical benefit, suggesting that in practical clinical settings, it can effectively balance treatment benefits and risks, offering additional value for clinical decision-making. Our findings are consistent with reports in cancer patients, where inflammatory markers calculated based on hematological parameters are advantageous for predicting disease risk and assessing prognosis.[41,42]

Furthermore, it has been noted that sustained hyperglycemia induces activation of inflammatory cells and enhances the expression of inflammatory mediators.[43] We further explored the correlation between inflammatory markers and blood glucose levels. In the DM group, no significant correlation was observed between inflammatory markers and blood glucose levels. This may be attributed to the fact that all enrolled patients were hospitalized individuals who had received pharmacological treatment, resulting in better control of both blood glucose levels and inflammatory status. In contrast, in the case group, a highly significant correlation was observed between MHR and HbA1c, suggesting that the presence of tuberculosis may exacerbate the difficulty of blood glucose control in patients with diabetes by influencing inflammatory

responses and metabolic status. Given the instability of fasting blood glucose and the challenges in monitoring HbA1c in diabetic patients, we propose that MHR can be considered a potential monitoring tool to indirectly assess the trends in HbA1c levels in patients with diabetes complicated by tuberculosis.

Additionally, we found that TG levels were significantly correlated with fasting blood glucose in both patient groups. This is consistent with current research, which indicates that TG levels are closely related to blood glucose levels. In patients with diabetes mellitus, insulin resistance can attenuate the inhibitory effect of insulin on triglyceride lipolysis, thereby leading to elevated triglyceride levels. Elevated triglycerides release more free fatty acids. These free fatty acids further impair insulin sensitivity and reduce glucose uptake and utilization by peripheral tissues, thereby creating a vicious cycle.[44] Notably, no significant correlation was observed between TG and HbA1c in our study. We speculate that this may be related to short-term fluctuations in blood glucose levels caused by acute illness, stress response, or other factors before the study participants visited the clinic, leading to changes in fasting blood glucose levels. While these short-term fluctuations in blood glucose are correlated with changes in TG levels, they are not sufficient to affect HbA1c, which reflects long-term blood glucose control. Therefore, the correlation between TG and fasting blood glucose observed in our study likely reflects short-term metabolic changes rather than long-term blood glucose control status.

This study is subject to several limitations. First, as a retrospective investigation, its design permits only an initial exploration of the risk factors for tuberculosis in patients with diabetes mellitus, without establishing causality. Second, given that all enrolled patients were hospitalized individuals who had received pharmacological treatments, their disease status and associated indices may have been influenced by the treatments, thereby introducing potential selection bias into the results. Third, the study only included patients with diabetes complicated by tuberculosis, excluding those with other comorbidities such as AIDS or malnutrition. Therefore, the sensitivity and accuracy of the predictive model established in this study may be affected when applied to patient populations with other comorbidities. Future studies should further investigate the applicability of this model in a broader range of patient populations. Fourth, the lack of external validation limits the generalizability and extrapolation of the study results. Future research should address these limitations through prospective designs and multicenter validation to more accurately assess the relationship between diabetes and tuberculosis.

Conclusion

This study pioneers the exploration of the predictive capacity of inflammatory biomarkers for the risk of PTB in patients with diabetes mellitus, offering a novel perspective for the early diagnosis of diabetes complicated by active tuberculosis. The results demonstrate that the combined application of TG with MLR, MHR, PNR, and PMR serves as a robust predictor for active tuberculosis risk in diabetic patients. Therefore, clinical managers should monitor inflammatory biomarkers in diabetic patients to identify and intervene in high-risk populations for tuberculosis infection at an early stage. This approach can more effectively manage patients' conditions, optimize treatment plans, and reduce the incidence of diabetes complicated by tuberculosis. However, given the limitations of this study, future research should conduct multicenter, large-sample, and multi-population studies involving external validation and cost-effectiveness analyses to better evaluate the application value of inflammatory biomarkers in diabetes complicated by active tuberculosis.

Abbreviations

NLR, neutrophil-to-lymphocyte ratio; NHR, neutrophil to high-density lipoprotein ratio; NMR, neutrophil-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; PNR, platelet-to-neutrophil ratio; PMR, platelet-to-monocyte ratio; LMR, lymphocyte-to-monocyte ratio; LHR, lymphocyte to high-density lipoprotein; MHR, monocyte to high-density lipoprotein ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; AISI, aggregate inflammation systemic index.

Data Sharing Statement

The data are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The study was conducted in accordance with the principles outlined in Declaration of Helsinki and was approved by the Ethics Committee of the Third People's Hospital of Kunming (approval number: KSLL2023032040). The information of participants involved in the study will be strictly confidential. De-identification methods will be used to minimize the risk of personal information leakage and to protect the privacy of each participant. Regarding compensation, since the study is retrospective, participants did not receive any compensation.

Consent for Publication

All authors have read and approved the manuscript.

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Author Contributions

The reported work has been significantly contributed to by all the authors. Their contributions encompass a range of areas, including conceptualization, study design, data acquisition, execution, analysis, and interpretation. Moreover, drafting, revising, and critically reviewing the article involved the participation of all authors. They have provided their final approval for the version intended for publication and have reached a consensus on the target journal. Additionally, all authors acknowledge their responsibility for every aspect of the work.

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Disclosure

The authors declare that there is no conflict of interest for this work.

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