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ORIGINAL RESEARCH

# Age-Stratified Effects of Diabetes Mellitus on Central Nervous System Tuberculosis Risk and Combined Effects with Neutrophil-to-Lymphocyte Ratio

Muxing Chen, Xinxin Fan, Yan Chen, Fan Zhang, Zhixiong Yao, Youfei Lin, Xiaohong Chen, Di Wu

Department of Tuberculosis, Fuzhou Pulmonary Hospital of Fujian Province, Fuzhou, Fujian, People's Republic of China

Correspondence: Xiaohong Chen; Di Wu, Email cxhong6886@126.com; fkyywd@163.com



**Purpose:** To investigate the relationship between diabetes mellitus (DM) and the risk of central nervous system tuberculosis (CNS-TB), to analyze the age-dependent characteristics of this association, and to assess the combined effects of DM and neutrophil-to-lymphocyte ratio (NLR).

**Patients and Methods:** We retrospectively analyzed clinical data of 862 extrapulmonary tuberculosis patients admitted to Fuzhou Pulmonary Hospital from April 2018 to April 2024, including 685 non-CNS extrapulmonary tuberculosis (non-CNS EPTB) patients and 177 CNS-TB patients. Baseline demographic and laboratory characteristics were compared between groups. Age-stratified analysis (≤40 years, 41–60 years, >60 years) was performed to evaluate the age-dependent nature of the association between diabetes and CNS-TB risk. Multivariate logistic regression analysis was used to identify independent risk factors for CNS-TB, and to assess the combined effects and interaction between diabetes and NLR.

**Results:** The prevalence of DM was significantly higher in the CNS-TB group than in the non-CNS EPTB group (24.29% vs 12.26%, $P<0.001$), with significantly elevated NLR ($P<0.001$). Age-stratified analysis revealed that the association between diabetes and CNS-TB risk exhibited significant age dependence, with no significant correlation in the ≤40 years group (OR=1.52, 95% CI: 0.47–4.94, $P=0.506$), but significant associations in the 41–60 years group (OR=2.80, 95% CI: 1.40–5.63, $P=0.003$) and >60 years group (OR=2.22, 95% CI: 1.20–4.13, $P=0.010$). Multivariate analysis confirmed DM (adjusted OR=2.116, 95% CI: 1.382–3.241, $P<0.001$) and NLR (adjusted OR=1.051, 95% CI: 1.022–1.080, $P<0.001$) as independent risk factors for CNS-TB. Combined effects analysis demonstrated that patients with both diabetes and high NLR (>4.194) had the highest risk of CNS-TB (adjusted OR=4.833, 95% CI: 2.737–8.535, $P<0.001$), with a proportion of 38.4%. However, formal interaction analysis indicated no evidence of a statistically significant additive interaction (RERI=0.198, 95% CI: −2.772–3.169, $P=0.896$).

**Conclusion:** DM is an independent risk factor for CNS-TB, significantly increasing risk in individuals aged >40 years. DM and NLR independently contribute to CNS-TB risk, supporting clinical risk assessment and prevention strategies incorporating metabolic and inflammatory biomarkers.

**Keywords:** central nervous system tuberculosis, diabetes mellitus, neutrophil-to-lymphocyte ratio, age stratification, combined effects

## Introduction

Extrapulmonary tuberculosis, particularly tuberculous meningitis affecting the central nervous system, constitutes a significant global public health challenge. According to the World Health Organization (WHO), approximately 10.8 million tuberculosis cases were reported worldwide in 2023,[1] with extrapulmonary tuberculosis accounting for 15–20%.[2,3] Central nervous system tuberculosis (CNS-TB), a severe manifestation of extrapulmonary tuberculosis, comprises 5–8% of extrapulmonary tuberculosis cases,[4,5] with an in-hospital mortality rate reaching 42.12%.[6] Even with aggressive therapy, more than half of CNS-TB survivors develop varying degrees of neurological sequelae.[7]

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Diabetes mellitus (DM), a prevalent metabolic disorder, currently affects over 589 million individuals globally (aged 20–79 years).[8] The relationship between diabetes and tuberculosis pathogenesis has garnered considerable attention, with co-morbidity rates continuing to rise and reaching up to 45% in certain regions.[9] Evidence has indicated that individuals with diabetes exhibit a threefold higher risk of developing tuberculosis,[10,11] often presenting with more severe clinical manifestations, increased bacterial burden, higher treatment failure rates, and elevated recurrence rates.[12] Diabetes may further exacerbate disease severity and adverse prognostic outcomes in CNS-TB by compromising blood-brain barrier integrity and intensifying neuroinflammatory responses.[13,14] Additionally, the neutrophil-to-lymphocyte ratio (NLR), an accessible inflammatory marker, demonstrates significant correlations not only with tuberculosis severity, treatment response, and unfavorable prognosis,[15–17] but also with diabetes outcomes.[18]

Recent years have witnessed advancements in understanding the pathogenesis of extrapulmonary tuberculosis, particularly CNS-TB. However, the synergistic effects of diabetes and inflammatory responses in CNS-TB development remain inadequately elucidated. Furthermore, questions regarding whether the association between diabetes and CNS-TB exhibits an age-dependent pattern, and whether diabetes and NLR demonstrate interactive effects, have not been systematically investigated. In clinical practice, the critical issue of stratifying risk based on patients' diabetic status and NLR levels to guide targeted prevention and early intervention strategies remains unresolved.

In light of these considerations, this retrospective case-control study aims to systematically evaluate the association between diabetes and CNS-TB, and explore the age-dependent characteristics of this relationship. Concurrently, we will analyze the correlation between NLR and CNS-TB, as well as potential interactions between diabetes and NLR. Our research is characterized by a substantial sample size, stringent inclusion and exclusion criteria, and robust statistical methodology, particularly employing an integrative analytical framework that combines age stratification with combined effects analysis to comprehensively assess CNS-TB risk factors. The findings will provide clinicians with effective tools for identifying high-risk populations, thereby contributing to improved early diagnosis, risk stratification, and precision treatment strategies for CNS-TB, ultimately reducing CNS-TB-associated disease burden and mortality.

# Materials and Methods

## Study Design and Patient Selection

This retrospective case-control study enrolled extrapulmonary tuberculosis patients hospitalized at Fuzhou Pulmonary Hospital between April 2018 and April 2024. Following systematic screening of an initial consecutive series of 1408 extrapulmonary tuberculosis patients, study participants were meticulously selected according to predefined eligibility criteria (Figure 1). Inclusion criteria included adult patients (age ≥18 years) with confirmed extrapulmonary tuberculosis. Exclusion criteria comprised patients with incomplete clinical documentation (n=464) and those with immunodeficiency disorders (including Human immunodeficiency virus (HIV) infection) or receiving immunosuppressive therapy (n=36). Incomplete clinical documentation was defined as the absence of one or more essential variables required for the primary multivariable regression analyses, including: complete blood count parameters (neutrophil (NEU), lymphocyte (LYM), platelet (PLT)), T-lymphocyte subset measurements ($CD3^+$, $CD4^+$, $CD8^+$, $CD45^+$ T-cell counts), nutritional biomarkers (albumin (ALB) and hemoglobin (Hb)). The final analytical cohort consisted of 862 eligible patients: 177 with CNS-TB and 685 with non-central nervous system extrapulmonary tuberculosis. Among the 177 CNS-TB patients, 43 presented with concomitant DM while 134 were non-diabetic.

All data exclusions were systematically applied to the initial cohort prior to CNS-TB diagnostic classification to minimize outcome-dependent selection bias. To ensure that the exclusion process did not introduce systematic bias related to diabetes status—particularly whether a disproportionate number of diabetic patients were excluded from either group—we performed a retrospective comparative analysis of the initial 1408-patient cohort before any exclusions. Among the 1408 initially screened patients, the Non-CNS EPTB group comprised 1110 patients (including 129 with diabetes mellitus), while the CNS-TB group comprised 298 patients (including 61 with diabetes mellitus). Chi-square analysis demonstrated a statistically significant difference in diabetes prevalence between the two groups ($\chi^2$ =15.007, $P$<0.001), with diabetes present in 20.5% (61/298) of CNS-TB patients versus 11.6% (129/1110) of Non-CNS EPTB patients. This finding confirms that the association between diabetes and CNS-TB risk was present in the original cohort

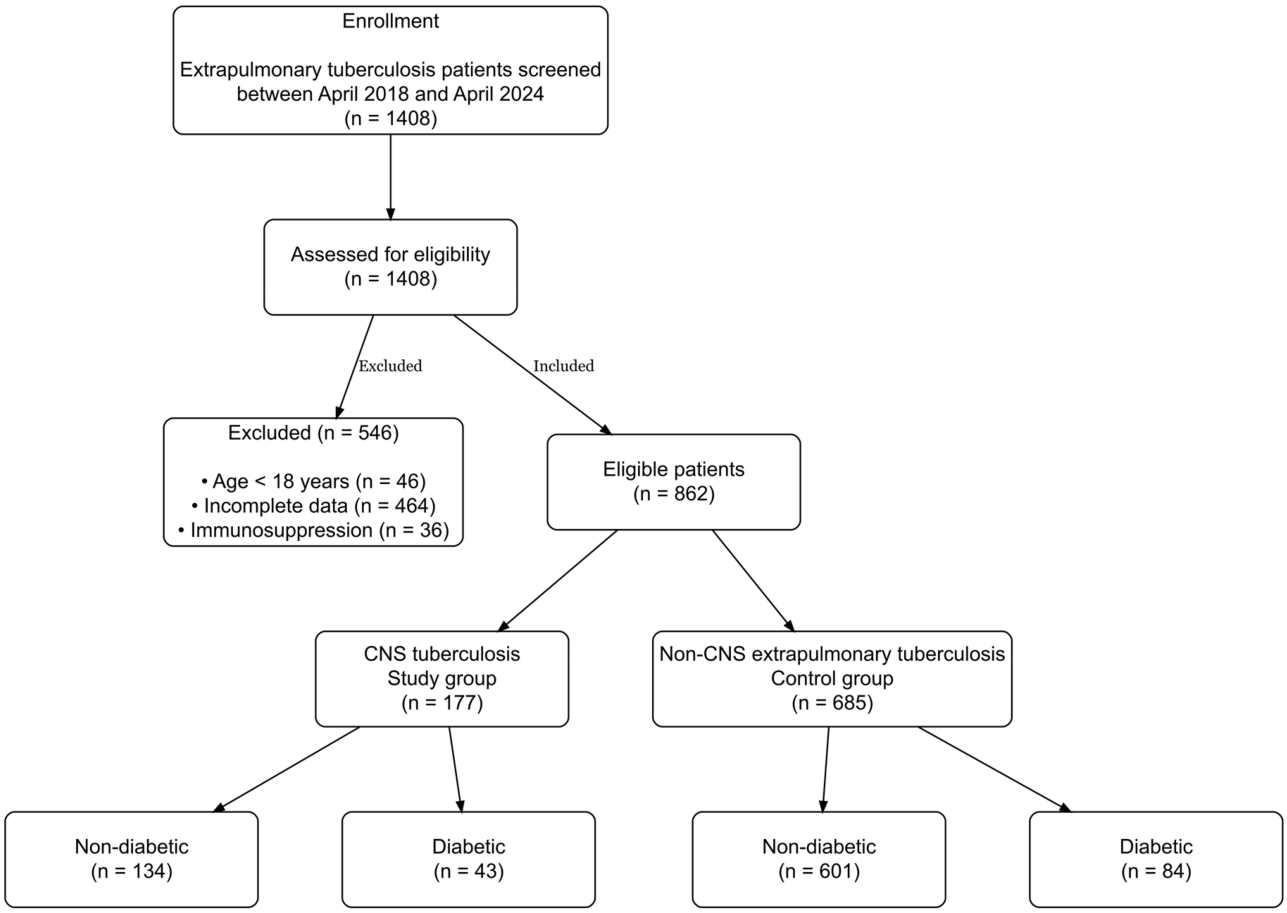


**Figure 1** Distribution of extrapulmonary tuberculosis (EPTB) sites among the study cohort.

prior to any data exclusions, thereby validating that subsequent patient exclusions for incomplete data did not artificially create or obscure the observed relationship between diabetes and CNS-TB.

Our research team has undertaken three distinct yet complementary investigations utilizing this cohort of 862 patients to address different clinical questions. The first study,[19] published in *Infection and Drug Resistance*, employed propensity score matching to characterize immuno-inflammatory patterns in tuberculous lymphadenitis compared to other forms of extrapulmonary tuberculosis. The second study,[20] published in *BMC Infectious Diseases*, comprehensively evaluated age-stratified T-lymphocyte immune characteristics ($CD3^+$, $CD4^+$, $CD8^+$, $CD45^+$) and nutritional parameters (Hb, ALB) in CNS-TB patients, identifying pronounced T-cell depletion in the 25–54 years age group.

The present analysis specifically examines DM as a risk factor for CNS-TB, with particular emphasis on age-stratified effects and interaction with NLR—aspects not evaluated in the second study. While the second study focused on T-lymphocyte subset patterns across age groups, it did not assess DM as an independent risk factor or explore DM-NLR interactions. Our findings demonstrate that DM significantly increases CNS-TB risk exclusively in individuals aged >40 years (41–60 years: OR=2.80, P=0.003; >60 years: OR=2.22, P=0.010), with no significant association observed in the ≤40 years group (OR=1.52, P=0.506). Furthermore, patients with concomitant DM and elevated NLR exhibit the highest CNS-TB proportion (38.4%, adjusted OR=4.833).

While utilizing the same patient cohort, each investigation explores distinct clinical characteristics and risk factor associations. For methodological transparency, we incorporated laboratory parameters (ALB, Hb, and T-lymphocyte subsets) reported in our second study[20] into the multivariable regression models of the present study as covariates for confounder adjustment rather than as primary analytical targets.


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## Diagnostic Criteria and Data Collection

Extrapulmonary tuberculosis diagnosis was established based on bacteriological, histopathological, or clinical evidence confirming tuberculous infection involving extra-pulmonary organs.[21,22] CNS-TB diagnosis was determined using either:[22,23] microbiological evidence (detection of *Mycobacterium tuberculosis* or related pathogenic evidence in cerebrospinal fluid), or comprehensive clinical-radiological criteria, including characteristic neuroimaging abnormalities, cerebrospinal fluid biochemical abnormalities (elevated protein levels, decreased glucose and chloride concentrations), and favorable response to anti-tuberculosis therapy. CNS-TB diagnosis was independently confirmed by two senior tuberculosis specialists employing a double-blind methodology. DM diagnosis was established according to the guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition),[24] encompassing both previously diagnosed diabetes and newly diagnosed diabetes during the current hospitalization. For newly diagnosed cases, blood samples (glucose, glycated hemoglobin) were obtained within 24 hours of admission and prior to anti-tuberculosis therapy and corticosteroid administration. Specifically, the diagnosis was based on the presence of typical diabetes symptoms (including polydipsia, polyuria, polyphagia, and unexplained weight loss) in combination with any of the following: (1) random plasma glucose ≥11.1 mmol/L; (2) fasting plasma glucose≥7.0 mmol/L (fasting defined as no caloric intake for at least 8 hours); (3) 2-hour plasma glucose during an oral glucose tolerance test≥11.1 mmol/L; or (4) glycated hemoglobin ≥ 6.5%. For asymptomatic patients, the diagnosis was confirmed by repeated testing on a -separate day. Clinical data were systematically extracted from the hospital's electronic medical record system by two trained independent investigators, with discrepancies resolved through consensus discussion.

## Variables

This study analyzed the following clinical parameters and their associations with CNS-TB: DM status and NLR. NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. PLR was calculated as the absolute platelet count divided by the absolute lymphocyte count. Additional analytical variables encompassed demographic characteristics (gender, age), clinical features (body mass index [BMI], tuberculosis treatment history, concurrent pulmonary tuberculosis status), hematological parameters (NEU, LYM, PLT), Hb, ALB, and immunological markers ($CD3^+$, $CD4^+$, $CD8^+$, $CD45^+$ T-lymphocyte subsets). All laboratory assessments were performed on blood samples collected within 24 hours of hospital admission: Laboratory measurements including complete blood count, T-lymphocyte subsets, and serum albumin were performed as previously described.[19,20] All enrolled patients possessed comprehensive clinical documentation with no missing data values.

## Statistical Analysis

Statistical analyses were performed using R statistical software version 4.4.2. Continuous variables were assessed for normality using the Shapiro–Wilk test. Non-normally distributed continuous variables are presented as median (interquartile range) [M(IQR)] and compared using the Mann–Whitney *U*-test. Categorical variables are presented as frequencies (percentages) and analyzed using Pearson's $\chi^2$ test or Yates' corrected $\chi^2$ test when appropriate. To specifically address potential confounding by age, age-stratified analyses were performed across three categories (≤40 years, 41–60 years, >60 years). Age-adjusted odds ratios (ORs) were calculated by including age as a continuous covariate within each stratum to account for residual confounding. Homogeneity of effects across age strata was assessed using the Breslow-Day test. Multivariable logistic regression models were constructed to evaluate the association strength between DM and CNS-TB, with adjustment for potential confounding factors. In the absence of a standardized clinical threshold, NLR was dichotomized into low (≤4.194) and high (>4.194) groups based on the median value of the 862 included patients. This approach ensured balanced group sizes and maximized statistical power for subsequent analyses. Combined effects analyses were conducted to explore synergistic interactions between DM and NLR. Additive interaction was quantified using relative excess risk due to interaction (RERI), attributable proportion (AP), and synergy index (SI). Multiplicative interaction was assessed through likelihood ratio testing. Multiple comparison corrections were applied using the Bonferroni method. Two-tailed *P*-values <0.05 were considered statistically significant.

# Results

## Baseline Characteristics of the Study Population

This study enrolled 862 patients with extrapulmonary tuberculosis, comprising 685 patients with non-central nervous system extrapulmonary tuberculosis (non-CNS EPTB) and 177 patients with CNS-TB. Table 1 presents the comparison of key baseline characteristics between the two groups. No significant differences were observed between groups regarding age [median: 50.0 years (32.0–64.0) vs 53.0 years (35.0–65.0), $W$=63521, $P$=0.326] or sex distribution [males: 72.12% vs 68.36%, $\chi^2$=0.80, $P$=0.373]. However, the prevalence of DM was significantly higher in the CNS-TB group compared to the non-CNS EPTB group [24.29% vs 12.26%, $\chi^2$=15.26, $P$<0.001].

Regarding inflammatory markers, the CNS-TB group demonstrated significantly enhanced inflammatory responses. The NLR was markedly elevated in the CNS-TB group [median: 6.15 (3.57–10.31) vs 3.78 (2.32–6.14), $W$=80690, $P$<0.001]. Similarly, the PLR was significantly higher in the CNS-TB group than in the non-CNS EPTB group [median: 302.33 (202.17–468.66) vs 239.00 (156.99–356.38), $W$=47426, $P$<0.001] (Table 1).

Additional clinical and laboratory parameters, including ALB, Hb, and T-lymphocyte subsets, were comprehensively analyzed and reported in our previous study.[20] These parameters also demonstrated significant differences between groups and provided the foundation for subsequent multivariable regression analyses to identify independent risk factors for CNS-TB and establish risk stratification models based on multiple risk factor combinations.

## Demographic and Clinical Characteristics of CNS-TB Patients Stratified by Diabetes Status

Within the cohort of 177 CNS-TB patients, we conducted a subgroup analysis stratified by diabetes status, comprising 134 patients (75.7%) without diabetes and 43 patients (24.3%) with DM. Table 2 presents the comparative baseline

**Table 1** Baseline Characteristics of CNS-TB and Non-CNS EPTB Patients

| Variables | Non-CNS EPTB Group (n = 685) | CNS-TB Group (n = 177) | *W* | OR (95% CI) | *P* |
|---|---|---|---|---|---|
| Age (years, *M* ($Q_1$, $Q_3$)) | 50.00 (32.00, 64.00) | 53.00 (35.00, 65.00) | *W*= 63521 | – | 0.326 |
| NEU, *M* ($Q_1$, $Q_3$) | 4.45 (3.28, 6.08) | 4.90 (3.63, 6.93) | *W*=67439 | – | 0.021 |
| LYM, *M* ($Q_1$, $Q_3$) | 1.18 (0.86, 1.61) | 0.82 (0.57, 1.20) | *W*=39082 | – | <0.001 |
| PLT, *M* ($Q_1$, $Q_3$) | 278.00 (219.00, 357.00) | 248.00 (190.00, 324.00) | *W=70495* | – | <0.001 |
| NLR, *M* ($Q_1$, $Q_3$) | 3.78 (2.32, 6.14) | 6.15 (3.57, 10.31) | *W*=80690 | – | <0.001 |
| PLR, *M* ($Q_1$, $Q_3$) | 239.00 (156.99, 356.38) | 302.33 (202.17, 468.66) | *W*=47426 | – | <0.001 |
| Sex, n (%) | | | $\chi^2$=0.80 | | 0.373 |
| Female | 191 (27.88) | 56 (31.64) | | 0.84 (0.58–1.2) | |
| Male | 494 (72.12) | 121 (68.36) | | 1.00 (Reference) | |
| DM, n (%) | | | $\chi^2$=15.26 | | <0.001 |
| No | 601 (87.74) | 134 (75.71) | | 1.00 (Reference) | |
| Yes | 84 (12.26) | 43 (24.29) | | 2.30 (1.52–3.47) | |

**Abbreviations**: OR, odds ratio; CI, confidence interval; NS-TB, Central nervous system tuberculosis; Non-CNS EPTB, Non-central nervous system extrapulmonary tuberculosis; NEU, neutrophil (×$10^9$/L); LYM, lymphocyte (×$10^9$/L); PLT, platelet (×$10^9$/L); NLR, Neutrophil-to-Lymphocyte ratio; PLR, Platelet-to-Lymphocyte Ratio; DM, Diabetes mellitus.

**Table 2** Baseline Characteristics of CNS-TB Patients by Diabetic Status

| Variables | No Diabetes (n = 134) | Diabetes (n = 43) | Statistic | *P* |
|---|---|---|---|---|
| Age, *M* ($Q_1$, $Q_3$) | 50.00 (30.00, 61.00) | 64.00 (52.00, 69.00) | *W*=1606 | <0.001 |
| BMI, *M* ($Q_1$, $Q_3$) | 19.21 (17.87, 21.48) | 19.72 (18.44, 20.95) | *W*=2596.5 | 0.331 |
| NEU, *M* ($Q_1$, $Q_3$) | 4.69 (3.64, 6.48) | 5.31 (3.74, 7.30) | *W*=2455.5 | 0.146 |
| LYM, *M* ($Q_1$, $Q_3$) | 0.84 (0.60, 1.20) | 0.78 (0.55, 1.16) | *W*=2941.5 | 0.837 |

(*Continued*)


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**Table 2** (Continued).

| Variables | No Diabetes (n = 134) | Diabetes (n = 43) | Statistic | *P* |
|---|---|---|---|---|
| PLT, *M* ($Q_1$, $Q_3$) | 248.00 (195.25, 315.50) | 278.00 (176.00, 361.00) | *W*=2637 | 0.405 |
| NLR, *M* ($Q_1$, $Q_3$) | 5.98 (3.62, 9.98) | 7.94 (3.43, 11.85) | *W*=2615 | 0.364 |
| PLR, *M* ($Q_1$, $Q_3$) | 298.85 (196.24, 429.98) | 359.81 (211.53, 510.29) | *W*=2590 | 0.320 |
| Hb, *M* ($Q_1$, $Q_3$) | 114.5±19.3 | 112.5±19.9 | *t* = 0.558 | 0.579 |
| ALB, *M* ($Q_1$, $Q_3$) | 35.9±5.17 | 35.3±6.13 | *t* = 0.587 | 0.559 |
| $CD3^+$, *M* ($Q_1$, $Q_3$) | 705.50 (363.00, 994.00) | 747.00 (504.00, 1169.50) | *W*=2503.5 | 0.197 |
| $CD4^+$, *M* ($Q_1$, $Q_3$) | 380.50 (207.75, 609.75) | 353.00 (240.50, 618.50) | *W*=2772.5 | 0.712 |
| $CD8^+$, *M* ($Q_1$, $Q_3$) | 258.00 (139.50, 392.25) | 310.00 (206.00, 532.50) | *W*=2328 | 0.059 |
| $CD45^+$, *M* ($Q_1$, $Q_3$) | 1036.50 (570.00, 1393.25) | 1163.00 (698.50, 1727.50) | *W*=2543 | 0.248 |
| Sex, n (%) | | | $\chi^2$=0.96 | 0.326 |
| Female | 45 (33.58) | 11 (25.58) | | |
| Male | 89 (66.42) | 32 (74.42) | | |
| Treatment, n (%) | | | $\chi^2$=8.51 | 0.004 |
| Initial Treatment | 129 (96.27) | 35 (81.40) | | |
| Retreatment | 5 (3.73) | 8 (18.60) | | |
| PTB, n (%) | | | $\chi^2$=0.03 | 0.857 |
| Yes | 128 (95.52) | 42 (97.67) | | |
| No | 6 (4.48) | 1 (2.33) | | |

**Notes**: Lymphocyte subsets were analysed, with $CD3^+$ representing total T lymphocytes (cells/μL), $CD4^+$ indicating T helper cells (cells/μL), $CD8^+$ representing cytotoxic T cells (cells/μL), and $CD45^+$ indicating total lymphocytes (cells/μL). "Initial Treatment" denotes patients receiving anti-tuberculosis therapy for a new episode of tuberculosis; "Retreatment" indicates patients with a history of prior anti-tuberculosis treatment who are now receiving therapy for relapse, treatment failure, or re-infection.

**Abbreviations**: Hb, hemoglobin (g/L); ALB, albumin (g/L).

characteristics between these subgroups. Patients with diabetes were significantly older than their non-diabetic counterparts [median age: 64.0 years (IQR: 52.0–69.0) versus 50.0 years (30.0–61.0), $P<0.001$]. Regarding tuberculosis treatment history, the diabetic subgroup demonstrated a substantially higher proportion of retreatment cases compared to the non-diabetic subgroup [18.60% versus 3.73%, $P<0.01$].

No significant disparities were identified between subgroups regarding sex distribution, body mass index, or the prevalence of concurrent pulmonary tuberculosis ($P>0.05$). With respect to immunological parameters, no significant differences were observed between subgroups in inflammatory biomarkers, including NLR and PLR ($P>0.05$). Nutritional indicators, encompassing Hb levels and ALB concentrations, exhibited comparable values across both subgroups ($P>0.05$). In the analysis of T-lymphocyte subsets, $CD8^+$ T-cell counts demonstrated a non-significant trend toward elevation in the diabetic subgroup [310.0 (206.0–532.5) versus 258.0 (139.5–392.3) cells/μL, $W=2328$, $P=0.059$]. The remaining T-cell populations ($CD3^+$, $CD4^+$, $CD45^+$) showed no significant inter-group differences ($P>0.05$).

## Age-Dependent Association Between Diabetes and CNS-TB Risk

Given the significant age disparity between diabetic and non-diabetic patients within the CNS-TB cohort ($P<0.001$), we conducted an age-stratified analysis to investigate the influence of DM on CNS-TB risk across different age demographics. The study population was stratified into three distinct age categories: ≤40 years (n=310), 41–60 years (n=290), and >60 years (n=262) (Table 3).

The age-stratified analysis revealed a pronounced age-dependent association between DM and CNS-TB susceptibility. Among patients aged ≤40 years, the proportion of CNS-TB was 26.7% (4/15) in diabetic individuals compared to 19.3% (57/295) in their non-diabetic counterparts, demonstrating no statistically significant difference [OR=1.52, 95% CI: 0.47–4.94, $P=0.506$]. Notably, the small number of diabetic patients in the ≤40 years subgroup (n=15) resulted in a wide confidence interval, suggesting limited statistical power to precisely estimate the association in this group. Conversely, In the 41–60 years age stratum, diabetic patients exhibited a substantially elevated CNS-TB proportion relative to non-

**Table 3** Association Between DM Status and Central Nervous System Involvement Stratified by Age

| Age Group | n | DM Status | CNS Status | | OR (95% CI) | Statistic | *P* |
|---|---|---|---|---|---|---|---|
| | | | Positive, n (%) | Negative, n (%) | | | |
| ≤40 years | 310 | Positive | 4 (26.7) | 11 (73.3) | 1.52 (0.47–4.94) | Fisher's exact test | 0.506 |
| | | Negative | 57 (19.3) | 238 (80.7) | | | |
| 41–60 years | 290 | Positive | 16 (34.8) | 30 (65.2) | 2.80 (1.40–5.63) | $\chi^2$ = 8.90 | 0.003 |
| | | Negative | 39 (16.0) | 205 (84.0) | | | |
| >60 years | 262 | Positive | 23 (34.8) | 43 (65.2) | 2.22 (1.20–4.13) | $\chi^2$ = 6.61 | 0.010 |
| | | Negative | 38 (19.4) | 158 (80.6) | | | |

**Notes**: All demographic, clinical, and laboratory variables (Sex, Age, Treatment history, DM, Cerebrovascular disease, PTB, BMI, PLR, NLR, Hb, ALB, $CD3^+$, $CD4^+$, $CD8^+$, $CD45^+$) were initially included in univariable analysis. Variables with $P<0.2$ were then entered into multivariable logistic regression. Only variables achieving statistical significance ($P<0.05$) in multivariable analysis were displayed.

diabetic individuals [34.8% (16/46) versus 16.0% (39/244), OR=2.80, 95% CI: 1.40–5.63, $P$=0.003]. Similarly, among patients aged >60 years, DM conferred a significant increase in CNS-TB risk [34.8% (23/66) versus 19.4% (38/196), OR=2.22, 95% CI: 1.20–4.13, $P$=0.010].

## Age-Adjusted Analyses

To address potential residual confounding by age within strata, we calculated age-adjusted odds ratios by including age as a continuous covariate in logistic regression models within each age stratum (Table 4). After age adjustment, diabetes mellitus remained significantly associated with CNS-TB in the overall sample (age-adjusted OR=2.30, 95% CI: 1.50–3.54, $P<0.001$). The age-stratified pattern persisted after adjustment: no significant association was observed in the ≤40 years group (age-adjusted OR=1.54, 95% CI: 0.47–5.07, $P$=0.480), while significant associations were detected in both the 41–60 years group (age-adjusted OR=2.72, 95% CI: 1.35–5.47, $P$=0.005) and the >60 years group (age-adjusted OR=2.28, 95% CI: 1.23–4.26, $P$=0.009). The minimal change between crude and age-adjusted ORs across all strata indicates limited residual age confounding within strata. The Breslow-Day test for homogeneity of odds ratios across age strata yielded non-significant results ($\chi^2$=0.80, df=2, $P$=0.669), indicating that the observed differences in effect sizes across age groups did not reach statistical significance for formal effect modification.

## Independent Risk Factors for CNS-TB Development

Given that previous studies have demonstrated close associations between nutritional status, inflammatory state, immune function, and tuberculosis development,[20] we incorporated nutritional indicators (BMI, ALB, Hb), inflammatory parameters (NLR, PLR), immunological markers ($CD3^+$, $CD4^+$, $CD8^+$, $CD45^+$ T-cell counts), and clinically relevant factors (DM) into a multivariable logistic regression model to identify independent risk factors for CNS-TB development. The multivariable analysis revealed (Table 5) that DM emerged as a strong independent risk factor for CNS-TB occurrence [adjusted OR=2.116, 95% CI: 1.382–3.241, $P<0.001$], indicating that diabetic patients demonstrated 2.116-fold higher odds of developing CNS-TB compared to their non-diabetic counterparts. Beyond diabetes, NLR emerged as a significant independent predictor when analyzed as a continuous variable. Each 1-unit increment in NLR was independently associated with a 5.1% increase in the odds of CNS-TB development (adjusted OR=1.051 per unit, 95% CI:

**Table 4** Age-Adjusted Odds Ratios for the Association Between Diabetes Mellitus and CNS Tuberculosis

| Age (Years) | n | CNS-TB | Non-CNS EPTB | Crude OR (95% CI) | Age-Adjusted OR* (95% CI) | *P* |
|---|---|---|---|---|---|---|
| Overall | 862 | 177 | 685 | 2.30 (1.52–3.47) | 2.30 (1.50–3.54) | <0.001 |
| ≤40 | 310 | 61 | 249 | 1.52 (0.47–4.94) | 1.54 (0.47–5.07) | 0.480 |
| 41–60 | 290 | 55 | 235 | 2.80 (1.40–5.63) | 2.72 (1.35–5.47) | 0.005 |
| >60 | 262 | 61 | 201 | 2.22 (1.20–4.13) | 2.28 (1.23–4.26) | 0.009 |

**Notes**: *Age-adjusted OR: Adjusted for age as a continuous variable within each stratum to account for residual confounding by age. Breslow-Day test for homogeneity of ORs across age groups: $\chi^2$=0.80, $df$=2, $P$=0.669.


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**Table 5** Univariable and Multivariable Analyses of Factors Associated with Central Nervous System Tuberculosis

| Variables | Univariate Analysis | | | | | Multivariate Analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *β* | *S. E* | *Z* | *P* | OR (95% CI) | *β* | *S. E* | *Z* | *P* | OR (95% CI) |
| DM | | | | | | | | | | |
| No | | | | | 1.00 (Reference) | | | | | 1.00 (Reference) |
| Yes | 0.831 | 0.21 | 3.949 | <0.001 | 2.396 (1.52 ~ 3.468) | 0.75 | 0.217 | 3.447 | <0.001 | 2.116 (1.382 ~ 3.241) |
| NLR | 0.068 | 0.013 | 5.215 | <0.001 | 1.07 (1.043 ~ 1.098) | 0.05 | 0.014 | 3.505 | <0.001 | 1.051 (1.022 ~ 1.08) |
| $CD3^+$ | −0.001 | 0.00 | −4.07 | <0.001 | 0.999(0.999 ~ 1) | −0.001 | 0.00 | −2.734 | 0.006 | 0.999 (0.998~ 1) |

1.022–1.08, *P*<0.001), demonstrating a dose-dependent relationship between systemic inflammatory burden and CNS-TB susceptibility. Among immunological parameters, $CD3^+$ T-lymphocyte absolute count served as an independent protective factor [adjusted OR=0.999, 95% CI: 0.998–1.000, *P*=0.006].

## Combined Effects of Diabetes and NLR on CNS-TB Risk

To further evaluate the combined effects of DM and inflammatory status, patients were stratified by NLR using the overall median value of 4.194 from the entire cohort of 862 patients as the cutoff, and combined with diabetes status for integrated analysis. The multivariable-adjusted combined effects analysis demonstrated (Table 6) a progressive risk escalation across risk factor combinations. Compared to the reference group without diabetes and with low NLR (CNS-TB proportion: 11.4%), both single-risk-factor groups exhibited significantly elevated CNS-TB risk: the group with high NLR but without diabetes showed an adjusted OR of 2.647 (95% CI: 1.780–3.937, *P*<0.001), while the group with diabetes but low NLR demonstrated an adjusted OR of 2.987 (95% CI: 1.521–5.867, *P*=0.001). Remarkably, patients with concomitant diabetes and elevated NLR (above the median of 4.194) exhibited the highest disease susceptibility, with an adjusted OR of 4.833 (95% CI: 2.737–8.535, *P*<0.001) and a proportion rate of 38.4%, suggesting a potential additive effect between these two risk determinants.

Although the combined effects analysis demonstrated that patients concomitantly exposed to DM and elevated NLR (>4.194) experienced the highest CNS-TB risk (adjusted OR=4.833, 95% CI: 2.737–8.535), subsequent interaction analysis revealed no statistically significant synergistic interaction between these two risk factors (Table 7). None of the additive interaction measures achieved statistical significance: the relative excess risk due to interaction (RERI=0.198, 95% CI: −2.772 to 3.169, *P*=0.896), the attributable proportion due to interaction (AP=0.041, 95% CI: −0.56 to 0.642, *P*=0.894), and the synergy index (SI=1.055, 95% CI: 0.216 to 1.893, *P*=0.899). Similarly, multiplicative interaction testing yielded non-significant results (product-term coefficient *β*=−0.49, 95% CI: −1.35 to 0.37, *P*=0.260; likelihood ratio test *P*=0.263). These findings suggest that DM and elevated NLR exert independent additive effects without deviation from additivity, indicating absence of sufficient-cause synergism in conferring CNS-TB susceptibility.

# Discussion

Through systematic analysis of 862 patients with extrapulmonary tuberculosis, this study confirms that DM is a significant independent risk factor for CNS-TB (adjusted OR=2.116, 95% CI: 1.382–3.241, *P*<0.001), indicating that diabetic patients demonstrate 2.116-fold higher odds of developing CNS-TB compared to their non-diabetic counterparts.

**Table 6** CNS-TB Risk Stratification by DM and NLR Status

| Risk Factor Combination | Total (n) | CNS-TB (n) | CNS-TB Proportion (%) | Adjusted OR* (95% CI) | *P*-value |
|---|---|---|---|---|---|
| No DM, Low NLR | 377 | 43 | 11.4 | 1.00 (Reference) | – |
| No DM, High NLR | 358 | 91 | 25.4 | 2.647 (1.780–3.937) | <0.001 |
| DM, Low NLR | 54 | 15 | 27.8 | 2.987 (1.521–5.867) | 0.001 |
| DM, High NLR | 73 | 28 | 38.4 | 4.833 (2.737–8.535) | <0.001 |

**Note**: *Adjusted for age, sex, BMI, and other potential confounders.

**Table 7** Interaction Analysis Between DM and Elevated NLR

| Interaction Measure | Estimate | 95% CI | *P*-value |
|---|---|---|---|
| **Additive Interaction** | | | |
| RERI | 0.198 | (−2.772, 3.169) | 0.896 |
| AP | 0.041 | (−0.56, 0.642) | 0.894 |
| SI | 1.055 | (0.216, 1.893) | 0.899 |
| **Multiplicative Interaction** | | | |
| $\beta$ coefficient | −0.49 | (−1.35, 0.37) | 0.260 |
| Likelihood ratio test | – | – | 0.263 |

**Abbreviations**: RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; SI, synergy index.

This finding is consistent with a large meta-analysis by Asori et al,[25] which included 16,847 cases and found that diabetes more than doubled the risk of meningitis, including tuberculous meningitis. Similarly, Jeon et al[10] concluded from a systematic review of 13 observational studies that diabetes increased the overall tuberculosis risk three-fold (RR=3.11, 95% CI: 2.27–4.26). A 2024 Cochrane systematic review[26] further reinforced this association, demonstrating that diabetes possibly increases the risk of developing TB disease overall (low certainty), probably increases the risk in the short term (<10 years; moderate certainty), and may increase the risk in the long term (≥10 years; low certainty), with hazard ratios ranging from 1.52 to 2.44. A 2025 review on immune dysregulation of diabetes in tuberculosis,[27] reported that diabetes mellitus increases TB disease risk by 1.5- to 3.5-fold, with 75% of the global DM burden concentrated in low- and middle-income countries where TB remains endemic. Importantly, our study offers methodological advantages in sample size and research design compared to previous investigations, as we specifically focused on the CNS-TB subgroup among extrapulmonary tuberculosis patients and conducted age-stratified analysis, revealing an age-dependent effect that has received limited attention in previous literature.

Mechanistically, diabetes promotes CNS-TB development through multiple pathways. Elevated blood glucose concentrations resulting from insulin resistance or decreased insulin production provide a conducive environment for bacterial growth, thereby increasing susceptibility to intracranial infection.[25] Hyperglycemia exerts profound immunosuppressive effects through multiple mechanisms, including impaired cytokine production, defective leukocyte recruitment, compromised pathogen recognition, dysfunction of macrophages and natural killer cells, as well as inhibited complement activation with consequent antibody suppression.[14,28] Under hyperglycemic conditions, the blood-brain barrier (BBB) undergoes pathological structural alterations characterized by compromised barrier integrity and enhanced vascular permeability, thereby facilitating the infiltration of infectious pathogens, particularly *Mycobacterium tuberculosis*, and subsequent initiation of tuberculous meningitis.[14,29] Hyperglycemia induces oxidative stress, inflammatory response, and Advanced glycation end products accumulation, leading to increased BBB permeability and dysfunction.[29]

Our age-stratified analysis revealed that the association between diabetes and CNS-TB risk demonstrates significant age dependence, with no statistically significant association detected in the ≤40 years age group (OR=1.52, 95% CI: 0.47–4.94, *P*=0.506), but significant associations in the 41–60 years (OR=2.80, 95% CI: 1.40–5.63, *P*=0.003) and >60 years groups (OR=2.22, 95% CI: 1.20–4.13, *P*=0.010). Age-adjusted analysis confirmed that diabetes mellitus is an independent risk factor for CNS-TB (overall aOR=2.30, *P*<0.001). The association appeared stronger in middle-aged and older groups (aOR=2.72 and 2.28) compared to the ≤40 years group (aOR=1.54). Notably, the small number of diabetic patients in the youngest subgroup (n=15) limited the precision of the effect estimate, as reflected in its wide confidence interval (95% CI: 0.47–5.07). This indicates substantial uncertainty, meaning our data can neither confirm nor rule out an association in this age stratum. This imprecision, stemming from the limited number of diabetic patients (n=15) in the youngest stratum, reduced the statistical power to detect heterogeneity across age groups. Consequently, although a trend of increasing ORs with age was observed (aOR: 1.54 → 2.72 → 2.28), the Breslow-Day test for heterogeneity did not reach statistical significance (*P*=0.669). This non-significant heterogeneity test should be interpreted with caution, as it may reflect insufficient power rather than true homogeneity of effects. Larger studies with adequate representation across all age groups are needed to definitively establish whether age modifies the association between DM and CNS-TB risk.

These findings are consistent with results from van Veen et al[30] who demonstrated that diabetes is a strong independent risk factor for mortality in adult bacterial meningitis, with this risk being more pronounced in individuals over 40 years of age. Although our study differs, which primarily focused on tuberculous meningitis rather than general bacterial meningitis, both studies highlight the modulating effect of age on infection risk. Previous studies have similarly indicated that advanced age constitutes a risk factor for disseminated extrapulmonary tuberculosis.[31,32]

The biological plausibility of this age-dependent effect can be explained by immunosenescence—the progressive deterioration of immune system function with advancing age.[33] Immunosenescence is characterized by diminished innate and adaptive immune responses, thereby increasing susceptibility to bacterial infections.[34] In elderly patients with diabetes, the combined burden of metabolic dysregulation and age-related immune decline creates a synergistic vulnerability to CNS-TB. This dual impairment—hyperglycemia-induced immune dysfunction superimposed on immunosenescence—provides a mechanistic explanation for the substantially elevated CNS-TB risk observed in diabetic individuals over 40 years of age in our study. Furthermore, older diabetic patients often have longer disease duration, potentially greater accumulation of microvascular complications affecting cerebral perfusion, and higher prevalence of other comorbidities, collectively contributing to the heightened susceptibility to CNS-TB.

NLR, as a biomarker for assessing systemic inflammatory status, has demonstrated important predictive value in various infectious diseases, including tuberculosis.[35,36] Our study identified NLR as an independent risk factor for CNS-TB, with each unit increase associated with a 5.1% elevation in CNS-TB risk, demonstrating a dose-dependent relationship between systemic inflammatory burden and CNS-TB susceptibility. This finding corroborates results from Guo et al[37] who observed that elevated NLR was significantly associated with early neurological deterioration and poor outcomes in patients with tuberculous meningitis. A recent prospective study involving 148 confirmed TBM cases found that while cerebrospinal fluid NLR showed no significant correlation with TBM severity, serum NLR demonstrated a significant positive correlation with disease severity, reinforcing the clinical utility of systemic rather than local NLR measurements in TBM prognostication.[38] As a systemic inflammation biomarker, NLR integrates responses from both innate and adaptive immune systems.[35,39] In CNS-TB pathogenesis, hyperactivated neutrophils directly compromise blood-brain barrier integrity by releasing inflammatory mediators such as matrix metalloproteinases (MMPs) and tumor necrosis factor-α (TNF-α), facilitating hematogenous dissemination of Mycobacterium tuberculosis to the central nervous system.[40] Lymphocytopenia reduces Mycobacterium tuberculosis clearance capacity, thereby increasing CNS-TB risk,[41] which aligns with our finding that decreased $CD3^+$ T lymphocyte count represents an independent risk factor for CNS-TB. Consequently, elevated NLR not only reflects an imbalance between neutrophil-dominated pro-inflammatory states and lymphocyte-mediated protective immune function but also constitutes a key pathophysiological mechanism in CNS-TB development, emerging as an independent predictor of CNS-TB occurrence.[37]

The combined effects analysis demonstrated a progressive risk escalation across risk factor combinations. Patients with concomitant diabetes and elevated NLR (above the median of 4.194) exhibited the highest disease susceptibility, with an adjusted OR of 4.833 (95% CI: 2.737–8.535, $P<0.001$) and a proportion rate of 38.4%, suggesting an additive effect between these two risk determinants.

From an epidemiological perspective, the distinction between independent additive effects and synergistic interaction has critical implications for pathogenesis understanding and intervention design. Our analysis revealed that diabetes and NLR exert independent additive effects (RERI=0.198, 95% CI: −2.772 to 3.169, $P=0.896$), indicating that these risk factors operate through mechanistically distinct pathways rather than converging on shared biological mechanisms. Diabetes primarily increases CNS-TB susceptibility via hyperglycemia-induced immune dysfunction and blood-brain barrier compromise,[14,25] whereas elevated NLR reflects systemic inflammatory dysregulation and neutrophil-mediated immunopathology.[35,40] This mechanistic independence carries three key clinical implications. First, it validates dual-pathway risk assessment, wherein diabetic status and inflammatory biomarkers must be evaluated as complementary rather than redundant indicators. Second, it suggests that controlling one risk factor will not automatically mitigate risk conferred by the other—contrasting with synergistic scenarios where single-target interventions yield disproportionate benefits. Third, optimal CNS-TB prevention requires parallel management of metabolic and inflammatory pathways through combined glycemic control and anti-inflammatory strategies. Seguel et al[42] documented similar independent additive effects of interferon-γ and lymphocyte stability on tuberculosis risk in wildlife, reinforcing the biological

plausibility that distinct immune and metabolic factors can independently contribute to tuberculosis susceptibility without synergistic amplification.

This study possesses several notable methodological strengths. First, we incorporated a substantial cohort of extrapulmonary tuberculosis patients (n=862), enhancing the statistical power and reliability of our analyses, which facilitated robust evaluation of specific subgroups including CNS-TB. Second, our age-stratified analytical approach (≤40 years, 41–60 years, and >60 years) effectively revealed the age-dependent nature of the diabetes-CNS-TB association, providing valuable insights into differential risk patterns across age cohorts. Third, our analytical strategy extended beyond conventional multivariable logistic regression to include a stratified risk classification scheme that categorized patients into four distinct risk gradient groups (non-diabetes/low NLR, diabetes/low NLR, non-diabetes/high NLR, diabetes/high NLR). This classification framework clearly demarcates progressive risk gradients and identifies the highest-risk population (diabetes with high NLR), offering a practical tool for clinical risk stratification. It merits emphasis that although the present study shares a cohort with our previous study[20] focusing on age-stratified T-lymphocyte immune profiles, it systematically evaluates age-dependent DM effects (>40 years threshold) and combined risk patterns with NLR, providing independent evidence for clinical risk stratification.

Several methodological limitations warrant consideration. First, the single-center design restricted to hospitalized patients may introduce selection bias toward more severe cases, limiting external validity and generalizability to outpatient or community-based settings. Second, our stringent exclusion criteria—particularly the omission of HIV-positive individuals, patients with autoimmune disorders, and those receiving immunosuppressive therapy—substantially limit generalizability to immunocompromised populations, thereby reducing relevance to global TB control strategies in high HIV-TB co-infection burden settings. Third, the absence of detailed diabetes characterization, including glycemic control indicators (glycated hemoglobin), diabetes duration, treatment regimens, and complications, precludes assessment of dose-response relationships and potential surveillance bias wherein diabetic patients may undergo more intensive monitoring leading to higher CNS-TB detection rates. Finally, despite adjustment for key covariates, residual confounding from unmeasured socioeconomic, nutritional, and behavioral factors remains possible in this observational study. Future multicenter prospective cohort studies incorporating comprehensive diabetes phenotyping and broader demographic representation will be essential to substantiate these findings.

## Conclusion

This investigation establishes that diabetes mellitus is independently associated with higher odds of CNS-TB in older patients, while no significant association was observed in younger individuals, suggesting age-dependent vulnerability. Elevated NLR demonstrated an independent association with CNS-TB risk through distinct inflammatory pathophysiological mechanisms. Although risk stratification revealed that diabetic patients with elevated NLR experienced the highest CNS-TB burden, formal interaction analysis detected no significant additive or multiplicative interaction between diabetes and NLR, indicating that diabetes and NLR exert independent additive rather than synergistic effects. These findings provide evidence for developing age-stratified risk assessment frameworks incorporating diabetic status and inflammatory biomarkers to facilitate targeted screening, earlier diagnosis, and personalized management strategies in CNS-TB prevention and control.

## Abbreviations

CNS-TB, central nervous system tuberculosis; NLR, Neutrophil-to-lymphocyte ratio; non-CNS EPTB, non-CNS extrapulmonary tuberculosis; DM, diabetes mellitus; HIV, Human immunodeficiency virus; EPTB, extrapulmonary tuberculosis; Hb, Hemoglobin; ALB, Albumin; BMI, body mass index; PLR, platelet-to-lymphocyte ratio; PTB, pulmonary tuberculosis; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; SI, synergy index; BBB, blood-brain barrier.

## Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

## Ethics Statement

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board/Ethics Committee of Fuzhou Pulmonary Hospital of Fujian Province (approval number: 2018-006[Research]-01). The Institutional Review Board/Ethics Committee of Fuzhou Pulmonary Hospital of Fujian Province waived the requirement for individual informed consent due to the retrospective nature of the study and because all patients had previously provided written consent at admission for their clinical data to be used in future research. All patient data were anonymized and deidentified prior to analysis to ensure confidentiality.

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## Disclosure

The authors report no conflicts of interest in this work.

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