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ORIGINAL RESEARCH

Distinctive Immuno-Inflammatory Pattern in Tuberculous Lymphadenitis: A Retrospective Cohort Study with Propensity Score Matching

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Purpose: Tuberculous lymphadenitis (TBL) represents a common form of extrapulmonary tuberculosis (EPTB), yet its immunological characteristics compared to other EPTB forms remain poorly characterized. We aimed to compare immunological parameters between TBL and non-TBL patients to elucidate site-specific immune phenotypes.

Patients and Methods: We conducted a retrospective single-center study at Fuzhou Pulmonary Hospital, China (April 2018-April 2024). From 1,408 EPTB patients screened, 862 met inclusion criteria after excluding immunocompromised patients, those with incomplete data, or age <18 years. Patients were stratified into TBL (n=337) and non-TBL EPTB (n=525) groups. To mitigate confounding, we implemented 1:1 propensity score matching based on demographic factors (age, sex) and nutritional status (BMI, hemoglobin, albumin), yielding 323 matched pairs. We compared inflammatory markers (neutrophil count, neutrophil-to-lymphocyte ratio [NLR]) and immunological parameters (lymphocyte count and T lymphocyte subsets: CD3+, CD4+, CD8+, CD45+) between groups using Mann–Whitney *U*-tests and Spearman correlation analyses.

Results: In matched cohorts, TBL patients demonstrated markedly higher lymphocyte counts than non-TBL patients (1.27 vs 1.04×10^9/L, $P<0.001$) despite comparable neutrophil counts (4.45 vs 4.49×10^9/L, $P=0.724$), resulting in significantly lower NLR (3.58 vs 4.38, $P=0.001$). T lymphocyte subset analysis revealed substantially elevated absolute counts in TBL patients: CD3+ (1000.00 vs 829.00 cells/μL, $P<0.001$), CD4+ (555.00 vs 474.00 cells/μL, $P=0.007$), CD8+ (372.00 vs 305.00 cells/μL, $P<0.001$), and CD45+ (1393.00 vs 1196.00 cells/μL, $P<0.001$). Lymphocyte counts strongly positively correlated with all T cell subsets (CD3+: $r=0.72$, CD4+: $r=0.72$, CD8+: $r=0.55$; all $P<0.001$), while higher NLR values were associated with lower T cell subset counts.

Conclusion: TBL patients exhibit distinctive immunological characteristics, including lower NLR values and elevated T lymphocyte subset counts compared to other EPTB forms. These findings provide novel insights into site-specific immune responses to Mycobacterium tuberculosis infection, enhancing our understanding of the pathophysiological mechanisms underlying different manifestations of tuberculosis.

Keywords: tuberculous lymphadenitis, extrapulmonary tuberculosis, neutrophil-to-lymphocyte ratio, t lymphocyte subsets, propensity score matching, site-specific immunity

Introduction

Tuberculosis remains a significant global public health challenge, with approximately 10.8 million new cases and 1.25 million deaths reported in 2023.[1] While pulmonary disease is most common, the epidemiological landscape of tuberculosis is undergoing substantial transformation, with extrapulmonary tuberculosis (EPTB) now constituting 15–20% of global tuberculosis cases and showing a persistent growth trajectory.[2,3] In China, this trend is even more pronounced, with EPTB accounting for 24.6% of all tuberculosis cases.[4] Notably, tuberculous lymphadenitis (TBL) represents the most prevalent form of EPTB in China, comprising 15.8% of all EPTB manifestations.[4] This evolving epidemiological pattern, characterized by increasing EPTB prevalence and the predominance of TBL, underscores the clinical imperative for comprehensive investigations into the distinctive pathophysiological mechanisms and immunological characteristics of TBL.

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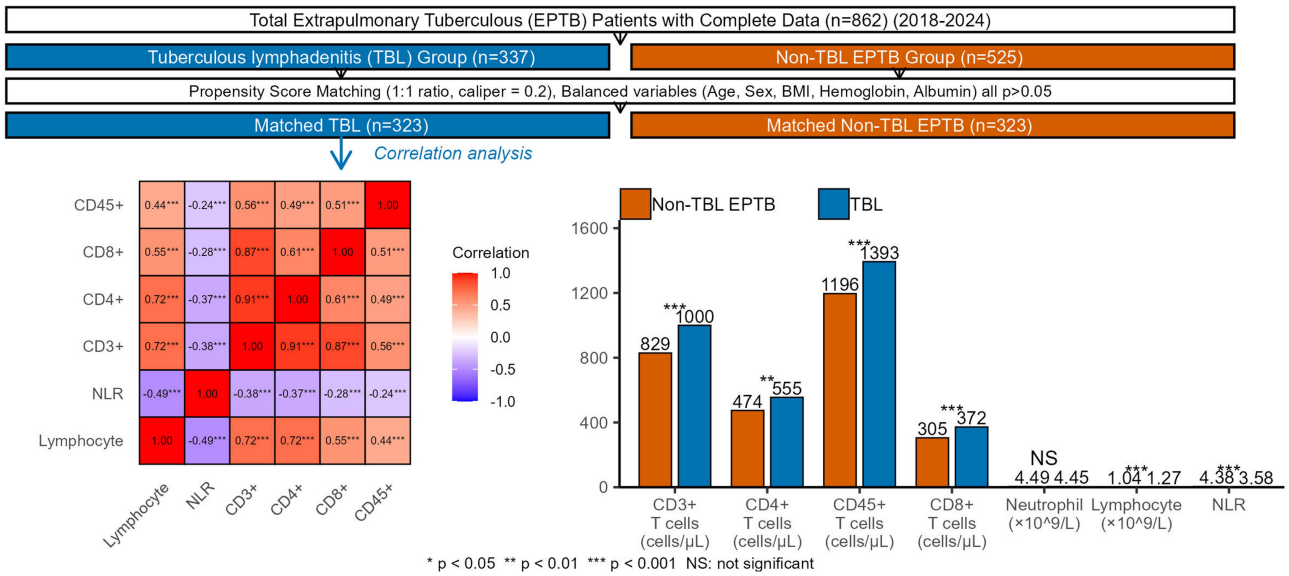
Graphical Abstract



The host immune response plays a critical role in determining tuberculosis disease manifestation and outcome.[5,6] Immune cells and inflammatory biomarkers serve as key mediators in the immunopathological mechanisms of tuberculosis,[7,8] with their quantitative and qualitative alterations potentially reflecting disease-specific patterns. Peripheral blood T lymphocyte analysis provides a crucial window into the immune status of tuberculosis patients, offering invaluable insights for evaluating disease severity, activity, therapeutic efficacy, and prognostic outcomes.[9] CD4+ T cells contribute to anti-tuberculosis immunity primarily through cytokine production, macrophage activation, and regulation of granuloma formation and inflammatory responses.[10–12] Complementarily, CD8+ T lymphocytes exert control over mycobacterial dissemination via cytotoxic effector functions and production of antimicrobial peptides.[12] The neutrophil-to-lymphocyte ratio (NLR), an accessible and well-established marker of systemic inflammatory response, has demonstrated substantial utility in tuberculosis diagnosis, disease activity assessment, and therapeutic monitoring.[8,13,14] These immunological parameters potentially reflect site-specific pathogenic mechanisms and could therefore exhibit distinctive patterns across different anatomical presentations of tuberculosis.

Current scientific literature on T lymphocyte subsets and the NLR has predominantly focused on pulmonary tuberculosis patients. These investigations have elucidated characteristic immunological alterations, including dysregulated T lymphocyte subset distribution and significant perturbations in NLR levels.[9,15] However, despite TBL being one of the most prevalent manifestations of EPTB,[4,6] systematic investigations into the immunological profile of TBL patients remain comparatively limited. Particularly lacking are comprehensive analyses of T lymphocyte subset composition and NLR dynamics in TBL compared to other EPTB forms. Recent studies suggest potentially distinct pathophysiological mechanisms and immune response patterns between different anatomical presentations of tuberculosis.[6,16] For instance, multiple studies have demonstrated distinct cytokine profiles in TBL compared to pulmonary tuberculosis,[17,18] while Hasan et al observed differential expression of cytokines across various EPTB manifestations.[19] These preliminary findings highlight the importance of site-specific immune investigations, as the unique microenvironment of lymph nodes —characterized by organized lymphoid structures and specialized antigen-presenting cells—likely shapes a distinctive immune response against Mycobacterium tuberculosis. Therefore, in-depth characterization of the immunological features specific to TBL holds substantial translational significance for improved understanding of pathogenesis, development of targeted diagnostic approaches, and optimization of therapeutic interventions.

To address this critical knowledge gap, we conducted a large-scale retrospective cohort study involving 862 EPTB patients, comparing immunological profiles between TBL (n=337) and non-TBL EPTB (n=525) patients. Our study uniquely employs propensity score matching methodology to mitigate confounding effects from demographic factors and nutritional parameters, thereby isolating the true immunological differences between these clinical entities. Through systematic assessment of T lymphocyte subset distribution patterns and inflammatory markers, complemented by network correlation analysis among immunological parameters, our research comprehensively characterizes the distinctive immune signature of TBL. We hypothesized that TBL patients would exhibit a unique immunological profile compared to other EPTB forms, reflecting site-specific pathophysiological mechanisms. Our findings illuminate significant differences in the immune microenvironment between TBL and other EPTB manifestations, characterized by a lymphocyte-predominant rather than neutrophil-driven inflammatory pattern. These observations not only enhance our understanding of the immunopathological characteristics of TBL and provide novel perspectives on its pathogenesis, but also establish crucial evidence for developing targeted immunomodulatory approaches and optimizing treatment response evaluation frameworks for this distinct patient population.

Material and Methods

Study Population

This single-center retrospective study was conducted at Fuzhou Pulmonary Hospital of Fujian Province, China, from April 2018 to April 2024. Among 1,408 EPTB patients initially screened, 862 met the eligibility criteria and were included in the final analysis (Figure 1).

EPTB was diagnosed according to WHO guidelines and Chinese national tuberculosis control program technical guidelines,[20,21] based on at least one of the following criteria: (1) bacteriological evidence (positive culture or molecular testing for Mycobacterium tuberculosis from extrapulmonary specimens); (2) histopathological findings consistent with tuberculosis (granulomatous inflammation with or without caseous necrosis); or (3) strong clinical and radiological evidence of active tuberculosis with appropriate response to anti-tuberculosis treatment in cases without bacteriological or histopathological confirmation.For TBL specifically, diagnosis was established based on fine-needle aspiration cytology, excisional biopsy, or molecular testing of lymph node specimens demonstrating evidence of Mycobacterium tuberculosis infection.

Inclusion criteria were: (1) age ≥18 years; (2) confirmed EPTB diagnosis; and (3) complete clinical data availability. Exclusion criteria comprised: (1) immunosuppressive conditions (eg, Human immunodeficiency virus (HIV) infection or long-term immunosuppressant use, n=36); (2) incomplete clinical data (n=464); and (3) age <18 years (n=46).Patients were ultimately categorized into two groups: TBL group (n=337) and non-TBL EPTB group (n=525).

Variables

Study data encompassed baseline demographic characteristics (age, sex), body mass index (BMI), tuberculosis treatment history (initial treatment vs retreatment), pulmonary tuberculosis comorbidity, and laboratory parameters. All laboratory specimens were collected within 24 hours of admission before initiating anti-tuberculosis treatment. Laboratory indicators included: (1) hematological parameters: neutrophil (NEU) count, lymphocyte (LYM) count, NLR, and hemoglobin (Hb); (2) biochemical parameter: serum albumin (ALB); and (3) immunological markers: T lymphocyte subsets (CD3+, CD4+, CD8+, CD45+) counts and percentages, CD3/CD4 ratio.

The laboratory parameters were obtained using the following methods: hematological indices (white blood cell count, absolute neutrophil count, neutrophil percentage, absolute lymphocyte count, and hemoglobin) were measured via an automated hematology analyzer (Mindray BC-6800, China); serum albumin levels were determined via the bromocresol green method; and T lymphocyte subsets (CD3+, CD4+, CD8+, and CD45+) were analyzed via flow cytometry (BD FACSCanto II, USA) from the first blood sample collected after admission. All laboratory tests were performed according to standardized operating procedures, with the initial test results recorded in the hospital information system used for analysis. All clinical data were independently extracted from the electronic medical record system by two trained researchers, with discrepancies resolved through consensus discussion. The clinical dataset was complete for all 862 patients with no missing values.

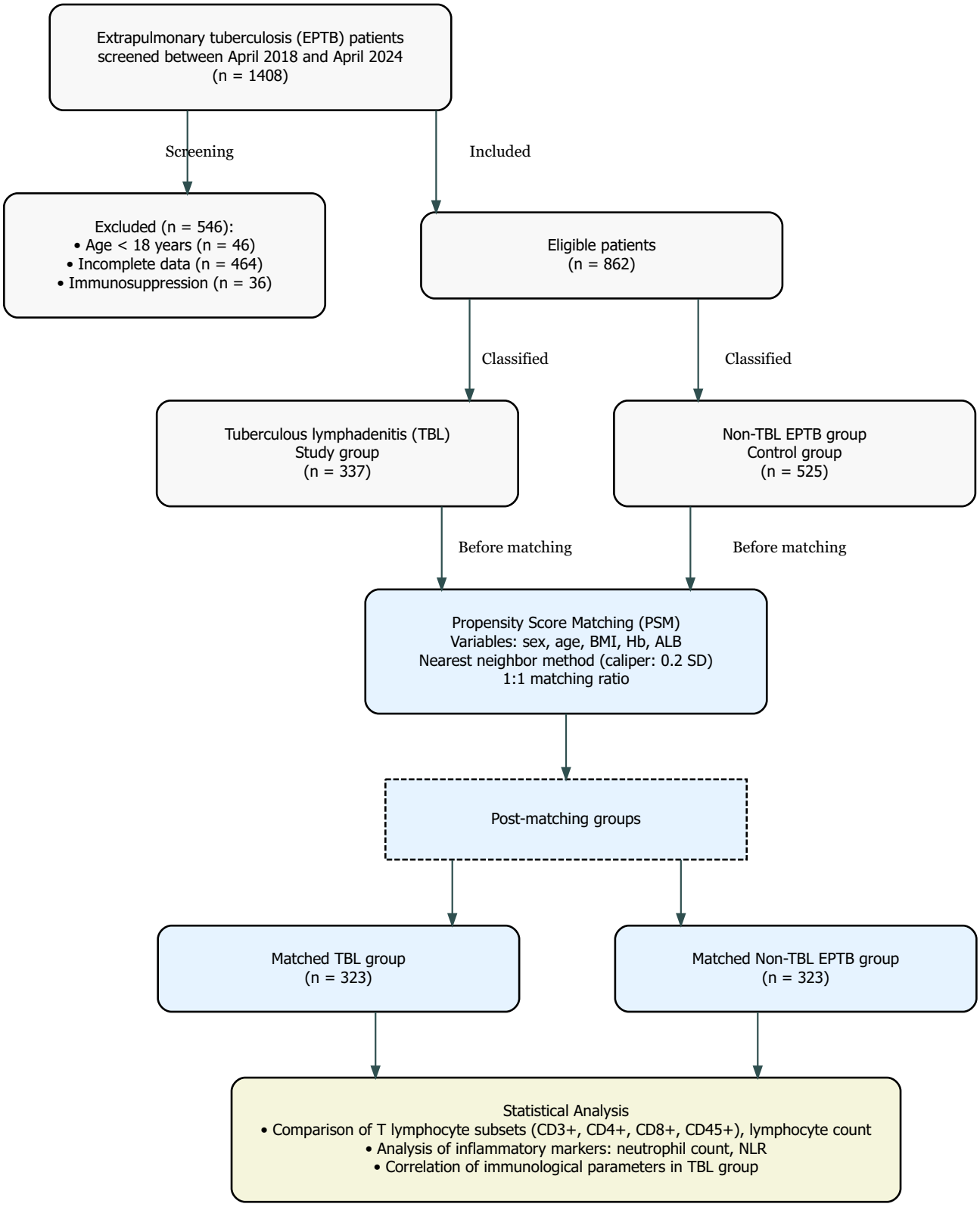


Figure 1 Flow Diagram of Patient Selection and Propensity Score Matching Process.

Statistical Analysis

All statistical analyses were performed using R software (version 4.3.3). As continuous variables demonstrated non-normal distribution by Shapiro–Wilk test, they were presented as median and interquartile range [*M*(*IQR*)], while categorical variables were presented as frequencies and percentages [n(*%*)]. To minimize selection bias and balance baseline characteristics, propensity score matching was implemented using the MatchIt package, with the model including sex, age, BMI, hemoglobin, and albumin. Patients were matched using the nearest neighbor method with a caliper width of 0.2 standard deviations and a 1:1 matching ratio, yielding 323 patients in each group. Balance assessment using standardized mean differences (SMD) and P-values confirmed adequate balance (SMD<0.1 for most covariates). Between-group comparisons employed Wilcoxon rank-sum test for continuous variables and chi-square test or Fisher's exact test for categorical variables. Correlations among immunological parameters were evaluated using Spearman's rank correlation coefficient and visualized with heatmaps. Statistical significance was defined as $P<0.05$ (*$P<0.05$, **$P<0.01$, ***$P<0.001$). The distribution and balance of variables before and after matching were visualized using density plots and Love plots, following STROBE guidelines for reporting observational studies.

Results

Balancing Baseline Characteristics Through Propensity Score Matching

To mitigate selection bias and balance baseline characteristics, propensity score matching (PSM) was employed to achieve a 1:1 ratio between the TBL group (n=337) and non-TBL EPTB group (n=525), yielding 323 patients in each matched group. The propensity score model incorporated sex, age, body mass index (BMI), hemoglobin, and albumin levels. The comparison of baseline characteristics before and after matching is presented in Table 1.

Analysis of Demographic Matching Effectiveness

Propensity score matching successfully balanced demographic characteristics between the groups (Table 1). The median age, which differed significantly before matching (TBL group: 43.00 years vs non-TBL EPTB group: 54.00 years, $W=68740.5$, $P<0.001$, SMD=0.399), was no longer significantly different after matching (44.00 years vs 50.00 years, $W=48432.5$, $P=0.116$, SMD=0.132). Similarly, the gender distribution was imbalanced before matching (female proportion in TBL group: 36.5% vs non-TBL EPTB group: 23.6%, $\chi^2=16.03$, $P<0.001$, SMD=0.284) but achieved balance after matching (33.7% vs 30.0%, $\chi^2=0.86$, $P=0.353$, SMD=0.080). Albumin levels, which were significantly different before matching (37.50 vs 36.00, $W=100480$, $P=0.001$, SMD=0.184), showed no significant difference after matching (37.50 vs 36.50, $W=54936$, $P=0.243$, SMD=0.036). BMI, neutrophil count, and hemoglobin levels showed no significant differences either before or after matching.

Assessment of Propensity Score Distribution and Standardized Mean Differences

The effectiveness of propensity score matching is visually demonstrated by the density distribution plot of propensity scores (Figure 2) and the Love plot of standardized mean differences (Figure 3). Figure 2 illustrates substantial overlap in propensity score distribution between the matched groups, while Figure 3 shows that standardized mean differences for all variables were reduced to acceptable levels after matching, with most variables having SMD<0.1 and only age slightly exceeding this threshold (SMD=0.132) but without statistical significance.

Comparison of Treatment History and Comorbidities

The proportions of tuberculosis treatment history (initial treatment vs retreatment) and pulmonary tuberculosis comorbidity showed no significant differences between the groups, either before or after matching (all P values >0.05) (Table 1).

Persistent Immunological Differences After Matching

Notably, several key immunological parameters remained significantly different between the groups even after adjustment for potential confounders ((Table 1, Figure 4). The TBL group demonstrated significantly higher lymphocyte counts compared to the non-TBL EPTB group (1.27 vs 1.04, $W=64088.5$, $P<0.001$, SMD=0.359), while NLR was significantly lower in the TBL group (3.58 vs 4.38, $W=43968$, $P=0.001$, SMD=0.179).

Table 1 Baseline Characteristics Before and After Propensity Score Matching Between TBL and Non-TBL EPTB Patients

Variable	Before PSM					After PSM				
	TBL (*n* = 337)	Non-TBL EPTB (*n* = 525)	Statistic	*P*	SMD	TBL (*n* = 323)	Non-TBL EPTB (*n* = 323)	Statistic	*P*	SMD
Age, *M* (Q_1, Q_3)	43.00 (29.00, 58.00)	54.00 (36.00, 65.00)	W=68740.5	<0.001	0.399	44.00 (30.00, 58.50)	50.00 (31.00, 62.50)	W=48432.5	0.116	0.132
BMI, *M* (Q_1, Q_3)	19.96 (18.31, 22.31)	19.72 (17.89, 21.89)	W=94931.5	0.070	0.116	19.92 (18.07, 22.25)	19.83 (17.95, 21.92)	W=54433	0.339	0.051
NEU, *M* (Q_1, Q_3)	4.45 (3.25, 6.23)	4.55 (3.44, 6.25)	W=85009.5	0.333	0.015	4.45 (3.29, 6.26)	4.49 (3.49, 6.08)	W=51327	0.724	0.045
LYM, *M* (Q_1, Q_3)	1.27 (0.97, 1.75)	0.99 (0.68, 1.42)	W=113459	<0.001	0.268	1.27 (0.97, 1.75)	1.04 (0.72, 1.46)	W=64088.5	<0.001	0.359
NLR, *M* (Q_1, Q_3)	3.57 (2.14, 5.81)	4.57 (2.80, 8.09)	W=69884	<0.001	0.274	3.58 (2.15, 5.82)	4.38 (2.56, 7.07)	W=43968	0.001	0.179
Hb, *M* (Q_1, Q_3)	118.00 (102.00, 131.00)	118.00 (104.00, 129.00)	W=90365.5	0.594	0.030	119.00 (103.50, 131.00)	119.00 (104.00, 129.50)	W=52341	0.941	0.008
ALB, *M* (Q_1, Q_3)	37.50 (33.30, 40.60)	36.00 (32.30, 39.30)	W=100480	0.001	0.184	37.50 (33.20, 40.50)	36.50 (32.90, 39.90)	W=54936	0.243	0.036
CD3%, *M* (Q_1, Q_3)	71.00 (63.00, 77.00)	72.00 (62.00, 78.00)	W=87322	0.749	0.003	71.00 (63.00, 77.00)	72.00 (62.50, 78.00)	W=50957.5	0.611	0.011
CD3, *M* (Q_1, Q_3)	1002.00 (674.00, 1354.00)	784.00 (517.00, 1115.00)	W=107239	<0.001	0.322	1000.00 (665.00, 1354.50)	829.00 (556.00, 1168.00)	W=60437.5	<0.001	0.227
CD4%, *M* (Q_1, Q_3)	39.00 (33.00, 45.00)	40.00 (33.00, 48.00)	W=83328	0.150	0.004	39.00 (33.00, 45.00)	40.00 (33.00, 47.00)	W=48776.5	0.153	0.012
CD4, *M* (Q_1, Q_3)	555.00 (356.00, 764.00)	450.00 (282.00, 658.00)	W=104090.5	<0.001	0.268	555.00 (354.50, 761.50)	474.00 (306.50, 689.00)	W=58598.5	0.007	0.174
CD8%, *M* (Q_1, Q_3)	27.00 (22.00, 33.00)	26.00 (20.00, 34.00)	W=92742	0.230	0.040	27.00 (22.00, 33.00)	26.00 (20.00, 33.00)	W=54513.5	0.322	0.076
CD8, *M* (Q_1, Q_3)	378.00 (247.00, 551.00)	289.00 (180.00, 438.00)	W=108084	<0.001	0.289	372.00 (245.50, 549.00)	305.00 (189.00, 460.50)	W=61279	<0.001	0.245
CD3/CD4, *M* (Q_1, Q_3)	1.46 (1.05, 1.91)	1.57 (1.06, 2.20)	W=81416	0.048	0.194	1.46 (1.05, 1.92)	1.58 (1.10, 2.20)	W=47546.5	0.052	0.199
CD45, *M* (Q_1, Q_3)	1400.00 (1033.00, 1915.00)	1141.00 (783.00, 1605.00)	W=108074	<0.001	0.212	1393.00 (1024.00, 1928.50)	1196.00 (845.00, 1651.00)	W=60906	<0.001	0.228
Sex, *n* (%)			χ^2=16.03	<0.001				χ^2= 0.86	0.353	
Female	123 (36.5)	124 (23.6)			0.284	109 (33.7%)	97 (30.0%)			0.080
Male	214 (63.5)	401 (76.4)			0.284	214 (66.3%)	217 226 (70.0%)			0.080
Treatment, *n* (%)			χ^2=0.11	0.738				χ^2=0.07	0.788	
Initial Treatment	308 (91.4)	475 (90.5)			0.032	294 (91.0)	291 (90.1)			0.032
Retreatment	29 (8.6)	50 (9.5)			0.032	29 (9.0)	32 (9.9)			0.032
PTB, *n* (%)			χ^2=0.34	0.557				χ^2=0.04	0.847	
No	324 (96.1)	499 (95.1)			0.053	310 (96.0)	308 (95.4)			0.030
Yes	13 (3.9)	26 (4.9)			0.053	13 (4.0)	15 (4.6)			0.030

Notes: Haematological parameters were measured as follows: neutrophil (NEU, $\times 10^9$/L), lymphocyte (LYM, $\times 10^9$/L), NLR, haemoglobin (Hb, g/L), and albumin (ALB, g/L). 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). The CD3+/CD4+ ratio reflects the proportion of total T lymphocytes (CD3+) to helper T cells (CD4+). Percentages are calculated relative to total lymphocyte populations.

Abbreviations: TBL, Tuberculosis of Lymph Nodes; Non-TBL EPTB, Extrapulmonary Tuberculosis other than Lymph Node Tuberculosis.

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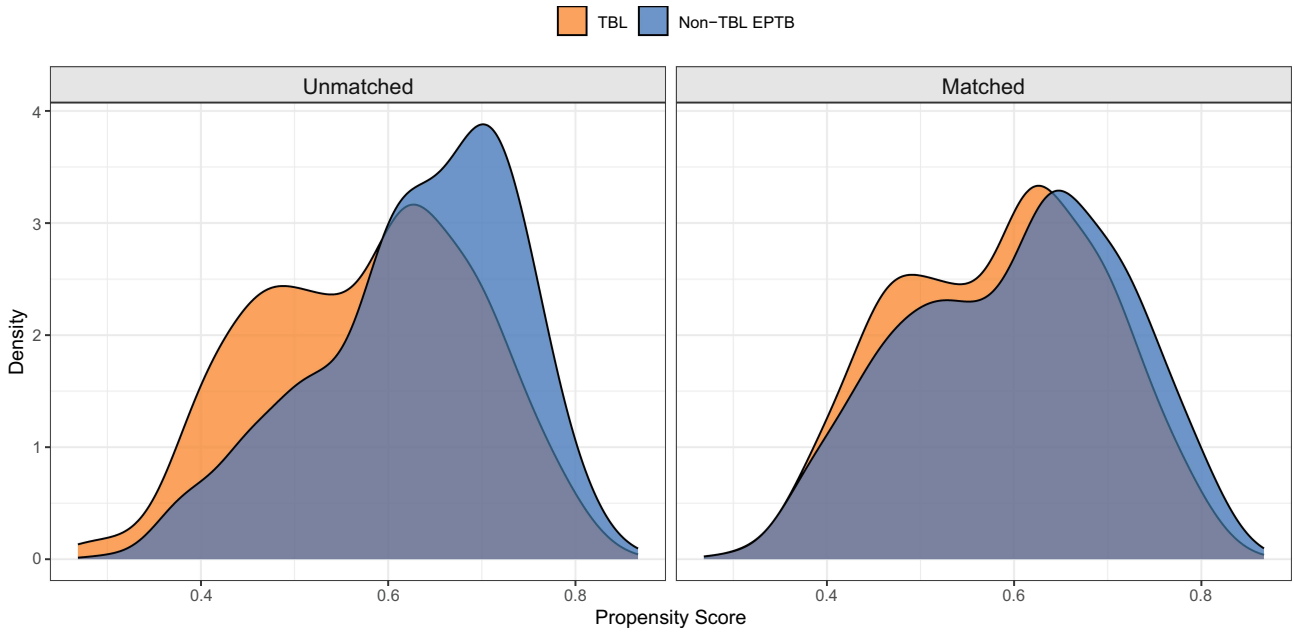

Figure 2 Propensity Score Distribution Density Plots Before and After Matching for TBL and Non-TBL EPTB Patients.

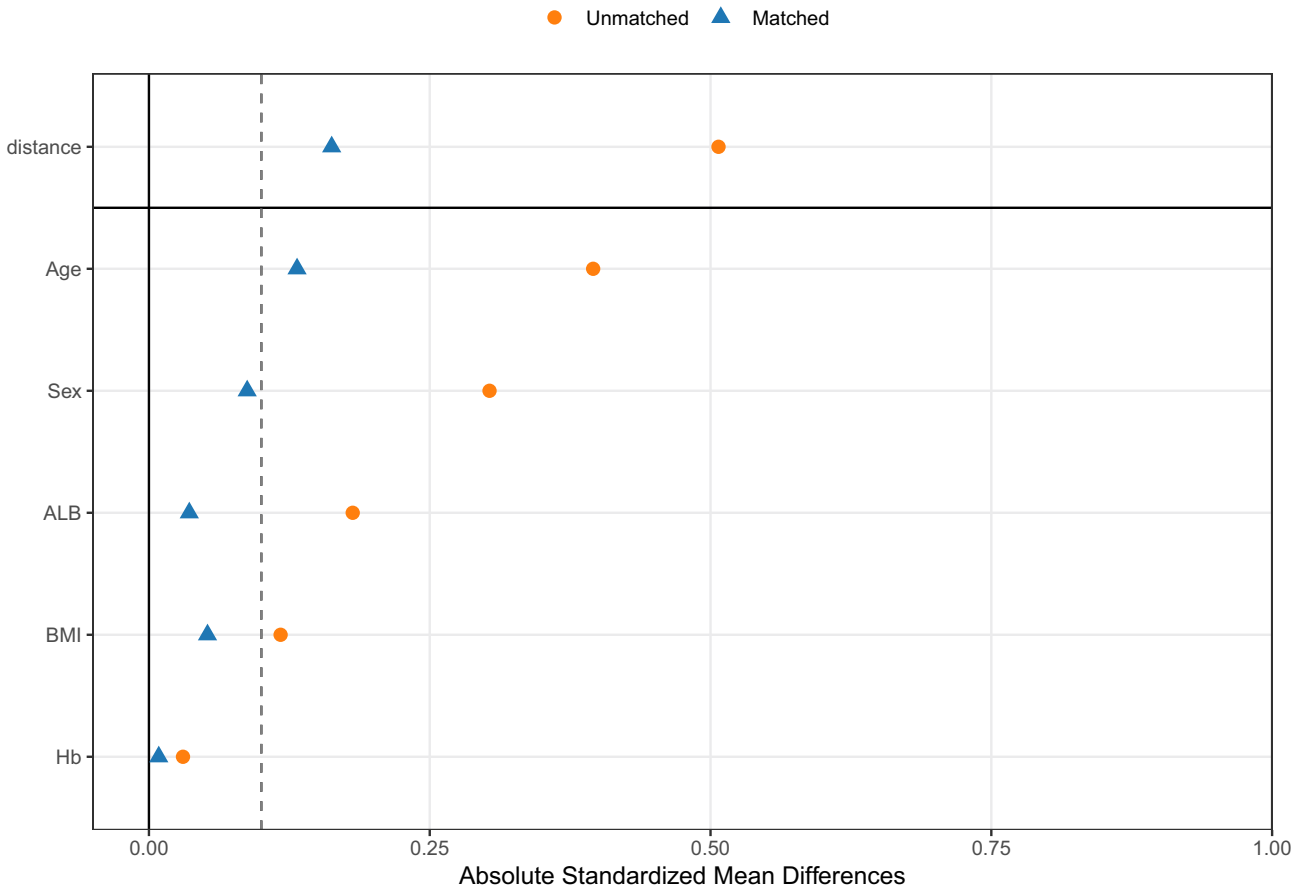

Figure 3 Love Plot of Standardized Mean Differences for Covariates Before and After Propensity Score Matching.

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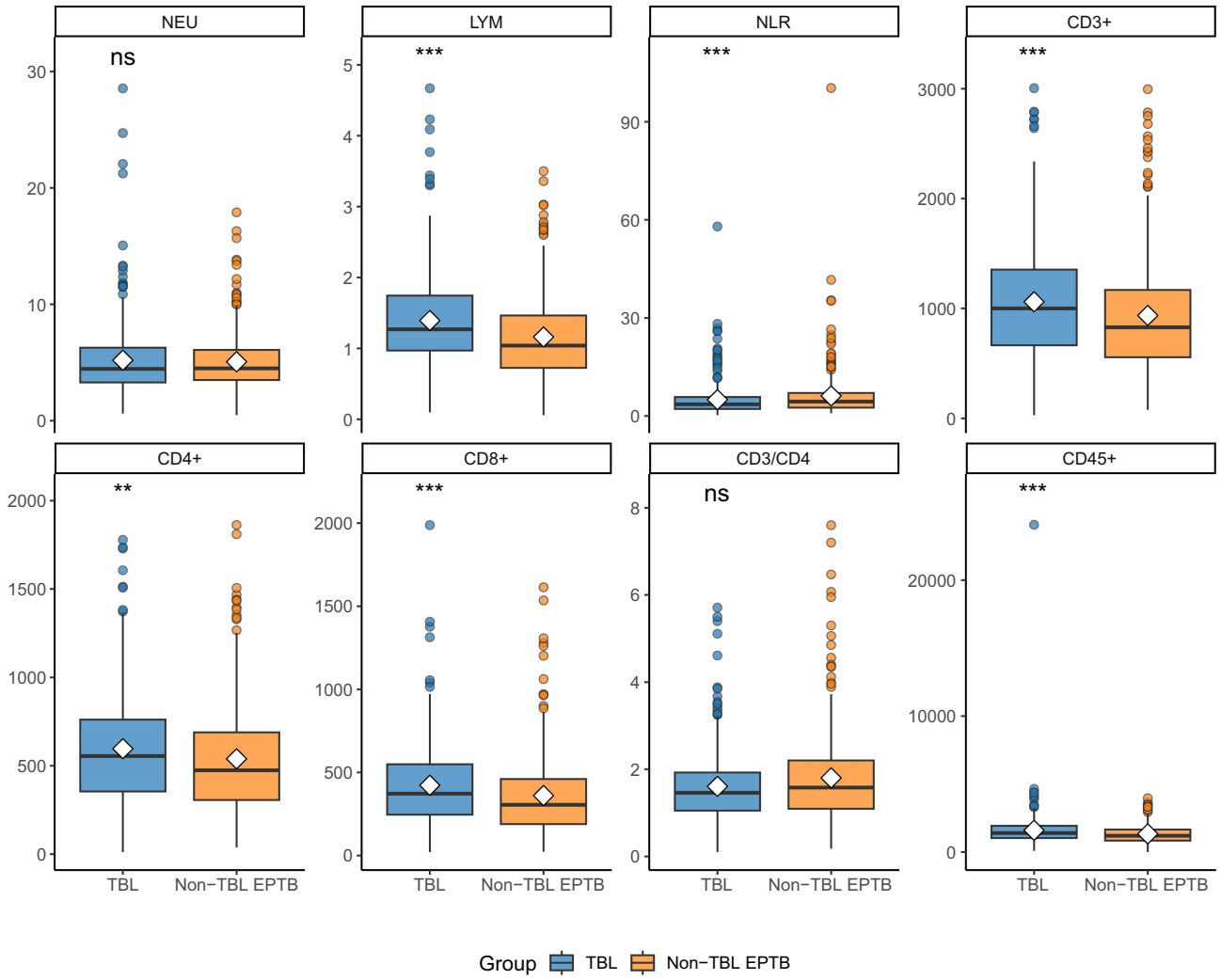

Figure 4 Comparison of Immunological Parameters Between Matched TBL and Non-TBL EPTB Patients.
Notes: 1. Each boxplot displays the median (horizontal line), interquartile range (box), mean (white diamond), and individual data points. 2. Statistical significance was determined using the Mann–Whitney *U*-test: *** p < 0.001, ** p < 0.01, ns = not significant (p ≥ 0.05).

In the analysis of T lymphocyte subsets, although the percentages of CD3, CD4, and CD8 cells showed no significant differences between groups, their absolute counts were significantly elevated in the TBL group. As shown in Figure 4, CD3 counts (1000.00 vs 829.00, W=60437.5, P<0.001, SMD=0.227), CD4 counts (555.00 vs 474.00, W=58598.5, P=0.007, SMD=0.174), CD8 counts (372.00 vs 305.00, W=61279, P<0.001, SMD=0.245), and CD45 counts (1393.00 vs 1196.00, W=60906, P<0.001, SMD=0.228) were all significantly higher in the TBL group compared to the non-TBL EPTB group. The CD3/CD4 ratio, which was significantly different before matching (P=0.048), showed a marginally non-significant difference after matching (1.46 vs 1.58, W=47546.5, P=0.052, SMD=0.199).

Correlation Analysis of Immunological Parameters in TBL Patients

We performed Spearman correlation analysis among lymphocytes, neutrophils, NLR and T lymphocyte subsets in the matched TBL group (n=323) (Figure 5). The correlation heatmap revealed multiple significant associations between immunological parameters.

Lymphocyte count exhibited significant positive correlations with all T lymphocyte subsets, including CD3+ (r=0.72, P<0.001), CD4+ (r=0.72, P<0.001), CD8+ (r=0.55, P<0.001), and CD45+ (r=0.44, P<0.001). NLR demonstrated

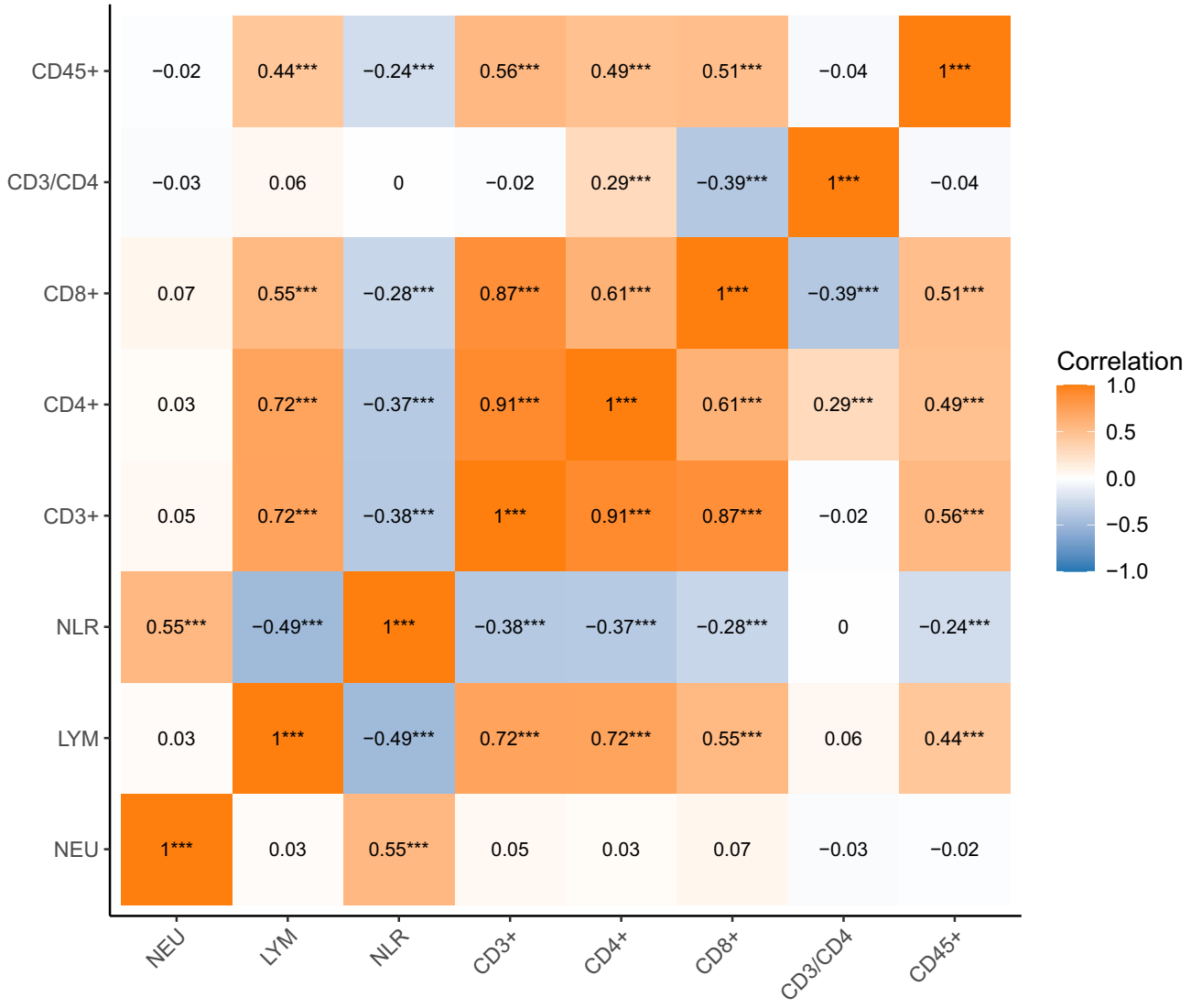

Figure 5 Correlation Heatmap Analysis of Immunological Parameters in TBL Patients.
Notes: 1. The colors represent Spearman correlation coefficients (r); orange indicates a positive correlation, and blue indicates a negative correlation. 2. The scale bar shows correlation coefficient values ranging from −1 to +1. Significance levels: *** (p < 0.001).

significant negative correlations with all T lymphocyte subsets, including CD3+ (r=−0.38, P<0.001), CD4+ (r=−0.37, P<0.001), CD8+ (r=−0.28, P<0.001), and CD45+ (r=−0.24, P<0.001).

Among T lymphocyte subsets, CD3+ cells showed very strong positive correlations with both CD4+ (r=0.91, P<0.001) and CD8+ cells (r=0.87, P<0.001). CD4+ and CD8+ cells demonstrated a substantial positive correlation (r=0.61, P<0.001), while the CD3/CD4 ratio exhibited a weak positive correlation with CD4+ (r=0.29, P<0.01) and a moderate negative correlation with CD8+ (r=−0.39, P<0.001). All these cellular subsets displayed moderate to strong positive correlations with CD45+ cells (r range: 0.49–0.56, all P<0.001).

Neutrophil count showed significant positive correlation only with NLR (r=0.55, P<0.001) and no significant correlations with any T lymphocyte subsets.

Discussion

In this retrospective analysis involving a large cohort of EPTB patients (n=862), we examined the immunological differences between TBL and other forms of EPTB while employing propensity score matching to adjust for demographic and nutritional confounders. Our findings demonstrate that even after balancing baseline characteristics, TBL patients exhibited distinct

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immunological profiles: significantly higher lymphocyte counts compared to the non-TBL EPTB group (1.27 vs 1.04, $P<0.001$), while neutrophil counts showed no significant difference between groups (4.45 vs 4.49, $P=0.724$), resulting in markedly lower NLR (3.58 vs 4.38, $P=0.001$). Additionally, TBL patients demonstrated consistently elevated absolute T lymphocyte subset counts, including CD3+ (1000.00 vs 829.00, $P<0.001$), CD4+ (555.00 vs 474.00, $P=0.007$), CD8+ (372.00 vs 305.00, $P<0.001$), and CD45+ (1393.00 vs 1196.00, $P<0.001$). Correlation heatmap analysis further revealed characteristic interaction patterns among immunological parameters in TBL patients, with neutrophils showing significant positive correlation with NLR ($r=0.55$, $P<0.001$), while lymphocyte counts demonstrated significant negative correlation with NLR (r=−0.49, $P<0.001$). Lymphocyte counts exhibited strong positive correlations with T lymphocyte subsets (CD3+: $r=0.72$, $P<0.001$; CD4+: $r=0.72$, $P<0.001$; CD8+: $r=0.55$, $P<0.001$), while NLR demonstrated significant negative correlations with these cellular subsets (CD3+: $r=-0.38$, $P<0.001$; CD4+: $r=-0.37$, $P<0.001$; CD8+: $r=-0.28$, $P<0.001$). These observations reveal a distinctive immuno-inflammatory signature in TBL that differs from other EPTB forms, characterized by enhanced lymphocytic immune responses rather than neutrophil-driven inflammation. This shift in immune balance likely reflects unique immuno-inflammatory regulatory mechanisms specific to TBL, closely associated with the distinctive microenvironment and localized immune surveillance function of lymph nodes as primary immune organs. The reduction in NLR as a systemic inflammatory marker, coupled with the universal elevation of T lymphocyte subset counts, suggests that TBL patients may exhibit more robust adaptive immune responses alongside relatively attenuated non-specific inflammatory reactions, an immuno-inflammatory pattern that potentially reflects distinctive pathophysiological mechanisms underlying this specific disease entity.

Our findings align with those reported by Kumar et al[22] in a prospective cohort study specifically comparing immunological characteristics between TBL and pulmonary tuberculosis patients. In their investigation of 45 patients (25 with TBL and 20 with pulmonary tuberculosis), Kumar et al observed significantly higher peripheral blood lymphocyte counts in TBL patients compared to the pulmonary tuberculosis group (2049.84 vs 1737.72 cells/mL), with similar trends in CD8+ cell subset levels, which closely corresponds with our observations. Notably, while Kumar's study utilized a smaller sample size and did not control for confounding factors such as nutritional status, our research validated these findings in a substantially larger cohort (n=646) using propensity score matching to adjust for demographic and nutritional parameters, thereby considerably enhancing the reliability of our conclusions. Furthermore, unlike Kumar et al, who used pulmonary tuberculosis as the comparison group, our study is the first to directly compare the immunological profiles of TBL with other forms of EPTB, revealing that even within the broader category of extrapulmonary disease, TBL exhibits a distinctive immunological phenotype. Our study demonstrated significantly elevated peripheral blood T-cell levels in TBL patients compared to those with other forms of EPTB, suggesting complex immunoregulatory mechanisms. Lymph nodes are secondary lymphoid organs that initiate and regulate adaptive immune responses, with their distinctive architecture providing crucial sites for immunological interactions.[23] Following Mycobacterium tuberculosis invasion, dendritic cells (DCs) capture and transport antigens to lymph nodes, where antigen presentation via MHC molecules initiates specific T-cell responses.[24,25] This localised immune response triggers rapid T-cell proliferation within lymph nodes, with activated T cells subsequently entering peripheral circulation through lymphatic drainage, accounting for the elevated levels of CD3+ (1000.00 vs 829.00, $P<0.001$),CD4+ (555.00 vs 474.00, $P=0.007$) and CD8+ (372.00 vs 305.00, $P<0.001$) T cells observed in peripheral blood. Furthermore, following colonization and proliferation within lymph nodes, Mycobacterium tuberculosis induces localized pathological alterations including congestion, edema, and caseous necrosis.[6] However, the inflammatory response remains relatively compartmentalized,[6] as evidenced by significantly lower NLR (3.58 vs 4.38, $P=0.001$), potentially attenuating the development of systemic immunosuppression.Furthermore, Novita et al's recent[26] investigation revealed characteristic expression patterns of chemokines and inflammatory cytokines (including CCR-2, IL-6, and IL-10) in TBL patients—molecules potentially involved in regulating lymphocyte recruitment and proliferation, thereby influencing T cell subset distribution. Our correlation analysis further supports this interpretation, with the negative relationship between NLR and T cell subsets suggesting that the immune response in TBL patients favors adaptive immunity rather than non-specific inflammatory reactions. These findings provide compelling evidence for the development of age- and gender-specific therapeutic approaches in clinical practice, potentially enhancing treatment outcomes through personalised intervention strategies.

This study provides robust evidence for the distinctive immunological profile of TBL compared to other EPTB forms, with significant clinical implications. Through a substantial sample size (n=862) and propensity score matching

methodology controlling for key confounding factors—including demographic characteristics and nutritional status—we established a matched cohort with strong statistical power (n=646). By directly comparing TBL with other EPTB manifestations rather than pulmonary tuberculosis, we address a critical gap in existing literature. Our comprehensive assessment encompassed multiple immunological parameters, from routine blood cell counts to detailed T lymphocyte subsets, with correlation analyses revealing interaction patterns within immune networks. Based on these findings, clinicians should pay particular attention to immunological status changes in TBL patients, especially the dynamics of T cell-mediated adaptive immune responses, which may aid in evaluating therapeutic efficacy and prognosis. Furthermore, identifying site-specific immunological signatures of tuberculosis establishes a foundation for developing targeted immunomodulatory strategies with potential to improve treatment outcomes.

Despite these strengths, several limitations warrant consideration. As a single-center investigation, the generalizability of our findings requires validation through multicenter studies. The observational design establishes associations rather than causality, and despite controlling for numerous measurable confounders, the influence of unmeasurable confounding factors cannot be excluded. Additionally, this study excluded HIV-positive individuals; considering that HIV infection significantly alters host immune responses, our findings should not be directly applied to HIV/TB co-infected populations. Moreover, our cohort was restricted to adult patients (≥18 years), precluding the extrapolation of these findings to pediatric populations with TBL, whose immune systems may exhibit fundamentally different responses to mycobacterial infection. Future research directions include exploring associations between these immunological parameters and treatment response or prognosis, investigating correlations between immunological phenotypes and lesion severity, and elucidating the molecular mechanisms underlying the distinctive immune microenvironment and regulatory networks in TBL.

Conclusion

Through propensity score-matched analysis of a large cohort, this study systematically reveals, for the first time, significant immunological distinctions between TBL and other EPTB forms. TBL patients exhibited lower NLR and elevated T lymphocyte subset counts, reflecting a distinctive lymphocyte-predominant inflammatory pattern. These findings suggest that Mycobacterium tuberculosis induces site-specific host immune responses at different anatomical locations, closely associated with the unique microenvironment of lymph nodes. This study provides novel insights into tuberculosis immunopathological mechanisms and establishes a foundation for developing targeted immunotherapeutic strategies.

Abbreviations

TBL, Tuberculous lymphadenitis; EPTB, extrapulmonary tuberculosis; Non-TBL EPTB, Extrapulmonary Tuberculosis other than Lymph Node Tuberculosis; NLR, Neutrophil-to-lymphocyte ratio; NEU, neutrophil; LYM, lymphocyte; Hb, Hemoglobin; ALB, Albumin; HIV, Human immunodeficiency virus.

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

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