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ORIGINAL RESEARCH

# Clinical Utility of Monocyte-to-Lymphocyte Ratio and Prognostic Nutritional Index in Diagnosing Smear-Negative Pulmonary Tuberculosis with Negative IGRA Results

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**Objective:** To evaluate the diagnostic usefulness of the monocyte-to-lymphocyte ratio (MLR) and the prognostic nutritional index (PNI) in smear-negative pulmonary tuberculosis (SN-PTB) patients with a negative interferon-γ release assay (IGRA) result.

**Methods:** Between January 2021 to December 2024, 548 consecutive patients suspected of having SN-PTB were enrolled at the Second People's Hospital of Fuyang. After exclusion, 276 patients with SN-PTB (SN-PTB group) and 272 with non-tuberculous (Non-TB) pulmonary infection (Non-TB group) were retrospectively analyzed. Laboratory parameters—including albumin (ALB), pre-albumin (PALB), C-reactive protein (CRP), fibrinogen (FIB), IGRA result, T-cell subsets ($CD3^+$, $CD4^+$, $CD8^+$), $CD4^+/CD8^+$ ratio, MLR, and neutrophil-to-lymphocyte ratio (NLR)—were compared between groups. Patients were further stratified by IGRA status (positive vs negative). Receiver-operating characteristic (ROC) curves were constructed to assess the diagnostic performance of individual and combined indices.

**Results:** In the IGRA-negative subgroup (SN-PTB group: n = 25; Non-TB group: n = 184), MLR was significantly higher in the SN-PTB group ($p = 0.008$) and PNI was significantly lower ($p < 0.001$). No significant differences were observed in ALB, FIB, CRP, PALB, or T-cell subsets in this subgroup. The combination of MLR and PNI—using a logistic regression-derived score—achieved the best discriminatory power, with an area under the ROC curve (AUROC) of 0.718 (95% CI: 0.656–0.774), sensitivity of 60.00%, and specificity of 82.38% at the optimal cut-off value.

**Conclusion:** MLR, PNI and their combination offer moderate diagnostic value for SN-PTB when the IGRA result is negative; the combined MLR+PNI index performs better than either marker alone. However, these findings should be interpreted with caution due to the limited sample size in the IGRA-negative subgroup, and further validation in larger cohorts is warranted.

**Keywords:** smear-negative pulmonary tuberculosis, interferon-gamma release assay, MLR, PNI, diagnostic value

## Introduction

Tuberculosis (TB), an infectious disease caused by Mycobacterium tuberculosis, poses a significant threat to global public health. According to the World Health Organization (WHO),[1] TB has reclaimed its position as the world's leading cause of death from a single infectious agent after being temporarily surpassed by coronavirus disease (COVID-19) over the preceding three years. TB now causes nearly twice as many deaths as HIV/AIDS. More than 10 million people continue to develop TB annually, with case numbers rising since 2021. Among patients diagnosed with pulmonary tuberculosis (PTB), a significant subset (approximately 20–50%) exhibit negative sputum acid-fast bacilli (AFB) smears, a condition termed smear-negative pulmonary tuberculosis (SN-PTB).[2–8] Diagnosing SN-PTB remains challenging.[9] The

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diagnostic delay in SN-PTB contributes significantly to ongoing transmission and adverse outcomes. Interferon-gamma release assays (IGRA), which measure T-cell-derived IFN-γ in response to M. tuberculosis-specific antigens, are valuable for detecting M. tuberculosis infection due to their high specificity and independence from BCG vaccination status. However, a critical limitation of IGRA is their inability to differentiate between active TB and latent TB infection (LTBI). Therefore, while IGRA can indicate infection, they cannot directly diagnose active SN-PTB. More critically, a substantial subset of patients with culture-confirmed SN-PTB yield false-negative IGRA results. This creates a distinct and diagnostically challenging subgroup—IGRA-negative SN-PTB patients—who are particularly problematic clinically. These individuals often present with non-specific symptoms and lack reliable microbiological or immunologic confirmation, leading to a high risk of misdiagnosis, prolonged diagnostic delays, postponed treatment initiation, and consequently, worsened prognosis and ongoing community transmission.

IFN-γ is a prominent host biomarker for TB infection and underpins IGRA, which are widely used in TB diagnostics. IGRA serve as important tools for identifying SN-PTB.[10] These assays only require venipuncture and eliminate the need for follow-up visits.[11] However, the occurrence of false-negative IGRA results in active TB—including SN-PTB—is frequently attributed to underlying immunosuppression, anergy, nutritional deficiencies, or early infection, which impair IFN-γ production. Consequently, an "IGRA-negative SN-PTB" cohort is defined by negative smears, delayed culture results, and negative IGRA findings, yet remains clinically infectious. This subgroup represents a critical gap in current diagnostic pathways, as no validated adjunctive biomarkers currently exist to aid in early diagnosis for these patients.

Novel diagnostic strategies for this population must therefore be grounded in the immunopathological features of TB itself. The monocyte-to-lymphocyte ratio (MLR) and prognostic nutritional index (PNI) are promising candidates that reflect the systemic inflammation and nutritional immunodeficiency characteristic of advanced TB.[9] The MLR quantitatively captures the dynamic interplay between innate and adaptive immune responses. Monocytosis, a hallmark of chronic inflammatory states like TB, indicates sustained antigenic stimulation and granulomatous inflammation, while lymphopenia reflects T-cell exhaustion and overall immunosuppression, commonly observed in active disease. Similarly, the PNI, calculated from serum albumin and lymphocyte count, serves as a composite marker integrating nutritional status and immune competence. Hypoalbuminemia signifies chronic catabolism and malnutrition, prevalent in consumptive diseases such as TB, while lymphocytopenia further underscores impaired cellular immunity.[12–14] Previous studies have demonstrated the utility of these biomarkers individually in various clinical contexts. For instance, MLR has shown predictive capacity for TB disease in both HIV-infected children and HIV-positive/negative adults, with high sensitivity and specificity.[15,16] Likewise, low PNI values, signifying malnutrition and/or adaptive immune impairment, have been associated with more severe TB manifestations and poorer anti-TB treatment outcomes.[17] Crucially, both indices are derived from inexpensive, routine blood tests, offering near-universal availability without additional cost or delay. Despite their potential, the utility of MLR and PNI, individually or in combination, specifically in the IGRA-negative SN-PTB population remains systematically underexplored.

This study aims to fill this critical knowledge gap by evaluating the diagnostic performance of MLR and PNI in patients with IGRA-negative SN-PTB. By comparing these indices against a control group with non-tuberculous pulmonary infections, we seek to determine their value as affordable and accessible rule-in tools for this diagnostically elusive patient subgroup. Our findings could provide clinicians with a practical adjunct for early intervention, ultimately improving treatment outcomes and interrupting transmission chains.

# Materials and Methods

## Patients

This was a retrospective study conducted over a defined period (January 2021 to December 2024), and all eligible patients during this timeframe were included: a case group of 276 patients with SN-PTB (SN-PTB group) and a control group of 272 patients with non-tuberculous (Non-TB) pulmonary infections (Non-TB group). Due to the exploratory nature of this study and the lack of prior AUROC data for MLR/PNI in the IGRA-negative SN-PTB population, a formal sample size calculation was not performed. All consecutive eligible patients during the study period were included to maximize the available data. The patient enrollment process, including the detailed inclusion and exclusion criteria, is summarized in Figure 1.

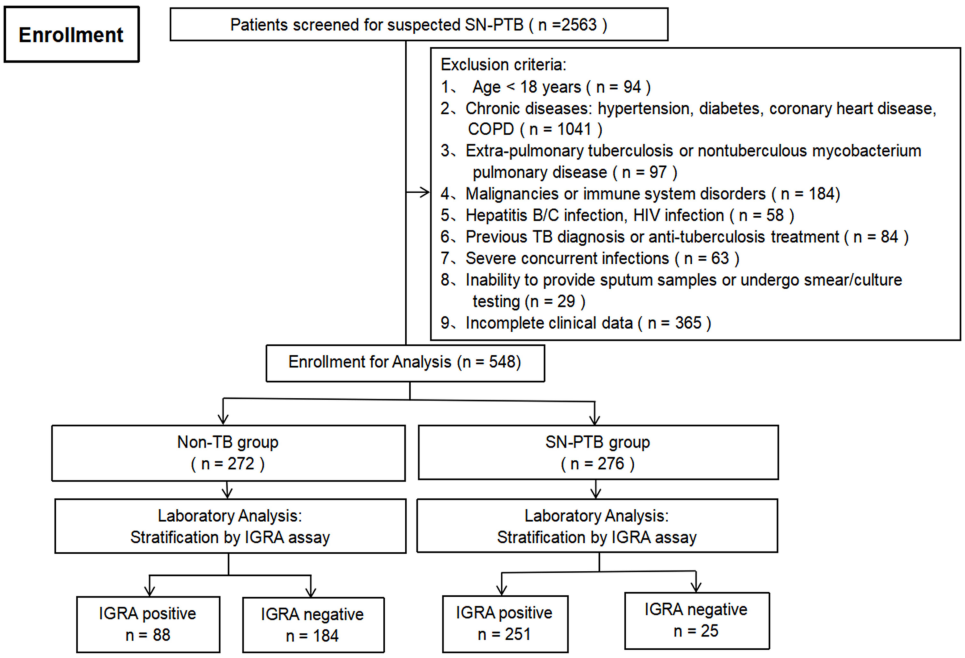


**Figure 1** Flowchart illustrating patient enrollment.
**Abbreviatons**: SN-PTB, smear-negative pulmonary tuberculosis; n, number; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; TB, tuberculosis; Non-TB, non-tuberculous; IGRA, Interferon-gamma release assay.

SN-PTB group: Three consecutive negative sputum smears plus one negative mycobacterial culture. Non-TB group: patients with pulmonary infections caused by pathogens other than Mycobacterium tuberculosis. Diagnostic criteria for SN-PTB: ① Typical TB symptoms and characteristic chest imaging findings, ② Response to anti-tuberculosis therapy, ③ Exclusion of other pulmonary diseases, ④ Strongly positive tuberculin skin test AND positive serum anti-TB antibodies, ⑤ positive sputum PCR/probe for M. tuberculosis, ⑥ Pathological confirmation of TB in extra-pulmonary tissues, ⑦ Acid-fast bacilli in bronchoalveolar lavage fluid, ⑧Histopathological confirmation of TB in bronchial/pulmonary tissues. Diagnosis required: Any 3 of criteria ①–⑥, OR, Criterion ⑦ or ⑧.

## Smear Acid-Fast Bacilli

Direct acid-fast staining of clinical specimens was performed using auramine O fluorescent stain (Baso Diagnostics, Zhuhai, China). When multiple AFB smear microscopy examinations were conducted, a positive result was recorded if ≥1 smear demonstrated acid-fast bacilli.

## Mycobacterium Tuberculosis Culture

Respiratory specimens were inoculated for mycobacterial culture with the automated MGIT 960 system (Becton, Dickinson and Company, USA) and by the modified Roche method. Isolates that demonstrated growth were presumptively identified by their susceptibility to P-nitrobenzoic acid and pyridine-2-carboxylic acid hydrazine.

## Interferon Gamma Release Assay

The IGRA was performed using a commercially available kit following the manufacturer's instructions. In brief, 3–5 mL of venous blood was collected from each participant into lithium heparin tubes. Peripheral blood mononuclear cells (PBMCs) were isolated using density-gradient centrifugation with Ficoll-Paque™. The purified PBMCs were stimulated with M. tuberculosis-specific antigens (ESAT-6 and CFP-10), a positive control (phytohaemagglutinin), and a negative control (culture medium alone). After incubation at 37°C for 16–24 hours under 5% $CO_2$, the concentration of IFN-γ in the supernatant was measured using an enzyme-linked immunosorbent assay (ELISA). A result was considered positive if the IFN-γ level in the antigen-stimulated well was at least twice that of the negative control and exceeded the


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manufacturer-defined cutoff. Results were interpreted as negative if the IFN-γ level did not meet these criteria. Indeterminate results occurred if the positive control failed or the negative control exceeded background levels; in such cases, the test was repeated or supplemented with further clinical evaluation.

## Study Indices

Baseline data including sex, age; laboratory data including albumin (ALB), prealbumin (PALB), C-reactive protein (CRP), Fibrinogen (FIB), IFN-γ, neutrophil count (NE), lymphocyte count (LY), monocyte count (MO), $CD3^+$ T-cells ($CD3^+$), $CD4^+$T-cells ($CD4^+$), $CD8^+$ T-cells ($CD8^+$), and $CD4^+/CD8^+$ ratio ($CD4^+$/ $CD8^+$) were collected. The laboratory data acquisition protocol is as follows: Fasting venous blood samples were collected from patients in the early morning hours.

Serum biochemical parameters, including ALB, PALB and CRP were measured with a HITACHI 7600 automated biochemistry analyzer. FIB levels were measured using the CS5100 (Sysmex, Kobe, Japan) automated coagulation analyzer with its corresponding reagents. Lymphocyte, mononuclear, and neutrophil counts were determined using an XE-2100 hematology analyzer (Sysmex, Kobe, Japan). The counts and percentages of $CD4^+$ and $CD8^+$ T cells were analyzed and recorded using an FC-500-MCL/MPL flow cytometer (Beckman Coulter, USA). Further, NLR, MLR and PNI were calculated using the following formulae. NLR = neutrophils/lymphocytes, MLR = monocytes/lymphocytes, PNI = albumin + 5 × lymphocytes.

## Statistical Analysis

SPSS 23.0 software was used for statistical analysis. Compliance with normal distribution was verified with the Shapiro–Wilk test, and the differences were assessed using Student's *t*-test. For the measurement data that do not conform to the normal distribution, the median and interquartile range were used, and the Mann–Whitney *U*-test was used for inter-group comparison. For categorical values, the chi-squared test method was used. A logistic regression model was employed to generate a combined score based on the MLR and PNI indices for the subsequent Receiver Operating Characteristic (ROC) curve analysis. The predictive value was evaluated using the Receiver Operating Characteristic (ROC) curve analysis. The difference was statistically significant ($p < 0.05$). Bootstrap Sensitivity Analysis: To assess the stability of the Area Under the Receiver Operating Characteristic Curve (AUROC) for the combined biomarker index (MLR+PNI) in the context of the imbalanced IGRA-negative subgroup, a bootstrap sensitivity analysis was performed. This involved generating 5000 bootstrap samples by randomly resampling with replacement from the original IGRA-negative cohort (n=209). The AUROC for the combined index was recalculated for each bootstrap sample to generate a distribution of 5000 AUROC values. The 95% confidence interval (CI) and standard error (SE) were derived from this distribution.

# Results

## Characteristics and Laboratory Parameters of Patients with Smear-Negative Pulmonary Tuberculosis and Non-Tuberculous Pulmonary Infection Patients

Table 1 A total of 548 patients were included in this study, comprising 276 individuals with SN-PTB and 272 with Non-TB. Significant differences were observed between the two groups across multiple baseline and laboratory parameters. Patients in the SN-PTB group were significantly younger than those in the Non-TB group (median age: 49.00 vs 54.00 years, $p = 0.006$). Sex distribution also differed markedly between groups ($\chi^2 = 17.298$, $p < 0.001$). Albumin (ALB) levels were significantly lower in the SN-PTB group (38.98 ± 5.38 g/L vs 40.69 ± 5.15 g/L, $p < 0.001$), whereas IFN-γ levels were substantially higher (median: 211.88 pg/mL vs 1.95 pg/mL, $p < 0.001$). The MLR was significantly elevated in SN-PTB patients (median: 0.36 vs 0.29, $p < 0.001$), while the PNI was significantly reduced (46.83 ± 7.14 vs 50.23 ± 6.40, $p < 0.001$). No statistically significant differences were observed in PALB, CRP, FIB, $CD3^+$, $CD4^+$, $CD8^+$ T-cell counts, $CD4^+/CD8^+$ ratio, or NLR between the two groups ($p > 0.05$).

Based on the serum levels of Interferon-γ, patients with smear-negative pulmonary tuberculosis were divided into IGRA-positive and IGRA-negative smear-negative pulmonary tuberculosis groups; patients with pulmonary infections were divided into IGRA-positive and IGRA-negative pulmonary infection groups. Select the indicators that have statistical significance in the comparison between smear-negative pulmonary tuberculosis and pulmonary infection

**Table 1** Characteristics and Laboratory Parameters of Patients with SN-PTB and Non-TB Patients

| Indicator | SN-PTB Group | Non-TB Group | Statistical Measure | *p*-values |
|---|---|---|---|---|
| Age (years) | 49.00 (30.00, 62.00) | 54.00 (39.00, 63.00) | −2.727 | 0.006^ |
| Sex (m/f) | 191/85 | 141/131 | 17.298 | < 0.001# |
| ALB (g/L) | 38.98 ± 5.38 | 40.69 ± 5.15 | 0.047 | < 0.001* |
| PALB (g/L) | 19.71 ± 6.88 | 20.35 ± 6.59 | 1.188 | 0.263* |
| CRP (mg/L) | 6.15 (1.20, 27.15) | 7.30 (1.80, 25.65) | −0.795 | 0.427^ |
| FIB (g/L) | 3.31 (2.43, 4.73) | 3.62 (2.75, 4.91) | −1.849 | 0.064^ |
| IFN-γ (pg/mL) | 211.88 (60.61, 646.90) | 1.95 (0.58, 28.98) | −15.21 | < 0.001^ |
| $CD3^+$ | 893.71 ± 389.30 | 1058.58 ± 389.42 | 0.004 | 0.052* |
| $CD4^+$ | 514.90 ± 239.30 | 557.23 ± 179.66 | 0.411 | 0.396* |
| $CD8^+$ | 322.00 (206.00, 462.00) | 415.50 (268.00, 554.00) | −1.895 | 0.066^ |
| $CD4^+/CD8^+$ | 1.63 (1.19, 1.95) | 1.34 (0.95, 1.98) | −1.29 | 0.197^ |
| MLR | 0.36 (0.23, 0.57) | 0.29 (0.20, 0.40) | −4.738 | < 0.001^ |
| PNI | 46.83 ± 7.14 | 50.23 ± 6.40 | 6.311 | < 0.001* |
| NLR | 2.47 (1.66, 3.89) | 2.35 (1.53, 3.58) | −1.361 | 0.174^ |

**Notes**: Data on serum ALB, PALB, $CD3^+$, $CD4^+$ and PNI are presented as means ± SD; Data on sex was tested using a chi-square statistic; Data on Age, CRP levels, FIB levels, IFN-γ levels, $CD8^+$, $CD4^+/CD8^+$, MLR and NLR are shown with the median and interquartile range; Data are presented as mean and standard deviation or median and inter-quartile range depending on data type and distribution (statistical tests: *Student's *t*-test, #Chi-square test, ^Mann–Whitney *U*-test); Age, ALB, PALB, CRP, IFN-γ, MLR, PNI, NLR (SN-PTB group: 276, Non-TB group: 272); FIB (SN-PTB group: 183, Non-TB group: 254; $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ (SN-PTB group: 122, Non-TB group: 26). SN-PTB group: Three consecutive negative sputum smears plus one negative mycobacterial culture. Non-TB group: patients with pulmonary infections caused by pathogens other than Mycobacterium tuberculosis.

**Abbreviations**: SN-PTB, smear-negative pulmonary tuberculosis; Non-TB, non-tuberculous; ALB, albumin; PALB, prealbumin; CRP, C-reactive protein; FIB, fibrinogen; IFN-γ, interferon-γ; $CD3^+$, $CD3^+$ T cells; $CD4^+$, $CD4^+$ T cells; $CD8^+$, $CD8^+$ T cells; $CD4^+/CD8^+$, $CD4^+/CD8^+$ ratio; MLR, monocyte to lymphocyte ratio; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio.

patients, Conduct separate comparisons between IGRA-positive smear-negative pulmonary tuberculosis patients and pulmonary infection patients, and between IGRA-negative smear-negative pulmonary tuberculosis patients and pulmonary infection patients.

## Comparison of Indicators Between IGRA-Positive Smear-Negative Pulmonary Tuberculosis Patients and Non-Tuberculous Pulmonary Infection Patients

Table 2 The median age of the smear-negative pulmonary tuberculosis group was 44 years, while that of the pulmonary infection group was 57 years. The age of patients in the smear-negative pulmonary tuberculosis group was significantly lower than that of the pulmonary infection group, and the age difference between the two groups was statistically significant ($Z = -4.631$, $p < 0.001$). There were no statistically significant differences between the two groups in the comparison of ALB, fibrinogen, PNI, and MLR.

## Comparison of Indicators Between IGRA-Negative Smear-Negative Pulmonary Tuberculosis Patients and Non-Tuberculous Pulmonary Infection Patients

Table 3 The MLR level in the smear-negative pulmonary tuberculosis group was significantly higher than that in the pulmonary infection group, with values of 0.39 (0.28, 0.7) and 0.27 (0.2, 0.39), respectively. Statistical analysis showed that the difference between the two groups was statistically significant ($Z = -2.651$, $p = 0.008$). The PNI level in the smear-negative pulmonary tuberculosis group was significantly lower than that in the pulmonary infection group, with values of 46.27 ± 6.55 and 51.42 ± 6.61, respectively. The difference between the two groups was statistically significant ($Z = 0.034$, $p < 0.001$).

**Table 2** Comparison of Indicators Between IGRA-Positive SN-PTB and Non-TB Patients

| Indicator | SN-PTB Group | Non-TB Group | Statistical Measure | *p*-values |
|---|---|---|---|---|
| Age (years) | 44.00 (27.00, 62.00) | 57.00 (47.00, 67.00) | −4.631 | <0.001 |
| ALB (g/L) | 39.31 ± 0.33 | 39.70 ± 0.41 | 5.432 | 0.533 |
| FIB (g/L) | 3.06 (2.33, 4.61) | 3.21 (2.71, 5.22) | −1.643 | 0.100 |
| MLR | 0.34 (0.23, 0.54) | 0.32 (0.22, 0.44) | −1.524 | 0.128 |
| PNI | 47.55 ± 0.44 | 48.14 ± 0.51 | 17.079 | 0.477 |

**Notes**: Data on serum ALB and PNI are presented as means ± SD; data on Age, FIB levels and MLR are shown with the median and interquartile range; Age, ALB, MLR and PNI (SN-PTB group: 251, Non-TB group: 88); FIB (SN-PTB group: 164, Non-TB group group: 83). SN-PTB group: Three consecutive negative sputum smears plus one negative mycobacterial culture. Non-TB group: patients with pulmonary infections caused by pathogens other than Mycobacterium tuberculosis.

**Abbreviations**: SN-PTB, smear-negative pulmonary tuberculosis; Non-TB, non-tuberculous pulmonary infection; ALB, albumin; FIB, fibrinogen; MLR, monocyte to lymphocyte ratio; PNI, prognostic nutritional index.

**Table 3** Comparison of Indicators Between IGRA-Negative SN-PTB and Non-TB Patients

| Indicator | SN-PTB Group | Non-TB Group | Statistical Measure | *p*-values |
|---|---|---|---|---|
| Age (years) | 55.00 (44.00, 59.00) | 50.00 (30.00, 61.00) | −1.717 | 0.086 |
| ALB (g/L) | 39.20 ± 5.02 | 41.37 ± 5.51 | 0.878 | 0.061 |
| FIB (g/L) | 4.15 ± 1.81 | 3.92 ± 1.36 | 1.392 | 0.515 |
| MLR | 0.39 (0.28,0.70) | 0.27 (0.20,0.39) | −2.651 | 0.008 |
| PNI | 46.27 ± 6.55 | 51.42 ± 6.61 | 0.034 | < 0.001 |

**Notes**: Data on serum ALB, FIB and PNI are presented as means ± SD; Date on Age and MLR are shown with the median and interquartile range; Age, ALB, PNI, MLR (SN-PTB group: 25, Non-TB: 184); FIB (SN-PTB group: 19, Non-TB group: 171); SN-PTB group: Three consecutive negative sputum smears plus one negative mycobacterial culture. Non-TB group: patients with pulmonary infections caused by pathogens other than Mycobacterium tuberculosis.

**Abbreviations**: SN-PTB, smear-negative pulmonary tuberculosis; Non-TB, non-tuberculous; ALB, albumin; FIB, fibrinogen; MLR, monocyte to lymphocyte ratio; PNI, prognostic nutritional index.

## Diagnostic Efficacy of Age, ALB, FIB, IFN-γ, MLR, and PNI in Distinguishing Smear-Negative Pulmonary Tuberculosis from Non-Tuberculous Pulmonary Infection Patients

Table 4 The diagnostic performance of various parameters—including Age, ALB, FIB, IFN-γ, MLR, and PNI—in differentiating smear-negative pulmonary tuberculosis from non-tuberculous pulmonary infection was evaluated using receiver operating characteristic (ROC) curve analysis. IFN-γ demonstrated the highest diagnostic accuracy with an area under the ROC curve

**Table 4** Diagnostic Efficacy of Age, ALB, FIB, IFN-γ, MLR, and PNI in Distinguishing Smear-Negative Pulmonary Tuberculosis from Non-Tuberculous Pulmonary Infection Patients

| Value | AUROC | Standard Error | 95% CI | Z Statistic | *p* | Youden Index | Cutoff | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|---|---|---|---|
| Age (years) | 0.548 | 0.0237 | 0.507–0.588 | 2.027 | 0.0426 | 0.1500 | ≤36.00 | 42.33 | 72.67 |
| ALB (g/L) | 0.584 | 0.0232 | 0.543–0.624 | 3.610 | 0.0003 | 0.1467 | ≤39.50 | 52.00 | 62.67 |
| FIB (g/L) | 0.569 | 0.0270 | 0.523–0.613 | 2.542 | 0.0110 | 0.1582 | ≤3.13 | 49.75 | 66.06 |
| IFN-γ (pg/mL) | 0.887 | 0.0138 | 0.859–0.911 | 28.033 | <0.0001 | 0.6633 | >28.98 | 89.00 | 77.33 |
| MLR | 0.610 | 0.0229 | 0.570–0.650 | 4.827 | <0.0001 | 0.1733 | >0.42 | 40.00 | 77.33 |
| PNI | 0.622 | 0.0228 | 0.582–0.661 | 5.352 | <0.0001 | 0.2300 | ≤46.55 | 48.00 | 75.00 |

**Notes**: $p < 0.05$ indicates a statistically significant difference between the groups. SN-PTB group: Three consecutive negative sputum smears plus one negative mycobacterial culture. Non-TB group: patients with pulmonary infections caused by pathogens other than Mycobacterium tuberculosis.

**Abbreviations**: AUROC, area under the ROC curve; 95% CI, 95% confidence interval for AUROC; ALB, albumin; FIB, fibrinogen; IFN-γ, interferon-γ; MLR, monocyte to lymphocyte ratio; PNI, prognostic nutritional index; SN-PTB, smear-negative pulmonary tuberculosis; Non-TB, non-tuberculous.

**Table 5** Differential Diagnostic Efficacy of Age in Discriminating Between IGRA-Positive Smear-Negative Pulmonary Tuberculosis and Non-Tuberculous Pulmonary Infections

| Value | AUROC | Standard Error | 95% CI | Z Statistic | *p* | Youden Index | Cutoff | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|---|---|---|---|
| Age (years) | 0.663 | 0.0295 | 0.611–0.711 | 5.512 | <0.0001 | 0.3547 | ≤36.00 | 44.36 | 91.11 |

**Abbreviation**: 95% CI, 95% confidence interval for AUROC.

(AUROC) of 0.887 (95% CI: 0.859–0.911, $p < 0.0001$). At a cutoff value of >28.98 pg/mL, it yielded a sensitivity of 89.00% and a specificity of 77.33%, with a Youden index of 0.6633. The remaining markers showed modest discriminatory power: Age (AUROC = 0.548, $p = 0.0426$) had a cutoff of ≤36 years, with sensitivity of 42.33% and specificity of 72.67%. ALB (AUROC = 0.584, $p = 0.0003$) at ≤39.5 g/L showed sensitivity of 52.00% and specificity of 62.67%. FIB (AUROC = 0.569, $p = 0.0110$) at ≤3.13 g/L yielded sensitivity of 49.75% and specificity of 66.06%. MLR (AUROC = 0.610, $p < 0.0001$) at >0.42 showed sensitivity of 40% and specificity of 77.33%. PNI (AUROC = 0.622, $p < 0.0001$) at ≤46.55 demonstrated sensitivity of 48.00% and specificity of 75.00%. All AUROC values were statistically significant ($p < 0.05$), indicating that each parameter had significant discriminatory ability, although IFN-γ was clearly superior in distinguishing between the two patient groups.

## The ROC Curve and Diagnostic Efficacy of Age in Distinguishing IGRA-Positive Smear-Negative Pulmonary Tuberculosis from Pulmonary Infection Patients Were Evaluated

Table 5 and Figure 2 The AUROC value for age was 0.663, with a standard error of 0.0295 and a 95% confidence interval ranging from 0.611 to 0.711. The Z-statistic was 5.512, with a corresponding p-value of less than 0.0001, indicating statistical significance. The Youden index was 0.3547, which indicated an optimal cutoff value of ≤36 years. At this cutoff, the sensitivity was 44.36% and the specificity was 91.11%.

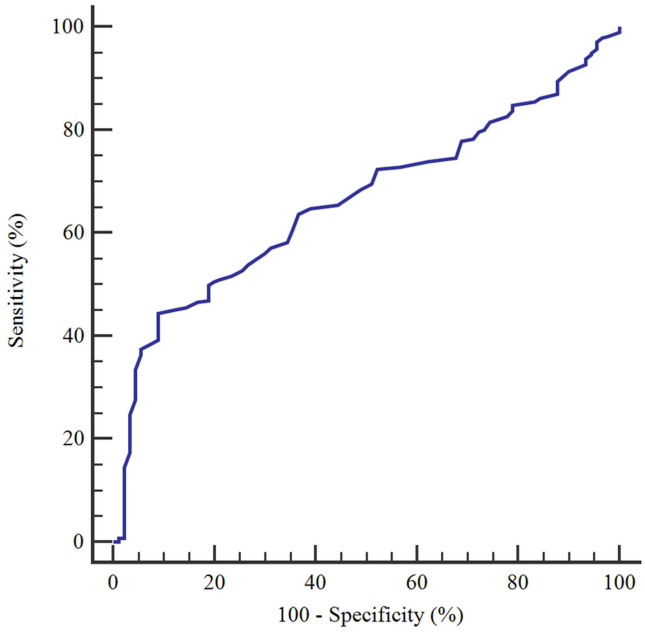


**Figure 2** ROC curves for baseline Age in the comparison of IGRA-positive smear-negative pulmonary tuberculosis and pulmonary infections patients.


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**Table 6** Differential Diagnostic Efficacy of MLR, PNI, and and Combined Test in Discriminating Between IGRA-Negative Smear-Negative Pulmonary Tuberculosis and Non-Tuberculous Pulmonary Infections

| Value | AUROC | Standard Error | 95% CI | Z Statistic | *p* | Youden Index | Cutoff | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|---|---|---|---|
| MLR | 0.662 | 0.0702 | 0.598–0.722 | 2.310 | 0.021 | 0.3257 | >0.350 | 64.00 | 68.57 |
| PNI | 0.713 | 0.0585 | 0.651–0.770 | 3.639 | 0.001 | 0.3810 | ≤46.700 | 60.00 | 78.10 |
| MLR+PNI | 0.718 | 0.0617 | 0.656–0.774 | 3.533 | 0.001 | 0.4238 | >0.139 | 60.00 | 82.38 |

**Abbreviations**: 95% CI, 95% confidence interval for AUROC; MLR, monocyte to lymphocyte ratio; PNI, prognostic nutritional index.

## The Diagnostic Efficacy of MLR, PNI, and the Combined MLR+PNI Index in Evaluating IGRA-Negative Smear-Negative Pulmonary Tuberculosis and Pulmonary Infection Patients

Table 6 and Figure 3 The diagnostic efficacy of the MLR, PNI, and combined MLR+PNI indices in evaluating smear-negative pulmonary tuberculosis and pulmonary infection patients is as follows: MLR Index: The AUC was 0.662, with a 95% CI ranging from 0.598 to 0.722. The Z-statistic was 2.310, and the p-value was 0.021, indicating statistical significance. The Youden index was 0.3257, corresponding to an optimal cutoff value of >0.35. At this cutoff, the sensitivity was 64.00%, and the specificity was 68.57%. PNI Index: The AUC was 0.713, with a 95% CI ranging from 0.651 to 0.770. The Z-statistic was 3.639, and the p-value was 0.001, indicating significant statistical significance. The Youden index was 0.381, corresponding to an optimal cutoff value of ≤46.7. At this cutoff, the sensitivity was 60.00%, and the specificity was 78.10%.

Combined MLR+PNI Index: The AUC was the highest at 0.718 (standard error 0.0617), with a 95% CI ranging from 0.656 to 0.774. The Z-statistic was 3.533, and the p-value was 0.001, indicating significant statistical significance. The Youden index was 0.4238, corresponding to an optimal cutoff value of >0.13867. At this cutoff, the sensitivity was 60.00%, and the specificity was 82.38%.

Bootstrap Analysis of the Combined Index: The bootstrap sensitivity analysis (5000 resamples) performed on the combined MLR+PNI index AUROC estimate of 0.718 yielded a 95% confidence interval of 0.682 to 0.754 with a standard error of 0.018.

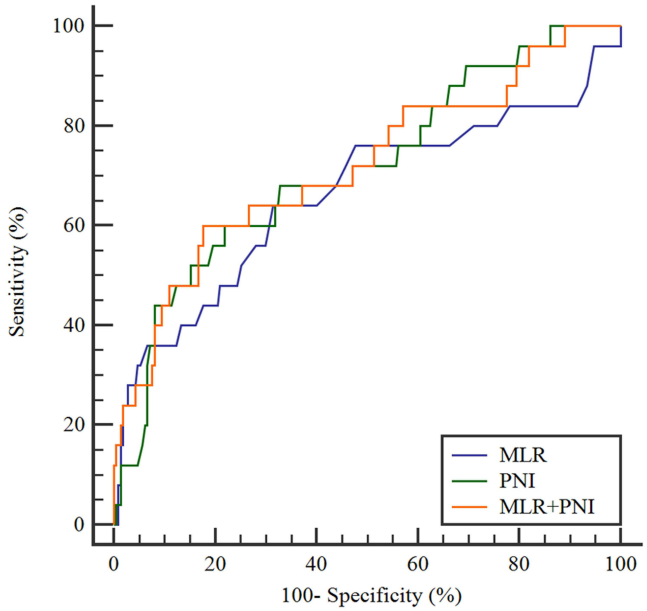


**Figure 3** ROC curves for baseline MLR, PNI and MLR+PNI in the comparison of IGRA-negative smear-negative pulmonary tuberculosis and pulmonary infections patients.

## Discussion

The absence of distinct clinical signs in SN-PTB poses a significant challenge in differentiating it from non-tuberculous pulmonary infections. Diagnosis of SN-PTB often necessitates a comprehensive approach that includes the exclusion of alternative conditions, consideration of non-specific patient history, imaging studies and laboratory findings, leading to considerable complexity in patient management.[18] Tuberculosis, as a chronic consumptive disease, often leads to a decline in nutritional and immune status in the late stages. This decline makes patients prone to secondary bacterial and fungal infections, thereby increasing disease burden and mortality risk.[19] Therefore, early identification of bacterionegative pulmonary tuberculosis can not only improve the prognosis of patients, but also facilitate more standardized management of tuberculosis cases, reduce the risk of transmission, and lower the incidence of tuberculosis.

In the present study, no statistically significant differences were observed in the levels of PALB, CRP, FIB, $CD3^+$ T-cells, $CD4^+$ T-cells, $CD8^+$ T-cells, or the $CD4^+/CD8^+$ ratio between the SN-PTB and Non-TB groups ($p > 0.05$). For instance, Hu Luo et al reported a significantly higher incidence of hypo-prealbuminemia and lower serum prealbumin levels in tuberculosis patients compared to controls.[20] CRP, an acute-phase reactant elevated in conditions like tuberculosis, can be measured via finger-prick blood using point-of-care devices, as shown by Chanda et al.[21] Chai et al showed elevated fibrinogen (FIB) in bacteria-negative pulmonary tuberculosis versus nontuberculous pulmonary infection.[18] Unlike their research, the lack of significant differences in our study may be attributed to population heterogeneity or differences in disease stage. Additionally, the unaltered T-cell profile in our SN-PTB patients could suggest an infection with Mtb strains of attenuated virulence.

The study confirmed that SN-PTB patients were predominantly male ($p < 0.001$), consistent with previous research highlighting the higher incidence of tuberculosis in males.[22,23] However, the finding that the SN-PTB group was younger than the Non-TB group contrasts with Tiamiyu AB's study,[24] which reported no significant age difference. This discrepancy may be due to variations in study populations or methodologies. The elevated MLR in SN-PTB patients ($p < 0.001$) likely reflects monocyte-driven granulomatous inflammation, a key pathological feature of tuberculosis. This aligns with previous studies indicating that MLR could be a potential biomarker for tuberculosis diagnosis and disease activity.[25] The reduced PNI in SN-PTB patients ($p < 0.001$) suggests compromised nutritional status, which is associated with impaired immune function and increased susceptibility to infections. This finding underscores the importance of nutritional assessment and support in the management of SN-PTB patients.[26] In this study, SN-PTB patients exhibited significantly higher IFN-γ levels compared to Non-TB patients. This is plausible given IFN-γ's critical role in activating mononuclear macrophages, which helps control the spread of Mycobacterium tuberculosis. As the sole type II interferon, IFN-γ plays a role in cells' antiviral, antitumor, and immune-regulatory functions. Its receptor's wide distribution reflects its pleiotropic effects in innate and adaptive immunity. Literature highlights that in anti-tuberculosis immunity, IFN-γ activates mononuclear macrophages, promoting their aggregation around lesions to control infection spread, thereby enhancing the body's bactericidal capacity.[27]

The MLR is calculated by dividing the monocyte count by the lymphocyte count, while the PNI is computed using albumin and lymphocyte levels. Both markers have been extensively utilized in various medical fields, including the prognosis assessment of cancer, infectious diseases, and the evaluation of nutritional risks in surgical patients.[28–33] This study demonstrates that "MLR elevation" and "PNI reduction" serve as significant discriminators for SN-PTB in IGRA-negative patients—a subgroup where conventional diagnostics falter. Three key implications emerge from these findings:

1. Pathophysiological Basis of Biomarker Dysregulation

   The elevated MLR reflects systemic immune imbalance characteristic of chronic M. tuberculosis infection. Monocytosis indicates sustained inflammatory responses, while lymphopenia suggests T-cell exhaustion-a hallmark of TB-associated immunosuppression.[34] Concurrently, reduced PNI signifies catabolic deterioration. This finding is consistent with the metabolic burden associated with tuberculosis as reported by Liu Qiuxia et al.[35] The PNI, which combines albumin and lymphocyte levels, is a valuable indicator of nutritional status and immune function. In patients with TB, a lower PNI reflects the catabolic state and nutritional depletion that are common in these patients, which can negatively impact their immune response and disease prognosis. This dual dysregulation

is particularly pronounced in paucibacillary SN-PTB, where pathogen persistence drives chronic immune activation without bacteriological confirmation.

2. Comparative Diagnostic Performance and Literature Comparison

   In the present study, the MLR demonstrated a sensitivity of 64.00%, a specificity of 68.57%, and an area under the receiver operating characteristic curve (AUROC) of 0.662 for discriminating IGRA-negative SN-PTB. This result is consistent with the diagnostic performance of MLR reported in other forms of tuberculosis. For instance, Chen et al reported an AUC of 0.663 for MLR in diagnosing spinal tuberculosis.[36] Similarly, Adane et al reported a higher AUROC of 0.88 for MLR in a broader TB population;[37] the superior performance in their study is likely attributable to the inclusion of a wider spectrum of tuberculosis patients, not confined to the challenging SN-PTB subtype. This pattern suggests that while MLR is a robust biomarker across TB manifestations, its diagnostic power may vary with the patient population studied. The study by Buttle et al reported that an elevated MLR was associated with low serum albumin levels in tuberculosis patients,[38] providing a plausible pathophysiological link between the inflammatory signal (MLR) and the nutritional component (albumin) of the PNI, thereby explaining their concurrent dysregulation in our cohort.

   Regarding the PNI, our study found an AUROC of 0.713 for identifying IGRA-negative SN-PTB. This value is closely aligned with the AUC of 0.764 reported for PNI in predicting adverse outcomes in patients with thoracolumbar tuberculosis,[39] indicating a consistent performance of this index across different forms and clinical contexts of tuberculosis. The AUROC values for both MLR and PNI observed in our study fall within the ranges reported in previous research involving patients with culture-confirmed tuberculosis, underscoring the generalizability of our findings.

3. Clinical Utility in Diagnostic Pathways

   The combined MLR+PNI index (AUROC=0.718) shows promise in diagnosing IGRA-negative patients with suspected SN-PTB. In resource-limited settings without advanced tests like Xpert MTB/RIF, a positive index result (0.139, specificity 82.38%) can support initiating empirical anti-TB treatment, minimizing over-treatment of non-TB pneumonias. However, its moderate sensitivity (60.00%) means a negative result does not rule out SN-PTB, Therefore, in high-risk individuals with a negative index result, clinicians should maintain a high index of suspicion and pursue further investigation or close monitoring. We propose integrating the MLR/PNI index as a cost-effective tool into the diagnostic workflow for IGRA-negative suspected SN-PTB patients. In primary care or resource-limited areas, for patients with typical symptoms and radiological features but IGRA-negative, immediate MLR and PNI calculation can guide treatment decisions. A positive index supports anti-TB treatment, while a negative result warrants referral for advanced diagnostics like bronchoscopy or Xpert MTB/RIF. This stratified approach optimizes resource use and improves early management of this challenging patient group, reinforcing the value of composite biomarkers in capturing TB's multifactorial pathogenesis.[40]

# Limitations and Research Implications

## Notable Constraints Include

Sample size imbalance: The IGRA-negative subgroup analysis was notably underpowered (SN-PTB: n=25 vs Non-TB: n=184). This imbalance may affect the robustness of the statistical significance, the generalizability of the findings, and the precision of the optimal cut-off value for the combined index. While the bootstrap sensitivity analysis performed supports the stability of the primary AUROC finding, the small sample size in the SN-PTB group still necessitates caution in interpreting the cut-off value and underscores the need for validation in larger, balanced cohorts. Future studies should validate MLR/PNI cutoffs in prospective cohorts with balanced IGRA-negative samples, especially in high-risk populations (eg, immunocompromised individuals). Integrating longitudinal monitoring of these indices to assess their utility in treatment response prediction would also be valuable.

## Retrospective Design

Potential selection bias in patient enrollment and unmeasured confounders (eg, comorbidities not fully excluded). Incomplete immunophenotyping: Partial data on CD4+/CD8+ subsets limits mechanistic exploration.

### Future Studies Should

Validate MLR/PNI cutoffs in prospective cohorts with balanced IGRA-negative samples, especially in high-risk populations (eg, immunocompromised individuals). Integrate longitudinal monitoring of these indices to assess their utility in treatment response prediction.

## Conclusion

This preliminary study identifies MLR and PNI as promising, low-cost biomarkers that may aid in the diagnosis of SN-PTB, especially when IGRA results are negative. Their combination captures underlying inflammation and nutritional status, offering valuable clinical insight. Nonetheless, our findings require prospective validation in larger cohorts before clinical application can be recommended. Future research should focus on establishing standardized cut-offs and integrating these indices into existing diagnostic pathways to improve patient triage and early treatment initiation.

## Data Sharing Statement

The data sets generated and analyzed in this study can be obtained from the corresponding author upon reasonable request.

## Ethical Approval

This study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki and was approved by the Ethics Committee of the Second People's Hospital of Fuyang City. Due to the retrospective nature of the study, the requirement for informed consent was waived, as authorized by the same ethics committee. All patient data were handled in strict compliance with ethical principles, ensuring confidentiality and anonymity throughout the research process. No personally identifiable information was used during data analysis or in the presentation of the results.

## Author Contributions

All authors have made substantial contributions to the conception and design of the study, the acquisition, analysis, and interpretation of data, and/or the drafting and critical revision of the manuscript. Each author has approved the final version for submission, consented to the choice of journal, and accepts responsibility for the accuracy and integrity of all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest in this work.

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