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*Original Article*

# The diagnostic value of combined detection of microRNA-155, TNF-α and IL-37 for active pulmonary tuberculosis in the elderly

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**Abstract:** Objective: To identify a panel of potential biomarkers consisting of microRNA-155 (miR-155), tumor necrosis factor-alpha (TNF-α), interleukin-37 (IL-37) for the diagnosis of active pulmonary tuberculosis (PTB) infection in elderly patients. Methods: The serum expression of miR-155 and TNF-α in patients was measured by RT-qPCR, and the serum IL-37 level was determined by ELISA. The correlation between their expression and the features of active PTB patients was also analyzed. The AUCs of miR-155, TNF-α and IL-37 in diagnosing active PTB was calculated according to the ROC curves. The sensitivity, specificity and Youden's index of the three biomarkers alone or in combination for the active PTB diagnosis in the elderly were assessed. Results: miR-155, TNF-α, and IL-37 were overexpressed in the sera of elderly patients with active PTB. miR-155, TNF-α and IL-37 serum levels were enhanced in the elderly patients with pulmonary and extrapulmonary TB relative to those with PTB only, and in patients with active TB infection in both lungs compared to those with unilateral lung infection. The AUCs of miR-155, TNF-α and IL-37 for the diagnosis of active PTB were 0.7920, 0.8734 and 0.7398, respectively. The combination of these three improved the sensitivity of the diagnosis (84.78%). Conclusion: miR-155, TNF-α and IL-37 were overexpressed in elderly patients with active PTB. The combined detection of serum miR-155/TNF-α/IL-37 expression has potential to serve as a diagnostic tool for active PTB in the elderly.

**Keywords:** MicroRNA-155, TNF-α, IL-37, active pulmonary tuberculosis, biomarkers

## Introduction

Tuberculosis (TB) induced by *Mycobacterium tuberculosis* contributes to the highest mortality from infectious diseases in the world, causing 1.5 million deaths in 2018 [1]. The lung is the most frequently affected organ in TB infection, with estimated lung involvement of 79 to 87% [2]. The major burden of pulmonary tuberculosis (PTB) is carried by the elderly, men, and clinically diagnosed patients, especially in China [3, 4]. Considering that TB is related to high mortality and morbidity if untreated [5], early diagnosis of PTB is the key to lowering mortality in the elderly.

There are currently no accurate tests available for predicting active TB, and interferon gamma release assays (IGRAs) are applied to screen latent TB infection [6]. Novel diagnostic tools and wider access to diagnosis are indispensable to slowing and eliminating the TB epidemic [7]. Differential expression of microRNAs (miRNAs) has been observed in active TB, indicating their possible application as biomarkers of disease development and the response to anti-TB treatment [8]. miRNAs are short RNAs of 19 to 25 nucleotides in length that modulate post-transcriptional silencing of target genes [9]. *Mycobacterium tuberculosis* often utilizes host miRNAs to potentiate pathogenicity by inhibiting host-mediated antibacterial pathways and modulating inflammation, autophagy, and apoptosis [10]. miR-155 demonstrated a fold change of 1.4 in peripheral blood mononuclear cells from the healthy control group and 3.7 in the active TB group upon *Mycobacterium tuberculosis* purified protein derivative stimulation [11]. However, the accuracy of miRNA-155 levels in pediatric cases of TB was higher than those in adults with TB [12]. Therefore, more diagnostic biomarkers should be added to the panel to

increase the diagnostic accuracy. On the other hand, the performance of new *Mycobacterium tuberculosis*-related cytokine responses, alone or in combination, in enhancing the sensitivity and specificity of immunodiagnostic assays has been investigated [13]. For instance, the IGRA and tumor necrosis factor-alpha (TNF-α) release assay considerably augmented the specificity for active TB (93%, $P = 0.001$) versus the sole IGRA, but not reducing the sensitivity (89%, $P = 0.67$) [14]. Moreover, interleukin-37 (IL-37) exerts a pathological role in TB via the inhibition of the release of pro-inflammatory factors and the stimulation of macrophages skewing to an M2-like phenotype [15]. Therefore, in this study, we assessed the sensitivity and specificity of miR-155, TNF-α, and IL-37 for active TB diagnosis among elderly subjects.

## Materials and methods

### *Ethical statements*

The Ethical Committee of Affiliated Nantong Hospital of Shanghai University (The Sixth People's Hospital of Nantong) (Code: 2022008) approved the protocol of the study. This retrospective study was implemented in compliance with the *Declaration of Helsinki*.

### *Study population*

This retrospective study included 92 elderly patients with active PTB and 86 healthy subjects without known TB risk factors from May 2021 to June 2022. The serum (5 mL) was collected separately from all subjects following the standard procedure of the Sixth People's Hospital of Nantong.

Inclusion criteria for elderly patients with active PTB were: (1) aged ≥ 65 years old; (2) patients with clinical symptoms and chest radiographs and HRCT images indicating TB (with or without extrapulmonary TB); (3) patients with positive sputum or bronchoscopy specimens or positive TB nucleic acid amplification tests; and (4) patients who never received TB treatment or received anti-TB treatment for no more than 14 days. Exclusion criteria: (1) patients who received anti-TB drugs for over two weeks, or (2) patients with no presence of TB indicated by HRCT images. Healthy subjects were the elderly aged ≥ 65 years (not significantly different from the age of the patients included). Who had no TB treatment and no history of exposure to or contact with patients with active PTB.

### *RT-qPCR*

Trizol (Beyotime, Shanghai, China) was utilized for total RNA extraction. TaqMan™ MicroRNA Reverse Transcription Kit (4366596, Thermo Fisher, Waltham, MA, USA) was used for cDNA synthesis from miRNA; Advantage RT-for-PCR Kit (639505, Takara Biotechnology Ltd., Dalian, Liaoning, China) was applied for cDNA synthesis from RNA. TB Green® Premix Ex Taq™aq cDNA synthesis from R and Applied Biosystems 7500 Real-Time PCR System were applied. The miR-155 expression was normalized using U6 as the endogenous control. For TNF-α gene expression analysis, GAPDH was utilized for normalization. The sequences were as follows: miR-155 5'-TGCTAATCGTGATAGGGG-3' (forward), 5'-GAACATGTCTGCGTATCTC-3' (reverse); TNF-α 5'-CTCTTCTGCCTGCTGCACTTTG-3' (forward), 5'-ATGGGCTACAGGCTTGTCACTC-3' (reverse); U6 5'-CTCGCTTCGGCAGCACAT-3' (forward), 5'-TTTGCGTGTCATCCTTGCG-3' (reverse); GAPDH 5'-GTCTCCTCTGACTTCAACAGCG-3' (forward), 5'-ACCACCCTGTTGCTGTAGCCAA-3' (reverse). The data were analyzed using the $2^{-\Delta\Delta Ct}$ method.

### *Determination of levels of IL-37 in the serum*

The concentration of IL-37 in the serum was read at 450 nm with the Human IL-37 ELISA Kit (ab300313, Abcam, Cambridge, UK) as per the manufacturer's recommendations.

### *Data analysis*

Statistical analyses and figure rendering were conducted using GraphPad Prism 8.02 statistical software (GraphPad, San Diego, CA, USA). Data were displayed as mean ± SD, and the comparison between the two groups were analyzed using unpaired *t* test. The receiver operating characteristic (ROC) curves were plotted to appreciate the value of miR-155, TNF-α, and IL-37 in differentiating PTB. The clinical data were compared using Fisher's exact test. Statistical significance was set at $P < 0.05$.

## Results

### *Demographics of the participants*

The demographics of the participants are listed in **Table 1**. Elderly patients with active PTB were enrolled, including 50 males and 42 females (median age of 75 years). There were 86 heal-

**Table 1.** Characteristics of elderly patients with active PTB and healthy controls

| Characteristics | active PTB (n = 92) | Healthy controls (n = 86) | *p* value |
|---|---|---|---|
| Mean age (mean ± SD) | 75.8±4.3 | 76.5±5.4 | 0.3385 |
| Sex | | | |
| Male | 50 | 48 | 0.8809 |
| Female | 42 | 38 | |
| TB site | | | |
| Pulmonary only (%) | 65 (70.65) | NA | |
| Pulmonary and extrapulmonary (%) | 27 (29.35) | NA | |
| Involvement of lung | | | |
| Unilateral (%) | 23 (25.00) | NA | |
| Bilateral (%) | 69 (75.00) | NA | |
| Serum albumin (mg/dL, mean ± SD) | 3.1±0.5 | 4.5±0.2 | < 0.0001 |
| White blood cell count (10^9/L, mean ± SD) | 2.49 ± 0.37 | 5.74 ± 0.82 | < 0.0001 |
| Lymphocyte count (10^9/L, mean ± SD) | 0.75 ± 0.13 | 2.45 ± 0.19 | < 0.0001 |

Note: PTB, Pulmonary Tuberculosis; SD, Standard Deviation; TB, Tuberculosis; NA, Not Applicable. Fisher's exact test was used to test the association between the two categories in the contingency table, and unpaired t test was used for comparison between the two groups.

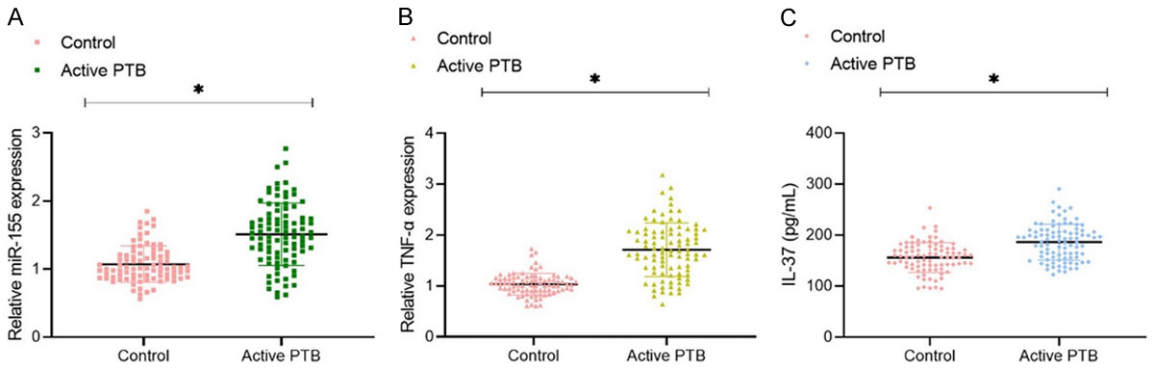


**Figure 1.** Expression of miR-155, TNF-α and IL-37 in the serum of patients with active PTB and healthy subjects. Detection of miR-155 (A) and TNF-α (B) expression in the sera of 128 elderly patients with active PTB and 86 healthy subjects using RT-qPCR. (C) IL-37 expression in the sera of 128 elderly patients with active PTB and 86 healthy subjects using ELISA. Groups were compared by unpaired *t* test. Significant differences are indicated by $*P < 0.05$. PTB, Pulmonary Tuberculosis; miR-155, microRNA-155; TNF-α, Tumor Necrosis Factor-alpha; IL-37, Interleukin-37.

thy subjects with a mean age of 76 years old, including 48 males and 38 females.

*Changes of miR-155, TNF-α and IL-37 in the serum of patients with active PTB*

The expression of miR-155, TNF-α and IL-37 in the sera of 92 elderly patients with active PTB and 86 healthy controls was examined. The serum levels of miR-155 and TNF-α was detected using RT-qPCR, and the results showed that the mRNA expression of miR-155 (**Figure 1A**) and TNF-α (**Figure 1B**) was highly expressed in elderly patients with active PTB. The IL-37 concentration in serum was evaluated by ELISA, and the result showed that IL-37 expression was elevated in elderly patients with active PTB as well (**Figure 1C**).

*Differential miR-155, TNF-α and IL-37 expression patterns were related to the clinical phenotypes of active PTB*

The patients were divided into miR-155 low expression group (n = 46), miR-155 high expression group (n = 46), TNF-α low expression group (n = 48), TNF-α high expression group (n = 44), IL-37 low expression group (n = 44), and IL-37 high expression group (n = 48) on the basis of their respective average expression values (1.512, 1.711, 186.417). The correlation analysis showed that the levels of miR-155, TNF-α

**Table 2.** The correlation between diagnostic marker expression and clinicopathological factors of patients

| Characteristics | N | miR-155 | | *p* value | TNF-α | | *p* value | IL-37 | | *p* value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Low (n = 46) | High (n = 46) | | Low (n = 48) | High (n = 44) | | Low (n = 44) | High (n = 48) | |
| Age | | | | | | | | | | |
| ≤ 75 | 47 | 23 | 24 | > 0.9999 | 26 | 21 | 0.6766 | 22 | 25 | > 0.9999 |
| > 75 | 45 | 23 | 22 | | 22 | 23 | | 22 | 23 | |
| Sex | | | | | | | | | | |
| Male | 50 | 23 | 27 | 0.5305 | 26 | 24 | > 0.9999 | 25 | 25 | 0.68 |
| Female | 42 | 23 | 19 | | 22 | 20 | | 19 | 23 | |
| TB site | | | | | | | | | | |
| Pulmonary only | 65 | 39 | 26 | *0.0055 | 41 | 24 | *0.0014 | 37 | 28 | *0.0110 |
| Pulmonary and extrapulmonary | 27 | 7 | 20 | | 7 | 20 | | 7 | 20 | |
| Involvement of lung | | | | | | | | | | |
| Unilateral | 23 | 17 | 6 | *0.0150 | 18 | 5 | *0.0042 | 16 | 7 | *0.0288 |
| Bilateral | 69 | 29 | 40 | | 30 | 39 | | 28 | 41 | |

Note: miR-155, microRNA-155; TNF-α, Tumor Necrosis Factor-alpha; IL-37, Interleukin-37; TB, Tuberculosis. Fisher's exact test was used to test the association between the two categories in the contingency table, *$P < 0.05$.

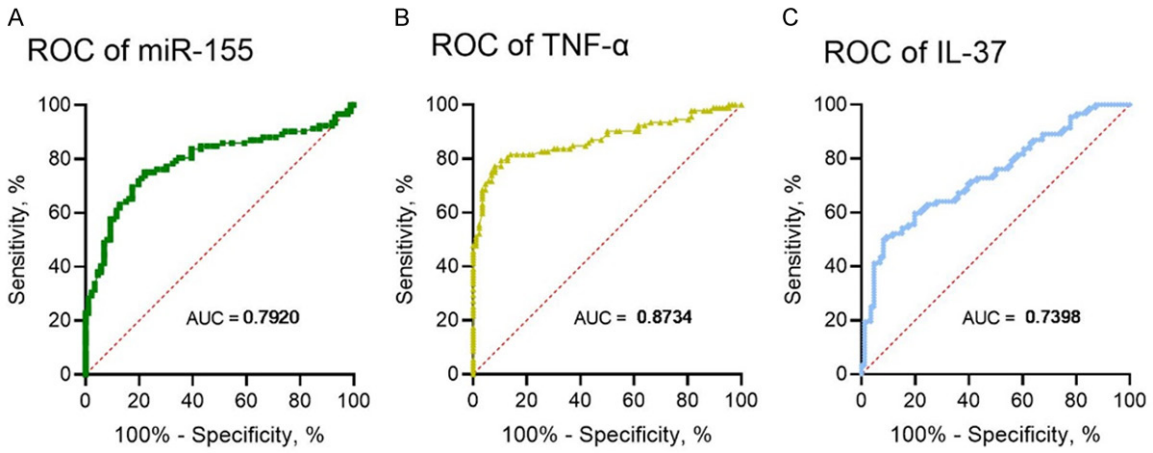


**Figure 2.** Diagnostic value of miR-155, TNF-α and IL-37 in the serum for active PTB. ROC curve analysis of miR-155 (A), TNF-α (B) and IL-37 (C). PTB, Pulmonary Tuberculosis; miR-155, microRNA-155; TNF-α, Tumor Necrosis Factor-alpha; IL-37, Interleukin-37.

and IL-37 were higher in the serum of elderly patients with pulmonary and extrapulmonary TB relative to elderly patients with pulmonary TB only. Serum expression of miR-155, TNF-α and IL-37 markers was higher in elderly patients with active PTB infection in both lungs compared to elderly patients with active PTB infection in one lung. By contrast, miR-155, TNF-α and IL-37 expression was independent of sex and age of these patients (**Table 2**).

*ROC curve of miR-155, TNF-α and IL-37 for the diagnosis of active PTB in the elderly*

The ROC curves demonstrated that the AUCs of miR-155, TNF-α and IL-37 in diagnosing active PTB in the elderly was 0.7920, 0.8734, and 0.7398, respectively (**Figure 2A-C**; **Table 3**).

*Comparison of sensitivity, specificity and Youden's index of three biomarkers alone and in combination*

The sensitivity of the biomarkers in descending order was TNF-α, miR-155, and IL-37. The sensitivity of the combination was 84.78%, while TNF-α ranked the highest regarding the Youden's index (0.69) (**Table 4**).

## Discussion

Commonly used procedures to diagnose TB include clinical manifestation, immunological,

**Table 3.** AUC of miR-155, TNF-α and IL-37 based on the ROC curves

| Test result variable | AUC | Standard error | Asymptotic 95% confidence interval | |
|---|---|---|---|---|
| | | | Lower bound | Upper bound |
| miR-155 | 0.792 | 0.035 | 0.7234 | 0.8606 |
| TNF-α | 0.8734 | 0.02758 | 0.8194 | 0.9275 |
| IL-37 | 0.7398 | 0.03685 | 0.6675 | 0.812 |

Note: miR-155, microRNA-155; TNF-α, Tumor Necrosis Factor-alpha; IL-37, Interleukin-37; ROC, Receiver Operating Characteristic; AUC, Area Under Curve.

**Table 4.** Sensitivity and specificity of miR-155, TNF-α and IL-37 expression in serum alone and in combination

| Test result variable | Optimal cut-off value | Sensitivity (%) | Specificity (%) | Youden's index |
|---|---|---|---|---|
| miR-155 | 1.24 | 75.00 | 77.91 | 0.53 |
| TNF-α | 1.26 | 77.17 | 91.86 | 0.69 |
| IL-37 | 178.7 | 59.78 | 80.23 | 0.40 |
| miR-155 + TNF-α + IL-37 | 1.24 | 84.78 | 55.81 | 0.41 |

Note: miR-155, microRNA-155; TNF-α, Tumor Necrosis Factor-alpha; IL-37, Interleukin-37.

microscopic, and radiographic observation, as well as bacterial culture, and fast and reliable diagnostic methods are still needed for effective TB management [16]. The requirement for novel biomarkers in TB stems from two important features of human *Mycobacterium tuberculosis* infection: its variable history and the indispensable role played by the minority bacillary subpopulations [17].

According to a review summarized by Alipoor *et al.*, miRNA profiles change with *Mycobacterium tuberculosis* infection, and the impact of miRNAs in TB infection is evident [18]. For instance, Kim et al. revealed that miR-199a-3p and miR-6886-3p can discriminate active TB from latent TB infection [19]. Compared with healthy controls, miR-155 expression was enhanced in the serum of elderly patients with active TB in our cohort. Interestingly, the AUC, specificity, and sensitivity of miR-155 in diagnosing periodontitis were 0.887, 78%, and 97.14%, respectively [20]. More specifically, sputum miR-155 may be a new non-invasive biomarker for accurate diagnosis of adult patients with active PTB [21]. The expression of miR-155 was increased significantly in the peripheral blood mononuclear cells of patients with active TB compared with that observed in the peripheral blood mononuclear cells of the healthy individuals [22]. The miR-155 detection in the serum, however, was surprisingly limited. In addition, we analyzed the correlation between miR-155 expression and clinicopathological features of elderly patients with active TB and found that miR-155 overexpression was related to pulmonary and extrapulmonary TB infection and bilateral pulmonary infection relative to pulmonary TB infection only and unilateral infection. A significant upregulation of miR-155 was also identified by Kathirvel *et al.* in children with active TB relative to healthy controls, with an AUC of 0.953 [23]. However, the diagnostic value of miR-155 was not the highest among the three biomarkers identified by Kathirvel *et al*. Therefore, we set out to probe more representative biomarkers.

TNF-α, an imperative cytokine of the immune system, is involved in the prevention and control of TB infection [24]. A critical influencer in containment versus spread of *Mycobacterium tuberculosis* is the character of the T-cell response in response to infection, during which a $CD4^+$ or $CD8^+$ T cell can simultaneously release two or more cytokines [25]. This immune response is dependent on T helper (Th) 1 cytokines, including TNF-α, and Th2 cytokines can inhibit the protective response of Th1, which makes a loop to maintain the normal immune response, thereby killing *Mycobacterium tuberculosis* without pathological damage caused by an excessive immune response [26, 27]. Acharya et *al.* found that TNF-α production from $CD38^+CD27^-CD4^+$ T cells showed the best diagnostic performance at a cutoff of 9.91% (96.15% specificity, 90.16% sensitivity) in TB [28]. In addition, calculation of *Mycobacterium*

*tuberculosis*-specific TNF-α not only differentiated active TB from latent TB infection, but also distinguished active TB from non-TB patients [29]. IL-37, a cytokine in the IL-1 family exerted extensive protective effects against inflammatory diseases, and can repress the levels of pro-inflammatory cytokines in favor to the levels of the anti-inflammatory ones [30]. Consistent with our findings, Wawrocki *et al.* revealed that co-expression of serum IL-18BP and IL-37 was the highest discriminative biomarker for the diagnosis of active PTB [31]. Here, we identified the combination of miR-155, TNF-α and IL-37 showed the highest sensitivity (84.78%) compared to their individual roles. Similarly, miR-155 expression was augmented in patients with rheumatoid arthritis relative to controls ($P < 0.001$) and related to TNF-α ($r = 0.94$, $P < 0.001$) [32].

In summary, as a retrospective study, the miR-155, TNF-α and IL-37 expression profile in the serum of elderly patients with active TB was measured. The impact of miR-155, TNF-α and IL-37 expression on the characteristics of elderly patients with active TB was determined. The role of miR-155, TNF-α and IL-37 expression in the diagnosis of active TB was investigated using the ROC curves. Our study does carry some limitations. First, serum miR-155, TNF-α and IL-37 expression only demonstrated capacity to distinguish elderly patients with active TB from healthy controls. Secondly, other miRNA and cytokine combinations may provide more efficient biomarkers, which warranted further research.

## Disclosure of conflict of interest

None.

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