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The diagnostic value and validation of IL-22 combimed with sCD40L in tuberculosis pleural effusion

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Abstract

Background There is substantial evidence indicating that cytokines play a role in the immune defense against tuberculosis. This study aims to evaluate the levels of various cytokines in pleural effusion to ditinguish between tuberculosis pleurisy and malignant pleurisy.

Methods A total of 82 participants with pleural effusion were included in the training cohort, and 76 participants were included in the validation cohort. The individuals were divided into tuberculosis and malignant pleurisy groups. The concentrations of interleukin-1β (IL-1β), IL-4, IL-6, IL-10, IL-17 A, IL-17 F, IL-21, IL-22, IL-25, IL-31, IL-33, interferon-γ (IFN-γ), soluble CD40 ligand (sCD40L) and tumor necrosis factor-α (TNF-α) in pleural effusion were measured using a multiplex cytokine assay. The threshold values were calculated according to the receiver operating characteristic (ROC) curve analysis to aid in diagnosing tuberculosis pleurisy. Furthermore, the combined measure was validated in the validation cohort.

Results The levels of all 14 cytokines in pleural effusion were significantly higher in participants with tuberculosis compared to those with malignant pleurisy (all $P < 0.05$). The area under the curve (AUC) was ≥ 0.920 for the IL-22, sCD40L, IFN-γ, TNF-α and IL-31, which were significantly increased in tuberculous pleural effusion (TPE) compared to MPE in the training cohort. Threshold values of 95.80 pg/mL for IFN-γ, 41.80 pg/mL for IL-31, and 18.87 pg/mL for IL-22 provided ≥ 90% sensitivity and specificity in distinguishing between tuberculosis pleurisy and malignant pleurisy in the training cohort. Among these, IL-22 combined with sCD40L showed the best sensitivity and specificity (94.0% and 96.9%) for diagnosing tuberculosis pleurisy, and this finding was validated in the validation cohort.

Conclusion We demonstrated that the levels of IL-1β, IL-4, IL-6, IL-10, IL-17 A, IL-17 F, IL-21, IL-22, IL-25, IL-31, IL-33, IFN-γ, sCD40L and TNF-α in pleural effusion had significant difference between tuberculosis pleurisy and malignant

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pleurisy. Specifically, IL-22 ≥ 18.87 pg/mL and sCD40L ≥ 53.08 pg/mL can be clinically utilized as an efficient diagnostic strategy for distinguishing tuberculosis pleurisy from malignant pleurisy.

Keywords Tuberculosis pleural pleurisy, Malignant pleural effusion, IFN-γ, IL-22, sCD40L

Background

Tuberculosis (TB) is a contagious disease and a leading cause of death worldwide among infectious diseases. TB is caused by the bacillus *Mycobacterium tuberculosis* (*M. tb*), which typically affects the lung but can affect other sites. Approximately a quarter of the world's population has been infected with *M.tb* [1]. Tuberculosis pleurisy is one of the most common sites of extrapulmonary TB, with an incidence of up to 30% in TB-endemic areas [2]. TPE and malignant pleural effusion (MPE) can present with similar symptoms such as cough, chest pain, and pleural effusion, making clinical differentiation difficult. The diagnosis of MPE remains a long-term clinical problem due to the low cytological examination detection rate (about 60%). Thoracoscopic biopsy is a high-performance diagnostic method for both TPE and MPE, but its invasiveness limits clinical application [3]. Definitive diagnosis of tuberculosis pleurisy requires histological evidence of caseating granulomas or microbiological evidence of the organism on smear or culture which is time-consuming, though GeneXpert could improve the diagnostic efficiency, it performs poorly in diagnosing TPE [4, 5]. Analyzing biomarkers such as adenosine deaminase (ADA) in pleural effusions can enhance the diagnostic accuracy for tuberculous pleurisy [6]. However, ADA activity may also be elevated in other conditions, such as pulmonary empyema and rheumatoid arthritis [7]. Therefore, identifying novel biomarkers is crucial for improving the diagnosis of tuberculous pleurisy.

Th1 and Th17 cells are the primary effector $CD4^+$ T cells involved in *M.tb* infection. Th1 cells are known to contribute to TB protection by secreting IFN-γ, which activates macrophages and stimulates phagocytosis, phagosome maturation, production of reactive nitrogen intermediates, and antigen presentation [8, 9]. Th17 cells secrete IL-17 and induce the expression of proinflammatory genes such as granulocyte colony-stimulating factor (G-CSF), CXC chemokines, IL-6, which promote neutrophilic inflammation and mediate tissue damage, thus playing a role in TB pathology [8, 10, 11]. Published studies suggest that Th17-related cytokine pathways, including IL-17, IL-21, IL-22, IL-23, may be manipulated by *M.tb* microorganisms for their survival benefits in primary tuberculosis (TB) [12]. It has been demonstrated that cytokines of IL-1β, IL-6, IL-17, IL-31, IL-33, TNF-α and IFN-γ may contribute to more efficient diagnosis strategies in the management of tuberculous pleurisy [13–17]. However, there was no synchronous comparison of the diagnostic value of each cytokine in tuberculous pleurisy.

In this study, we utilized a multiplex immunoassay kit that includes Th1 and Th17-related cytokines, as well as other cytokines. This approach enabled us to simultaneously compare the diagnostic efficacy of these cytokines in identifying TPE and MPE. We evaluated the levels of various cytokines in pleural effusion to determine whether they could discriminate between TPE and MPE, or if a combination of biomarkers could serve as biosignature for TPE.

Results

Characteristics of enrolled participants

In the training cohort, which consisted of 50 participants with TPE and 32 participants with MPE, we aimed to explore the differential expression of IL-1β, IL-4, IL-6, IL-10, IL-17 A, IL-17 F, IL-21, IL-22, IL-25, IL-31, IL-33, IFN-γ, sCD40L and TNF-α. The validation cohort, comprising 51 TPE participants and 25 MPE participants, was used to confirm the results proposed by the training cohort. The clinical characteristics of both cohorts are presented in Table 1. In the training cohort, there was no significant difference in sex (TPE vs. MPE, 74.0% vs. 68.8%, $P=0.606$) or average age (TPE vs. MPE, 47.6 years vs. 64.7 years, $P=0.108$) between tuberculosis pleurisy and malignant pleurisy group. The average age in the validation cohort had a statistical difference between the tuberculous pleurisy and malignant pleurisy group (TPE vs. MPE, 44.2 years vs. 66.5 years, $P=0.001$) but had no significant difference of sex (TPE vs. MPE, 66.7% vs. 48%, $P=0.139$). Eleven (22.0%) participants in the training cohort and fourteen (27.5%) participants in the validation cohort had positive result for *M.tb* on sputum smear or culture.

Pleural effusion levels and ROC curve of different cytokines in the training cohort

The levels of different cytokines in all participants of the training cohort are shown in Fig. 1. The level of IL-6 had the highest concentration but IL-25 had the lowest concentration in tuberculous and malignant pleural effusion. We found that the levels of all cytokines in the tuberculosis pleurisy group were significantly higher than malignant pleurisy group (Table 2). We used ROC curve analysis to determine the optimal cut-off value of each marker that discriminated TPE versus MPE (Fig. 2). The AUC, sensitivity, and specificity of each cytokine are shown in Table 2. The AUC of all cytokines were >0.7,

Table 1 The clinical characteristic of training cohort and validation cohort

	Tuberculous pleurisy ($n=50$)	Malignant pleurisy ($n=32$)	*P* value*
Training cohort			
Male/Female	37/13	22/10	0.623
Age, median (range)	47.6 (12.0–84.0)	64.7 (39.0–89.0)	0.108
Sputum smear or culture positive, n (%)	11 (22.0)	--	--
Validation cohort			
Male/Female	34/17	12/13	0.139
Age, median (range)	44.2 (14.0–87.0)	66.5 (44.0–84.0)	0.001
Sputum smear or culture positive, n (%)	14 (27.5)	--	--

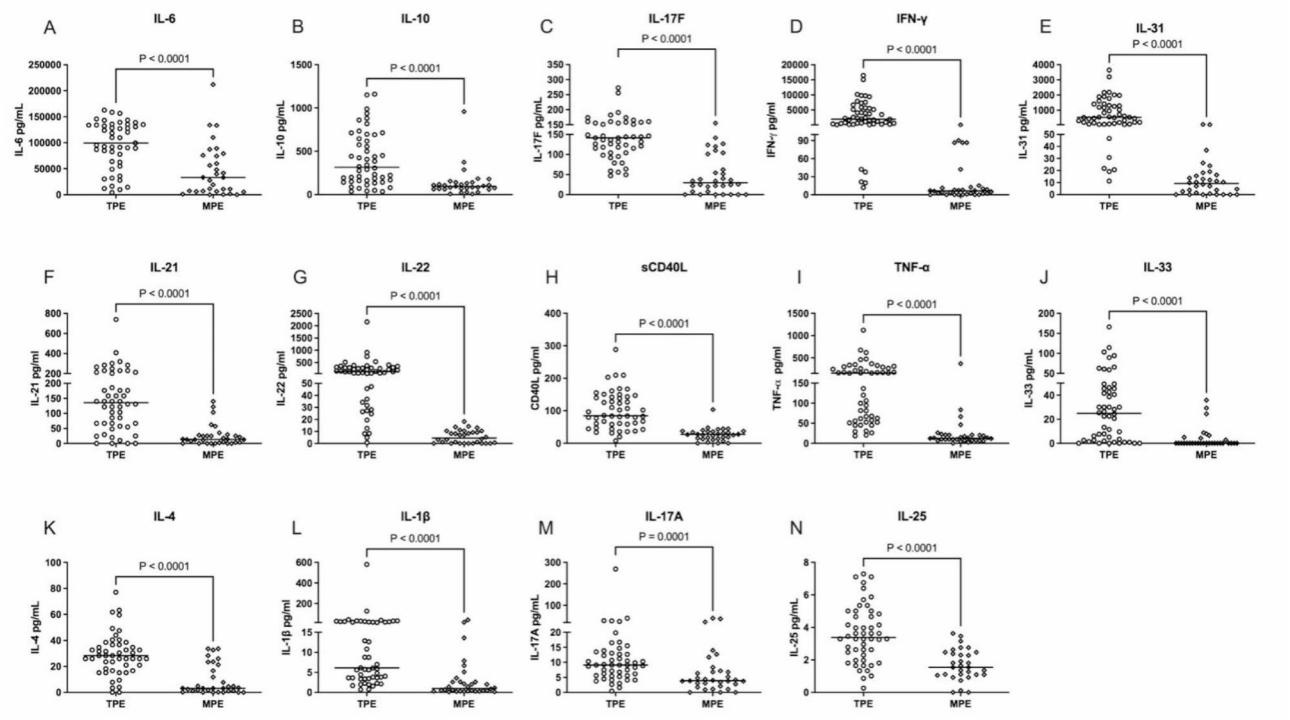

Fig. 1 The levels of IL-6, IL-10, IL-17 F, IFN-γ, IL-31, IL-21, IL-22, sCD40L, TNF-α, IL-33, IL-4, IL-1β, IL-17 A and IL-25 between TPE and MPE in training cohort were measured using a multiplex cytokines assay

with IL-22, sCD40L, IFN-γ, TNF-α, IL-17 F and IL-31 all having an AUC > 0.9. The sensitivity and specificity of IFN-γ, IL-31 and IL-22 were ≥ 90%.

Combined measure of IL-22 with sCD40L, TNF-α, IL-31 and IFN-γ in the training cohort

The AUC for IL-22, sCD40L, TNF-α, IL-31 and IFN-γ was ≥ 0.920, indicating a significant increase in these markers in TPE compared to MPE. These cytokines have proven to be highly effective in distinguishing TPE from MPE. Among them, IL-22 had the highest specificity, leading to diagnosis threshold ≥ 18.87 pg/mL, which was used in combination with sCD40L (53.08 pg/mL), TNF-α (25.96 pg/mL), IL-31 (41.80 pg/mL), and IFN-γ (95.80 pg/mL) (Fig. 3). As summarized in Table 3, IL-22 comnbined with sCD40L had the best sensitivity and specificity (94.0% and 96.9%, respectively). The sensitivity of IL-22 combined with IFN-γ, TNF-α and IL-31 were 92.0%, 98.0% and 94.0%, respectively, and the specificity were 96.9%, 87.5% and 93.8%, respectively.

Diagnostic performance of IL-22 combined with sCD40L in the validation cohort

We found that the combination of IL-22 with sCD40L provided the best sensitivity and specificity in the training cohort. Then we used 76 independent samples as a validation cohort to confirm the accuracy of this test. As shown in Table 4, the AUC for IL-22 and sCD40L were > 0.860 in the validation cohort. In the validation cohort, the median value of IL-22 was higher than in the training cohort (68.31 vs. 27.72 pg/ml), while the median value of sCD40L was lower (38.36 vs. 47.71 pg/ml). Howerer, the

Table 2 Pleural effusion levels and AUC of different cytokines in training cohort

Cytokines	Median (pg/mL)	TPE Median (pg/mL)	MPE Median (pg/mL)	AUC	*P* value	95% CI	Cut-off value (pg/mL)	Sensitivity (%)	Specificity (%)
IL-6	83681.00	99547.00	33268.00	0.793	< 0.001	0.689–0.898	76752.00	72.3	77.4
IFN-γ	258.00	1989.00	6.34	0.979	< 0.001	0.956-1.000	95.80	90.0	96.9
IL-10	165.40	314.00	94.28	0.830	< 0.001	0.735–0.924	141.10	82.0	80.7
IL-17 F	115.50	141.40	29.71	0.902	< 0.001	0.832–0.97	63.02	91.8	75.0
IL-31	84.32	529.40	9.20	0.979	< 0.001	0.957-1.000	41.80	90.0	93.8
IL-21	64.71	135.6	13.52	0.864	< 0.001	0.784–0.945	41.69	82.0	84.4
IL-22	27.72	132.20	4.51	0.959	< 0.001	0.919-1.000	18.87	90.0	100.0
TNF-α	56.66	157.40	12.54	0.938	< 0.001	0.875-1.000	25.96	96.0	87.5
sCD40L	47.71	84.74	27.34	0.921	< 0.001	0.861–0.980	53.08	78.0	96.9
IL-4	22.30	28.25	3.17	0.834	< 0.001	0.742–0.927	13.49	87.8	71.9
IL-33	5.60	24.91	0.00	0.843	< 0.001	0.758–0.929	5.07	72.0	80.7
IL-17 A	7.15	9.09	3.92	0.745	< 0.001	0.628–0.862	6.56	70.0	68.8
IL-1β	3.73	6.12	0.99	0.843	< 0.001	0.751–0.936	2.99	82.0	78.1
IL-25	2.63	3.38	1.54	0.829	< 0.001	0.742–0.916	2.55	72.0	80.7

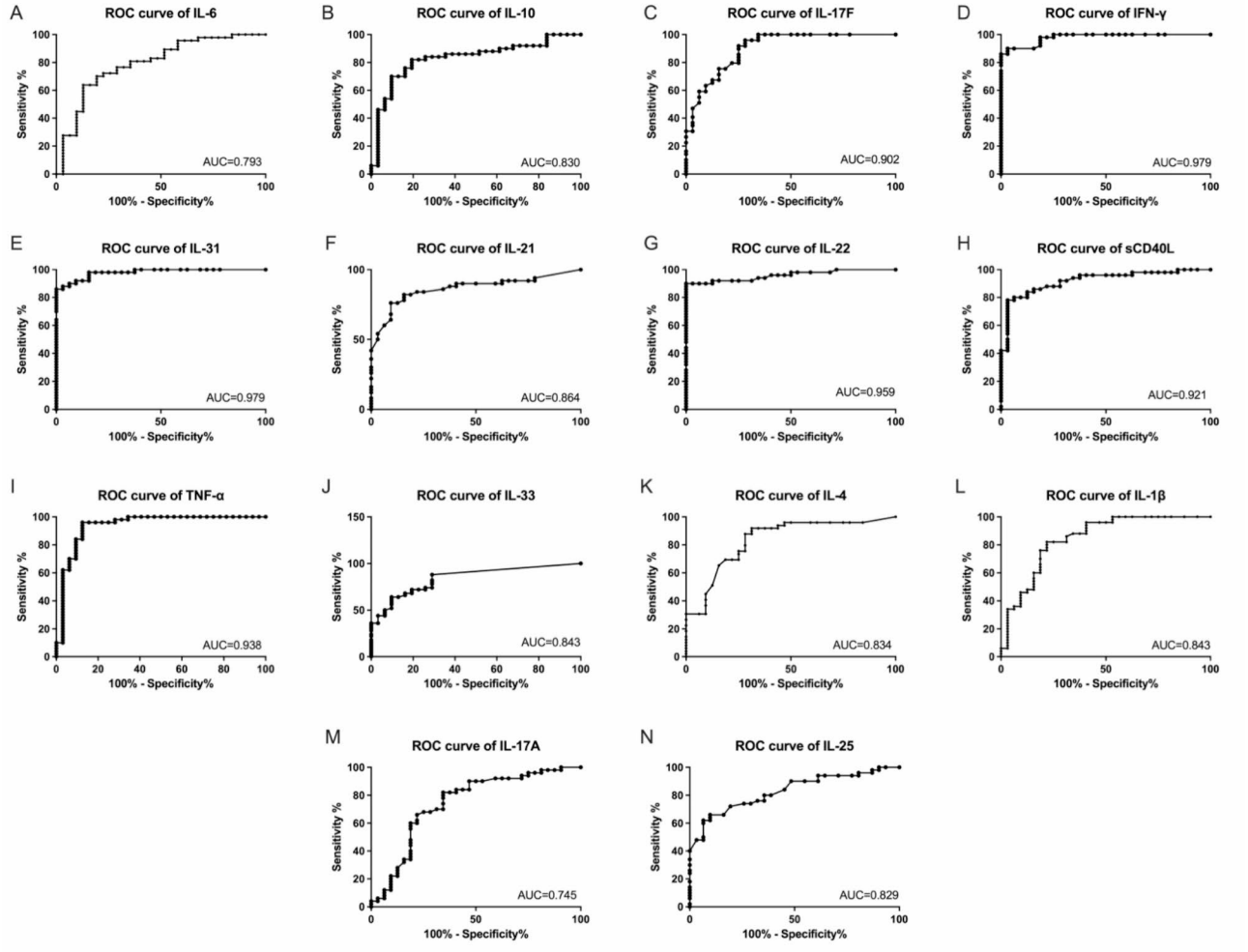

Fig. 2 The ROC curve analysis of different cytokines between TPE and MPE in training cohort. ROC: Receiver operating characteristic. AUC: Area under the curve

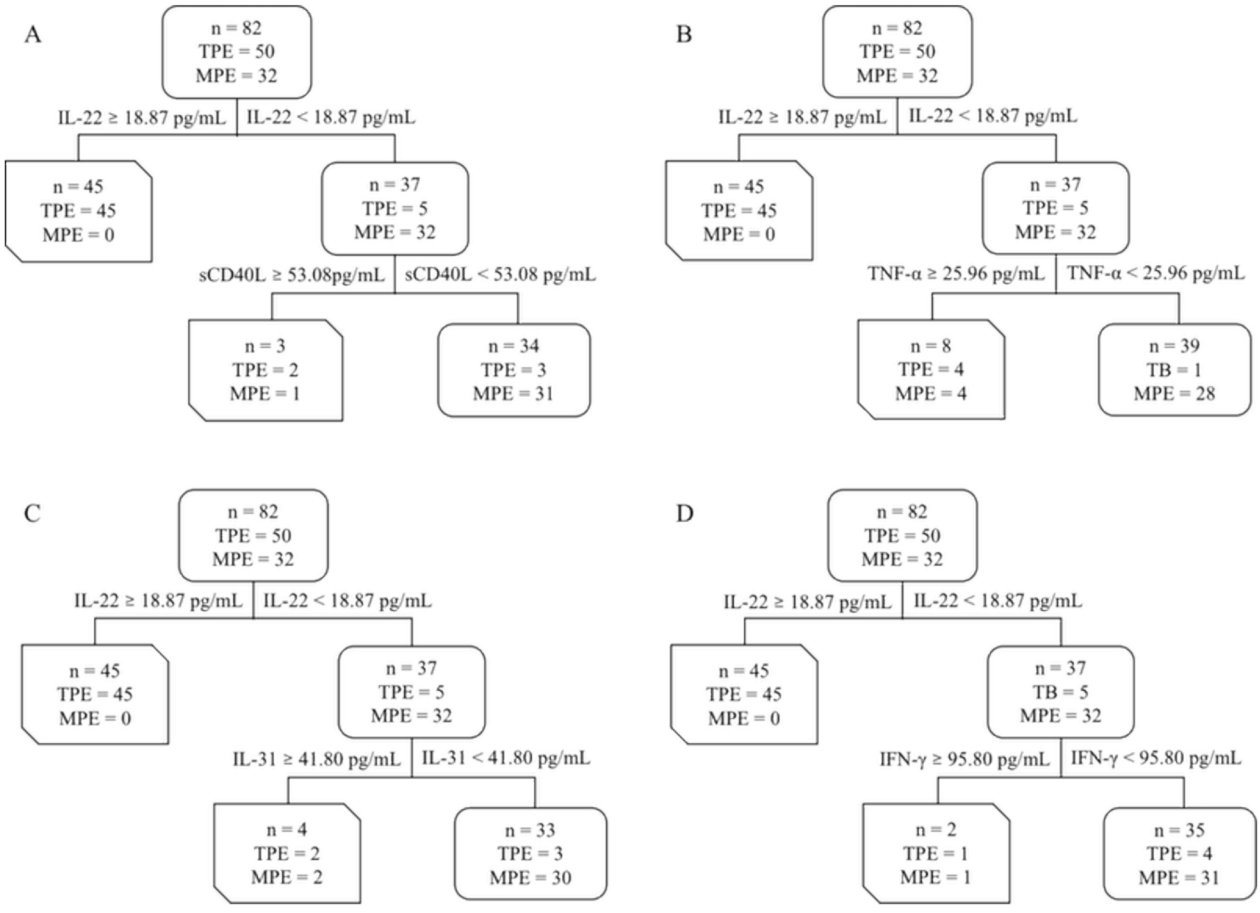

Fig. 3 Combined measure of IL-22 with sCD40L, TNF-α, IL-31 and IFN-γ in training cohort. (**A**) Combined measure of IL-22 with sCD40L between TPE and MPE. (**B**) Combined measure of IL-22 with TNF-α between TPE and MPE. (**C**) Combined measure of IL-22 with IL-31 between TPE and MPE. (**D**) Combined measure of IL-22 with IFN-γ between TPE and MPE. TPE: Tuberculosis pleural effusion. MPE: Malignant pleural effusion

Table 3 The sensitivity and specificity of IL-22 combined with sCD40L, TNF-α, IL-31 and IFN-γ in training cohort

	TPE	MPE	Sensitivity	Specificity	PPV	NPV
IL-22 combined with sCD40L	47/50	1/32	94.0%	96.9%	97.9%	91.2%
IL-22 combined with TNF-α	49/50	4/32	98.0%	87.5%	92.5%	96.6%
IL-22 combined with IL-31	47/50	2/32	94.0%	93.8%	95.9%	90.9%
IL-22 combined with IFN-γ	46/50	1/32	92.0%	96.9%	97.9%	88.6%

Table 4 Diagnostic performance of IL-22 combined with sCD40L in validation cohort

Cytokines	Median (pg/mL)	AUC	*P* value	95% CI	Cut-off value (pg/mL)	Sensitivity (%)	Specificity (%)
IL-22	68.31	0.956	< 0.001	0.910-1.000	3.44	96.0	92.2
sCD40L	38.36	0.869	< 0.001	0.761–0.977	31.27	88.0	82.4
IL-22 combined with sCD40L	--	--	--	--	--	90.2	88.0

cut-off values for IL-22 and sCD40L were lower in the training cohort compared to the training cohort (3.44 vs. 18.87, and 31.27 vs. 53.08 pg/ml, respectively). We nextly applied the threshold levels previously determined in the training cohort (IL-22 was 18.87 pg/mL and sCD40L was 53.08 pg/mL) to confirm their diagnostic efficacy in the validation cohort. As shown in Fig. 4, the combination of IL-22 with sCD40L can efficiently discriminate TPE versus MPE in the validation cohort, with a sensitivity of 90.2% and a specificity of 88.0%.

Discussion

Recently, single-cell profiling has revealed that TPE displayed obvious differences in the abundance of natural killed (NK) cells, $CD4^{+}$T cells and macrophages. These differences were notably associated with disease type

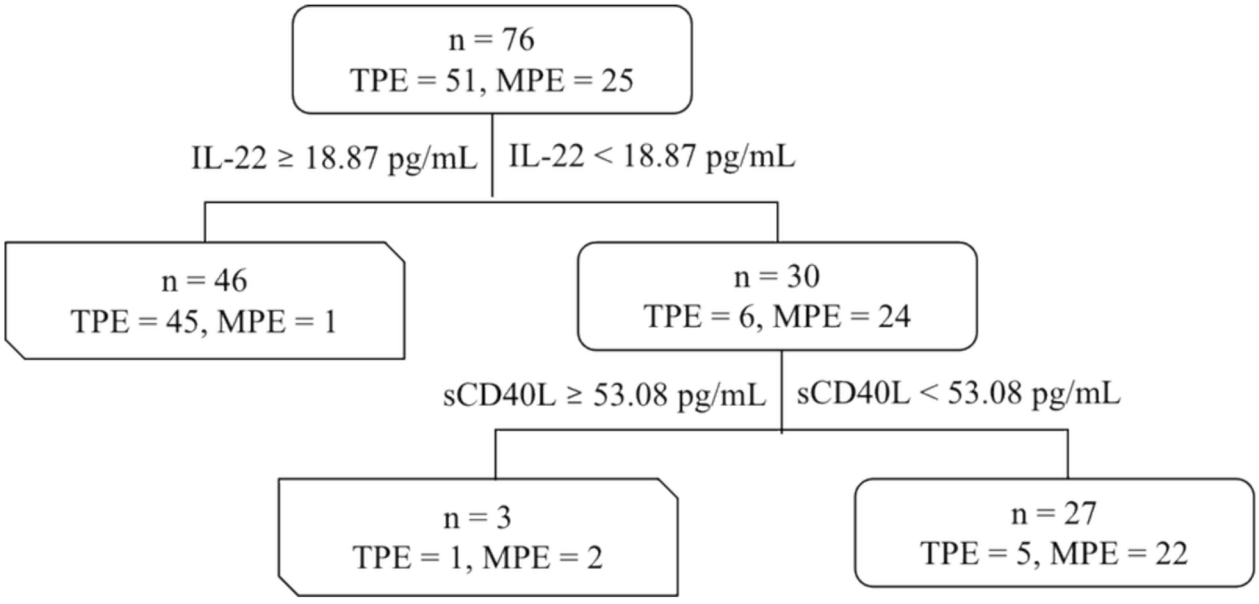

Fig. 4 Validation of diagnostic performance of IL-22 combined with sCD40L in validation cohort. TPE: Tuberculosis pleural effusion. MPE: Malignant pleural effusion

[18]. In TPE, a variety of cytokines are produced by these different cell types. NK cells can produce cytokines such as IFN-γ and TNF-α, which contribute to infection defense and influence the activity of other immune cells. $CD4^+$ T cells secrete IFN-γ, a cytokine essential for activating macrophages and enhancing their bactericidal activity as well as other cytokines like IL-2, IL-4, IL-10, and IL-17. These cytokines help regulate the immune response and maintain a balance between pro- and anti-inflammatory signals. Macrophages are known to release pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which play critical roles in the immune response to *M.tb* infection. These cells are crucial for the initial immune response, helping to contain the infection and mediate inflammation [19–22].

In the present study, we investigated the potential role of the various cytokines in pleural effusion, as biomarkers of disease by comparing participants with tuberculous pleurisy and malignant pleurisy. We demonstrated that multiple biomarkers detected in pleural effusion can contribute to a diagnostic signature for differentiating TPE from MPE. The diagnostic accuracy of these cytokines was evaluated using ROC curve analysis. Consistent with previous results [13–15], several cytokines were able to discriminate, with a good performance, TPE from MPE. Our analysis identified 6 cytokines IL-17 F, IL-22, IL-31, sCD40L, IFN-γ and TNF-α that performed well, with the AUC value>0.9. Among these, IL-22, IFN-γ and IL-31 achieved the highest sensitivity and specificity of ≥ 90%. Further combined measure revealed that IL-22 combining with sCD40L provided higher sensitivity and specificity, and this combination was verified in the validation cohort.

Published studies have suggested that Th17-related cytokine pathways played a crucial roles in tuberculosis infection [12]. IL17A secretion by $CD4^+$T lymphocytes is essential for eliminating primary infections and establishing an effective memory response by producing IFN-γ, which ultimately restricts bacterial growth [23, 24]. In participants with chronic TB, IL-17 A production appears to be decreased. Studies found that IL-17 levels in participants with tuberculous pleural effusion were higher than that in peripheral blood [25, 26]. In our study, we found that the levels of IL-17 A and IL-17 F in TPE were higher compared to MPE. However, the sensitivity and specificity of these cytokines were not superior to those of other cytokines. In some IL-17 Receptor Knock Out (IL-17RKO) mice models, it was found that IL-17 gene knockout did not affect the susceptibility or survival to *M.tb* infection [27, 28]. These murine models suggest that, while the functional IL-23/Th17 pathway is not crucial for primary protection against mycobacterial infections, it may comtribute to granuloma formation and inflammation [29]. Therefore, we speculated that IL-17 does not play a dominant role in anti-tuberculosis immunity, which may explain its lower diagnostic performance in pleural effusion. The current research suggests that IFN-γ has extremely high diagnostic accuracy for TPE [30–32]. In this study, the sensitivity and specificity of IFN-γ for diagnosing TPE were 90.0% and 96.9%, consistent with previous fingdings. Therefore, IFN-γ can be

used as a reference to evaluate the diagnostic accuracy of other cytokines.

IL-22 is a recently characterized cytokine from the IL-10 family, produced by Th 17 cells, γδ T cells, NKT cells, and newly described innate lymphoid cells. A role for IL-22 has also been described in host defense within barrier tissues such as the intestine, oral mucosa, skin and lung [33]. Research has demostrated that IL-22 is involved in tuberculosis immune responses [34]. Previous studies have reported higher concentrations of IL-22 in the bronchoalveolar lavage fluid (BALF) of active tuberculosis participants compared to healthy controls [35]. Liu et al. found a significantly higher level of IL-22 in the pleural fluid of TPE participants than in the blood [36]. CD40L and sCD40L belong to the tumor necrosis factor super family, and play dual roles in prothrombotic and proinflammatory processes. They are expressed in various tissues, including the immune system (in both B and T cells), the vascular wall, and activated platelets [37]. The interaction between CD40L and CD40 is crucial for the priming and expansion of antigen-specific $CD4^+$ T cells, including upregulation of CD25 expression and cytokine production [38, 39]. Studies reveal that CD40-deficient dendritic cells (DCs) fail to induce antigen-specific IL-17 responses after *M.tb* infection, highlighting the CD40-CD40L pathway as a potential traget to enhance adaptive immunity to TB [40, 41]. Research confirms that IL-22 combined with ADA may further improve diagnostic accuracy [42]. In this study, we evaluated combination of IL-22 with sCD40L, TNF-α, IL-31 and IFN-γ, and found that IL-22 combined with sCD40L had the best sensitivity and specificity among these combinations. It was validated in the independent cohort, where the combination showed a sensitivity of 90.2% and a specificity of 88.0%. Therefore, we speculate that the combined measure of IL-22 with sCD40L provides new insights into the distinguishing between TPE and MPE.

This study has several limitations. First, only malignant pleural effusion was included as the control group, which may limit the generalizability of our findings. Additionally, differentiating between parapneumonic pleural effusion and tuberculous pleural effusion remains challenging in clinical practice. Future studies should aim to include a broader range of control conditions to address this issue. Second, while we verified the combined measure of IL-22 with sCD40L in the validation cohort, the combination of IL-22 with other cytokines were not yet implemented. Future research should explore these additional combinations to fully evaluate their diagnostic potential.

Conclusions

In conclusion, this study compared the AUC, sensitivity and specificity of different cytokines in discriminating tuberculosis pleurisy with malignant pleurisy. We found that IL-22, IFN-γ and IL-31 had higher sensitivity and specificity. Notably, the combination of IL-22 with sCD40L proved to be an effective diagnostic strategy for identifying tuberculous pleurisy in clinical settings.

Materials and methods

Participants

From January 2011 to October 2013, totally 82 participants with pleural effusion were consecutively enrolled from Wuxi Fifth People's Hospital and Huashan Hospital of Fudan University as the training cohort. This cohort was used to explore the difference in various cytokines between tuberculous pleurisy and malignant pleurisy. From April 2018 to July 2021, totally 76 participants with pleural effusion from Wuxi Fifth People's Hospital, 905th Hospital of PLA Navy and Huashan Hospital of Fudan University were consecutively enrolled as the validation cohort to confirm the results proposed by the training cohort. In this study, subjects with human immunodeficiency virus (HIV), fungi or bacterial infection or intake immunosuppressive agents and glucocorticoids were excluded. Participants were divided into tuberculous pleurisy group and malignant pleurisy group. The tuberculous pleurisy group included confirmed and clinically diagnosed tuberculosis. The confirmed tuberculous pleurisy was diagnosed based on *M. tuberculosis* culture-positive from pleural effusion and/or confirmed tuberculosis infection via pleural biopsy. The clinical diagnosis of tuberculous pleurisy was made if one of the following criteria was met: positive acid-fast bacilli (AFB) smear or culture of *M. tuberculosis* in sputum, positive tuberculosis culture from other biologic specimens, clinical symptom and radiological evidence suggesting tuberculosis infection, and a positive response to antituberculosis medication without other identifiable causes of pleural effusion. The malignant pleurisy were participants with malignant tumor and the pleural effusion were found tumor cells.

Measurement of different cytokines in pleural effusion

The participants with pleural effusion provided informed consent and underwent bedside pleural puncture guided by ultrasound. During the procedure, 2 mL pleural effusion was extracted using a sterile tube, and then was centrifuged at 1500 rpm for 10 min. The supernatants were stored at -80 °C until analysis. 25uL of each pleural effusion samples was diluted 1:1 with the kit serum matrix. The levels of various cytokines in pleural effusion, including IL-1β, IL-4, IL-6, IL-10, IL-17 A, IL-17 F, IL-21, IL-22, IL-25, IL-31, IL-33, IFN-γ, sCD40L and TNF-α, were

measured simultaneously using the Bio-Plex Multiplex Immunoassay of Th17 cytokines (Bio-Rad Laboratories, Inc.USA), according to the instructions of the kit manufacturers. The data were analyzed with Bio-Plex 200 system (Bio-Rad Laboratories, Inc.,USA), and all the results were expressed in pg/mL.

Statistical analysis

The statistical analysis was performed with GraphPad Prism software (version 9.2.0; GraphPad Software, Inc.). The data were compared by using the non-parametric *Mann-Whitney* test and Chi-square test or Fisher's exact test. Significance was inferred for $P<0.05$. ROC curve analysis was performed to determine the discriminate ability of selected cytokines to distinguish tuberculosis pleurisy and malignant pleurisy with the overall accuracy assessed by AUC values. Sensitivity, specificity, positive and negative predictive values (PPV, NPV) were calculated. 95% confidence intervals (95% *CI*) were calculated using the Wilson method for proportions.

Abbreviations

TB	tuberculosis
M.tb	Mycobacterium tuberculosis
ADA	adenosine deaminase
IFN-γ	interferon-γ
IL	interleukin
G-CSF	granulocyte colony-stimulating factor
TNF-α	tumor necrosis factor-α
AFB	acid-fast bacilli
HIV	human immunodeficiency virus
sCD40L	soluble CD40 ligand
ROC	receiver operating characteristic
AUC	area under curve
PPV	positive predictive values
NPV	negative predictive values
CI	confidence intervals
TPE	tuberculosis pleural effusion
MPE	malignant pleural effusion
DCs	dendritic cells
NK	natural killed cells

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Author contributions

Yuzhen Xu, Jing Wu and Qiuju Yao contributed to the manuscript drafting and statistical analysis, Qianqian Liu, Huaxin Chen and Bingyan Zhang contributed to the methodology and enrollment of patients, Yuanyuan Liu, Sen Wang and Lingyun Shao contributed to the curation of data and supervision, Wenhong Zhang, Qinfang Ou and Yan Gao contributed to the study design and critical revision of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Our study was approved by the Ethics Committee of Huashan Hospital affiliated with Fudan University Ethics Committee (KY2021-978). All the experiments were performed in accordance with the Helsinki Declaration. Written informed consent was obtained from all of the participants prior to participation in our study.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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