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TANAFFOS

Diagnostic Accuracy of Interleukin 27 for the Diagnosis of Pleural Tuberculosis

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Background: Pleural tuberculosis (TB) is one of the most common forms of extra-pulmonary TB. Since diagnosis is challenging through microbiological tests, discovering new diagnostic techniques with higher accuracy could help us improve early detection and lead to better outcomes. This study aims to investigate the sensitivity and specificity of interleukin 27 (IL27) as a diagnostic test for pleural Tuberculosis.

Materials and Methods: The current study was conducted on 121 adult patients admitted to Masih Daneshvari Hospital due to pleural effusion with an unknown cause. 36 cases had transudative, and 85 cases had exudative pleural effusions. Among them, TB (33.1%) and malignant pleurisy (23.1%) were the most common causes. In addition to routine studies for pleural effusion workups, pleural interleukin-27 concentrations were measured by ELISA and compared between groups of TB-affected patients and those without TB**.**

Results: We found that the value 679 pg/ml was the most appropriate cut-off threshold for interleukin 27 in pleural fluid with 95% sensitivity, 69% specificity, 94% negative predictive value, and 73% positive predictive value (P value<0.001) for diagnosis of TB pleurisy. ADA levels were not significantly different between TB and non-TB cases.

Conclusion: Compared to other groups, interleukin 27 levels in patients with a final diagnosis of TB-pleurisy were significantly higher, indicating the significant value of this interleukin as a diagnostic biomarker.

Keywords: Tuberculosis; Pleurisy; Interleukin 27; Diagnostic test

INTRODUCTION

More than 50 different etiologies are currently responsible for pleural effusion (PE), including localized pleural pathologies, pulmonary diseases, systemic disorders, and medications (1). Pleural effusion due to tuberculosis (TB) is among the most prevalent reasons in the endemic regions (2, 3). Pleural TB is the second most prevalent extra-pulmonary TB, responsible for fewer than 1% of pleural effusions in developed countries and 30-80% in developing countries. TB pleurisy is found in approximately 31% of all TB patients (4); however, its diagnosis is rather difficult due to the low sensitivity of acid-fast staining smears for diagnosis, and the rather prolonged time required for mycobacterial culture (5).

Currently, clinical presentations, radiologic studies, and lab data (pleural fluid analysis, pleural biopsy, and molecular and microbiological studies) are used for diagnosis (6, 7). The golden standard for diagnosis of pleural TB (with a specificity of approximately 100%) is the isolation of Mycobacterium from pleural fluid or biopsy. Unfortunately, the sensitivity for pleural fluid culture is rather low. Therefore, pleural biopsy and direct observation of the granuloma in the tissue would be a specific (95%) substitute (8). Pleural biopsy, on the other hand, is an invasive procedure and should be performed by an expert with high skill. Moreover, sometimes the diagnosis gets more difficult, which necessitates further invasive measures, such as thoracoscopy, which subsequently increases the risk of incidence of potential side effects and even mortality following the procedure (9).

The mentioned reasons altogether necessitate seeking other possible alternatives that would be less invasive. Biomarkers have always been an interesting suggestion, and Adenosine Deaminase (ADA) is one of the markers that is frequently used to differentiate TB from other possible reasons for pleurisy. Common false-positive results are due to empyema, parapneumonic effusions, rheumatic effusions, lymphomatous effusions, and malignancies. False-negative results have also been documented (8, 10-13).

Several studies have suggested that interleukin 27 (IL27), which is a fraction of interleukin-12, might be useful in pleural TB diagnosis (3, 5, 14, 15). This marker is a hetero-dynamic cytokine (16), encompassing P28 and PRO3 subunits (17) and is mostly produced by antigen-activated cells; however, few studies have investigated the use of IL27 in the diagnosis of TB pleurisy. Our study aimed to investigate the accuracy of IL27 in the diagnosis or exclusion of pleural TB. We hypothesized that IL27 has more accuracy for the diagnosis of pleural TB than ADA. Furthermore, the recruitment of these two tests together could be considered as an effective strategy for diagnosis with more specificity and sensitivity.

MATERIALS AND METHODS

Case selection

This study was conducted among patients at least 18 years old who were admitted to Masih Daneshvari Hospital, the tertiary center of lung disease in Tehran, with pleural effusion of unknown etiology in a period of four months. Cases with a history of invasive procedures concerning the pleural cavity (thoracentesis, thoracoscopy, thoracic surgery, etc.) in the past 6 weeks, chest trauma in the past three months, hemothorax or chylothorax, and those who were discharged from the hospital without a final net diagnosis were excluded.

Sampling method

After radiologic confirmation of a pleural effusion, 2 mL of pleural fluid was collected in standard heparinized tubes and transferred to the immunology laboratory within 20 minutes. After that, cell counts, cytologic studies, Gram and Ziehl-Neelsen staining, and aerobic, anaerobic, and Löwenstein-Jensen cultures were performed on the specimens. Moreover, lactate dehydrogenase, protein, and glucose levels were measured in both the pleural fluid specimen and a simultaneous blood sample. R and D ELISA kits were used to measure the interleukin 27 concentrations.

Definitions

Based on the results, the patients were classified into one of the following groups: transudate PE, parapneumonic effusion, empyema, TB pleurisy, malignant PE, and other causes of exudative pleural effusion. Transudative and exudative effusions were identified by Light's Criteria (18).

Tuberculosis effusion was confirmed with the following criteria: 1) Presence of acid-fast bacilli in either the pleural fluid or biopsy sample OR growth of mycobacterium in Löwenstein-Jensen culture; 2) Granulomatous reaction in the pleural biopsy in the absence of other granulomatosis disorders; 3) Presence of

AFB in the sputum OR mycobacterial growth in Löwenstein-Jensen culture and simultaneous exudative pleural effusion.

Empyema was confirmed with the presence of pus in the pleural cavity or the isolation of microorganisms from the pleural fluid sample.

Statistical analysis

Frequencies and percentages described quantitative variables, and qualitative variables were described by median, mean, and IQR (interquartile range). Kolmogorov-Smirnov and Shapiro-Wilk tests were used to investigate the normal distribution of the data. To compare the medians of ADA and IL27 with other groups, we used the Mann-Whitney test. ROC curve was used to compare the diagnostic accuracy and establish the cut-off for interleukin 27 and ADA. For evaluating the critical point in the diagnosis of TB with IL27 and ADA levels, the indicators of optimal cut-off were used, such as CZ and J. Other related factors, such as sensitivity, specificity, positive and negative predictive values, test accuracy, and probability ratio, were calculated. All tests were performed at a significance level of 0.05.

Ethics

This study was reviewed and approved by the research medical ethics committee of Shahid Beheshti University of Medical Sciences (approval number: IR.SBMU.MSP.REC.1398.492) and was conducted under the Declaration of Helsinki and institutional ethics guidelines. Informed consent was received before every procedure, and cases were enrolled in the study if the patients were willing to. No additional medical cost was obliged to the patients, and their confidential information was not disclosed.

RESULTS

In the period of study, a total number of 154 patients underwent pleural fluid sampling, and 33 cases were rolled out due to the following reasons: 8 repeated cases, 4 cases with formerly known etiology, 3 cases due to chest tube insertion, 2 patients for history of recent chest trauma or surgery, 1 case for hemothorax, and 2 cases due to coagulated specimens. In a study involving 121 patients with a mean age of 58.4 years, 77 of whom were male, the final diagnosis remained unclear in 13 patients despite routine evaluations. Among the 121 cases, 36 were categorized as having transudative pleural effusions, while 85 had exudative pleural effusions. The most common causes of the exudative effusions were tuberculosis (TB) and malignant pleurisy. Table 1 shows the demographic, lab data, and final diagnosis of the patients.

The TB group was considered the reference, and the levels of IL27 and ADA were measured in all groups. The results demonstrated that the pleural levels of IL27 were statistically higher in TB cases compared to those with either transudative or non-TB etiologies of exudative pleurisy. In terms of pleural ADA levels, comparison between TB cases and individuals who had exudative pleural effusion other than TB revealed no significant differences. Next, to focus on TB pleurisy, transudative effusions and PMN-dominant exudates were excluded from analysis, leaving 71 cases with exudative pleurisy and lymphocyte dominance, including 36 TB patients. These cases were divided into two groups: TB and non-TB. Moreover, IL27 and ADA levels were compared between these two groups. These results are summarized in Table 2 and Figure 1.

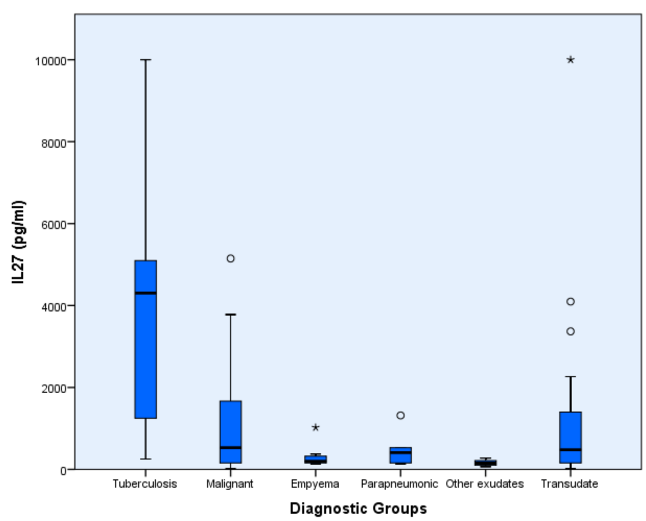

Figure 1. Pleural levels of IL27 among different diagnostic groups

The sensitivity and specificity of multiple levels of IL27 and ADA for the diagnosis of pleural TB were calculated using the ROC plot (Figure 2).

Finally, the best cut-off for IL27 and ADA pleural levels in order to diagnose TB pleurisy was calculated in each of the following groups: all pleurisy cases, exudative pleuritis, and exudative lymphocyte-dominant pleuritis, separately. Also, sensitivity, specificity, positive and negative predictive values, diagnostic accuracy, and positive and negative likelihood ratios were calculated and reported in detail (Table 3).

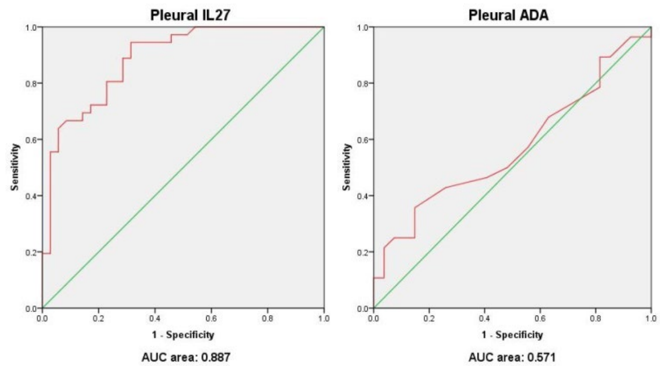

Figure 2. Receiver operator characteristic (ROC) plot of pleural levels of IL27 and ADA, discriminating pleural TB from other causes of exudative lymphocyte-dominant pleural effusion. Abbreviations: IL-27: interleukin 27; AUC represents the area under the curve

Table 1. Demographics, lab data, and final diagnosis of the 121 patients were enrolled in the study

Parameter		N (%)	Details
Age (y)		58.4±20.3	
Gender	**Male**	77 (63.6%)	
	Female	44 (36.4%)	
Medical conditions	**Diabetes Mellitus**	20 (16.5%)	
	Collagen vascular diseases	2 (1.7%)	
	HIV	2 (1.7%)	
ESR (mm/h)		62.4 ± 35.9	
Pleural fluid WBC (cell/mm3)		1185 ± 1494	
Pleural fluid PMNs		14 (11.6%)	
Pleural fluid ADA (IU/L)		36.0 ± 23.1	
Sputum AFB smear (+)		9 (9.3%)	From 96 sputum samples
Pleural fluid AFB smear (+)		3 (3.1%)	From 96 plural samples
Pleural fluid MTB culture (+)		5 (6.8%)	From 74 plural samples
Pleural fluid MTB PCR (+)		2 (10.5%)	From 19 plural samples
Diagnostic pleural pathology		37 (84.1%)	From 44 biopsy samples
Pleural fluid IL27 (pg/ml)		2091 ± 2371	
Final Diagnosis	**TB pleurisy**	40 (33.1%)	With or without concurrent pulmonary TB
	Malignant PE	28 (23.1%)	Primary or metastatic
	Empyema	8 (6.6%)	
	Parapneumonic effusion	5 (4.1%)	
	Other causes of exudative PE effusion	4 (3.3%)	
	Transudate	36 (29.8%)	

Abbreviations: HIV: human immunodeficiency virus; ESR: erythrocyte sedimentation rate; WBC: white blood cells; PMN: polymorphonuclear leukocyte; ADA: adenosine deaminase; AFB: Acid-fast bacillus; MTB: Mycobacterium tuberculosis; PCR: Polymerase chain reaction; IL-27: Interleukin 27; TB: Tuberculosis; PE: Pleural effusion

Table 2. Comparison of the pleural levels of IL27 and ADA among different groups of patients with pleural effusion

Diagnosis		N	**IL-27 (pg/ml)**					**ADA (IU/L)**				
			Mean	**SD**	**Median**	**IQR**	**P-VALUE**	**Mean**	**SD**	**Median**	**IQR**	**P-VALUE**
All cases with PE	**TB (Reference)**	40	4228	2995	4305	3847	-	41	24	34	10	-
	Malignant PE	28	1101	1304	529.9	1508	**<0.0001**	32	7	33	6	0.174
	Empyema	8	315	297	199.3	167	**<0.0001**	72	72	40	18	0.199
	Parapneumonic PE	5	510	481	408.7	374	**0.002**	33	4	33	6	0.621
	Other exudates PE	4	160	87	150.1	111	**0.001**	31	6	34	10	0.447
	Transudative PE	36	1062	1815	480.0	1243	**<0.0001**	28	5	30	8	**<0.0001**
LDEPE	**TB**	36	4077	2773	4305	3844	**<0.0001**	39	19	34	9	**0**
	Non-TB	35	913	1223	375	1022		33	6	33	6	

Abbreviations: N: number; IL-27: interleukin 27; ADA: Adenosine deaminase; SD: standard deviation; IQR: interquartile range; TB: Tuberculosis; PE: pleural effusion, LDEPE: Lymphocyte dominant exudative pleural effusion.

Table 3. The diagnostic accuracy of pleural IL-27 and ADA for the differentiation of TB from non-tuberculosis pleural effusions

Groups	Variable	AUC (95% CI)	p-value	Method	Optimal Cut-off	Sn.	Sp.	PLR	NLR	PPV	NPV	Diagnostic accuracy
Any PE	**IL-27**	0.888 (0.830-0.947)	<0.0001	J	**679.7**	0.95	0.68	2.96	0.07	0.59	0.97	0.77
				CZ	**764.3**	0.93	0.70	3.13	0.11	0.61	0.95	0.78
	ADA	0.660 (0.540-0.78)	0.012	J	35.5	0.45	0.84	2.85	0.65	0.58	0.76	0.71
				CZ	35.5	0.45	0.84	2.85	0.65	0.58	0.76	0.71
Exudative PE	**IL-27**	0.898 (0.835-0.962)	<0.0001	J	**679.2**	0.95	0.69	3.05	0.07	0.73	0.94	0.81
				CZ	**1038.5**	0.88	0.73	3.22	0.17	0.61	0.92	0.78
	ADA	0.566 (0.425-0.707)	0.358	J	36.5	0.39	0.80	1.94	0.77	0.63	0.60	0.61
				CZ	35.5	0.45	0.71	1.58	0.77	0.58	0.60	0.59
LDEPE	**IL-27**	0.877 (0.811-0.962)	<0.0001	J	**764.3**	0.93	0.65	2.71	0.10	0.71	0.91	0.79
				CZ	**764.3**	0.93	0.65	2.71	0.10	0.71	0.91	0.79
	ADA	0.571 (0.418 -0.725)	0.363	J	36.5	0.33	0.84	2.08	0.79	0.66	0.56	0.592
				CZ	35.5	0.41	0.72	1.48	0.58	0.58	0.56	0.571

Units: IL-27 (pg/ml); ADA (IU/L)

Abbreviations: AUC: area under curve; CI: Confidence Interval; Sn: sensitivity; Sp: specificity; PLR: positive likelihood ratio; NLR: negative likelihood ratio; PPV; positive predictive value; NPV: negative predictive value; IL-27: Interleukin 27; ADA: Adenosine deaminase; PE: Pleural effusion; LDEPE: Lymphocyte dominant exudative pleural effusion; CZ = Concordance Probability Method; J = Youden Index.

DISCUSSION

Pleural effusion due to TB is frequent, especially in endemic regions (2, 3), although its diagnosis is difficult due to the low sensitivity of the smear and the long period required for Mycobacterium culture (5). Clinicians frequently use ADA to differentiate TB from other etiologies causing pleurisy. False positive (empyema, parapneumonic effusions, rheumatoid effusions, lymphomatous effusions, and other malignancies) and false negative results for this test are frequently reported (8, 10-13). Therefore, obtaining a diagnostic biomarker with high specificity and sensitivity would significantly address the diagnostic challenges. Several studies have assessed the diagnostic accuracy of IL27 in pleural fluid samples using the ELISA method.

In 2012, Yang et al.(15) measured the concentration of IL27 in the serum and pleural fluid of 174 HIV-negative patients, including 68 patients with TB pleuritis, 63 malignant pleurisy, 22 infective pleurisy, and 21 transudative effusions (divided by Light's Criteria (18)). The concentration of IL27 in pleural fluid was significantly higher in TB pleurisy in comparison to the other groups ($p<0.001$) (15). This study resembles our study regarding the number and variety of patients. Similarly, our study reported significantly greater levels of IL27 in the TB pleurisy group ($p<0.0001$).

Another study in 2014 by Valdés et al. enrolled 519 patients admitted to the hospital due to pleural effusion (5). They excluded 88 cases of pleural effusions without clear etiologies and divided the rest of them into 6 groups: 70 tuberculosis effusions, 146 neoplastic effusions, 58 parapneumonic effusions, 28 empyema, 88 transudative effusions, and 41 other effusions. In these groups, measurement of the levels of pleural ADA, ADA_2, IL27, and Interferon-γ demonstrated significantly greater amounts of them in TB patients compared to others; however, IL27 showed lesser sensitivity and specificity in comparison with ADA and ADA_2 in the diagnosis of TB pleurisy. Nevertheless, the usage of either ADA or ADA_2 in combination with IL27 showed greater diagnostic sensitivity in comparison with ADA and ADA_2 alone. In this study, the diagnostic threshold for IL27, which was obtained by the ROC curve, was reported as 0.55 ng/ml. Moreover, this experiment revealed that elevated levels of IL27 could predict most of the TB pleuritis with 91.4% sensitivity and 85.1% specificity. They comprehended that the product of IL27 and ADA could significantly increase the diagnostic accuracy compared to each of the markers alone, which is supported by the study of Shu et al. (19). The product sensitivity and the possibility of a false-positive report were approximately 100% and null, respectively (5, 19).

The total number of cases and etiologies responsible for pleural effusion was greater in the Valdés et al. (5) study; however, the percentage of TB patients was higher in our study (16.2% versus 33.1%). Our study calculated the optimum diagnostic threshold at 0.679 ng/ml (close to 0.55ng/ml they obtained), with 95% sensitivity and 68% specificity. Moreover, differences in ADA levels were insignificant in our study.

Another study by Sun et al. (20) which was conducted on 76 patients with pleural effusion, the levels of IL27 in the serum and pleural fluid of 40 TB patients and 36 patients with malignancy were measured. The levels of IL27 were significantly higher in TB pleural effusions compared to malignancies ($p<0.05$). ROC curve defined that the best diagnostic threshold for IL27 for diagnosis of TB pleurisy would be 838 ng/L (with respective sensitivity and specificity of 95% and 97.2%). The total number of cases and their diversity in this study are rather limited compared to our study and the other similar studies. Therefore, the results of our study and those with significant diversity would be closer to the real clinical outcomes.

Skouras et al. (3) published a paper in 2015 that investigates the diagnostic accuracy of ADA, IL27, and their product for confirming or ruling out tuberculosis pleurisy. They obtained 121 patients with exudative pleural effusions, of which 10 cases were diagnosed with tuberculosis (8%). Others were composed of 69 malignancies (57%), 19 parapneumonic effusions (16%), and 23 effusions due to other reasons (19%). Their results revealed that IL27 and ADA alone were not reliable as mere indicators for pleural tuberculosis in the endemic regions. However, they could be used as diagnostic tools in regions with lower prevalence, considering time and cost-effectiveness. They suggested considering the ADA as a tool for ruling out the possibility of TB. In the endemic regions, the product of ADA and IL27 would have a more negative predictive value. This study has considered 15 different etiologies for pleural effusion, suggesting its strong designation; however, a few limitations can be witnessed. First, the sub-optimal power (60%) due to the small number of TB cases; second, the use of clinical criteria for diagnosis of TB; and third, the restored specimens for lab analysis. There is currently no clear information on the durability of IL27 in pleural fluid (3). Another important point is that this study did not enroll transudative effusions, which might falsely elevate the total number of true negatives and decrease the false positives, which leads to bias and false reports on increased specificity (11, 21).

Another study was conducted in our center by Dalil Roofchayee et al. and published in 2021 (22). This study aimed to investigate the utility of measuring cytokines in pleural fluid in the diagnosis of pleural tuberculosis. In this study, the levels of ADA, IL6, IL18, IL27, CXCL8, CCL-1, IP-10, and IL27 in the pleural fluid were compared in 30 TB patients and 58 non-tuberculosis patients (malignant pleurisy, parapneumonic effusion, and empyema). IL27 was significantly higher in the pleural fluid of TB patients (4725 versus 978 pg/ml, respectively, $p\leq0.001$) with a cut-off of 2363 pg/ml, sensitivity of 96.67, and specificity of 98.28 (22). Compared to our study, the cut-off of IL-27 and its specificity were higher in this study, which may be due to the different inclusion and exclusion criteria, especially the exclusion of transudative cases and various causes of exudative pleurisy.

Our study has some limitations. First, this study was conducted in a TB referral center, so the results may be different in other centers where the number of infected patients is less and other inflammatory causes of pleurisy, such as rheumatological diseases, are more common. Also, we did not consider the pre-test probability of TB in the patients before the investigation. The yield of the IL27 may be higher in patients who have a higher probability of TB (like a history of recent close contact with an active case of TB). However, the current study was performed in a tertiary pulmonary center in an endemic region with acceptable diagnostic facilities for every kind of pleural disease, so the results of the current report would be reliable for decision-making in the endemic regions.

CONCLUSION

The results of this study showed that measurement of the concentration of interleukin 27 in pleural fluid was a better diagnostic test than ADA levels for discrimination of TB pleurisy from other causes. The best threshold was 679pg/ml with a sensitivity of 0.95 and specificity of 0.68.

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