



# Assay of pleural fluid interleukin-6, tumour necrosis factor-alpha and interferon-gamma in the diagnosis and outcome correlation of tuberculous effusion <sup>☆</sup>

Chi-fong Wong<sup>a,\*</sup>, Wing-wai Yew<sup>a</sup>, Simon Kwok-fai Leung<sup>a</sup>, Chiu-yeung Chan<sup>b</sup>, Mamie Hui<sup>b</sup>, Carrie Au-Yeang<sup>b</sup>, Augustine Fun-bun Cheng<sup>b</sup>

<sup>a</sup>Tuberculosis & Chest Unit, Grantham Hospital, 125 Wong Chuk Hang Road, Aberdeen, Hong Kong, China

<sup>b</sup>Department of Microbiology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong, China

## KEYWORDS

Tuberculosis;  
Pleural effusion;  
Diagnosis;  
Outcome;  
Interleukin-6;  
Tumour Necrosis Factor;  
Interferon-gamma

**Summary Objective:** To assess the usefulness of interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF- $\alpha$ ) and interferon-gamma (IFN- $\gamma$ ) in the diagnosis and prediction of outcome of pleural tuberculosis.

**Patients and methods:** Pleural fluid from 32 TB and 34 non-TB patients was sent for assay of IL-6, TNF- $\alpha$  and IFN- $\gamma$ . Clinical parameters at presentation and residual pleural scarring at completion of treatment were assessed for pleural TB cases.

**Results:** The pleural fluid levels of IL-6, TNF- $\alpha$  and IFN- $\gamma$  in TB patients were significantly higher than those with non-TB effusions ( $P$  values of  $<0.001$ ,  $0.018$  and  $<0.001$ , respectively by independent  $t$ -test). Utility of these cytokines for diagnosis of pleural TB was evaluated using receiver operating characteristic (ROC) curve analysis. The cut-off values for IL-6, TNF- $\alpha$  and IFN- $\gamma$  determined in this analysis were 4000, 4 and 60 pg/ml respectively, and their sensitivity and specificity were 90.6% and 76.5%, 90.6% and 79.4%, 100% and 100%, respectively. The pretreatment pleural fluid IL-6 levels had a positive correlation with the number of febrile days after treatment (Pearson correlation test:  $r=0.60$ ,  $P=0.009$ ). A negative correlation was found between the percentage reduction in pleural fluid cytokines after 2 weeks treatment and the extent of residual pleural scarring (IL-6:  $r=-0.62$ ,  $P=0.041$ ; TNF- $\alpha$ :  $r=-0.65$ ,  $P=0.030$ ; IFN- $\gamma$ :  $r=-0.83$ ,  $P=0.002$ ).

**Conclusion:** Pleural fluid IL-6, TNF- $\alpha$  and IFN- $\gamma$  assays are useful in the diagnosis of pleural TB. The initial IL-6 level correlates with the number of febrile days. The percentage change of cytokines after 2 weeks of treatment also helps to predict residual pleural scarring.

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\*Corresponding author. Tel.: +852-2518-2644; fax: +852-2580-2493.

E-mail address: [wongcf2001@yahoo.com.hk](mailto:wongcf2001@yahoo.com.hk) (Chi-fong Wong).

## Introduction

Tuberculosis (TB) is still a common and important infectious disease worldwide.<sup>1</sup> Pleural TB is a common form of extrapulmonary involvement,<sup>2</sup>

and TB is a common cause of pleural effusion in areas with high disease prevalence.<sup>3-5</sup>

The diagnosis of pleural TB is made from the characteristic features demonstrated on histological examination of pleural tissue, or a positive culture of *Mycobacterium tuberculosis* in the pleural fluid or tissue. However, the sensitivities of these investigations are limited<sup>4,6</sup> and difficulty in diagnosis of pleural TB is sometimes encountered.

Pleural TB represents largely an immunological reaction in which a repertoire of cytokines is intimately involved in the pathogenesis. These include especially interleukin-1 (IL-1),<sup>7</sup> interleukin-8 (IL-8),<sup>8,9</sup> interleukin-6 (IL-6),<sup>9-11</sup> tumour necrosis factor (TNF),<sup>8,12-15</sup> and interferon-gamma (IFN- $\gamma$ ).<sup>7,8,12,14,16-21</sup> The measurement of levels of some of these cytokines has been shown to be helpful in the diagnosis of pleural TB.<sup>8,13,14,16-19</sup>

The present study was undertaken to evaluate the usefulness of pleural fluid IL-6, TNF- $\alpha$ , IFN- $\gamma$  in the diagnosis and outcome prediction of pleural TB.

## Materials and methods

### Patients

A prospective study was conducted in the Tuberculosis and Chest Unit of Grantham Hospital over one and a half year. Patients who were hospitalized from January 1999 to June 2000 for management of pleural effusion were enrolled into the study. Patients with the diagnosis of TB were regarded as study subjects. Patients with non-TB effusion constituted the control group for comparison.

### Thoracentesis

All studied patients underwent thoracentesis for diagnostic purpose. During thoracentesis, pleural fluid aspirated was sent for biochemical, cytological, and microbiological (including mycobacteriological) studies. About 10 ml of the pleural fluid was also saved and stored at  $-70^{\circ}\text{C}$  for cytokine assay later. Pleural biopsy was also performed at the same setting unless the diagnosis was already known at the time of thoracentesis.

### Cytokine assay

The assay of the cytokines in the pleural fluid samples was carried out in another laboratory of

which the staff was not involved in the clinical management of the patients. The levels of the cytokines were measured by the commercially available enzyme-linked immunosorbant assay (ELISA) kits (Central Laboratory of the Netherlands Red Cross; Amsterdam, Netherlands) that employed the quantitative 'sandwich' enzyme immunoassay technique in which a monoclonal antibody against the specific cytokine was coated onto polystyrene microtitre wells. A measured volume of the clinical specimen and eight standard solutions were placed on the wells, followed by addition of a biotinylated sheep antibody to the specific cytokine. After washing off the excess biotinylated antibody, horseradish peroxidase conjugated streptavidin was added. After final washing, a substrate was added. A colour product was then formed in proportion to the amount of cytokine present in the sample or the standard. From the measured colour absorbance, the concentration of the cytokine could be determined by interpolation with the standard curve.

## Diagnosis of Tuberculosis

TB effusion was diagnosed using one of the following criteria:

1. Pleural biopsy showing granulomatous inflammation together with stainable acid-fast bacilli.
2. *M. tuberculosis* isolated from the pleural fluid by culture.
3. Pleural biopsy showing granulomatous inflammation, but no stainable acid-fast bacilli, together with a good radiographic response to anti-tuberculous treatment.
4. No histological or bacteriological confirmation, but with other likely alternative diagnoses excluded, together with a good clinical and radiographic response to anti-tuberculous treatment.

All patients with pleural TB were given anti-TB treatment as in-patients for at least 2 weeks with no adjunctive corticosteroid therapy or therapeutic drainage. Radiographic resolution of the pleural effusion at 2 weeks was assessed. A repeated thoracentesis was performed unless resolution of pleural effusion rendered thoracentesis difficult or the procedure was refused by the patient.

Chest radiographs of all TB patients were assessed for residual pleural scarring after completion of anti-TB treatment.

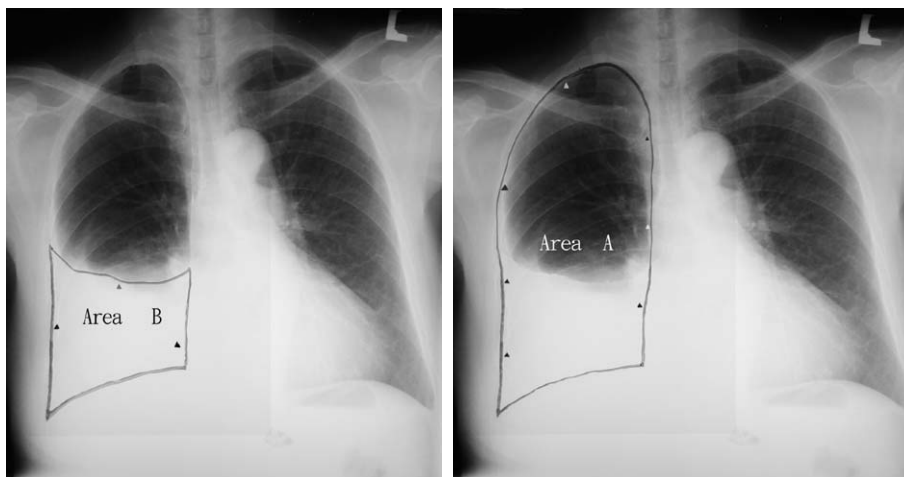


Figure 1 Assessment of extent of pleural effusion.

### Assessment of extent of pleural effusion and scarring

The amount of pleural effusion at presentation and after treatment was assessed by measurement of the area of radio-opacity due to pleural effusion and expressed as a percentage of the area of the ipsilateral lung field (Fig. 1). The presence of residual pleural scarring was defined as presence in any area of thickened pleural shadow of  $\geq 10$ mm on the chest radiograph or blunting of the costophrenic angle to  $\geq 90^\circ$ . The extent of residual pleural scarring was assessed by measurement of the area of radio-opacity from the pleural shadow and expressed as the percentage of the area of the ipsilateral lung field. All pleural effusion and pleural scarring assessments were done by a single investigator to avoid inter-observer bias in the assessment.

### Statistical Analysis

The statistical analysis of data was done using a computer software (SPSS Version 8.0). Independent *t*-test was used to compare the cytokine levels between TB and non-TB patients. Receiver operating characteristic curve analysis was used to determine an optimal cut-off value for diagnostic accuracy for each cytokine. Pearson correlation test was used to study the relation between cytokine levels and number of febrile days, and their correlation with the extent of residual pleural scarring. A *P*-value of less than 0.05 denotes the presence of statistical significance.

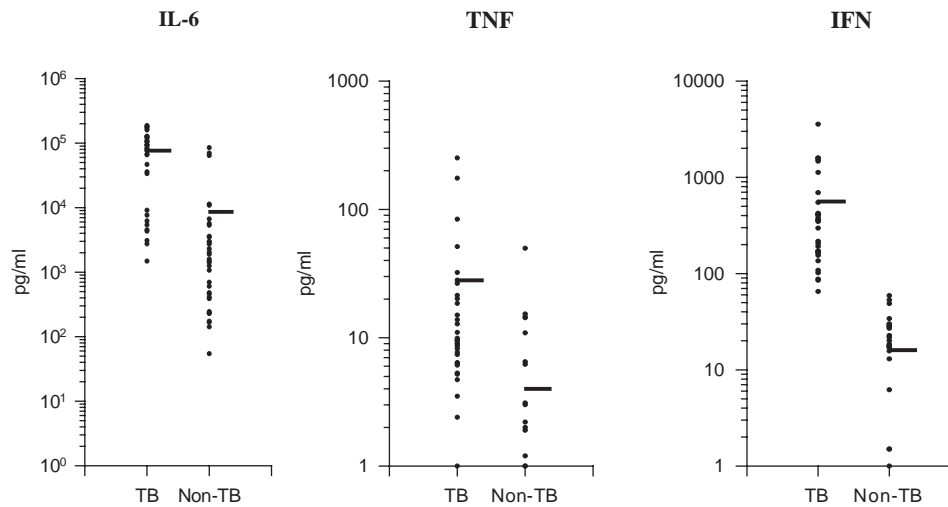
### Results

Thirty-two cases of pleural TB were enrolled into the study. They include 23 male and nine female patients with a mean age of 52.0 years (range: 17–85 years). All except two cases had diagnosis confirmed by either pleural biopsy showing granulomatous inflammation or pleural fluid growing *Mycobacterium tuberculosis*. Thirty-four cases of non-TB pleural effusion were recruited as control. They included 29 cases of malignant effusion (all due to metastatic carcinoma of lung) and five cases of transudative effusion (congestive heart failure = 4 and chronic renal failure = 1).

The individual values of the three cytokines are presented in Fig. 2.

Table 1 shows the mean levels of the three cytokines in the pleural fluid of 32 TB and 34 non-TB cases. The levels of IL-6, TNF- $\alpha$  and IFN- $\gamma$  in pleural fluid of the TB patients were significantly higher than those from non-TB effusions. Diagnostic utility of these cytokine measurements for TB effusion was evaluated using ROC curve analysis (Fig. 3). The cut-off values that give the best diagnostic accuracy for IL-6, TNF- $\alpha$  and IFN- $\gamma$  determined in this analysis were 4000, 4 and 60 pg/ml, respectively. Using these cut-off values, the sensitivity, specificity and the diagnostic accuracy obtained for each cytokine are shown in Table 2.

Eighteen of the 32 pleural TB cases had fever at presentation. There was no correlation found between the presence of fever and any of the pleural fluid cytokine levels. However, the pleural fluid IL-6 level was found to have a positive correlation to the number of febrile days after the commencement of anti-TB treatment ( $r = 0.60$ ,  $P = 0.009$ ) (Fig. 4).



**Figure 2** Individual values of pleural fluid levels of IL-6, TNF- $\alpha$  and IFN- $\gamma$  in pleural TB and non-TB effusion (horizontal bar representing the means of the values).

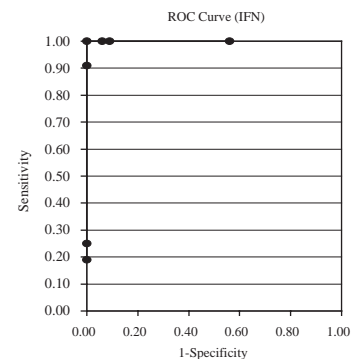
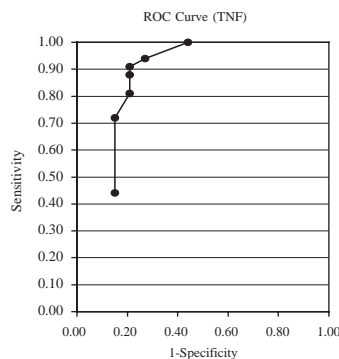
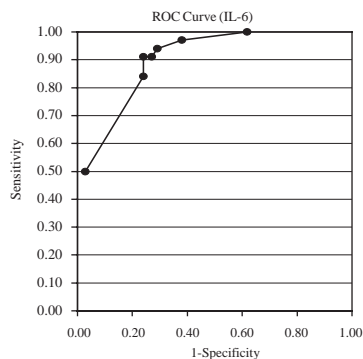
**Table 1** Values of IL-6, TNF- $\alpha$  and IFN- $\gamma$  in pleural fluid of patients with pleural TB and non-TB effusions

Cytokine	TB effusion (n: 32)		Non-TB effusion (n: 34)		P
	Mean (pg/ml)	SD	Mean (pg/ml)	SD	
IL-6	76,426	59,229	8,752	20,673	< 0.001
TNF- $\alpha$	27.5	52.2	4.2	9.2	0.018
IFN- $\gamma$	559.5	718.6	15.6	16.5	< 0.001

IL-6	1-Specificity	Sensitivity	LR+	LR-
80000	0.03	0.50	17.00	0.52
5000	0.24	0.84	3.50	0.21
<b>4000</b>	<b>0.24</b>	<b>0.91</b>	<b>3.79</b>	<b>0.12</b>
3500	0.27	0.91	3.37	0.12
3000	0.29	0.94	3.24	0.08
2500	0.38	0.97	2.55	0.05
1000	0.62	1.00	1.62	0.00

TNF	1-Specificity	Sensitivity	LR+	LR-
10	0.15	0.44	2.93	0.66
7	0.15	0.72	4.80	0.33
6	0.21	0.81	3.86	0.24
5	0.21	0.88	4.19	0.15
<b>4</b>	<b>0.21</b>	<b>0.91</b>	<b>4.33</b>	<b>0.11</b>
3	0.27	0.94	3.48	0.08
1	0.44	1.00	2.27	0.00

IFN	1-Specificity	Sensitivity	LR+	LR-
1000	0.00	0.19		0.81
500	0.00	0.25		0.75
100	0.00	0.91		0.09
<b>60</b>	<b>0.00</b>	<b>1.00</b>		<b>0.00</b>
50	0.06	1.00	16.67	0.00
40	0.09	1.00	11.11	0.00
10	0.56	1.00	1.79	0.00



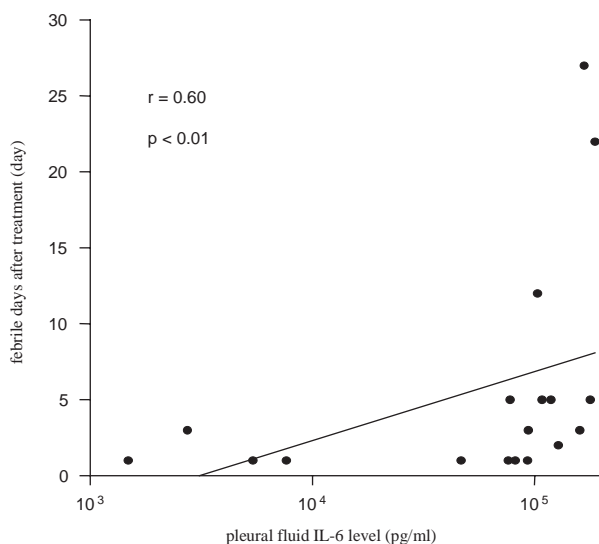
**Figure 3** Receiver operating characteristic curves for using IL-6, TNF- $\alpha$  and IFN- $\gamma$  for diagnosis of pleural TB (figures in bold representing the cut-off values for best diagnostic accuracy).

Chest radiograph was taken for monitoring of the amount of effusion for 29 TB patients after 2 weeks of anti-TB treatment. The amount of pleural effusion was assessed to be small (less than 15%

of the lung field) in 11 patients, and thus a second pleural tapping was not attempted. In the remaining 18 cases, 11 agreed to undergo a second thoracentesis and had fluid sent for cytokine assay.

**Table 2** Sensitivity, specificity and accuracy in the diagnosis of TB using the best cut-off value for IL-6, TNF- $\alpha$  and IFN- $\gamma$  in pleural fluid

	Cut-off ( pg/ml)	Sensitivity (%)	Specificity (%)	Diagnostic accuracy (%)
IL-6	4,000	90.6	76.5	83.3
TNF- $\alpha$	4	90.6	79.4	84.8
IFN- $\gamma$	60	100	100	100

**Figure 4** Correlation between pretreatment pleural fluid IL-6 level and the number of febrile days after treatment in patients with TB effusion ( $r$ : Pearson correlation coefficient).

Chest radiographs of 28 patients were evaluated after completion of TB treatment (one died of heart disease during treatment, one excluded because of bacillary multidrug-resistance and two were lost to follow-up). Eight cases (28.6%) had residual pleural scarring. There was no correlation between the pleural fluid cytokine levels and the presence or the extent of residual pleural scarring. However, on analysis of the cases in which a second pleural fluid specimen was taken for cytokine assay, a statistically significant negative correlation was found between the percentage reduction of cytokine levels after 2 weeks and the extent of residual pleural scarring (Fig. 5).

## Discussion

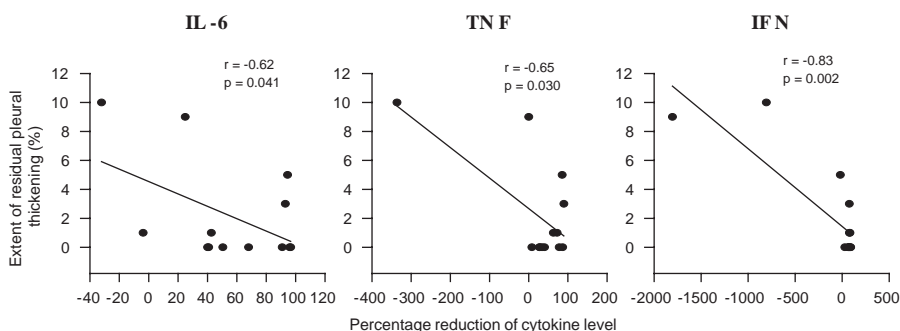
TB pleuritis depicts an inflammatory response to the mycobacteria in the pleural cavity. Mycobacterial antigens interact with previously sensitized T-lymphocytes and cause an immunological or

hypersensitivity reaction.<sup>22</sup> Many inflammatory cells including neutrophils, mononuclear cells, lymphocytes and mesothelial cells alongside a complex array of cytokines, are involved in granuloma formation and alteration of coagulation locally.<sup>23,24</sup> This reaction leads to an increase in permeability of pleural capillaries and impairment of clearance of proteins by the lymphatics, resulting in the formation of an exudative pleural effusion.

IL-6, TNF and IFN- $\gamma$  are three important cytokines putatively involved in the inflammatory process of the TB effusion. Although they are also found in other inflammatory or neoplastic conditions of the pleura, it has been reported in some studies that these cytokines are markedly elevated in TB as compared to the other conditions.<sup>7-9,11-21</sup> This is particularly true for IFN- $\gamma$  and the usefulness of this cytokine in differential diagnosis of pleural TB has been well reported.<sup>14,17-19</sup> However for IL-6, the diagnostic utility is somewhat conflicting.<sup>10,11</sup> For TNF, Ogawa et al. found elevation of pleural fluid TNF in both TB and parapneumonic effusion as compared to malignancy,<sup>14</sup> but other reports found elevation of TNF levels in TB when compared to other conditions.<sup>8,12,13,15</sup>

The results of our study showed a significant difference in the levels of all three cytokines in the pleural fluid between TB and non-TB patients. These cytokines, especially IFN- $\gamma$ , can be useful in enabling the diagnosis of TB pleural effusion. Our results largely corroborate those of other investigators. However, due to the relatively small sample size, the cut-off values derived in this study would preferably be tested on a larger number of patients with pleural effusion with different etiologies in the local community to determine whether the sensitivity and specificity would be acceptable for the test to be put to clinical use in the diagnosis of TB effusion.

Pleural fluid IL-6 level was also found to be very high and correlated with the number of febrile days after treatment. It might reflect the important role of this orchestrating cytokine in the induction and maintenance of inflammatory response<sup>25</sup> as well as its property of an endogenous pyrogen.<sup>26,27</sup>



**Figure 5** Relationship between the extent of residual pleural scarring and the percentage reduction in pleural fluid cytokine levels after 2 weeks ( $r$ : Pearson correlation coefficient).

There is currently scanty data on the role of pleural fluid cytokine measurement in the prediction of outcome of pleural TB, in particular the presence or extent of residual pleural thickening. De Pablo and colleagues found a higher fluid TNF level in those patients who developed pleural thickening than those without pleural thickening.<sup>28</sup> A recent study by Kunter and colleagues also demonstrate a correlation between the development and degree of pleural thickening and TNF level in the pleural fluid.<sup>29</sup> In Chinese TB patients, Hua and colleagues found higher levels of TNF and IL-1 $\beta$  in the pleural fluid of those with residual pleural thickening.<sup>15</sup> In our study, there was no correlation between the residual pleural scarring and the initial fluid levels of any of the three cytokines. However, a negative correlation was found between the extent of pleural scarring and the percentage decrease of the levels of cytokines in the pleural fluid. This might suggest that the association between residual pleural scarring and pleural inflammation rests more on the rate of resolution of the inflammation rather than its intensity on presentation. Thus, the proportional decrease in pleural fluid cytokine levels at 2 weeks might help in identifying the risk of subsequent development of pleural scarring. Confirmation of these findings with a larger sample size would be useful.

Furthermore, studies on possible therapeutic interventions in ameliorating this important sequel appear warranted. At the moment, evidence from randomized controlled trials regarding hastening of resorption of pleural effusion by corticosteroids is equivocal, and does not suggest the value of corticosteroids in reducing residual pleural thickening.<sup>30–33</sup> However, our findings subject to consolidation, might enable selection of a more homogenous patient population for such intervention studies.

## Conclusion

Pleural fluid IL-6, TNF- $\alpha$  and IFN- $\gamma$  assays are useful in the diagnosis of pleural TB. The percentage change of these cytokines after 2 weeks of treatment also helps to predict the outcome of pleural TB.

## Acknowledgements

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