Th1/Th2 Cytokine Profiles Differentiating Tuberculous from Malignant Pleural Effusions: A Systematic Review and Meta-Analysis

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Abstract

To clarify which one has a different predominance of Th1 and Th2 immune responses in malignant and tuberculous pleural effusions. We did a meta-analysis of the results published previously to assess the levels of Th1/Th2 cytokines in two types of pleural effusion, and evaluated its ability to distinguish TPE from MPE. We queried the PubMed and Embase databases for studies indexed from 2000 up to March 2021. We included studies that (a) diagnosis of TPE and MPE by on culture, or pleural biopsy tissue provided; (b) compared levels of Th1/Th2 cytokines in pleural effusion between TPE and MPE. Pooled data by using a random-effects model or fixed-effects model, standardized mean differences (SMD) across studies comparing TPE and MPE. We also performed Egger test to *assess of publication bias*. Of 917 identified studies, a total of 42 studies were selected in the meta-analysis. Compared with malignant subjects, tuberculous subjects had a significant higher level of TNF- α [2.22, (1.60–2.84)], an elevated level of IFN- γ [3.30, (2.57–4.40)] in pleural effusion, a situation where the Th1 immune response dominates. Conversely, Interleukin-4 (IL-4) and IL-10 (Th2 cytokines) levels were higher in MPE than TPE. Besides, they were shown to be statistically insignificant tiny effects were [-0.15, (-0.94–0.63)], [-0.04, (-0.21–0.12)] respectively. We confirmed that pleural effusions caused by tuberculosis, a situation in which the Th1 cytokines are predominant. The slight preponderance of Th2 cytokines in malignant pleural effusions, which are not convincing enough to prove.

Introduction

Malignant and tuberculous pleural effusions are the two most common types of exudative pleural effusions, both of which can be seen with the typical accumulation of lymphocytes. [1, 2]. The naïve CD4⁺ T cells are activated by antigen-MHC complex, then differentiate toward functional subsets T-helper 1(Th1) or T-helper 2 (Th2) lineage[3]. Th1 cytokines, including interleukin (IL)-2, tumor necrosis factor (TNF)- α , and interferon (IFN)- γ , Instead IL-4, IL-5, and IL-10 are considered to be Th2 cytokines[4]. IL-6 as an inflammatory cytokine, produced by monocytes, macrophages, and dendritic cells[5, 6]. IL-6 has emerged as an important regulator of Th1/Th2 differentiation, promoting the induction of Th2 differentiation is dependent upon IL-4, inhibiting Th1 differentiation by upregulating suppressor of cytokine signaling (SOCS)-1 expression[7].

Immune responses mediated by either the Th1 or Th2 subset dominate, depending on different types of pleural effusion. Tuberculous pleural effusion (TPE) is a Th1-dominant disease[8]. The Th1-dominated immune response is thought to be a considered important factor in the containment of mycobacteria, and the main immune effector mechanism involves classically activated macrophages that arise in response to Th1 cytokine signals[9]. Instead, Malignant pleural effusion (MPE) is suggestive of Th2 cytokine-predominant conditions[10, 11]. Although Some reports have shown that a bias towards a *Th2* predominant state in MPE, some reports *did not clearly* show predominance[12].

Therefore, in this study, we performed a meta-analysis of all available studies to quantitatively evaluate the levels of Th1/Th2 cytokine profiles in TPE and MPE, as well as to assess the potentially diagnostic

value of these cytokines in discriminating TPE from MPE.

Materials And Methods

This meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement [13]. An approval from institutional review board was not necessary as we extracted only summary information from previously published articles.

Search strategy

A systematic search was conducted in PubMed, Embase databases from 2000 up to March 2021 (Zeng Y.L. and Qi Y.). We selected eligible studies documenting the levels of pleural effusion about Th1/Th2 cytokine profiles. The following key words were used to search in the above databases: malignant pleural effusion, tuberculous pleural effusion, tumor necrosis factor-alpha, TNF- α , *interferon gamma*, IFN- γ , interleukin 2, IL-2, interleukin 4, IL-4, interleukin 5, IL-5, interleukin 6, IL-6, interleukin 10, IL-10. The details of the strategy are available in Supplementary Methods.

Study selection and data extraction

Inclusion criteria: 1) original and human studies; 2) studies with a title or abstract including the terms “tuberculous and malignant pleural effusion” and “cytokines”; 3) studies reporting the pleural effusions levels of TNF- α , IFN- γ , IL-2, IL-4, IL-5, IL-6, IL-10 in patients; 4) malignant pleural effusion was diagnosed by malignant cells shown in pleural fluid or pleural biopsy; 5) tuberculous pleural effusion was diagnosed by Ziehl–Neelsen stains or positive mycobacteria culture, or pleural biopsy tissue samples were positive; 6) the full text of studies can be found in the database. No limitation was applied for the histological type of malignant pleural effusion, *stages of cancer*, severities of the disease, or region and race of the study subjects. We extracted demographic details from each included study: the country of origin, surname of the first author, year of publication, sample size, research design, age. The standard deviation (SD), median, *interquartile range* (IQR) pleural effusions levels of Th1/Th2 cytokine profiles were extracted for each potentially included study. The data extraction was conducted by two independent investigators via a form created for this study. Divergences were resolved by consensus or by consulting a senior investigator.

Quality evaluation

We used the Newcastle-Ottawa Scale (NOS) to assess methodological quality of studies describing differences in levels of Th1/Th2 cytokine profiles in TPE and MPE, and considered any study with a score of 6 or more (the highest score is 9) as being of good quality. The results are displayed in Supplementary Methods. Two reviewers independently evaluated the quality of each study.

Statistical analysis

The outcomes were all continuous variables: tuberculous and malignant pleural effusions levels of Th1/Th2 cytokine profiles. Data provided as mean and standard deviation were extracted. Data provided as median and interquartile range (IQR) was transformed to mean and standard deviation through according to the method devised by S.P. Hozo (2005)[14]. We used standardized mean differences (SMD) and 95% CI to assess the levels of Th1/Th2 cytokine profiles in TPE compared to MPE. The Cochran's Q test, I^2 statistic and P value were used to value the heterogeneity. A $P \geq 0.1$ or $I^2 \leq 50\%$ was considered as no significant heterogeneity, and the fixed-effects model (FEM) was applied; otherwise, the random-effects model (REM) was used. We used the sensitivity analysis to value the robustness. Subgroup analyses stratified studies by covariables including country, design, etiology, publishing year and quality scores were analyzed to explore potential sources of heterogeneity. The software *RevMan* 5.2 and *STATA version 14.0* was used for the statistical analyses and images. Begg's test were used in assessing the asymmetry of the funnel plot. $p < 0.05$ was considered as publication bias, and if present, the trim-and-fill method was adopted to determine the influence of publication bias on results.

Results

Table 1. Included all original studies of characteristics about Th1/Th2 cytokine profiles in tuberculous and malignant pleural effusions.

						Heterogeneity(%)		<i>p</i> value
Cytokines	No. of Studies	No. of patients	Assay methodology	SMD (95%)	Model	ρ	<i>P</i>	
TNF- α	19 [15-33]	TPE:571 MPE:661	ELISA (N=19)	2.22	Random	95	<0.001	<0.001
IFN- γ	20 [12, 16, 17, 19, 28, 32, 34-47]	TPE:728 MPE:992	ELISA (N=20)	3.82	Random	97	<0.001	<0.001
IL-2	3 [35, 48, 49]	TPE:179 MPE:210	ELISA (N=1) Others (N=2)	-0.07	Fixed	46	0.16	0.47
IL-4	6 [12, 19, 35, 40, 49, 50]	TPE: MPE:	ELISA (N=4) Others (N=2)	-0.15	Random	92	<0.001	0.70
IL-6	12 [21, 26, 31, 39, 48-55]	TPE:361 MPE:731	ELISA (N=7) Others (N=5)	3.53	Random	98	<0.001	<0.001
IL-10	8 [12, 19, 20, 28, 34, 48-50]	TPE:280 MPE:549	ELISA (N=5) Others (N=3)	0.17	Random	66	0.005	0.25

Characteristics of included studies.

A total of 917 potentially relevant studies identified from the database were retrieved, of which 43 studies were included in the final meta-analytical processes. The study selection process was detailed in *Fig. 1*. In addition, we provided the details of the selected studies in *Table 1*. Considering the large number of included studies for TNF- α and IFN- γ , we only selected the results of ELISA measurements, but other methods of measurements were included in the remaining cytokines [included cytometric bead array (CBA), chemiluminescent enzyme immunoassay (CLEIA), radioimmunoassay (RIA)]. One study was finally excluded due to cytometric bead array measuring IFN- γ levels [56]. The quality ratings for each study and characteristics of studies included are presented in Supplementary Methods.

The levels of Th1/Th2 cytokine profiles in in TPE and MPE

Analysis of TNF- α

In a pooled analysis of all 19 trials, the results revealed that there was a significant increase in the pleural effusion levels of TNF- α in tuberculous subjects compared to malignant subjects [2.22, (1.60–2.84, $p < 0.00001$)] (*Fig. 2*). However, there was statistically significant heterogeneity among studies (I^2 95%). Subsequently, sensitivity analysis (*Fig. S1*) was conducted by excluding one by one at a time, none of the magnitude and direction of the effect size was substantially altered. We showed that pooled SMD appreciably had stability and reliability, implying that the higher TNF- α levels in tuberculous pleural effusion. To examine the sources of the heterogeneity, we perform subgroup analysis stratified by variables, including country, design, etiology, publishing year and quality scores into the meta-regression. In stratified analyses (*Table S1*), there was no reliable evidence that for the above variables was the main source of heterogeneity. We consider that the remaining higher heterogeneity is due to differences in ELISA manufacturers, and severities of the disease of selected studies. In this analysis there was publication bias on Begg's Test ($p < 0.05$). We therefore used the trim-and-fill method to adjust for publication bias and examined its effect on the pooled SMD (*Supplementary Methods*), yielding an adjusted effect (SMD= 1.038, 95% CI 0.328–1.748, $p < 0.01$).

Analysis of IFN- γ

Pooled analysis of all 20 trials revealed that there was a significant increase in the pleural effusion levels of IFN- γ in tuberculous subjects compared to malignant subjects [3.82, (2.97–4.66, $p < 0.00001$)] (*Fig. S2*), with statistically significant between-study heterogeneity (I^2 97%). Subsequently, we performed the sensitivity analysis shows that there is a considerable variation in one trial ([19, 32, 36, 44, 47]). After the deletion of that trial, the remaining results proved to be stable through sensitivity analysis, the random-effects model of pooled SMD [3.30, (2.57–4.40, $p < 0.00001$)] (*Fig. 3*). Based on our pooled data, suggesting that the higher IFN- γ levels in tuberculous pleural effusion. However, despite a decrease in heterogeneity (I^2 from 97% to 95%) with the removal of that trial, substantial heterogeneity still existed. To explore possible sources of heterogeneity, we further performed subgroup analyzes stratified for the following categories: country, design, etiology, publishing year and quality scores into the meta-regression. In stratified analyses (*Table S2*), there was no reliable evidence that for the above variables was the main source of heterogeneity. While Egger's test indicates evidence of publication bias ($p < 0.05$). The trim and fill method imputed 3 missing studies to add to the left of the funnel plot to ensure symmetry (random-effects model), the pooled SMD was adjusted [2.567, 95% CI 1.750–3.384, $p < 0.001$] (*Supplementary Methods*).

Analysis of IL-2

As can be seen in *Fig. 4*, although pooled analysis of all 3 included trials revealed that the fixed-effects model of pooled SMD [-0.07, (-0.28–0.13, $p < 0.00001$)], suggested that IL-2 levels were higher in malignant subjects compared to tuberculous subjects, they were not statistically significant [p

=0.47 >0.05]. The reason for this result is probably due to the small number of included studies. An assessment of publication bias was not accomplished due to fewer than 10 trials were included.

Analysis of IL-4

Pooling the data from the 6 trials revealed that the random-effects model of pooled SMD [-0.15, (-0.94–0.63)] with statistically significant between-trial heterogeneity (I^2 92%), and the results of this are presented in *Fig. 5*. In malignant subjects had a significantly higher levels of IL-4 compared with than tuberculous subjects, but were not statistically significant (p =0.70 >0.05).

Analysis of IL-10

A meta-analysis of the data from 8 trials about IL-10 was performed, and the results of this are presented in *Fig. S3a*, a random-effects model of pooled SMD [0.17, (-0.12–0.46)]. However, there was statistically significant heterogeneity among the above results (I^2 66%, p < 0.00001). We excluded 2 studies[48, 50] according to the results of Galbraith radial plot (*Fig. S3b*), the heterogeneity was decreased appreciably (I^2 from 66 to 0%) shown in *Fig. 6*. On the basis of 6 remaining trials revealed that the fixed-effects model of pooled SMD [-0.04, (-0.21–0.12)], suggesting that the higher IL-10 levels in malignant subjects.

Analysis of IL-6 between TPE and MPE

IL-6 was the most commonly measured inflammatory cytokine. On the basis of total 12 trials, the random-effects model of pooled SMD was [3.53, (2.16–4.90)], with substantial heterogeneity between studies (I^2 = 98%, p < 0.00001) in *Fig. 7*. The pooled results confirmed that levels of IL-6 in TPE were higher than patients with MPE. To assess the stability of the pooled results of the meta-analysis of IL-6, sensitivity analysis was conducted by excluding one by one at a time. None of the magnitude and direction of the effect size was substantially altered, indicating that our results were robust. Furthermore, we also excluded 2 slight offset trials[21, 53], suggested by sensitivity analysis (*Fig. S4a*). After the deletion of 2 trial, the remaining results proved to be stable through sensitivity analysis (*Fig. S4b*), which had no appreciable change on the pooled SMD [1.92, (1.13–2.71)], but the heterogeneity was decreased (I^2 from 98 to 94%) (*Fig. S4c*). To test the robustness of our results, we perform stratified analyses to detect the sources of the heterogeneity in this study in *Table S3*. Among the total 12 trials, 7 studies used ELISA measurements and the remaining 5 studies used other measurements (included 2 of CBAs, 2 of RIAs, and 1 of CLEIA). Consequently, we consider that main heterogeneity arises from differences in measurement methods. However, insignificant differences in between-group heterogeneity was found in some stratified analyses, meanwhile measurement methods did not indicate additional sources of heterogeneity. In this analysis there was no publication bias on Egger test (p = 0.150, *Supplementary Methods*).

Discussion

To the best of our knowledge, this is the first large-scale meta-analysis to systematically investigate the levels of Th1/Th2 cytokines in MPE and TPE. Our results showed that in TPE, a situation in which the level of Th1 cytokine profile was predominant compared to MPE. We confirmed that TPE was an immune response dominated by Th1 polarization. Although significant heterogeneity was detected, subsequent through sensitivity analysis and Galbraith radial plot to exclude trials with extreme SMDs, which diminished *heterogeneity* and get more stable results. We considered differences in ELISA manufacturers and severities of the disease may be responsible for the heterogeneity. Despite the slightly bias toward Th2 cytokines in malignant pleural effusions, the pooled SMD was not statistically significant.

Exudative pleural effusion is a vicious loop of interactions between immune system and pleural or parenchymal disease like tuberculosis infection, malignancy or inflammation. It results in abnormal accumulation of fluid in the pleural space via altering the permeability of the pleural membranes to enhance plasma extravasation. Tuberculosis and malignant disease are among most frequent causes of exudative pleural effusions. The T helper cells are known to have important bearing on the pathogenesis of exudative pleural effusion and host defense.

Th1 cells have been observed to have an anti-infectious role in tuberculosis[57]. Th1-mediated host immunity inhibits further multiplication of *Mycobacterium tuberculosis* (Mtb) via the secretion of IFN- γ and other Th1 cytokines, which activate macrophages, promote phagosome maturation to stimulate phagocytosis, and stimulate the production of reactive nitrogen intermediates[58]. TNF- α , it is essential for stimulating the chemotaxis of inflammatory cells to sites of infection, and *leads* to *granulomatous* response to containment disease progression[59]. Normally, IL-6 was manifested in its role as a proinflammatory cytokine, induces the production of acute phase proteins to promote inflammation. Nevertheless, macrophages infection with Mtb induced production of IL-6 inhibited of macrophage response to IFN- γ , resulting in the inability to eradicate Mtb infection[60]. The increased IL-6 levels could also contribute to increased expression of suppressor of cytokine signaling (SOCS) in TB[61]. SOCS1 was regarded as an important mediator, inhibits macrophage IFN- γ secretion that in turn accounted for hampered Mtb clearance early by macrophages [62]. Consistent with the results of other studies, our study found higher levels of IL-6 in TPE, which suggested that IL-6, as an important cytokine may be involved in the formation process of TPE and play an important role in the occurrence and development of pulmonary tuberculosis (PTB).

Different from Th1 cytokines, IL-10 is considered as an inhibitory and anti-inflammatory Th2 cytokine that negatively regulates IFN- γ mediated host immunity, limits pathogen clearance in the early immune response to Mtb and mediates long-term chronic infection[63]. Besides, the IFN- γ /IL-10 ratio could be a useful objective marker of the clinical severity of tuberculosis[64]. Also, the IL-4 is a classic Th2 cytokine that may subvert mycobacterial containment in macrophages by perturbing Th1-related pathways and regulatory T cells (Tregs)[65].

Early studies have suggested that Th1 and Th2 cell producing cytokines plays important roles in the immune microenvironment of tumors, Th1 cytokines relevant to antitumor immunity, whereas Th2 cytokines are related to tumor invasiveness and metastasis[66]. Notably, in advanced cancer often found a shift from Th1 to Th2 T cells in the tumor environment, associated with impaired Th1 cell-mediated immunity along with progression of cancer[67, 68]. Anthony et al have reported that patients with advanced squamous cell carcinoma were found diminish Th1 antitumor immune response but stronger underlying Th2 immune response[69]. This shift was further demonstrated in malignant effusions[70]. Accordingly, these studies collectively point to a shift from Th1 to Th2 T cell response in the microenvironment of tumors may play a crucial role in the development and progression of tumor. Moreover, evidence indicates that tumor-derived TGF- β induced overexpression levels of IL-10, leading to drive the shift in the Th1/Th2 balance toward Th2 response and inhibiting the Th1 response[71]. The balance of these Th1/Th2 cytokines in the MPE remains controversial. We speculate that the shift from Th1 to Th2 along with tumor progression may explain this discrepancy about whether Th2 cytokines predominates in malignant pleural effusions in our study, but this needs to be studied further.

As future studies clarify the role of Th1/Th2 cytokine profiles and their effect on the local immune response, new therapeutic approaches to immunotherapy may be developed. Currently, the useful therapeutic strategy to cytokine/anti-cytokine therapy is that supplementation of anti-inflammatory recombinant cytokines as well as neutralizing cytokines or antagonizing receptors by monoclonal antibodies (mAbs). Recombinant IL-2 has been used successfully for *cancer* therapy and was approved for the treatment for metastatic renal-cell carcinoma in 1992 and for metastatic melanoma in 1998 by FDA. Infliximab, a chimeric anti-TNF α monoclonal antibody, has been demonstrated to be an effective therapy for rheumatoid arthritis, Crohn's disease, ankylosing spondylitis and other autoimmune diseases. Despite these beneficial effects of infliximab treatment in autoimmune diseases, it carries the risk of TB occurrence and latent tuberculosis reactivation[72]. Based on the immunosuppressive ability of IL-10 in tumor immunity, therapeutic strategies targeting the IL-10 signaling pathway have evolved considerably in cancer immunotherapy[73]. In addition, overexpression of IL-4 and IL-13 receptors on cancer cells as specific targets *for receptor-directed* cancer immunotherapy[74]. Our study confirms changes in the Th1/Th2 cytokine profiles of patients with TPE and MPE, which may be helpful for future investigation about cytokine therapy.

Moreover, combining multiple biomarkers has previously been shown to enhance diagnostic accuracy. It was found that the combination of TNF- α and adenosine deaminase 2 (ADA₂), could be could improve the specificity and accuracy of diagnosis for the differentiation of TPE from MPE[28]. Future studies are needed to determine if Th1/Th2 cytokines confers *supplementary* diagnostic value for PE.

There are some unavoidable limitations of our study that are deserving of attention. First, significant heterogeneity was observed in some of our results, although stratified analyses were done, we did not identify the source of heterogeneity. Second, some of trials provide only the median and IQR levels of cytokines, which we converted to mean and standard deviation by Hozo et al.'s method, which might lead

to the estimates of the data are slightly skewed. Third, the sample size included in studies on Th2 cytokines was relatively small, only six trials were included in the pooled results respectively. Fourth, we did not examine the effect of the stages of cancer on cytokine levels in the included studies, which might lead to heterogeneity and deviation in this analysis. Fifth, few studies have reported the primary tumor causing malignant pleural effusions and the histological type of primary tumor, future studies should be continued to investigate its effect on cytokine levels.

Conclusion

In summary, this systematic review and meta-analysis confirms that pleural effusions caused by tuberculosis, a situation in which the Th1 cytokines is predominant, but malignant pleural effusions are slightly bias toward Th2 cytokines is not sufficiently convincing to prove. Our findings support the concept that these cytokines are likely to serve *supplementary* diagnostic value for the differentiation of TPE from MPE. Moreover, it is important to know the role of cytokines derived from T helper cell on the pathogenesis of diseases and host defense, which may provide new clues for the treatment of cytokine immunotherapy.

Declarations

Acknowledgments

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Contributions

Z.Y.L. conceived and designed the study; Z.Y.L. and Q.Y. performed the systematic literature search and quality assessment; Z.Y.L., Q.Y. and Z.H. analyzed the data; Z.Y.L drafted the initial manuscript; W.L.W reviewed the manuscript and critically edited and revised the manuscript. All authors approved the final version of the manuscript as submitted.

Competing interests

The authors declare that there are no other competing financial interests

Data availability

The data sets supporting the results of this article are included within the article and its supplementary material.

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Figures

Figure 1

PRISMA flow chart of the selection of studies.

Figure 2

Forest plot for combined 19 studies comparing TNF- α levels in tuberculous pleural effusions and malignant effusions. Standardized mean-difference (the pleural effusion levels of TNF- α of tuberculous subjects minus that of malignant subjects) was estimated by meta-analysis.

Figure 3

Forest plot for combined 19 studies comparing IFN- γ levels in tuberculous pleural effusions and malignant effusions. Standardized mean-difference (the pleural fluid levels of IFN- γ of tuberculous subjects minus that of malignant subjects) was estimated by meta-analysis.

Figure 4

Forest plot for combined 3 studies comparing IL-2 levels in tuberculous pleural effusions and malignant effusions. Standardized mean-difference (the pleural effusion levels of IL-2 of tuberculous subjects minus that of malignant subjects) was estimated by meta-analysis.

Figure 5

Forest plot for combined 6 studies comparing IL-4 levels in tuberculous pleural effusions and malignant effusions. Standardized mean-difference (the pleural effusion levels of IL-4 of tuberculous subjects minus that of malignant subjects) was estimated by meta-analysis.

Figure 6

Forest plot for combined 6 studies comparing IL-10 levels in tuberculous pleural effusions and malignant effusions. Standardized mean-difference (the pleural effusion levels of IL-10 of tuberculous subjects minus that of malignant subjects) was estimated by meta-analysis.

Figure 7

Forest plot for combined 12 studies comparing IL-6 levels in tuberculous pleural effusions and malignant effusions. Standardized mean-difference (the pleural fluid levels of IL-6 of tuberculous subjects minus that of malignant subjects) was estimated by meta-analysis.

Supplementary Files

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