Research Article

Diagnostic Value of Soluble Form of Mer Tyrosine Kinase (sMerTK) in Tuberculous Pleural Effusion and Malignant Pleural Effusion

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Objectives. With the development of proteomics, it has been indicated that differentially expressed proteins are biological markers for the diagnosis of different types of pleural effusion (PE). The aim of our study was to explore the value of sMerTK (soluble form of Mer tyrosine kinase) in the differential diagnosis of tuberculous pleural effusion (TPE) and malignant pleural effusion (MPE). In addition, we also wanted to explore whether MerTK was associated with IL-1β and TNF-α, which are inflammatory factors related to pleural effusion. *Methods*. We screened all patients who underwent thoracoscopy and had a definite diagnosis. In total, 136 patients were enrolled in this study and classified into two groups, with 64 patients in the TPE group and 72 patients in the MPE group. The concentrations of sMerTK in the TPE and MPE groups were detected by ELISA. The diagnostic accuracy was determined by generating receiver operating characteristic (ROC) curves and calculating the area under the curve (AUC). Correlations between the expression level of sMerTK and those of the inflammatory factors interleukin 1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) were also studied using Pearson's linear correlation analysis. *Results*. The concentrations of sMerTK were $5,278.77 \pm 2,479.98$ ng/L and 859.91 ± 540.45 ng/L in the TPE and MPE groups, respectively. The concentration of sMerTK in TPE was shown to be significantly higher than that in MPE ($P < 0.05$). The area under the ROC curve for sMerTK in distinguishing TPE from MPE was 0.958, with a cutoff value of 2,122 ng/L. The sensitivity and specificity for sMerTK were 98.61% and 90.63% ($P < 0.05$). The expression levels of sMerTK in these two groups were not correlated with those of the inflammatory factors IL-1β and TNF-α ($P > 0.05$). *Conclusions*. The expression level of sMerTK in PE could be a potential biomarker for common use in the diagnosis of TPE and MPE.

1. Introduction

Pleural effusion (PE) is a common clinical finding characterized by pathological fluid accumulation in the pleural cavity. The pleural cavity is a potential space between the visceral and parietal pleura. A normal person has a thin layer of fluid in the pleural cavity. This fluid provides lubrication during breathing. Approximately 500~1,000 mL of fluid is formed and absorbed in the pleural cavity every day. The formation and absorption of fluid in the pleural cavity occur in a dynamic balance. PE can occur for any reason when liquid

production increases or liquid absorption decreases. Despite the variety of conditions associated with effusions, many are idiopathic, and these effusions tend to follow a benign course [1]. Effusions can be divided into transudative PE and exudative PE. Clinically, transudative PE is commonly seen in hypoproteinemia, heart failure, and other diseases. By combining the patient's primary disease and the diagnostic criteria of Light [2], transudative PE is relatively easy to diagnose. However, exudative PE is commonly seen in tuberculosis (TB) and tumors. Although malignant pleural effusion (MPE) can be diagnosed by simple pleural fluid

TABLE 1: Demographic data of PE patients.

	TPE ($n = 64$)	MPE ($n = 72$)	P value
Age (years)	57.72 ± 15.68	60.48 ± 9.20	$P > 0.05*$
Sex (n)	M: 36 (56.3%)	M: 40 (55.6%)	$P > 0.05^{\#}$
	F: 28 (43.7%)	F: 32 (44.4%)	
ADA (U/L)	41.98 ± 14.69	13.20 ± 7.81	$P < 0.05*$
LDH (U/L)	623.84 ± 331.74	472.5 ± 310.7	$P < 0.05*$
LDH pleural/serum ratio	>0.6	>0.6	$P > 0.05^{\#}$
CEA in PE (ng/ml)	2.14 ± 5.26	84.10 ± 101.72	$P < 0.05*$
Protein (g/L)	44.74 ± 7.28	41.69 ± 8.59	$P < 0.05*$
Leukocyte count (10^6/L)	$1,480 \pm 346$	$1,040 \pm 268$	$P < 0.05*$
Lymphocyte (%)	88.00 (75.5–93.5)	76.5 (61.75–90.0)	$P < 0.05*$
Neutrophil (%)	5 (1–12.75)	7 (1.5–12)	$P > 0.05*$
Protein pleural/serum ratio	> 0.5	> 0.5	$P > 0.05^{\#}$
sMerTK	$5,278.77 \pm 2,479.98$	859.91 ± 540.45	$P < 0.05*$
IL-1β (pg/ml)	3.87 ± 2.36	2.08 ± 1.83	$P < 0.05*$
TNF-α (pg/ml)	379.95 ± 165.42	284.03 ± 129.32	$P < 0.05*$

TPE: tuberculous pleural effusion; MPE: malignant pleural effusion; F: female; M: male; ADA: adenosine deaminase; LDH: lactate dehydrogenase; CEA: carcinoembryonic antigen; PE: pleural effusion; sMerTK: soluble form of Mer tyrosine kinase; IL-1β: interleukin 1 beta; TNF-α: tumor necrosis factor alpha; *Used t-test; #Used Chi-squared or Fisher's exact test.

cytology, this method has significant limitations, including a highly variable sensitivity, ranging from as low as 11.6% to as high as 71%. Additionally, both tuberculous pleural effusion (TPE) and MPE are lymphocytic PEs, which are difficult to identify [3, 4].

At present, the clinical detection methods for TPE and MPE mainly include (1) the detection of acid-fast bacilli and tumor cells in the pleural sediment, which has a sensitivity of only 30-60%; (2) a tuberculosis bacillus culture carried out with PE fluid, which has a long culture cycle and a very low positive rate; (3) thoracoscopic pleural biopsy, which has a high positive rate but is invasive and expensive and therefore cannot be used for patients with economic difficulties and a poor physical condition; and (4) biochemical indicators commonly used in clinical practice, such as adenosine deaminase (ADA) and lactate dehydrogenase (LDH), which are often affected by various factors, resulting in poor sensitivity or specificity [5]. At present, the most common causes of exudative PE are cancer and infection in the pleural space [6]. The prognoses of these two diseases are completely different, so the identification of these forms of PE is particularly important. All the diagnostic methods described above have shortcomings, so more accurate and convenient diagnostic methods need to be found.

In recent years, with the development of proteomic technology, many scholars have found that differentially expressed proteins have significant clinical value as biological markers for the differential diagnosis of PE [7]. MerTK is a member of the TAM (Tyro-3, Axl, and Mer) family. Previous studies [8] have shown that MerTK contributes to regulating the innate immune response to apoptotic cells (ACs) by inhibiting dendritic cell (DC) activation in animal models, and

MerTK is a potent suppressor of the T cell response. As the pathogenesis of tuberculosis is closely related to the activation and apoptosis of T cells [9], the expression of MerTK may be potentially associated with tuberculosis. However, their correlation, especially between tuberculous pleural effusion and MerTK, has not been reported. Furthermore, studies have shown that MerTK is linked to tumorigenesis in some cancers, such as melanoma, astrocytoma, gastric cancer, and non-small cell lung cancer [10]. McIver [11] found a small molecule that inhibited the expression of the MerTK protein. MerTK protein inhibitors have dual therapeutic effects on tumors with MerTK expression (such as lung cancer and acute leukemia [12]), which are mainly exerted by reducing the survival and invasion of cancer cells and stimulating the antitumor immune response [11]. In conclusion, MerTK is closely related to tuberculosis and malignant tumors, and the concentration of its soluble form is feasibly detected, which also provides a basis for our study.

2. Materials and Methods

2.1. Study Design and Patients. Patients treated from April 2017 to September 2019 at the First Hospital of Jilin University were studied. The following inclusion criteria were used: patients of any sex with PE who were diagnosed with TPE or MPE using a thoracoscope. The exclusion criteria were as follows: (1) patients who had been clearly diagnosed with tuberculosis or a malignant tumor in the past and received regular antituberculosis treatment, anti-infection treatment, chemoradiotherapy, or immunotherapy; (2) patients who had bloody pleural effusion or transudative hydrothorax; and (3) patients who had severe heart disease (heart failure), liver disease, immune system disease, etc. The included patients
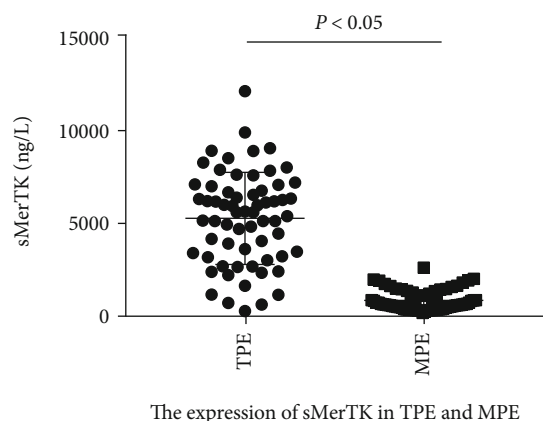
FIGURE 1: The expression levels of sMerTK in the TPE and MPE groups. The concentration of sMerTK in TPE was significantly higher than that in MPE ($P < 0.05$).

were classified into two groups—the TPE and MPE groups—according to the pathological diagnosis of their PE by thoracoscopy. The authors had access to information that could identify individual participants during data collection. This study has been approved and registered by the ethics committee of the First Hospital of Jilin University.

2.2. Sample Analysis. Each patient's pleural fluid was extracted by thoracocentesis and analyzed. Biomarkers were quantified in the pleural fluid supernatant. To obtain the supernatant, the pleural fluid was centrifuged at 1,500 revolutions per minute for 5 minutes. After the supernatant was extracted, it was centrifuged at 4,000 revolutions per minute for 10 minutes. After the first separation of the supernatant, the residual cells were taken as samples to observe the cell morphology. The concentration of the soluble form of MerTK in the supernatant was determined using a MerTK ELISA kit from ABCAM (Cambridge, MA, USA) according to the instructions. The experimental procedures for detecting the level of the inflammatory cytokines IL-1β and TNF-α in PE fluid were followed according to the instructions of the ELISA kit from BD Biosciences (San Jose, CA, USA) and ABCAM (Cambridge, MA, USA). The concentration of a standard product was taken as the horizontal coordinate, and the OD value of the standard product was taken as the vertical coordinate. Excel was used to draw the required standard curve and generate the corresponding linear regression equation. The OD value of a sample was substituted into the regression equation to obtain the concentration of the sample.

2.3. Statistical Analysis. Statistical analysis was performed using the Statistical Package for Social Sciences version 19 software (IBM Corp., Armonk, NY, USA) and the GraphPad Prism 7 software (GraphPad Software, San Diego, CA, USA). A P value less than 0.05 was considered statistically significant. If the continuous measurement was a normal distribution, the data are presented as the average (SD); otherwise, the data are presented as the median (IQR). The classification variable is presented as the count
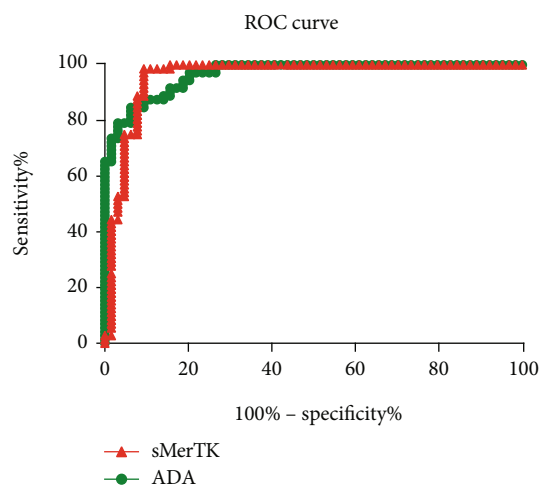

FIGURE 2: The ROC curves of sMerTK and ADA. The ROC curve for differentiating TPE from MPE. The AUCs for sMerTK and ADA were 0.958 and 0.966, respectively. The optimal cutoff values for sMerTK and ADA were 2,122 ng/L and 21.44 U/L.

(%). An independent-sample t-test and the Chi-squared or Fisher's exact test were used for comparing the differences between the groups. Receiver operating characteristic (ROC) curves were constructed to identify the diagnostic value of the sMerTK expression level. The areas under curves (AUC) were calculated with 95% confidence intervals (CI). The Youden index was performed to determine optimal cutoff values for each indicator. The Pearson linear correlation method was used to study the correlations between the expression level of sMerTK and the levels of various inflammatory factors, such as IL-1β and TNF-α, in PE. The correlation coefficient was expressed as r.

3. Results

The study population comprised 136 patients (76 males and 60 females) aged between 18 and 85 years old. In total, 64 patients had TPE, and 72 patients had MPE. The characteristics of the included patients are summarized in Table 1. The concentrations of ADA and LDH in the TPE group were significantly higher compared to the MPE group ($P < 0.05$). Meanwhile, carcinoembryonic antigen (CEA) in MPE was higher than that in TPE ($P < 0.05$), but the protein of the PE was lower in MPE than in TPE. The leukocyte count and the lymphocyte in TPE were significantly higher than those in MPE.

The concentrations of sMerTK were $5,278.77 \pm 2,479.98$ ng/L and 859.91 ± 540.45 ng/L in the TPE and MPE groups, respectively. The concentration of sMerTK in TPE shown in Figure 1 was significantly higher than that in MPE ($P < 0.05$). The ROC curve using sMerTK and ADA to differentiate TPE from MPE can be seen in Figure 2. The AUC and optimal cutoff value for ADA were 0.966 and 21.44 U/L, respectively. The sensitivity and specificity for ADA were 84.72% and 93.75% ($P < 0.05$). The AUC and optimal cutoff value for sMerTK were 0.958 and 2,122 ng/L, respectively. The sensitivity and specificity for sMerTK were 98.61% and 90.63% ($P < 0.05$).
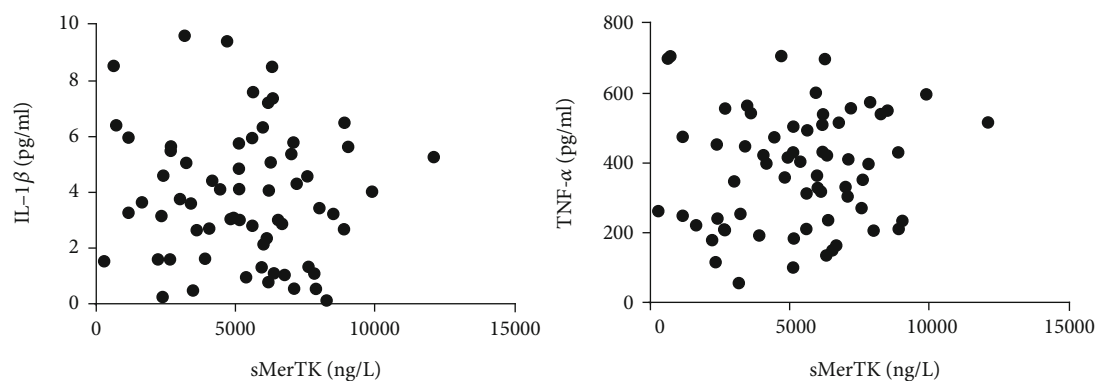
FIGURE 3: The correlation of the concentration of sMerTK in the TPE group with those of IL-1β and TNF-α. The concentration of sMerTK in the TPE group was not correlated with the concentrations of IL-1β and TNF-α ($P > 0.05$) by the Pearson linear correlation method.
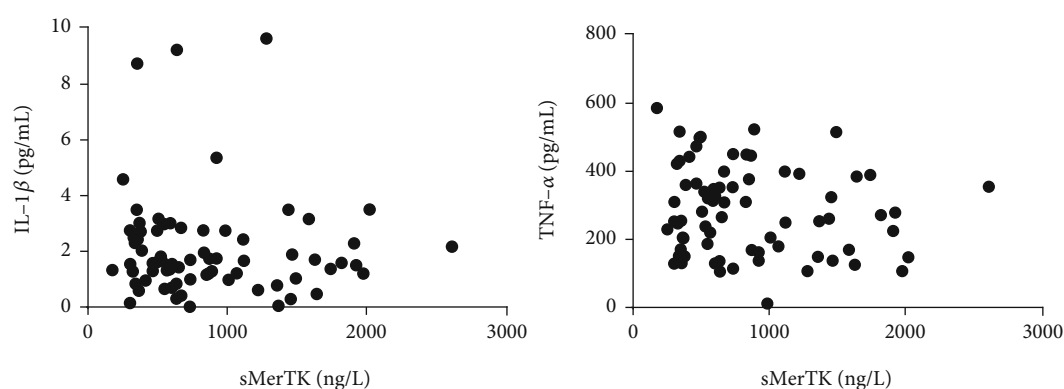

FIGURE 4: The correlation of the concentration of sMerTK in the MPE group with those of IL-1β and TNF-α. Correlations of sMerTK with IL-1β and TNF-α in the MPE groups were not found ($P > 0.05$) by the Pearson linear correlation method.

TABLE 2: The sMerTK in the lung cancer and non-lung cancer groups.

	Lung cancer ($n = 51$)	Non-lung cancer ($n = 21$)	P value
sMerTK (ng/L)	815.79 ± 520.16	967.06 ± 586.07	$P > 0.05$ *

*Used t-test.

A significant difference was found in the concentration of IL-1β and TNF-α between the TPE and MPE groups ($P < 0.05$) (Table 1). But the concentrations of sMerTK in the TPE (Figure 3) and MPE (Figure 4) groups were not correlated with the concentrations of IL-1β and TNF-α ($P > 0.05$) by the Pearson linear correlation method.

Most patients had pleural effusion due to lung cancer in the MPE group. However, there was no statistical significance between the lung cancer and non-lung cancer groups ($P > 0.05$) (Table 2).

Tables 3 and 4 show the distribution of histological diagnoses in the MPE group. The distribution was as follows: 41 for lung adenocarcinoma, 6 for small cell lung cancer, 4 for squamous cell lung carcinoma, 5 for breast cancer, 4 for gastric cancer, 4 for mesothelioma of the pleura, 3 for unknown, 2 for rectal cancer, 2 for lymphoma, and 1 for esophageal cancer.

4. Discussion

PE is a common problem in internal medicine practice. However, exudative PE requires careful differential diagnosis that includes tuberculosis and metastatic cancers, which are often found to be the cause in a large number of patients [6, 13, 14]. According to statistics, more than 1.5 million people develop PE each year in the United States [15]. Additionally, tuberculosis remains a major health problem worldwide, leading to 1.8 million deaths annually [16]. Lung cancer is the most common fatal cancer. Its prevalence is increasing in Korea. It is the leading cause of cancer mortality in many countries [17, 18]. However, the methods for diagnosing TPE and MPE are not both sensitive and specific, so a more effective and economical diagnostic method for these two diseases is essential for proper treatment.

MerTK, which is a member of the receptor tyrosine kinase family, is expressed in many tissues of the body and participates in a variety of physiological functions. Tyrosine kinases are a set of catalytic enzymes that phosphorylate tyrosine residues. The main mechanism of these enzymes involves transferring a phosphorus atom from an ATP molecule to the target tyrosine residue, participating in the transduction of cellular signals and causing changes in the expression levels of certain genes, thus driving a series of pathological and physiological changes [19].

TABLE 3: Distribution of histological diagnoses in the MPE group and the corresponding sMerTK values.

	$N = 72$	sMerTK (ng/L)
Lung cancer	51 (70.8%)	815.79 (251.91, 2,615.01)
Breast cancer	5 (6.9%)	1,347.31 (851.92, 1,744.37)
Gastric cancer	4 (5.6%)	440.60 (175.24, 668.85)
Mesothelioma of the pleura	4 (5.6%)	1,328.88 (603.12, 2,024.23)
Unknown	3 (4.2%)	1,252.8 (592.64, 1,912.96)
Rectal cancer	2 (2.8%)	446.59 (342.85, 550.33)
Lymphoma	2 (2.8%)	897.26 (303.02, 1,822.23)
Esophageal cancer	1 (1.4%)	834.83

TABLE 4: The sMerTK in pleural effusion caused by different histological types of lung cancer.

Histologic type of lung cancer	sMerTK (ng/L)	$N = 51$
Adenocarcinoma	847.77 ± 508.04	41 (80.4%)
Small cell	811.60 ± 728.64	6 (11.7%)
Squamous cancer	494.29 ± 177.04	4 (7.8%)

Studies have shown that ectopic expression of MerTK is found in human lymphocytes and leukemia cells, while no expression of MerTK is found in mature lymphocytes or lymphoid bone marrow precursor cells. Researchers have found high expression of MerTK in 30%-50% of children with B-lymphoblastic leukemia or T-lymphoblastic leukemia, in 70%-90% of patients with chronic myeloid leukemia and in a portion of patients with multiple myeloma [20]. Another study [21] found that knocking down the expression of MerTK could reduce phagocytosis by phagocytic cells and confirmed that the sustained expression of MerTK could activate the clearance of apoptotic cells. In addition, apoptotic cells could induce the expression of PDL1 through MerTK, indicating that tumor cells can regulate apoptosis through MerTK-mediated immunosuppression. Therefore, MerTK is an important molecule associated with tumor expression and cell death [22] and becomes a tumor promoter when overexpressed. Other scholars have found that MerTK is associated with tumorigenesis in some cancers, such as melanoma, astrocytoma, gastric cancer, and non-small cell lung cancer. MerTK may be a therapeutic target in some of these tumor types [10]. McIver [11] found that small molecules inhibited the expression of the MerTK protein, and MerTK protein inhibitors have dual therapeutic effects on tumors that express MerTK (such as lung cancer and acute leukemia) [23], which are mainly exerted by reducing the survival, invasion, and metastasis of cancer cells and stimulating the antitumor immune response. In summary, MerTK is closely related to tumor cells, which provides a new idea for use in studying MerTK in MPE.

The main immunoprotective mechanism against tuberculosis is cellular immunity. Macrophages secrete a large number of cytokines, such as IL-1, IL-6, and TNF-α, after infection by *Mycobacterium tuberculosis* (Mtb). These inflammatory factors cause lymphocytes and monocytes to gather at the site of invasion, gradually forming granulomas and limiting the further spread and killing of *Mycobacterium tuberculosis*. Some studies have shown that during tuberculosis infection, we can detect the expression of markers related to the activation of M2 macrophages, such as CD16, CD163, MerTK, CD206, AMAC1, and CD200R1. This indicates that the MerTK protein is also involved in the immune mechanism described here during tuberculosis infection [24]. Moreover, studies have shown that the MerTK expression level may be positively correlated with the disease severity [25]. Therefore, we hypothesized that MerTK may also be highly expressed in TPE.

In this study, our results showed that the soluble form of MerTK was highly expressed in both TPE and MPE, as we hypothesized, but surprisingly, the expression level in the TPE group was significantly higher than that in the MPE group ($P < 0.05$). The occurrence of this phenomenon is considered related to the significantly increased activity of M2-type macrophages in tuberculosis [26]. The sMerTK concentration was applied to differentiate TPE from MPE, in which the AUC was 0.958 and the cutoff value was 2,122 ng/L. Although ADA's AUC is 0.966, which is slightly higher than that of sMerTK, the sensitivity and specificity for sMerTK were both higher than 90%. In addition, we found that there was no significant difference in the expression value of sMerTK between pleural effusion caused by lung cancer and other tumors. Meanwhile, we found that the value of sMerTK in squamous cell carcinoma patients was lower than that in adenocarcinoma and small cell lung cancer patients. However, in view of the small numbers of patients, we did not perform any statistical analysis. In conclusion, this study indicates that sMerTK has a high sensitivity and specificity in the differential diagnosis of TPE and MPE, which is helpful for identifying the etiology of PE, and can be used as a potential biomarker in the differential diagnosis of PE.

Existing studies have shown that MerTK is involved in cellular immunity [8]. We have confirmed through the above experiments that there is a significant difference in the concentration of sMerTK between TPE and MPE. In exploring the specific mechanism of action, based on a large amount of data [27–30], we found that there were some common inflammatory factors in TPE and MPE, such as IL-1β, TNF-α, IL-1, IL-6, c-reactive protein, and the erythrocyte sedimentation rate. In our study, although we did not find a direct relationship between any specified inflammatory factors and MerTK, we selected two inflammatory factors, IL-1β and TNF-α, which are closely related to pleural effusion. We found that IL-1β and TNF-α were highly expressed in both PE groups, which was consistent with previous studies [31, 32]. However, the levels of IL-1β and TNF-α were not correlated with the concentration of sMerTK in either the TPE group or the MPE group. Still, we can conduct further studies about other inflammatory factors in follow-up studies.

This study identifies the potential use of sMerTK in differentiating malignant and tuberculous pleural effusions. However, due to the small sample size and some of the confounding factors that we cannot rule out in this study, it still requires a prospective validation study to determine the

clinical utility of sMerTK, including its sensitivity and specificity. In addition, this study was designed as a single-index study. To be useful, sMerTK should be evaluated in parapneumonic effusions or other types of PE in the future. Additionally, in our study, the inflammatory factors of IL-1β and TNF-α were not correlated with the concentration of sMerTK; therefore, additional relevant samples can be collected, and multiple indicators, such as other inflammatory indicators, can be combined to identify the etiology of PE. At present, no studies have shown that the expression level of sMerTK is correlated with the prognosis of TPE or MPE patients, which can also be taken as a research area for further exploration.

Data Availability

The datasets are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors disclose no conflicts of interest.

Authors' Contributions

Shucheng Hua and Lei Song are responsible for conceptualization. Zhenzhen Zhang and Han Liu are responsible for data curation. Shuai Wang and Jing Jie are responsible for formal analysis. Han Liu and Jing Jie are responsible for investigation. Han Liu and Zhenzhen Zhang are responsible for writing—original draft. Lei Song, Shuai Wang, and Shucheng Hua are responsible for writing—review and editing. Lei Song and Shucheng Hua contributed equally to this work.

Acknowledgments

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