Clinical and blood gas characteristics of mycoplasmal pleural effusion and tuberculous pleural effusion in pediatric patients: a retrospective case-control study

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Research Article

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Abstract

Background

Mycoplasma pneumoniae pneumonia-related pleural effusion (MP-PPE) and tuberculous pleural effusion (TPE) are common pediatric respiratory diseases. This study aimed to investigate their clinical characteristics, serum markers, and pleural fluid characteristics in pediatric patients.

Methods

The clinical and imaging characteristics, serum inflammatory indicators, pleural fluid analysis, and biochemistry and blood gas analysis results from 98 children aged 2–14 years who were hospitalized in the Pediatric Respiratory Department of Shengjing Hospital of China Medical University from 2018 to 2021 for MP-PPE or TPE were retrospectively examined.

Results

There were 28 (40%) males and 44 (60%) females in the MP-PPE group and 18 (69%) males and 8 (31%) females in the TPE group ($p < 0.05$). There was no statistically significant between-group difference in the age ranges of the MP-PPE group (2–13 years, mean age 7.55 ± 3.29 years) and TPE group (5–14 years, mean age 9.69 ± 3.70 years) ($p > 0.05$). The duration of fever before admission was 12.54 ± 6.95 and 7.77 ± 4.00 days in the MP-PPE and TPE groups, respectively ($t = 2.324$, $p < 0.05$). The duration of cough before admission was 15.04 ± 6.86 and 5.90 ± 4.81 days in the MP-PPE and TPE groups ($t = 3.972$, $p < 0.05$). Serum neutrophil percentage and C-reactive protein, procalcitonin, interleukin-6, lactate dehydrogenase (LDH), D-dimer, and alanine transaminase levels were significantly higher in the MP-PPE group than in the TPE group. CD3+, CD3 + CD8+, CD3 + CD4+, CD16 + CD56+, and CD19 + counts were lower in the MP-PPE group. There were significant between-group differences in white blood cell count and hemoglobin, fibrinogen, and immunoglobulins (IgA, IgM, and IgG) levels ($p > 0.05$). There was no significant between-group difference in adenosine deaminase level ($p > 0.05$). Finally, while there were significant between-group differences in pleural fluid pH, $PaCO_2$, and pleural fluid lactate and blood gas glucose levels ($p < 0.05$), there was no significant between-group difference in pleural fluid PaO_2 ($p > 0.05$).

Conclusions

Serum and pleural fluid LDH levels were elevated in the MP-PPE group compared to the TPE group. Our findings could be used to help distinguish MP-PPE from TPE. Blood gas analysis results revealed that the MP-PPE group had a higher pH and was predominantly alkaline compared with the TPE group, which is also a significant finding for differentiating MP-PPE from TPE.

Background

Mycoplasma pneumoniae (MP) is a common cause of community-acquired pneumonia in childre[1]. In recent years, its incidence has increased, as has the prevalence of macrolide-resistant MP (MRMP) pneumonia[2]. MRMP is often characterized by a prolonged, severe, rapidly progressing fever and is prone to pleural effusion and atelectasis. The increase in MP drug resistance has led to a gradual rise in the incidence of severe refractory MP pneumonia and pleural effusion complications[3].

A previous study has reported MP as the causative agent in 19% of severe pneumonia cases with parapneumonic effusion and pustular pleural effusion[4], and the incidence of pleural effusion in MP pneumonia was reportedly 20.3–20.7%[5]. Another study found that patients with MP pneumonia who required intensive care had a significantly higher incidence of pleural effusion than those who did not (65% vs. 10%, $p < 0.001$)[6].

Tuberculosis (TB) is another major cause of pleural effusion in pediatric patients, with approximately 12–38% of primary TB cases in children whose condition is complicated with pleural effusion [7], primarily in children aged > 5 years. The differentiation of pleural effusion caused by TB from other causes is clinically challenging. Thoracentesis and pleural fluid analysis remain the preferred methods for diagnosing tuberculous pleural effusion (TPE). However, pleural fluid culture has a 20–70% sensitivity and requires a relatively long time to provide results[8].

We reviewed all available cases of patients hospitalized in our pediatric respiratory department and who were diagnosed with pleural effusion from 2018–2021. This study aimed to retrospectively examine patients with *Mycoplasma pneumoniae* pneumonia-related pleural effusion (MP-PPE) or TPE, as confirmed by pleural fluid analysis, and analyze the characteristics of pleural fluid obtained from MP-PPE and TPE patients. To the best of our knowledge, this is the first study to report the clinical features and blood gas findings associated with MP and tuberculosis infections in pediatric patients with pleural effusion.

Methods

Study participants

In this retrospective study, we identified all children aged 2–14 years who were admitted to the Department of Pediatric Respiratory Medicine, Shengjing Hospital of China Medical University from 2018 to 2021, and diagnosed with MP infection or tuberculosis infection with pleural effusion. The diagnostic criteria were referenced to the diagnosis and treatment of mycoplasma pneumoniae pneumonia in children with integrated traditional Chinese and Western medicine Expert Consensus (formulated in 2017) [9].We included all patients with pleural fluid, biochemical, and pleural fluid blood gas analyses. The clinical, laboratory, and imaging data of participants were obtained by retrospectively searching the hospital's diagnosis system, and written informed consent from parents or guardians for diagnosis, treatment, laboratory tests, and thoracentesis were obtained from all study participants. All the included

participants presented with cough, fever, and abnormal findings on chest imaging at admission. The diagnostic criteria for MP-PPE include (i) symptoms of acute respiratory infection, such as cough, fever, and wheezing; (ii) inflammatory infiltration with pleural effusion on chest computed tomography (CT) and further confirmation of the depth of pleural effusion on chest ultrasound; (iii) positive serum MP-IgM and positive MP ribosomes findings for a nasopharyngeal swab or bronchoalveolar lavage fluid; and (iv) no hematologic diseases or other underlying diseases, such as cardiac diseases. The diagnostic criteria for TPE were as follows: (i) antecedent symptoms, such as fever and night sweats; (ii) inflammatory infiltration with pleural effusion on chest CT and further confirmation of the depth of pleural effusion on chest ultrasound; (iii) positive interferon-gamma release assay results; and (iv) no other pathogenic infections, hematologic diseases, or other underlying diseases, such as cardiac diseases.

Study design and procedures

A retrospective case-control study design was used. Relevant clinical data, including sex, age, duration of fever before admission, and duration of cough before admission, were collected from the included participants. Blood-related laboratory tests were conducted, including parameters such as complete blood count/white blood cell (WBC × 10^9/L); platelet (PLT) count; C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), alanine transaminase (ALT), total protein (TP), albumin, lactate dehydrogenase (LDH), fibrinogen (FIB), D-dimer (DD), immunoglobulin (IgA, IgM, IgG) levels; and absolute lymphocyte count. Pleural fluid-related laboratory tests included parameters such as pleural fluid pH and PaO_2, $PaCO_2$, lactate (Lac), blood gas glucose levels. Pleural fluid complete blood count included total cell count, WBC count, neutrophil percentage (N%), and monocyte percentage(L%). Pleural fluid biochemistry analysis included protein, chloride, glucose, and adenosine deaminase (ADA) levels. Lung imaging results were also collected. The clinical data of the MP-PPE and TPE groups were compared and analyzed.

Statistical analysis

Statistical analyses were conducted using the SPSS.26 statistical software [IMB, SPSS Inc., Chicago, United States] for data processing and analysis. Measurement data conforming to the normal distribution are presented as mean ± standard deviation. The t-test was used to compare the two groups. Measurement data not conforming to the normal distribution are presented as medians and interquartile ranges, and the rank-sum test was used for comparisons between the two groups. For count data, the χ^2 test was used for comparisons between groups. Differences with $p < 0.05$ were considered statistically significant.

Results

Characteristics of participants in the MP-PPE and TPE groups

A total of 98 pediatric patients with pleural effusion who underwent pleural fluid blood gas analysis via thoracentesis were included in the two groups: 72 (73%) had MP pneumonia and 26 (27%) had tuberculosis. There were 28 males (40%) and 44 females (60%) in the MP-PPE group and 18 males (69%)

and 8 females (31%) in the TPE group. The between-group difference in sex was statistically significant ($p<0.05$). The age range of participants in the MP-PPE group was 2–13 years, with a mean age of 7.55±3.29 years, and the age range of participants in the TPE group was 5–14 years, with a mean age of 9.69±3.70 years; the difference was not statistically significant ($p>0.05$). The duration of fever before admission was 12.54±6.95 days in the MP-PPE group and 7.77±4.00 days in the TPE group; this difference was statistically significant (t=2.324, $p<0.05$). Furthermore, the duration of cough before admission was 15.04±6.86 days in the MP-PPE group and 5.90±4.81 days in the TPE group; the difference was statistically significant (t=3.972, $p<0.05$) (Table 1).

Table 1.Basic clinical characteristics of participants in the MP-PPE and TPE groups.

	MP-PPE group	TPE group	t/χ²	*P*
Participants [n (%)]	72 (73%)	26 (27%)		
Sex				
Male [n (%)]	28 (40%)	18 (69%)	7.061	0.008
Female [n (%)]	44 (60%)	8 (31%)		
Age (y)	7.55±3.29	9.69±3.70	1.938	0.053
Duration of fever (d)	12.54±6.95	7.77±4.00	2.324	0.025
Duration of cough (d)	15.04±6.86	5.90±4.81	3.792	0.001

Differences with $p<0.05$ considered statistically significant.

Abbreviations: MP-PPE: *Mycoplasma pneumoniae* pneumonia-related pleural effusion; TPE: tuberculous pleural effusion

Laboratory test findings

Neutrophil percentage（N%）, lymphocyte percentage (L%), and CRP, procalcitonin (PCT), interleukin-6 (IL-6), LDH, DD, and ALT levels were higher in the MP-PPE group than in the TPE group; the differences were statistically significant ($p<0.05$). PLT count, TP level, albumin level, erythrocyte sedimentation rate (ESR), and lymphocyte subpopulation count were lower in the MP-PPE group than in the TPE group; the differences were statistically significant ($p<0.05$). Between-group differences in WBC count and hemoglobin (HB), FIB, and immunoglobulin (IgA, IgM, and IgG) levels were non-significant ($p>0.05$) (Table 2).

Table 2. Comparison of blood-related indicators between the MP-PPE and TPE groups.

	MP-PPE group M (P25，P75)	TPE group M (P25，P75)	Z	*P*
WBC (×10^9/L)	9.8 (8.1，**11.91**)	7.71 (6.58，**10.94**)	1.694	0.09
N%	79.45 (68.22，**85.25**)	56.5 (49.5，**64.2**)	4.048	<0.001
L%	13.55 (7.825，**22.62**)	28.9 (21.2，**36.3**)	3.578	<0.001
HB (g/L)	117 (110，**128**)	113 (106，**124**)	1.173	0.241
PLT (×10^9/L)	280 (206，**325**)	420 (365，477)	3.178	0.001
CRP (mg/L)	81.6 (63.5，**182**)	24 (14.25，**51**)	3.167	0.002
PCT (ng/ml)	0.767 (0.198，1.98)	0.111 (0.172，**0.158**)	3.909	<0.001
IL-6 (pg/ml)	94.86 (45.67，**214.1**)	33.4 (22.99，51.635)	2.912	0.004
TP (g/L)	59.2(56.2，62.7)	64.6(60.8，68.45)	2.877	0.004
Albumin (g/L)	30(27.7，33.1)	35.8(33.5，37.25)	3.736	<0.001
ALT (U/L)	26 (15，**51**)	8 (6，**11.5**)	2.381	0.023
LDH (U/L)	546 (379，**1,030**)	229 (195.5，**413.5**)	3.562	<0.001
IgG (g/L)	8.865 (6.98，**13.175**)	9.61 (7.92，**12.2**)	0.383	0.702
IgA (g/L)	1.245 (0.737，**1.69**)	1.11 (1.00，**1.5**)	0.104	0.917
IgM (g/L)	1.775 (0.966，**2.66**)	1.57 (1.195，**1.765**)	0.673	0.501
ESR (mm/min)	43(32.75，54)	59(45，71)	2.44	0.015
FIB (g/L)	4 (3.6，4.6)	4.4 (4.05，4.5)	1.754	0.079
DD (ug/L)	2,192 (1,141，**3,521**)	1,210 (741，**2,291.5**)	2.262	0.024
CD3+ count	604. (340.25，1,211.75)	1,377 (990.25，1,897)	2.975	0.003
CD3+CD8+ count	249.5 (165，455.75)	515 (394.75，872.25)	2.45	0.014
CD3+CD4+ count	252.5 (189.25，652.75)	651.5 (518，1,122.25)	2.869	0.004
CD16+CD56+ count	65.5 (53，123.5)	246.5 (136.5，411.75)	3.29	0.001
CD19+ count	223.5 (132.25，394.5)	358.5 (326.5，462)	2.45	0.014

Differences with $p<0.05$ considered statistically significant.

Abbreviations: MP-PPE: *Mycoplasma pneumoniae* pneumonia-related pleural effusion; TPE: tuberculous pleural effusion; WBC: white blood cell count; N%: neutrophil percentage; L%: lymphocyte percentage; HB: hemoglobin CRP: C-reactive protein, PCT: procalcitonin, IL-6: interleukin-6, LDH: lactate dehydrogenase,

DD: D-dimer, ALT: alanine transaminase; PLT: platelets, TP: total protein, ESR: erythrocyte sedimentation rate

[Insert Table 2]

[Insert Figure 1]

[Insert Figure 2]

Receiver operating characteristic (ROC) curve analysis was performed to determine the sensitivity and specificity of the differences in blood-related indicators between the two groups for diagnosis of the two types of pleural effusions (Figure1Figure 2). The results showed that N% [area under the ROC curve (AUC) 0.884, sensitivity 83%, specificity 92%, p<0.05], CRP level (AUC 0.8, sensitivity 77%, specificity 85%, p<0.05), PCT level (AUC 0.87, sensitivity 80%, specificity 85%, p<0.05), IL-6 level (AUC 0.776, sensitivity 60%, specificity 100%, p<0.05), LDH level (AUC 0.973, sensitivity 94%, specificity 100% p<0.05), DD level (AUC 0.714, sensitivity 71%, specificity 69%, p<0.05), and ALT level (AUC 0.898, sensitivity 89%, specificity 85%, p<0.05) exhibited high sensitivity and specificity for the diagnosis of MP-PPE (Table 3). TP level (AUC 0.766, sensitivity 77%, specificity 71%, p<0.05), albumin level (AUC 0.852, sensitivity 92%, specificity 69%, p<0.05), ESR (AUC 0.732, sensitivity 69%, specificity 82%, p<0.05), and L% (AUC 0.836, sensitivity 85%, specificity 71%, p<0.05) showed high sensitivity and specificity for the diagnosis of TPE (Table 4).

Table 3. ROC curve analysis for diagnosis of MP-PPE showing AUC and cutoff points of blood-related indicators with high sensitivity and specificity.

Indicator	AUC	*P*	Asymptotic 95% confidence interval		Cutoff point	Sensitivity	Specificity
			Lower limit	Upper limit			
N	0.884	0<0.001	0.787	0.98	89.9	0.83	0.92
CRP	0.8	0.002	0.67	0.93	88	0.77	0.85
PCT	0.87	0<0.001	0.77	0.97	7.15	0.8	0.85
IL-6	0.776	0.004	0.647	0.904	20.9	0.6	100
LDH	0.973	0<0.001	0.701	0.974	1,593	0.93	100
DD	0.714	0.024	0.557	0.871	1,141	0.71	0.69
ALT	0.905	0<0.001	0.798	0.997	58	0.89	0.85

Differences with p<0.05 considered statistically significant.

Abbreviations: MP-PPE: *Mycoplasma pneumoniae* pneumonia-related pleural effusion; N%: Neutrophil percentage; CRP: C-reactive protein, PCT: procalcitonin, IL-6: interleukin-6, LDH: lactate dehydrogenase,

DD: D-dimer, ALT: alanine transaminase; ROC: receiver operating characteristic; AUC: area under the receiver operating characteristic curve

Table 4. ROC curve analysis for diagnosis of TPE showing AUC and cutoff points of blood-related indicators with high sensitivity and specificity.

	AUC	*P*	Asymptotic 95% confidence interval		Cutoff point	Sensitivity	Specificity
			Lower limit	Upper limit			
Total protein	0.766	0.005	0.625	0.907	64.5	0.77	0.71
Albumin	0.852	0<0.001	0.742	0.962	41.9	0.92	0.69
ESR	0.732	0.015	0.563	0.901	39	0.69	0.82
L%	0.836	0<0.001	0.717	0.955	8.7	0.85	0.71

Differences with $p<0.05$ considered statistically significant.

Abbreviations: ROC: receiver operating characteristic; AUC: area under the receiver operating characteristic curve; TPE: tuberculous pleural effusion; ESR: erythrocyte sedimentation rate; L%:monocyte percentage.

Blood count, biochemistry, and blood gas results

Pleural fluid blood count in the MP-PPE group indicated significant differences in pleural fluid WBC count and TP, glucose, and LDH levels compared to the TPE group ($p<0.05$); there was no significant between-group difference in ADA level ($p>0.05$). Further comparison of the pleural fluid blood gas analysis results between the two groups indicated significant differences in pleural fluid pH, $PaCO_2$, Lac, and blood gas glucose in the MP-PPE group compared to the TPE group ($p<0.05$); there was no statistically significant difference in pleural fluid PaO_2 levels between the two groups ($p>0.05$) (Table 5).

Table 5.Characteristics of routine, biochemical and blood gas analysis of pleural effusion the MP-PPE and TPE groups.

	MP-PPE group **M (P25，P75)**	TPE group **M (P25，P75)**	Z	*P*
Pleural fluid WBC (×10^9/L_)	1,054 (451，2,957)	3,416 (2,595，9,259)	2.717	0.007
Pleural fluid neutrophil percentage (%)	14.6 (5.7，37.8)	8.6 (4.2，24.2)	1.262	0.207
Pleural fluid monocyte percentage (%)	85.4 (62.2，94.3)	91.4 (75.8，95.8)	1.262	0.207
Pleural fluid total protein (g/L)	44.9 (40.9，49.3)	50.9 (48.9，52)	2.846	0.004
Pleural fluid chloride (mmol/L)	104.7 (101，107.7)	106.2 (104.3，107.8)	1.249	0.212
Pleural fluid glucose (mmol/L)	5.57 (4.54，6.49)	4.56 (3.42，5.23)	2.511	0.012
ADA	49 (34，69)	46 (42，63)	0.167	0.867
Pleural fluid LDH (U/L)	2,318 (863，2,834)	472 (360，828)	3.867	<0.001
Pleural fluid pH	7.523 (7.474，7.581)	7.427 (7.327，7.468)	2.846	0.004
Pleural fluid $PaCO_2$ (mmHg)	28.6 (25.3，34.3)	36.7 (32.1，41.4)	2.627	0.009
Pleural fluid PaO_2 (mmHg)	129 (109，143.3)	116.5 (100.5，136)	0.785	0.432
Pleural fluid blood gas GLU (mmol/L)	5.9 (4.9，6.7)	5.1 (3.7，5.7)	2.423	0.015
Pleural fluid blood gas Lac (mmol/L)	3 (2.3，4)	5.2 (3.3，6.1)	2.937	0.003

Differences with *p*<0.05 considered statistically significant.

Abbreviations: MP-PPE: *Mycoplasma pneumoniae* pneumonia-related pleural effusion; TPE: tuberculous pleural effusion; WBC: white blood cells; ADA: adenosine deaminase; LDH: lactate dehydrogenase; GLU: glucose; Lac: pleural fluid lactate

[Insert Table 5]

ROC curve analysis was performed to determine the sensitivity and specificity of the differences in pleural fluid indicators between the two groups（Figure 3，Figure 4）. The results showed that pleural fluid pH (AUC 0.787, sensitivity 77%, specificity 82%, p<0.05), blood gas glucose (AUC 0.744, sensitivity 51%, specificity 100%, p<0.05), LDH (AUC 0.877, sensitivity 71%, specificity 100%, p<0.05), and glucose (AUC 0.753, sensitivity 60%, specificity 100%, p<0.05) exhibited high sensitivity and specificity for diagnosis of MP-PPE, with cutoff points of 7.49 for pH, 5.7 mmol/L for blood gas glucose, 6 mmol/L for glucose, and 2,484 U/L for LDH (Table 6). Pleural fluid WBC count (AUC 0.744, sensitivity 91%, specificity 63%, p<0.05),

TP level (AUC 0.787, sensitivity 91%, specificity 71%, $p<0.05$), $PaCO_2$ (AUC 0.765, sensitivity 64%, specificity 96%, $p<0.05$), and blood gas Lac level (AUC 0.796, sensitivity 91%, specificity 60%, $p<0.05$) exhibited high sensitivity and specificity for diagnosis of TPE, with cutoff points of 641×10^9/L for white blood cell count, 55 g/L for albumin, 28.4 mmHg for blood gas $PaCO_2$, and 5.3 mmol/L for blood gas lactate (Table 7).

[Insert Figure 3]

[Insert Figure 4]

Table 6. ROC curve analysis for diagnosis of MP-PPE showing AUC and cutoff points of pleural fluid-related indicators with high sensitivity and specificity.

Indicator	AUC	P	Asymptotic 95% confidence interval		Cutoff point	Sensitivity	Specificity
			Lower limit	Upper limit			
PH	0.787	0.004	0.61	0.964	7.49	0.77	0.82
Pleural fluid blood gas GLU	0.744	0.015	0.6	0.888	5.7	0.51	100
Pleural fluid GLU	0.753	0.012	0.615	0.891	6	0.6	100
Pleural fluid LDH	0.885	<0.001	0.776	0.977	2,318	0.71	100

Differences with $p<0.05$ considered statistically significant.

Abbreviations: MP-PPE: *Mycoplasma pneumoniae* pneumonia-related pleural effusion; TPE: tuberculous pleural effusion; ROC: receiver operating characteristic; AUC: area under the receiver operating characteristic curve; GLU: glucose; LDH: lactate dehydrogenase

Table 7. ROC curve analysis for diagnosis of TPE showing AUC and cutoff points of pleural fluid-related indicators with high sensitivity and specificity.

Indicator	AUC	P	Asymptotic 95% confidence interval		Cutoff point	Sensitivity	Specificity
			Lower limit	Upper limit			
Lac	0.796	0.003	0.66	0.933	5.3	0.91	0.6
Pleural fluid WBC	0.774	0.007	0.615	0.933	641	0.91	0.63
Pleural fluid total protein	0.787	0.004	0.656	0.918	55	0.91	0.71
$PaCO_2$	0.765	0.009	0.571	0.959	28.4	0.64	0.96

Differences with $p<0.05$ considered statistically significant.

Abbreviations: TPE: tuberculous pleural effusion; ROC: receiver operating characteristic; AUC: area under the receiver operating characteristic curve; WBC: white blood cell

Lesion laterality and site

There were 12 bilateral (17.14%) and 60 unilateral (82.86%) cases in the MP-PPE group, whereas all the cases in the TPE group were unilateral. There were 49 right-side (68%) and 23 left-side (32%) cases in the MP-PPE group and 10 right-side (38%) and 16 left-side (62%) cases in the TPE group; the difference was statistically significant ($p<0.05$)(Table 8).

Table 8. Comparison of lesion involvement between the MP-PPE and TPE groups.

	MP-PPE group	TPE group	χ^2	*P*
Bilateral involvement [n (%)]	12 (17.14%)	0		
Unilateral involvement [n (%)]	60 (82.86%)	26 (100%)		
Right side [n (%)]	49 (68%)	10 (38%)	6.983	0.008
Left side [n (%)]	23 (32%)	16 (62%)		

Differences with $p<0.05$ considered statistically significant.

Abbreviations: MP-PPE: *Mycoplasma pneumoniae* pneumonia-related pleural effusion; TPE: tuberculous pleural effusion

Discussion

This study investigated clinical characteristics, serum markers, and pleural fluid in pediatric patients with mycoplasma pneumoniae pneumonia-related pleural effusion (MP-PPE) and tuberculous pleural effusion

(TPE). We found that serum and pleural fluid lactate dehydrogenase levels were elevated in the MP-PPE group compared to the TPE group. Furthermore, the MP-PPE group had a higher pH and was predominantly alkaline compared with the TPE group, and this finding can be used for differentiating MP-PPE from TPE.

Pleural fluid is secreted by the parietal pleura, wherein hydrostatic pressure is high and the fluid is absorbed through venous capillaries of the visceral pleura. This process forms a dynamic equilibrium between filtration and absorption under normal conditions; however, if this equilibrium is disrupted, pleural effusion can develop due to increased secretion from the parietal pleura or abnormal absorption from the venous capillaries of the visceral pleura [10]. Infection is a common cause of pleural effusion in children. Common pathogens that cause pleural effusion include bacteria, viruses, MP, and TB. However, the incidence of MP infection has been increasing steadily, and more drug-resistant cases have emerged in recent years; therefore, the number of cases of pleural effusion due to MP infection and the severity of these cases have increased in recent years [11]. According to the World Health Organization, there are approximately 1 million TB patients worldwide[12], with extrapulmonary TB accounting for 15% of reported cases of TPE. TB infection remains another major cause of pleural effusion in pediatric patients.

The exact pathophysiology of pleural effusion in MP pneumonia is currently unknown. Most studies have suggested that the development of pleural effusion is associated with direct MP invasion, persistent infection, or the immune response generated by the body[13]. Some studies have found that, older age and prolonged duration of fever were associated with the development of pleural effusion in in children with MP pneumonia. In addition, mechanical ventilation, severe pneumonia, and lack of response to conventional MP pneumonia treatment were significantly associated with MP-PPE[14]. The results of the present study showed that the duration of fever and cough before admission was significantly longer in the MP-PPE group than in the TPE group. Moreover, the maximum fever temperature was higher, suggesting a more pronounced inflammatory response to MP infection. The underlying mechanism possibly involves the close adhesion of MP with respiratory epithelial cells through adhesion proteins on the cell membrane surface, which destroys the integrity of the respiratory mucosa[15]. This produces many inflammatory mediators at early stages, leading to lung damage and induces autoimmune reactions[16]. Pleural effusions are associated with severe MP pneumonia, resulting in more intense inflammatory responses. Studies have shown that fever duration of >10 days was significantly higher in the MP-PPE group than in the general MP pneumonia group and that a long duration of fever indicated a persistent inflammatory response in the body and excessive infiltration of lymphocytes into the airway, causing immunopathological damage through the release of inflammatory factors[17]. The present study also showed that the duration of fever in the MP-PPE group was significantly longer than that in the TPE group, which is consistent with the above-mentioned previous study findings.

Various inflammatory factors are involved in the immune response following MP infection. It has been suggested that high CRP and LDH levels and low L% are associated with MP-PPE development[18]. The results of the present study indicated that blood N% and CRP, PCT, IL-6, LDH, DD, and ALT levels were significantly higher in the MP-PPE group tan in the TPE group, suggesting the involvement of all these

inflammatory factors in the immune response after MP infection, wherein higher values of these indicators reflect a more severe inflammatory response. Platelets are considered inflammatory agents that can release inflammatory mediators, such as chemokines and cytokines, during the acute phase, thus aggravating the inflammatory response[19]. CRP is an acute temporal reactive protein that is a major component of the non-specific immune response. A previous study has reported that the MP-PPE group presented with a long duration of fever, significantly elevated serum CRP level, and poor control of inflammation[20]. PCT is a 116-amino acid glycoprotein secreted by thyroid C cells that exist in a free form in the serum; it is a sensitive indicator of infection[21]. Abnormally elevated serum PCT level is positively correlated with the condition of patients with bacterial infections, burns, pancreatitis, and polytrauma[22]. The inflammatory response to MP pneumonia with pleural effusion is more severe, resulting in elevated PCT; however, this indicator is more often associated with a bacterial infection[23].

DD is a specific marker that reflects fibrinolytic activity[24]. In recent years, DD has been considered a specific marker of the fibrinolytic system and an indicator for monitoring the severity of disease and inflammation [25]. Previous studies[26] have reported higher DD levels in children with MP pneumonia than in healthy children and in patients with severe MP pneumonia than in those with milder disease, especially in cases of severe MP pneumonia with extrapulmonary complications[27]. Studies have also shown that MP pneumonia patients with elevated DD levels have more severe clinical symptoms and chest imaging findings than those with normal DD levels[28]. Elevated serum DD levels in patients with refractory MP pneumonia (RMPP) indicate excessive inflammation and prolonged endothelial injury[29] and are believed to be an early predictor of the development of RMPP and associated complications[30]. These inflammatory factors are closely associated with the inflammatory response after MP infection. In the present study, levels of these indicators were significantly elevated in the MP-PPE group compared to the TPE group, with statistically significant differences. To the best of our knowledge, as no previous comparisons of DD between MP-PPE and TPE patients have been reported, more clinical studies are required for further confirmation.

LDH is a glycolytic enzyme is a non-specific biomarker of inflammation. Elevated LDH levels are common in several diseases, including inflammatory diseases. Destruction of respiratory tract and lung tissue cells by an MP infection releases intracellular LDH into the blood, causing serum LDH level to increase. LDH is a good predictor of refractory MP pneumonia and is recommended as an indicator for steroid therapy in MP pneumonia[31]. In the present study, we found that LDH level was significantly elevated in the MP-PPE group, which is consistent with the results of previous studies[31]. In addition, the present study compared LDH in the pleural fluid and found that the serum LDH level of 546 (range: 379–1,030) U/L and pleural fluid LDH level of 2,318 (range: 863–2,834) U/L in the MP-PPE group were significantly higher than the serum LDH level of 229 (range: 195.5–413.5) U/L and pleural fluid LDH level of 472 (range: 360–828) U/L in the TPE group. ROC curve analysis showed that the serum LDH level (AUC) was significantly higher in the MP-PPE group than in the TPE group. The pleural fluid LDH level was also significantly higher in the MP-PPE group, with serum LDH (AUC 0.973, sensitivity 93%, specificity 100%, $p<0.05$) and pleural fluid LDH levels (AUC 0.877, sensitivity 71%, specificity 100%, $p<0.05$) at cutoff points of 1,593 U/L and 2,482 U/L, respectively, noted as the most accurate for the diagnosis of MP-PPE.

Serum albumin is a negative acute phase protein synthesized by the liver, and its level decreases rapidly during acute infection. This decrease is considered a biomarker of local and systemic inflammation and has major clinical value in predicting the severity and outcomes of pneumonia[32]. The results of the present study showed that serum total protein and albumin levels were significantly lower in the MP-PPE group than in the TPE group, suggesting a more intense inflammatory response in the MP-PPE group. It has been suggested that IL-6 plays a major role in the early stage of the immune response and that elevated IL-6 level is associated with disease severity and duration[33]. This further suggests an excessive immune response during hypoxia in MP pneumonia[34]. Furthermore, it has been suggested that the body produces pro-inflammatory cytokines, such as IL-6 and IFN-γ, to clear pathogens and promote tissue repair after MP infection. Therefore, serum IL-6 level is elevated in cases of severe MP pneumonia compared to mild cases in the MP group[35]. In the present study, the difference in serum IL-6 levels between the MP-PPE and TPE groups was statistically significant, suggesting a stronger inflammatory response after MP infection than after TB infection, which is consistent with the above-mentioned findings.

T lymphocytes in the peripheral blood are the principal immune cells that maintain immune homeostasis in humans. An abnormal change in the number of T lymphocytes may occur upon infection by external pathogens, resulting in immune dysfunction. T lymphocytes play a key role in the adaptive immune response after infection. Dendritic cells and monocytes serve an antigen-presenting role to activate CD4+ T lymphocytes, release immunomodulatory cytokines, and assist in coordinating cytotoxic CD8+ T lymphocyte function[36]. Lymphocytes are susceptible to apoptosis during severe infection, resulting in a significant decrease in CD4+ T, CD8+ T, and B lymphocytes. At the same time, inflammatory cells are activated in large numbers and release various pro- and anti-inflammatory factors, ultimately leading to severe immune dysfunction[37]. Luchsinger *et al.* [38]found that peripheral blood CD19+ B lymphocyte counts were lower in patients with severe pneumonia than in patients with mild pneumonia, but there was no significant difference in IgA, IgM, and IgG levels between patients with severe and mild pneumonia. In the present study, we analyzed the differences in absolute blood T lymphocyte subpopulation counts between the two groups and found that the differences in CD3+, CD3+CD8+, CD3+CD4+, CD16+CD56+, and CD19+ counts between the MP-PPE and TPE groups were statistically significant ($p<0.05$). In addition, the median counts in the MP-PPE group were significantly lower than those in the TPE group, indicating that T lymphocyte counts were significantly decreased after MP infection, especially in severe cases of pleural effusion, suggesting possible excessive inflammatory response and immune dysfunction.

The pathogenesis of tuberculous pleural effusion is currently believed to involve rupture of a subpleural caseous focus and entry of mycobacterial antigens, resulting in the entry of TPE into the pleural cavity. Inflammation in the parietal pleura can obstruct the lymphatic stomata and lead to pleural effusion[39]. The presence of mycobacteria in the pleural cavity activates CD4+ T lymphocytes, thereby triggering a delayed hypersensitivity response[40]. Thus, T lymphocytes play a crucial role in protective immunity against tuberculosis. In the present study, the median CD3+, CD3+CD8+, CD3+CD4+, CD16+CD56+, and CD19+ counts were higher in the TPE group than in the MP-PPE group; the differences were statistically

significant. This suggests the presence of immune dysfunction following MP infection and an excessive inflammatory response, whereas lymphocytes provide a protective effect after TB infection and tend to promote the activation of various T lymphocyte subpopulations.

ADA, an enzyme involved in purine metabolism, catalyzes the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively, thereby releasing ammonia[41]. ADA is present in various cells, especially in activated T cells, and it plays a major role in lymphocyte differentiation. Production of ADA in the pleural cavity reflects T cell and monocyte activation in pleural effusions[42]. Previous studies have concluded that the sensitivity and specificity of ADA in pleural effusions for diagnosis of TPE were 88%–100% and 81%–97%, respectively[43]. ADA level of >40 U/L is usually diagnostic of pleural TB[44], with sensitivity and specificity of 92%–93% and 90%–92%, respectively[45]. Similarly, elevated pleural ADA levels are considered diagnostic of pleural TB in children. However, a significant proportion of children with pleural TB still have pleural ADA values below the 40 U/L threshold[7]. In the present study, there was no statistically significant difference in ADA levels between the TPE and MP-PPE groups; however, to the best of our knowledge, because there have been no previous studies comparing ADA in pleural effusions between patients with TPE and MP-PPE, more studies are still required to further confirm this correlation.

It has been suggested that ADA, LDH, and pleural fluid protein levels were higher in TPE patients than in non-TPE patients and that increased lymphocytes and decreased N% may help differentiate TPE patients from non-TPE patients[46]. In the present study, serum levels of the relevant inflammatory indicators were significantly lower in the TPE group than in the MP-PPE group, but serum TP level, albumin level, ESR, and L% were higher than in the MP-PPE group; the differences were statistically significant (p<0.05). ROC curve analysis showed that the serum TP level of >64.5 g/L (AUC 0.766, sensitivity 77%, specificity 71%, p<0.05), albumin level of >41.9 g/L (AUC 0.852, sensitivity 92%, specificity 69%, p<0.05), ESR of >39 mm/min (AUC 0.732, sensitivity 69%, specificity 82%, p<0.05), and L% of >8.7% (AUC 0.836, sensitivity 85%, specificity 71%, p<0.05) resulted in maximum sensitivity and specificity for the diagnosis of TPE (p<0.05).

Previous studies [47]have concluded that the pleural fluid of patients with PT is usually colorless or yellowish and may be clear, cloudy, or serous. In nearly 70% of cases, it is an exudate with high protein levels (nearly 50 g/L). Glucose levels in the pleural fluid are lower than those in the serum, and the pH is generally normal. LDH level is usually higher than in the serum, usually >500 U/L. Cytological examination indicates multiple cell types in 90% of cases, with lymphocytes predominating (>50%). However, a predominance of neutrophils can be observed in the first two weeks of disease and can persist in up to 10% of cases; the number of mesothelial cells does not usually exceed 5%. Glucose concentrations in pleural effusions and serum glucose change in tandem, and low pleural fluid glucose concentrations are mostly observed in cases of tuberculosis, malignant pleurisy, rheumatoid arthritis, and pneumonia complicated by pleurisy[48]. The present study results indicated a statistically significant difference in pleural fluid WBC count and TP, glucose, and LDH levels between the MP-PPE and TPE groups (p<0.05). Furthermore, the median WBC count and pleural fluid TP level were lower in the MP-PPE

group than in the TPE group, whereas the median pleural fluid glucose and LDH levels were higher in the MP-PPE group than in the TPE group. There were no statistically significant differences between the two groups in pleural fluid N% or monocyte percentage ($p>0.05$).

Further pleural fluid blood gas analysis revealed statistically significant differences in the pleural fluid pH, $PaCO_2$, and Lac and blood gas glucose levels in the MP-PPE group compared to the TPE group ($p<0.05$). Previous studies[49] have indicated that Lac level was significantly lower in the MP group than in the non-MP group, and ROC curve analysis yielded a diagnostic threshold of 4.02 mmol/L to diagnose an MP infection. Lac is a product of anaerobic metabolism in body tissues, and its level is significantly elevated in tissue hypoxia and deficient perfusion. Although MP infection damages host cells, the pathogenic mechanism primarily disrupts the immune response,' therefore, the Lac level was reportedly significantly lower in the MP group than in the non-MP group. This is consistent with the results of the present study, in which Lac level was 3 mmol/L in the MP-PPE group, which is significantly lower than the median Lac level of 5.2 mmol/L in the TPE group. The pH in the MP-PPE group was higher than that in the TPE group (median 7.523 vs. 7.427 respectively, $p<0.05$) because MP infection is not dominated by anaerobic metabolism. $PaCO_2$ was lower in the MP-PPE group than in the TPE group (median 28.6 mmHg vs. 36.7 mmHg respectively, $p<0.05$), suggesting that the blood gas analysis of pleural effusions is likely to indicate alkalinity after MP infection. However, more studies are needed to further confirm these results.

ROC curve analysis was performed to determine the sensitivity and specificity of the differences in pleural fluid indicators between the two groups. The results showed that pleural fluid pH (AUC 0.787, sensitivity 77%, specificity 82%, $p<0.05$), blood gas glucose level (AUC 0.744, sensitivity 51%, specificity 100%, $p<0.05$), glucose level (AUC 0.753, sensitivity 60%, specificity 100%, $p<0.05$), and LDH level (AUC 0.877, sensitivity 71%, specificity 100%, $p<0.05$) exhibited high sensitivity and specificity for differentiation of MP-PPE, with cutoff points of 7.49, 5.7 mmol/L, 6 mmol/L, and 2,484 U/L, respectively, at which the diagnosis of MP-PPE is most accurate. Pleural fluid WBC count (AUC 0.744, sensitivity 91%, specificity 63%, $p<0.05$), TP level (AUC 0.787, sensitivity 91%, specificity 71%, $p<0.05$), $PaCO_2$ (AUC 0.765, sensitivity 64%, specificity 96%, $p<0.05$), and blood gas Lac level (AUC 0.796, sensitivity 91%, specificity 60%, $p<0.05$) exhibited high sensitivity and specificity for the diagnosis of TPE, with cutoff points of >641 × 10^9/L for WBC count, >55 g/L for albumin level, >28.4 mmHg for blood gas $PaCO_2$, and >5.3 mmol/L for blood gas Lac level, at which the diagnosis of TPE is most accurate. Among these, the AUC of pleural fluid LDH was 0.877, and its accuracy for the diagnosis of MP-PPE was the highest.

Studies have found that MP in pleural effusion was associated with slow absorption of lesions on chest radiography in pediatric patients with MP pneumonia[50]. Another study found that patients with MP pneumonia with pleural effusion had a larger surface area of lesion involvement on chest radiography at admission[51]. Therefore, most studies have suggested that pleural effusion in MP pneumonia indicates a severe lesion on chest radiography and prolonged absorption[14]. Previous studies have reported that most children with tuberculous pleural effusion are involved in one lung and less in two side[52].However, to the best of our knowledge, no studies have compared the degree of MP-PPE lesion involvement with

that of TPE lesion involvement. In the present study, the disease involvement of lesion sites between the two groups was compared, and it was found that the lesion sites of children with MP-PPE can occur both unilaterally and bilaterally, but TPE was found to occur only unilaterally. Further comparison of lesion involvement between the right and left lungs revealed that most MP-PPE cases involved the right side, whereas the majority of TPE cases involved the left side; the difference was statistically significant ($p<0.05$). This may be because the pathogenesis of MP pneumonia is dominated by airway injury, and its anatomical features predispose the right side of the airway and lungs to damage from infection.

Our study is the first large-scale retrospective investigation of the clinical, hematologic, and pleural gas characteristics of MP-PPE and TPE in children.Our results may provide clinicians with a new method to distinguish MP-PPE and TPE in children .The present study results should be interpreted within the context of some limitations. First, the number of case samples included in this study is small because pleural effusion must reach a certain depth, and thoracentesis can only be performed after ultrasound localization and obtaining consent from a guardian. Consequently, relatively few patients are candidates for thoracentesis. In addition, the pleural fluid samples were centrifuged immediately after thoracentesis; then, blood gas analyses were performed. Specimen quality may have been impacted if the specimen was not immediately centrifuged; such cases were eliminated.

In conclusion, this study was the first comprehensive comparative analysis of clinical, blood, and pleural fluid data between MP-PPE and TPE patients. We conclude that serum N% and CRP, PCT, IL-6, LDH, DD, and ALT levels were significantly higher, whereas CD3+, CD3+CD8+, CD3+CD4+, CD16+CD56+, and CD19+ counts were lower in the MP-PPE group than in the TPE group. This suggests that various inflammatory factors are involved in the immune response after MP infection and that excessive inflammatory response and immune dysfunction is present when accompanied by pleural effusion. In contrast, serum and pleural fluid LDH levels were elevated compared to the TPE group, suggesting that LDH can be used as a more sensitive indicator to distinguish MP-PPE from TPE. Blood gas analysis results indicated that the pH in the MP-PPE group was more alkaline compared to the TPE group, which was also a significant finding for differentiating MP-PPE from TPE. We believe that our study makes a significant contribution to the literature because MP-PPE and TPE are commonly observed in pediatric patients. The study findings could be used to help distinguish MP-PPE from TPE.

List Of Abbreviations

AUC	Area under the receiver operating characteristic curve
CT	Computed tomography
MP	*Mycoplasma pneumoniae*
ROC	Receiver operating characteristic
MP-PPE	*Mycoplasma pneumoniae* pneumonia-related pleural effusion

TPE	Tuberculous pleural effusion
MRMP	Macrolide-resistant *Mycoplasma pneumoniae*
TB	Tuberculosis
WBC	White blood cell
PLT	Platelet
CRP	C-reactive protein
PCT	Procalcitonin
IL-6	Interleukin-6
ALT	Alanine transaminase
TP	Total protein
LDH	Lactate dehydrogenase
FIB	Fibrinogen
DD	D-dimer
Ig	Immunoglobulin
ADA	Adenosine deaminase
Lac	Lactate
PCT	Procalcitonin
ESR	Erythrocyte sedimentation rate
HB	Hemoglobin

Declarations

Ethics approval and consent to participate:

This study was performed in strict accordance with the human subject protection guidance of Ministry of Science and Technology of China.The study was approved by the institutional ethics review board at Shengjing Hospital Affiliated to China Medical University Reference no:2021PS213J.Verbal informed consent was obtained for all the investigations, and written informed consent was obtained from the parents of each participant in the study prior to enrollment. This study used currently existing sample

collected during the course of routine medical care and did not pose any additional risks to the patients. All patient data were anonymized prior to the analysis.

Consent for publication:

Not applicable.

Availability of data and materials:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests:

The authors declare that they have no conflict of interest.

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Authors' contributions:

LC:Conceptualization, Writing Original draft preparation, Software, Validation; QC: Reviewing,Collect clinical data, statistics; YS and XC : Reviewing and Editing. All authors read and approved the final manuscript.

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Figures

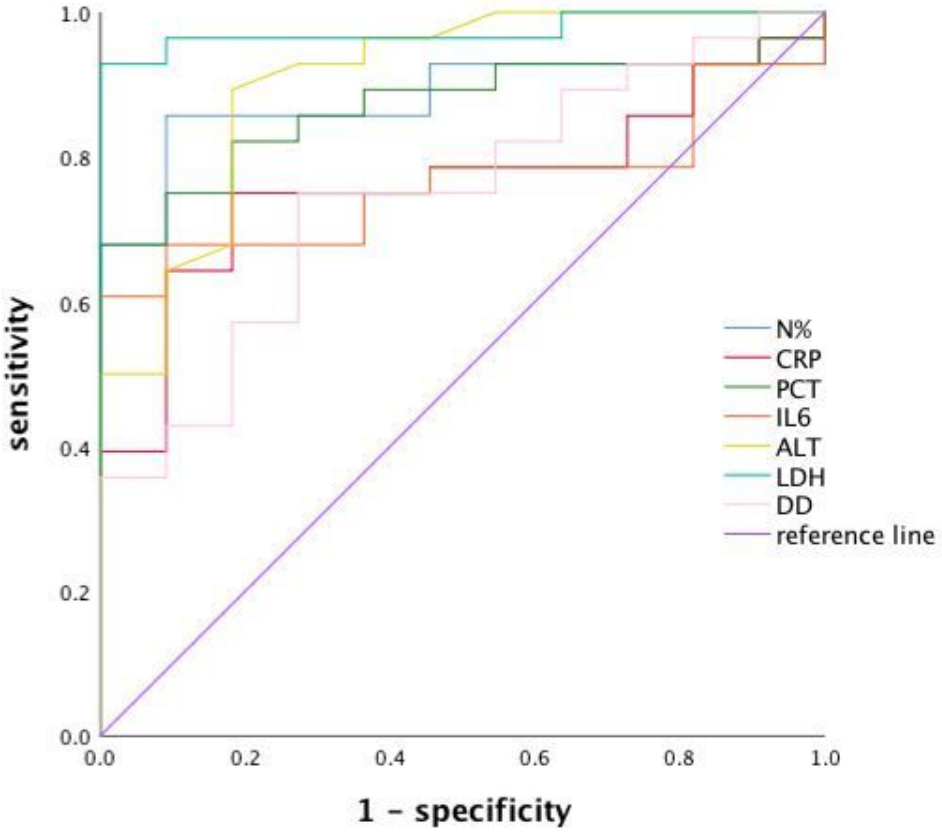

Figure 1

Receiver operating characteristic (ROC) curve analysis

Analysis of blood neutrophil percentage (N%), C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), lactate dehydrogenase (LDH), D-dimer (DD), and alanine transaminase (ALT) indicated high

sensitivity and specificity for diagnosis of *Mycoplasma pneumoniae* pneumonia-related pleural effusion (MP-PPE). $p<0.05$.

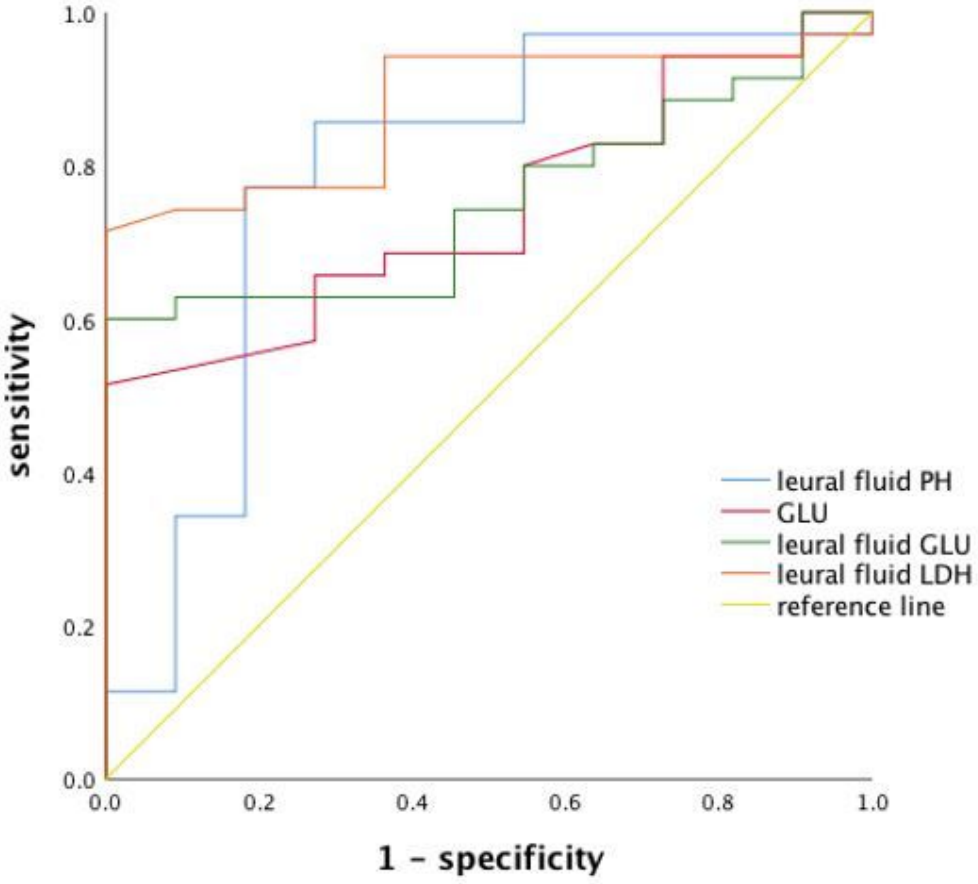

Figure 2

Receiver operating characteristic (ROC) curve analysis

Analysis of total protein, albumin, erythrocyte sedimentation rate (ESR), and lymphocyte percentage in blood indicated high sensitivity and specificity for diagnosis of tuberculous pleural effusion (TPE). $p<0.05$.

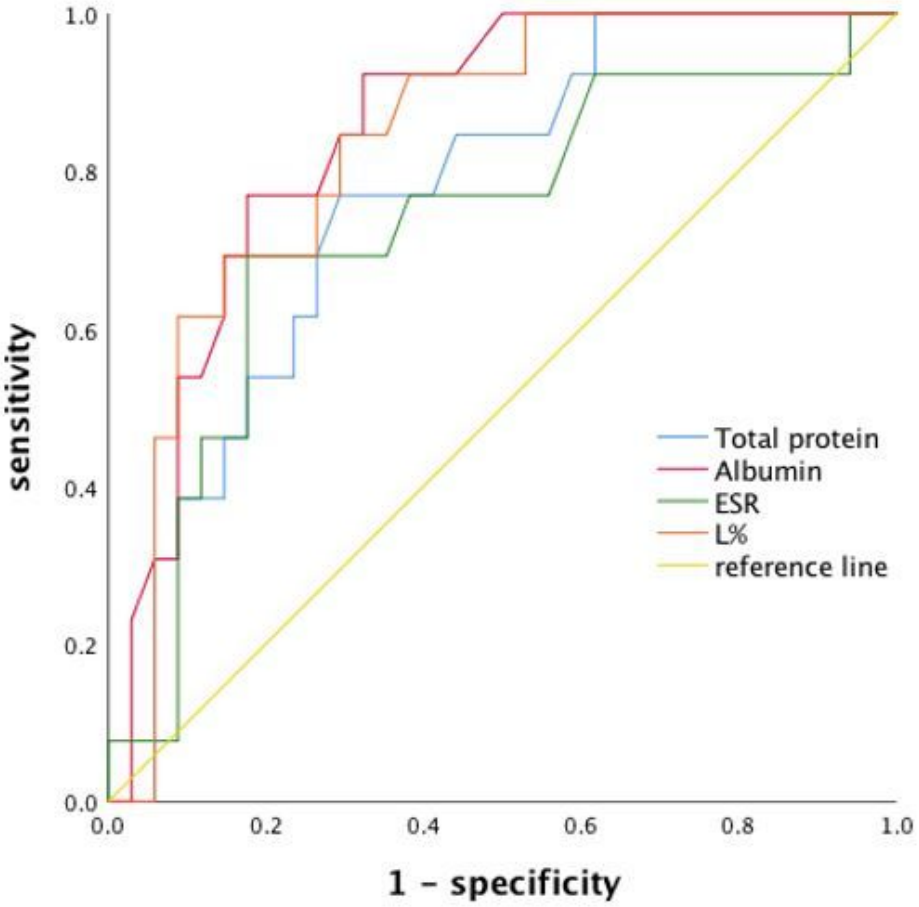

Figure 3

Receiver operating characteristic (ROC) curve analysis

Analysis of the sensitivity and specificity of pleural fluid pH, blood gas glucose, glucose, and lactate dehydrogenase (LDH) for diagnosis of *Mycoplasma pneumoniae* pneumonia-related pleural effusion (MP-PPE). $p<0.05$.

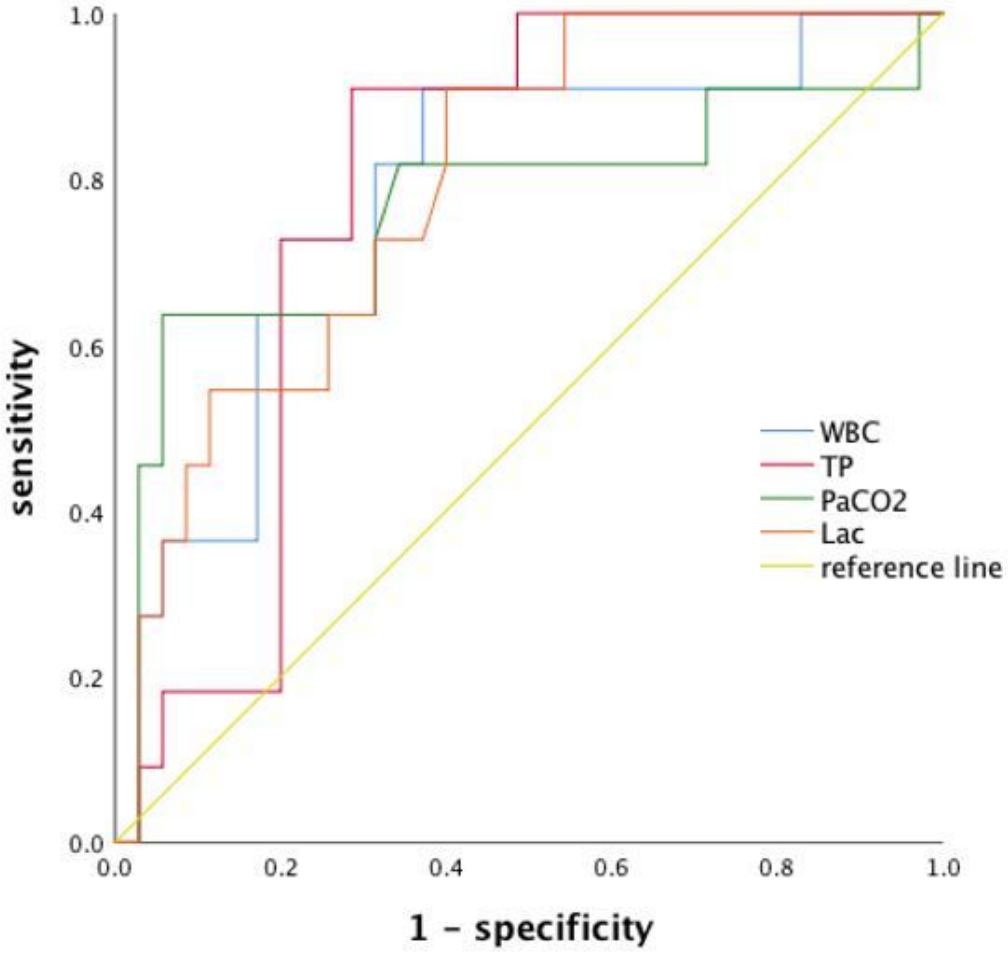

Figure 4

Receiver operating characteristic (ROC) curve analysis

Analysis of the sensitivity and specificity of pleural fluid white blood cell count, total protein, $PaCO_2$, and Lac for diagnosis of tuberculous pleural effusion (TPE). $p<0.05$.