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Analysis of the Role of D-Dimer, Interleukin-6, and Interleukin-18 in Differential Diagnosis of Pediatric Refractory *Mycoplasma pneumoniae* Pneumonia

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Abstract: *Objective:* To analyze the value of D-dimer (D-D), interleukin-6 (IL-6), and IL-18 in the differential diagnosis of children with refractory *Mycoplasma pneumoniae* pneumonia (RMPP). *Methods:* The medical records of 92 children with *Mycoplasma pneumoniae* pneumonia (MPP) treated in the hospital were selected for retrospective analysis from January 2023 to January 2024. After comprehensive examinations such as computed tomography examination of the chest, 48 children with general *Mycoplasma pneumoniae* pneumonia (GMPP) were put in the GMPP group and 44 children with RMPP were grouped in the RMPP group. The IL-6, IL-18, and D-D levels were compared between the two groups, and the receiver operating characteristic (ROC) curves were plotted to analyze their value for differential diagnosis of RMPP. *Results:* The levels of IL-6, IL-18, and D-D in the RMPP group were higher than those in the GMPP group ($P < 0.05$); the ROC curves showed that the specificity of the differential diagnosis of IL-6, IL-18, and D-D was higher, and their diagnostic value was significant. *Conclusion:* Determination of IL-6, IL-18, and D-D levels in children with MPP can further diagnose the children's condition, which can help physicians formulate targeted treatment plans, and is of great significance to the improvement of the children's condition, which is worthy of attention.

Keywords: Refractory *Mycoplasma pneumoniae* pneumonia; D-dimer; Interleukin-6; Interleukin-18; Differential diagnosis

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1. Introduction

Mycoplasma pneumoniae pneumonia (MPP) is a respiratory disease that often occurs in children, mainly due to *Mycoplasma pneumoniae* (MP) infection. The clinical treatment is mostly based on antibiotics, but with the enhancement of drug resistance in children, the effect of conventional antibiotic treatment is weakened, increasing the difficulty of treatment for children's conditions and gradually progressing to refractory

Mycoplasma pneumoniae pneumonia (RMPP), which can aggravate lung damage and even involve other organs, endangering their lives [1]. Therefore, it is crucial to diagnose the type of MPP in children as early as possible, adjust the treatment plan to the actual situation, and promote the recovery of the children's condition. With in-depth clinical research, it is found that the occurrence and development of RMPP are closely related to the immune damage of children, and interleukin (IL-6), IL-18, and other immune-related cytokines can provide a reliable reference value for the prediction of RMPP [2]. D-dimer (D-D) is a special fibrin degradation product, which is a specific marker for the fibrinolytic system, and can provide a reference for the assessment of the severity of the disease and the long-term prognosis of the children. Therefore, IL-6, IL-18, and D-D measurements are valuable in diagnosing the condition of children with RMPP [3]. Based on this, the present study was conducted to analyze the value of D-D, IL-6, and IL-18 in differential diagnosis of pediatric RMPP.

2. General information and methods

2.1. General information

92 children with MPP who presented to the hospital from January 2023 to January 2024 were selected, including 48 males and 44 females; their ages ranged from 6 months to 10 years, with a mean age of 6.45 ± 2.33 years. Inclusion criteria: (1) all were consistent with the diagnostic criteria of MPP [4]; (2) complete personal data. Exclusion criteria: (1) those who suffered from bronchial asthma, tuberculosis, and other lung diseases; (2) those who suffered from immune diseases; (3) those who suffered from severe tumors; (4) those who suffered from congenital heart disease, limb deformities, and organ defects. All of them received chest computed tomography examination with the presence of lung shadows and positive mycoplasma pathogenesis, but after 5 days of treatment with macrolide antibiotics, the children were seen to be significantly better and were classified as generalized *Mycoplasma pneumoniae* pneumonia (GMPP). If the treatment time was > 7 days, but did not see improvement or the condition continued to aggravate, it was classified as RMPP. There were 48 children in the GMPP group, male:female was 25:23, aged 6 months–12 years (6.49 ± 2.34) years. There were 44 children in the RMPP group, male:female was 23:21, aged 6 months–12 years (6.42 ± 2.36) years. The two groups were comparable in terms of age and gender ($P > 005$) and met the conditions of the Medical Ethics Committee (202301).

2.2. Methods

5 ml of morning fasting venous blood was collected from the cubital vein. The blood was then centrifuged at 3000 rpm for approximately 5 minutes. The supernatant was used to measure the levels of D-D, IL-6, and IL-18 using enzyme-linked immunosorbent assay (ELISA).

2.3. Observation indexes

The D-D, IL-6, and IL-18 levels of children were recorded and analyzed for their diagnostic sensitivity and specificity.

2.4. Statistical methods

The data were analyzed by SPSS20.0 software, the measurement data were expressed as mean ± standard deviation (SD), and *t*-test was performed; the count data were expressed as %, and Fisher's exact probability method or χ^2 test was used. The value of D-D, IL-6, and IL-18 in the differential diagnosis of RMPP was analyzed by plotting the receiver operating characteristic (ROC) curve, a higher area under the ROC curve (AUC)

value suggested that the diagnostic value was more significant, and $P < 0.05$ suggested that the difference was statistically significant.

3. Results

3.1. Comparison of D-D, IL-6, and IL-18 levels between the two groups

The levels of D-D, IL-6, and IL-18 in the RMPP group were higher than those of the GMPP group ($P < 0.05$), as shown in **Table 1**.

Table 1. Comparison of D-D, IL-6, and IL-18 levels between groups (mean ± SD)

Groups	Number of cases	D-D (mg/L)	IL-6 (pg/mL)	IL-18 (pg/mL)
GMPP group	48	0.43 ± 0.12	17.65 ± 3.52	315.42 ± 72.65
RMPP group	44	1.36 ± 0.66	31.52 ± 9.88	376.58 ± 116.53
t	-	9.596	9.119	3.048
P	-	< 0.001	< 0.001	0.003

3.2. Analysis of the value of D-D, IL-6, and IL-18 for differential diagnosis of RMPP

The results of the ROC curve showed that the AUC of D-D, IL-6, and IL-18 for differential diagnosis of RMPP was 0.910, 0.924, and 0.661, respectively, all of which had a certain degree of accuracy; whereas the sensitivity was 88.64%, 96.36%, and 43.18%, and the specificity was 97.92%, 93.75% and 91.67%, which had a good differential diagnostic value, as shown in **Table 2** and **Figure 1**.

Table 2. The value of D-D, IL-6, and IL-18 in the differential diagnosis of RMPP

Indicators	AUC	SE	*P*	95% CI	Optimum cut-off value	Sensitivity	Specificity	Jordan index
D-D	0.910	0.040	< 0.001	0.832–0.960	0.62 mg/L	88.64%	97.92%	0.866
IL-6	0.924	0.035	< 0.001	0.850–0.969	22.28 pg/mL	96.36%	93.75%	0.801
IL-18	0.661	0.059	< 0.001	0.554–0.756	400.62 pg/mL	43.18%	91.67%	0.349

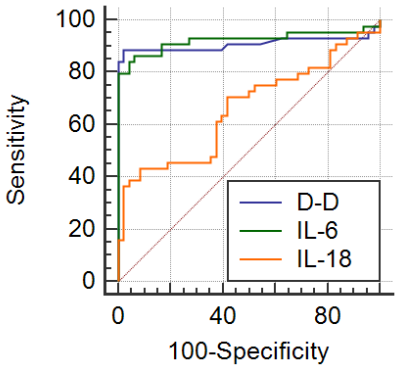

Figure 1. Value of D-D, IL-6, and IL-18 in differential diagnosis of RMPP

4. Discussion

MPP is a common respiratory illness primarily affecting children. It is mainly caused by MP infection, which is highly infectious. The bacteria enter the respiratory mucosa and ciliated epithelial cells through droplets,

leading to the release of toxic substances such as hydrogen peroxide. This causes cellular membrane damage. Additionally, once inside the body, MP stimulates the production of autoantibodies and immune complexes, which can lead to complications such as encephalitis and nephritis, severely threatening the child's life [5]. Therefore, it is important to diagnose the condition of children as early as possible and provide targeted treatment. RMPP develops when MPP does not respond to treatment. RMPP is characterized by a certain level of resistance to macrolide antibiotics. Therefore, accurate differential diagnosis of the child's condition, along with developing an effective treatment plan tailored to the specific situation, is crucial for promoting recovery [6].

In this study, the levels of D-D, IL-6, and IL-18 in the RMPP group were higher than those in the GMPP group ($P < 0.05$), indicating that these indicators can be used for the differential diagnosis of the children's conditions. As IL-6 is a 26 kD peptide, which can effectively regulate the growth and differentiation of B cells and promote the synthesis of acute phase proteins by hepatocytes; it is a common clinical inflammatory factor and its level will rise significantly when the body is infected, thus it is positively correlated with inflammatory response. At the same time, secreted by macrophages and monocytes, it has a wide range of biological activities, can induce and promote the activation of the peripheral blood monocyte system, promote neutrophil apoptosis, resulting in immune suppression, leading to a decline in immunity, which can reflect on the severity of the child's condition, and can be used as one of the indicators of differential diagnosis of RMPP [7]. D-D is a protein degradation product that reflects the activation of the body's coagulation and fibrinolytic systems. Elevated levels of D-D indicate increased blood coagulability and dysfunction of vascular endothelial function. Monitoring these levels can help predict the patient's condition and provide reliable data for analyzing treatment effectiveness, thereby aiding physicians in better understanding and managing the patient's health [8]. IL-18 is a multifunctional pro-inflammatory cytokine that can induce the production of various other cytokines. It promotes cellular and humoral immune responses based on the surrounding cytokine environment and, in conjunction with IL-12, stimulates the production of numerous inflammatory factors. This can lead to localized inflammatory responses and exacerbate organ damage. IL-18 may be involved in the pathological and physiological processes of children with RMPP, serving as a potential biomarker for predicting RMPP. Thus, its role in diagnosis should be given significant attention [9]. The AUCs of D-D, IL-6, and IL-18 for differential diagnosis of RMPP were 0.910, 0.924, and 0.661, respectively, as analyzed by the ROC curve, which is of high value. It can be seen that the determination of D-D, IL-6, and IL-18 levels effectively provides a reliable reference for the differential diagnosis of children's conditions, further improves the detection rate of children with RMPP, and effectively prevents missed diagnosis and misdiagnosis, and the specificity of the differential diagnosis of children with RMPP with D-D, IL-6, and IL-18 is more than 90%, which can be used as a highly effective indicator for the differential diagnosis of children with RMPP [10].

5. Conclusion

In summary, the value of D-D, IL-6, and IL-18 differential diagnosis of RMPP children is significant and can provide a reliable reference for physicians to formulate an effective treatment plan. Therefore, in the diagnosis and treatment of MPP children, the measurement of D-D, IL-6, and IL-18 levels should be emphasized, in order to further improve the therapeutic effect and prognosis.

Disclosure statement

The authors declare no conflict of interest.

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