Original Article

The predictive values of soluble B7-DC in children with refractory mycoplasma pneumoniae pneumonia

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Background: Refractory mycoplasma pneumoniae pneumonia (RMPP) is a serious mycoplasma pneumoniae infection and is difficult to diagnose early. The levels of serum soluble B7-dendritic cell (sB7-DC) in children with mycoplasma pneumoniae pneumonia (MPP) were assessed to explore the clinical significance of sB7-DC levels in RMPP.

Methods: A total of 65 patients with mycoplasma pneumoniae pneumonia (MPP) were enrolled in this study between January 2017 and December 2018. The patients were divided into the general mycoplasma pneumoniae pneumonia (GMPP) (n=30) and RMPP groups (n=35); the data of 20 normal children served as a control group (n=20). An enzyme-linked immunoassay kit was used to detect the expression of soluble B7-dendritic cell (sB7-DC) and other inflammatory factors. Binary logistic regression was performed to identify the independent predictors of RMPP. Receiver operating characteristic (ROC) curves were drawn to evaluate the value of each independent risk factor in the early diagnosis of RMPP.

Results: The results showed that compared to the GMPP group, children in the RMPP group had a significantly longer hospital stay and had a significantly longer fever duration ($P<0.05$). The values of interferon-gamma (IFN-γ), interleukin 17 (IL-17), and sB7-DC in the RMPP group were significantly higher than those in the normal control and GMPP groups (all $P<0.05$). The results of the correlation analysis showed that sB7-DC was positively correlated with IFN-γ and IL-17 and these indicators could be used in combination to evaluate the severity of the disease. The binary logistic regression analysis identified IL-17 and sB7-DC as independent risk factors for RMPP ($P<0.05$). The ROC curve analysis showed that the cut-off values of IL-17 and sB7-DC were 309.6 pg/L and 1,109.7 pg/mL, respectively. The areas under the curve (AUCs) of IL-17 and sB7-DC were 0.741 and 0.794, respectively. The sensitivity of IL-17 to RMPP prediction was 83.3%, and the specificity was 62.9%. The sensitivity and specificity of sB7-DC to RMPP were 86.7% and 62.9%, indicating that sB7-DC had the highest predictive power for RMPP.

Conclusions: The level of serum sB7-DC may play an important role in the early diagnosis of RMPP. Our research results provide a theoretical basis for the early diagnosis of RMPP.

Keywords: Mycoplasma pneumoniae pneumonia; refractory mycoplasma pneumoniae pneumonia; soluble B7-dendritic cell (sB7-DC); children

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Introduction

Mycoplasma pneumoniae (MP) is one of the main pathogens causing community-acquired pneumonia (CAP) in children. Studies have shown that mycoplasma pneumoniae pneumonia (MPP) may account for 40% of CAP cases, and approximately 20% of MPP patients require hospitalization (1,2). Most MP infections in children are mild and self-limited; however, a small number of patients require hospitalization and may sometimes experience various pulmonary and extrapulmonary complications.

Macrolides are the first choice of antibiotics for pediatric patients. However, some patients treated with macrolide antibiotics for ≥7 days do not show any improvement on clinical and radiological examinations. Such cases of MP are classified as refractory mycoplasma pneumoniae pneumonia (RMPP) (3-5). It is currently believed that RMPP is mainly caused by MP directly invading the lung and bronchial tissues, or by MP stimulating excessive immunological inflammation responses in the body (6-8), including the strong expression of cytokines and a highly activated cell-mediated immune response. Many literatures have reported the correlation between cytokines, chemokines or other inflammatory biomarkers and RMPP (9). Clinical indicators, such as C-reactive protein (CRP), erythrocyte sedimentation rate, D-dimer, and lactate dehydrogenase (LDH), are usually elevated (5,10). In addition, studies have shown that 35 α- Percentage of hydroxybutyrate dehydrogenase (HBDH) (7), the percentage of neutrophils and cluster of differentiation CD8+ (CD8+) T cells, interleukin (IL)-6, interleukin (IL)-10, interferon γ (IFN-γ) and serum chemokines such as C-X-C motif chemokine 10 (CXCL10)/IP-10 may be potential biomarkers of RMPP (11-13). A previous study showed that interleukin (IL)-17, interleukin (IL)-8, and tumor necrosis factor alpha (TNF-α) cytokines in the bronchoalveolar lavage fluid of patients are increased, the increase of IL-17, IL-8, and TNF-α is greater in RMPP patients than general mycoplasma pneumoniae pneumonia (GMPP) patients, and an increase in the IL-17 level is associated with an increase in lung lesions (14). However, these cytokines still lack specificity in the diagnosis of RMPP.

The early clinical manifestations of RMPP are non-specific; thus, the early diagnosis of RMPP can be difficult. Sensitive predictors that can detect RMPP early need to be identified. This study sought to identify independent factors related to RMPP by analyzing and comparing the differences in the clinical characteristics and laboratory data of MPP and RMPP cases and to provide a basis for the early clinical diagnosis of RMPP. Notable differences in soluble B7-dendritic cell (sB7-DC) concentration were found between healthy individuals, patients with RMPP, and those with GMPP in the collected data, and these data attracted our attention. Thus, we conducted this study to reveal the relationship between sB7-DC concentration and RMPP to verify the role of sB7-DC in the early diagnosis of RMPP. We present the following article in accordance with the STARD reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-86/rc).

Highlight box

Key findings

- We found that serum soluble B7-DC (sB7-DC) level can be used as an early predictor of refractory mycoplasma pneumoniae pneumonia (RMPP).

What is known and what is new?

- The early clinical manifestations of RMPP are non-specific, and there is a lack of sensitive predictors for the early detection of RMPP.
- We found that the sB7-DC and interleukin (IL)-17 levels of children with RMPP were significantly increased, and that sB7-DC has a higher predictive value than IL-17 for RMPP.

What is the implication, and what should change now?

- Given the increase in the number of cases of RMPP and that the early symptoms of RMPP are non-specific, RMPP can be challenging to diagnose. Our findings may assist in the early diagnosis and intervention of RMPP.

Methods

Study population and data collection

This retrospective study comprised 20 normal individuals and 65 children who were diagnosed with MPP during their hospitalization at the Children's Hospital of Soochow University between January 2017 and December 2018. The study was conducted at the Children's Hospital of Soochow University. Before entering the study, the corresponding author (Zheng-Rong Chen) evaluated and screened all the subjects to ensure they met the research qualification criteria. This was a convenient sample of children with MPP; the subjects were registered when the corresponding author was scheduled for work in the hospital. The children were aged ≥1 year and all met the MPP diagnosis criteria and treatment expert consensus (2015 version)

for children (10). The clinical manifestations included fever, cough, dyspnea, and abnormal lung auscultation, and the laboratory findings included new infiltrates on chest radiography, serum mycoplasma pneumoniae-immunoglobulin M (MP-IgM) >1.1, and nasopharyngeal aspirate MP-deoxyribonucleic acid >1.0×10^5 copies/L (10). Patients were excluded from the study if they had immunodeficiency, a non-infectious interstitial lung disease, tuberculosis, a history of recurrent wheezing or asthma, bronchopulmonary dysplasia, a severe heart, liver, or kidney disease, a malignant tumor, or incomplete case information.

The following definition for RMPP was adopted: (I) fever persisting for ≥7 days; or (II) radiological deterioration despite appropriate antibiotic therapy, including macrolide antibiotic therapy (5). All the other subjects were considered to have GMPP (5). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study protocol was approved by the Ethical Review Committee of the Children's Hospital of Soochow University (No. 2020CS078). Written informed consent was obtained from the parents or legal guardians of all the subjects prior to their being included in the study.

When the children attended the hospital for treatment during the onset of an illness, after the children were diagnosed with GMPP or RMPP, the laboratory tests were performed within 24 h of admission, and the results of these tests, including the white blood cell (WBC) count, platelet (PLT) count, CRP level, LDH level, alanine aminotransferase (ALT) level, aspartate aminotransferase (AST) level, and other data, were recorded. General patient information was also collected, including sex, age, total fever duration, and medical history. An enzyme-linked immunoassay (ELISA) kit was used upon admission to detect sB7-DC and other inflammatory factors according to the instructions provided by the manufacturer (kit for detecting inflammatory factors: Sigma-Aldrich; St. Louis, MO, USA; kit for detecting sB7-DC: Thermo Fisher; Carlsbad, CA, USA). The imaging data and laboratory examination data of each patient were reviewed by corresponding professional doctors, who knew nothing of the subjects' information, including the final disease diagnosis.

Reagents

The ELISA kit used to detect interferon-gamma (IFN-γ), interleukin (IL)-4, and IL-17 was purchased from Sigma-Aldrich (St. Louis, MO, USA), and the ELISA kit used to detect sB7-DC was purchased from Thermo Fisher (Carlsbad, CA, USA).

Statistical analysis

SPSS 25.0 statistical software was used for the data analysis. The normally distributed measurement data are expressed as the mean ± standard deviation ($\bar{x}\pm s$), and an independent sample *t*-test was used to conduct comparisons between 2 groups. The skewed distribution data are expressed as the median value (25th–75th interquartile range), and the Mann-Whitney U rank-sum test was used to conduct comparisons between 2 groups. The differences were considered statistically significant if the P value was <0.05. The χ^2 test was used for comparisons between groups for the categorical variables. A Spearman correlation analysis was used to determine the correlations of the non-normally distributed data. A binary logistic regression analysis of the risk factors related to RMPP was also performed (the variable selection criterion was P<0.05). Receiver operating characteristic (ROC) curves were drawn, and the areas under the curve (AUCs) were used to evaluate the predictive value of each independent risk factor in the formation of RMPP. The closer the AUCs were to 1.0, the higher the authenticity of the detection method. The higher the sensitivity, the higher the diagnostic accuracy, and the higher the specificity, the lower the misdiagnosis rate. Indeterminate results were considered false-positive or false-negative results and not incorporated into the final analysis.

Results

Characteristics of the study subjects

This study analyzed the clinical data of 65 children with MPP and 20 normal children. *Figure 1* shows the research process adopted for this study. The GMPP group comprised 30 patients (35.3%), and the RMPP comprised 35 patients (41.2%). The average ages of the GMPP group and RMPP group were 4.6±2.9 and 4.8±2.6 years, respectively; the difference between the 2 groups was not statistically significant (P>0.05; *Table 1*). There was no significant difference in terms of sex between the GMPP and RMPP groups (P>0.05; *Table 1*). The results of the univariate analysis showed that compared to the GMPP group, children in the RMPP group had a significantly longer hospital stay, a significantly longer fever duration,

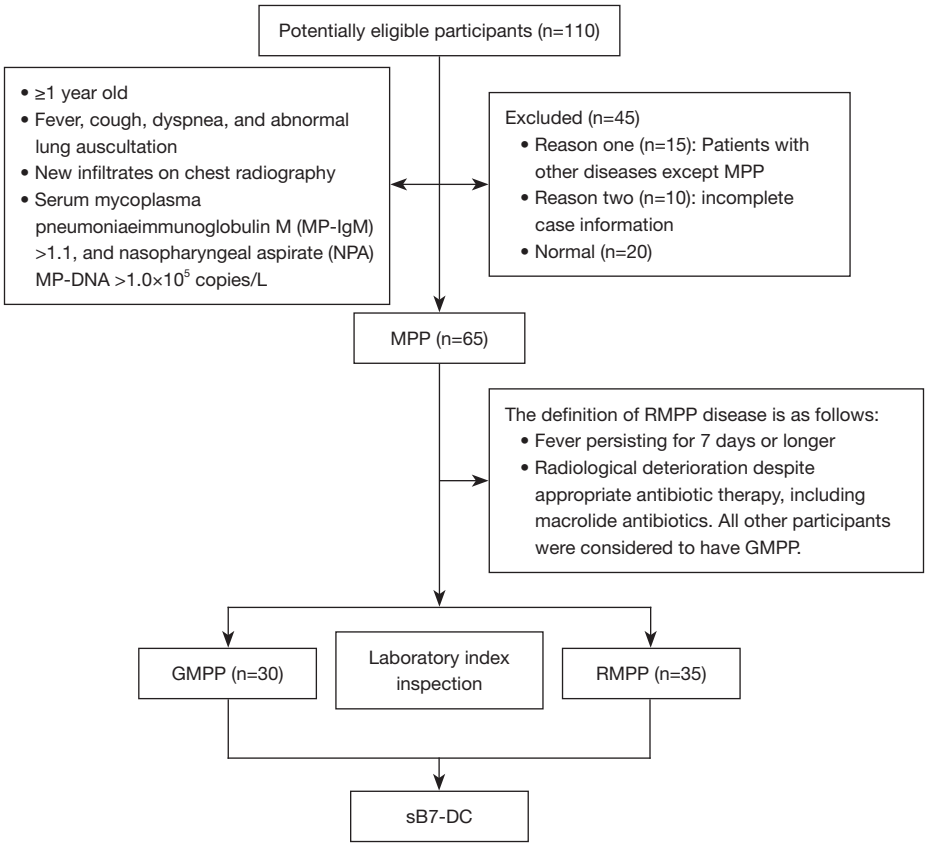

Figure 1 Flow diagram of research on the screening of the predictive factors related to the early diagnosis of RMPP. MP, mycoplasma pneumoniae; MPP, mycoplasma pneumoniae pneumonia; GMPP, general mycoplasma pneumoniae pneumonia; RMPP, refractory mycoplasma pneumoniae pneumonia; sB7-DC, soluble B7-dendritic cell.

significantly higher levels of WBC, total immunoglobulin (Ig) G, and IgM, and significantly lower levels of cluster of differentiation 3-cluster of differentiation 19+ (CD3-CD19+) and cluster of differentiation 19+ cluster of differentiation 23+ (CD19+CD23+) based on the laboratory test administered within 24 hours of admission (all P<0.05, *Table 1*).

An ELISA kit was used to detected the expression of sB7-DC and inflammatory factors, and a statistical analysis was performed. The results showed that the values of IFN-γ, IL-17, and sB7-DC in the RMPP group were significantly higher than those in the normal control and GMPP groups, (all P<0.05; *Figure 2*). There was no difference in the values of IL-4 in the 3 groups, and there was no statistically significant difference among the groups (P>0.05; *Figure 2*).

Correlation analysis of sB7-DC levels with IgG, IgM, CD3-CD19+, CD19+CD23+, IFN-γ, and IL-17

The WBC levels of the children in the GMPP and RMPP groups were normal. A correlation analysis was conducted to determine the factors related to sB7-DC. The results showed that the level of sB7-DC was positively correlated with the IFN-γ and IL-17 levels (Spearman r=0.363, P<0.05; Spearman r=0.441, respectively, P<0.0001, *Table 2*).

Predictive value of the sB7-DC level for RMPP

The statistical analysis identified 9 variables (i.e., hospitalization time, total fever duration, IgG, IgM, CD3-CD19+, CD19+CD23+, IFN-γ, IL-17, and sB7-DC) as

Table 1 Clinical and laboratory characteristics of the GMPP and RMPP patients

Variables	GMPP (n=30)	RMPP (n=35)	P value
Characteristics			
Male/female	14/16	16/19	0.939
Age, years	4.6±2.9	4.8±2.6	0.766
Hospitalization time (d)	7 (6, 9)	11 (9, 14)	<0.001
Signs and symptoms			
Total fever duration (d)	6.4±1.81	12.8±5.6	<0.001
Lung rales, n (%)	11 (36.7)	15 (42.9)	0.612
Lung wheezing, n (%)	8 (26.7)	7 (20.0)	0.525
Laboratory characteristics			
WBC ($\times10^9$/L)	6.6 (5.0, 8.0)	8.0 (6.3, 10.7)	0.048
N%	58.3 (46.1, 65.3)	62.5 (48.2, 73.2)	0.421
L%	36.4 (28.7, 46.3)	32.7 (20.2, 43.1)	0.263
PLT ($\times10^9$/L)	259.0 (204.0, 310.3)	292.0 (257.5, 336.5)	0.062
CRP (mg/L)	7.5 (3.3, 17.8)	11.5 (4.9, 35.6)	0.167
ALT (U/L)	13.4 (10.0, 17.1)	14.4 (11.2, 21.4)	0.157
AST (U/L)	30.4 (25.6, 37.6)	32.7 (25.1, 43.0)	0.563
LDH (U/L)	377.7 (318.1, 451.2)	450.5 (323.9, 534.9)	0.171
Humoral immunity			
IgG/g·L^{-1}	7.9±3.3	9.7±3.1	0.031
IgA/g·L^{-1}	0.77 (0.38, 1.28)	1.25 (0.56, 1.94)	0.186
IgM/g·L^{-1}	1.2 (0.9, 1.5)	1.7 (1.2, 2.0)	0.036
Cellular immunity			
CD3+	64.4±8.7	67.6±10.3	0.185
CD3+CD4+	34.2±6.5	34.4±7.7	0.900
CD3+CD8+	25.1±6.6	28.4±8.2	0.09
CD4/CD8	1.6 (1.0, 1.7)	1.1 (1.0, 1.6)	0.195
CD3-CD19+	21.1 (18.2, 29.4)	16.0 (12.1, 19.6)	0.002
CD3-CD (16+56+) +	9.6 (7.3, 14.4)	11.5 (7.1, 17.8)	0.545
CD19+CD23+	10.3 (8.3, 13.3)	7.5 (5.8, 10.9)	0.025

Data are expressed as the mean ± standard deviation or median (25th–75th interquartile range). GMPP, general mycoplasma pneumoniae pneumonia; RMPP, refractory mycoplasma pneumoniae pneumonia. WBC, white blood cell count; N%, proportion of neutrophils; L%, proportion of lymphocytes; PLT, platelets; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; LDH, lactate dehydrogenase; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M.

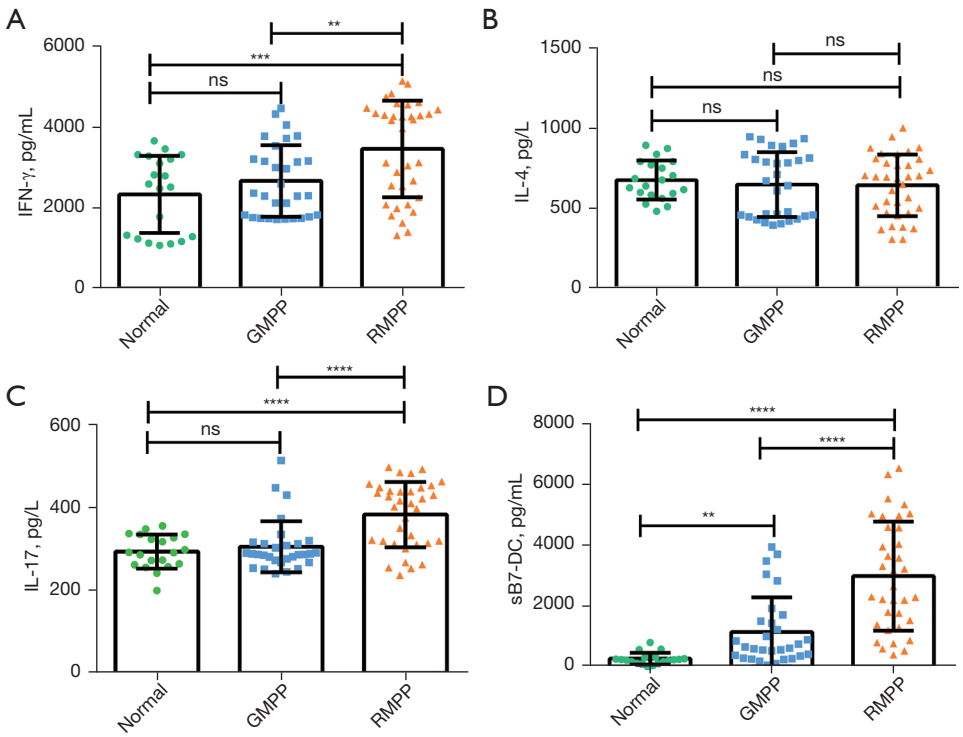

Figure 2 The IFN-γ, IL-4, IL-17, and sB7-DC results for the normal, GMPP, and RMPP groups. IFN-γ, interferon-gamma; IL-4, interleukin 4; IL-17, interleukin 17; sB7-DC, soluble B7-dendritic cell; GMPP, general mycoplasma pneumoniae pneumonia; RMPP, refractory mycoplasma pneumoniae pneumonia. **, P<0.01, ***, P<0.001, ****, P<0.0001, ns means no significance.

Table 2 Correlation analysis of the serum B7-DC level with IgG, IgM, CD3-CD19+, CD19+CD23+, IFN-γ, and IL-17

	IgG	IgM	CD3-CD19+	CD19+CD23+	IFN-γ	IL-17
Spearman r	0.152	0.184	–0.219	–0.116	0.363	0.441
P value	0.226	0.142	0.080	0.358	0.003	0.000

IgG, immunoglobulin G; IgM, immunoglobulin M; IL-17, interleukin 17; IFN-γ, interferon-gamma.

Table 3 Independent risk factors for RMPP

Characteristics	Proportion (%)	OR	95% CI	P
IL-17 ≥309.6 (pg/L)	82.9	1.012	1.003–1.022	0.010
sB7-DC ≥1,109.7 (pg/mL)	82.9	1.001	1.000–1.001	0.012

RMPP, refractory mycoplasma pneumoniae pneumonia; IL-17, interleukin 17; sB7-DC, soluble B7-dendritic cell.

significant risk factors for RMPP (P<0.05, *Table 1*, *Figure 1*). This study excluded the following high-level indicators: hospitalization time and total fever duration. These 7 variables were included in the binary logistic regression analysis. The binary logistic regression analysis revealed that after adjusting for confounding factors, IL-17 and sB7-DC were independent risk factors for RMPP (P<0.05, *Table 3*). The proportions of IL-17 ≥309.6 pg/L and sB7-DC ≥1,109.7 pg/mL in the GMPP group were 30.0% and 33.3%, respectively, while those in the RMPP group were 82.9%, indicating that there were more patients with IL-17 ≥309.6 pg/L and sB7-DC ≥1,109.7 pg/mL in the RMPP

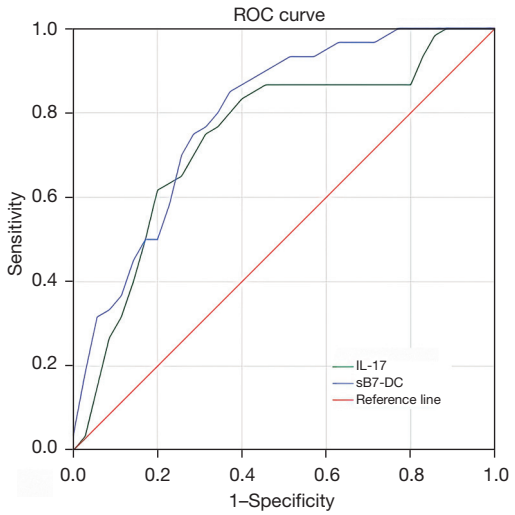

Figure 3 ROC curves of IL-17 and sB7-DC for predicting RMPP. The AUCs of IL-17 and sB7-DC were 0.741 and 0.794, respectively. ROC, receiver operating characteristic; IL-17, interleukin 17; sB7-DC, soluble B7-dendritic cell; RMPP, refractory mycoplasma pneumoniae pneumonia; AUC, area under the curve.

group than the GMPP group. The AUCs of IL-17 and sB7-DC were 0.741 [95% confidence interval (CI): 0.616, 0.866] and 0.794 (95% CI: 0.686, 0.902), respectively (*Figure 3*). The sensitivity of IL-17 to RMPP prediction was 83.3%, and the specificity was 62.9%. The sensitivity and specificity of sB7-DC to RMPP were 86.7% and 62.9%, respectively, indicating that sB7-DC had the highest predictive power for RMPP (P<0.001). No major adverse event was observed during any of the performing the index test or the reference standard.

Discussion

MPP is traditionally believed to be a self-limited disease; however, the incidence of RMPP has continued to increase because of the increase in resistance to macrolide antibiotics (2). Thus, for pediatricians, the early recognition and timely treatment of RMPP are essential to prevent disease progression. Studies have shown that fever for >10 days, LDH (9,15), serum D-D levels (5), pleural effusion, extrapulmonary complications, pulmonary X-ray consolidation ≥2/3 and CRP >40 mg/L are risk factors for the early evaluation of RMPP, but these factors are not independent risk factors for RMPP, and have certain limitations in the early diagnosis of RMPP (16).

In this retrospective study, 65 MPP patients were included, and the different clinical characteristics of the RMPP and GMPP patients were compared. According to the diagnostic criteria for RMPP, 35 patients were diagnosed with RMPP and 30 with GMPP. A statistical analysis of the clinical characteristics of the 65 children with MPP showed that the hospitalization time and fever duration of the children in the RMPP group were longer than those of children in the GMPP group, indicating that the children in the RMPP group had a longer clinical course. The laboratory examination results revealed that the IgG, IgM, IFN-γ, IL-17, and sB7-DC levels in the RMPP group were higher than those in the GMPP group, while the CD3-CD19+ and CD19+CD23+ levels in the RMPP group were lower than those in the GMPP group; this may be related to the severity of the disease. A further statistical analysis showed that a IL-17 level ≥309.6 pg/L and a sB7-DC level ≥1,109.7 pg/mL were highly correlated with the occurrence of RMPP.

B7-DC is a co-stimulatory molecule and a new member of the B7 family (17). B7-DC messenger ribonucleic acid has been detected in the liver, lung, and spleen and is preferentially expressed in bone marrow-derived and splenic dendritic cells (18,19). B7-DC shares the programmed cell death protein 1 receptor with B7-homolog 1 (B7-H1), which is thought to mediate immune self-tolerance (20). Anti-B7-DC monoclonal antibody therapy has been shown to exacerbate the phenotype of allergic diseases (21-24). A previous study showed that B7-DC, IFN-γ, and IL-13 are involved in regulating the allergic asthma phase (25). Another previous study showed that B7-DC is involved in the asthma response phase, and promotes the development of pathogenic type II helper T cells and their migration and activation to the lungs (23). The mechanism underlying the involvement of B7-DC in MPP has not yet been reported.

Inflammatory cytokines are also involved in the pathogenesis of MP infections. In our study, we found that the levels of IL-17 and IFN-γ in the RMPP group were higher than those in the GMPP group (P<0.01), which may be related to the severity of the disease in children with MPP. The expression of B7-DC in inflamed lungs is limited (23). In the present study, sB7-DC levels were positively correlated with IL-17 levels. IL-17 is involved in the inflammatory response of patients with RMPP, which suggests that sB7-DC levels may be used to evaluate both the inflammatory response and severity of the disease. A further analysis revealed that sB7-DC and IL-17 levels were independent risk factors for RMPP, and the ROC

curve analysis showed that sB7-DC was better than IL-17 at predicting RMPP, and had a sensitivity of 86.7% and a specificity of 62.9% for RMPP. Thus, sB7-DC has an important value in the early prediction of RMPP, and the role of sB7-DC in the pathogenesis of RMPP needs to be further explored.

Our study had some limitations. First, as this was a retrospective study, there may have been a selection bias. Further prospective studies are recommended. Second, the number of patients included in this study was relatively small.

Conclusions

sB7-DC and IL-17 levels are independent risk factors for the development of RMPP. The sB7-DC and IL-17 levels of children with RMPP were significantly increased, indicating that the patient population may have developed RMPP. sB7-DC has a higher predictive value than IL-17 for RMPP; thus, sB7-DC detection is beneficial for the early diagnosis of RMPP.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-86/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-86/dss

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-86/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-86/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study protocol was approved by the Ethical Review Committee of the Children's Hospital of Soochow University (No. 2020CS078). Written informed consent was obtained from the parents or legal guardians of all the subjects prior to their being included in the study.

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