Original Article

Predictive value of immune-related parameters in severe *Mycoplasma pneumoniae* pneumonia in children

Chaoyue Jiang, Siwen Bao, Weifeng Shen, Chun Wang

Department of Laboratory Medicine, The First Hospital of Jiaxing, Affiliated Hospital of Jiaxing University, Jiaxing, China

Contributions: (I) Conception and design: C Jiang; (II) Administrative support: W Shen; (III) Provision of study materials or patients: S Bao, W Shen; (IV) Collection and assembly of data: C Wang, S Bao; (V) Data analysis and interpretation: C Jiang, C Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Chun Wang, PhD. Department of Laboratory Medicine, The First Hospital of Jiaxing, Affiliated Hospital of Jiaxing University, No. 1882 Zhonghuan South Road, Jiaxing 314001, China. Email: wangchun821001@163.com.

Background: The severity of *Mycoplasma pneumoniae* pneumonia (MPP) is strongly correlated with the extent of the host's immune-inflammatory response. In order to diagnose the severity of MPP early, this study sought to explore the predictive value of immune-related parameters in severe MPP (sMPP) in admitted children.

Methods: We performed a database analysis consisting of patients diagnosed at our medical centers with MPP between 2021 and 2023. We included pediatric patients and examined the association between complete blood cell count (CBC), lymphocyte subsets and the severity of MPP. Binary logistic regression was performed to identify the independent risk factors of sMPP. Receiver operating characteristic (ROC) curves were used to estimate discriminant ability.

Results: A total of 245 MPP patients were included in the study, with 131 males and 114 females, median aged 6.0 [interquartile range (IQR), 4.0–8.0] years, predominantly located in 2023, and accounted for 64.5%. Among them, 79 pediatric patients were diagnosed as sMPP. The parameters of CBC including white blood cell (WBC) counts, neutrophil counts, monocyte counts, platelet counts, and neutrophil-to-lymphocyte ratio (NLR), were higher in the sMPP group (all $P<0.05$). The parameters of lymphocyte subsets including $CD3^+$ T cell ratio ($CD3^+$%) and $CD3^+CD8^+$ T cell ratio ($CD3^+CD8^+$%), were lower in the sMPP group (all $P<0.05$). And $CD3^-CD19^+$ B cell ratio ($CD3^-CD19^+$%) was higher in the sMPP group. Logistic regression analysis showed that age, $CD3^-CD19^+$%, and monocyte counts were identified as independent risk factors for the development of sMPP (all $P<0.001$). The three factors were applied in constructing a prediction model that was tested with 0.715 of the area under the ROC curve (AUC). The AUC of the prediction model for children aged ≤5 years was 0.823 and for children aged >5 years was 0.693.

Conclusions: The predictive model formulated by age, $CD3^-CD19^+$%, and monocyte counts may play an important role in the early diagnosis of sMPP in admitted children, especially in children aged ≤5 years.

Keywords: *Mycoplasma pneumoniae* pneumonia (MPP); pediatrics; risk factor; severity prediction

Submitted May 03, 2024. Accepted for publication Aug 15, 2024. Published online Sep 13, 2024.
doi: 10.21037/tp-24-172
View this article at: https://dx.doi.org/10.21037/tp-24-172

Introduction

Mycoplasma pneumoniae pneumonia (MPP) is a major cause of community-acquired pneumonia (CAP) in children, accounting for 10–40%, most of which occur over 5 years old (1,2). MPP is usually manifested as mild symptoms, but some might progress to severe MPP (sMPP), which can involve a variety of complications and sequelae, such as pleural effusion, atelectasis, bronchiolitis obliterans, and multi-organ damage, all of which pose a life-threatening risk (3). In recent years, there has been a gradual increase in the incidence of

sMPP in children (3). In order to minimize the complications and mortality associated with sMPP, early detection of sMPP and aggressive intervention are important.

Mycoplasma pneumoniae (MP) infection leads to host immune damage and inflammatory injury, the severity of MPP appears to be related to the host innate immunity to the MP (4,5). Therefore, it makes sense to look for relevant immune inflammation indicators to predict disease severity. Correlative studies have shown that MP infection causes both cellular and humoral immunity, however, reports of this correlation with disease severity and complications are inconclusive (6).

Complete blood cell count (CBC) is a routine hospitalization test that can provide some indication of immunity and inflammation levels. Lymphocyte subsets analysis is an important indicator of cellular and humoral immunity and provides an overall picture of the patient's immune function, status, and homeostasis. The aim of this study is to assess the changes in inflammatory and immune responses and their correlation with disease severity by analyzing CBC and lymphocyte subsets in pediatric inpatients with MP infection. We present this article in accordance with the STARD reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-172/rc).

Methods

Study subjects

Pediatric patients aged under 14 years with pneumonia as the first diagnosis were retrospectively reviewed from January 2021 to December 2023 in the Affiliated Hospital of Jiaxing University. The case group included hospitalized children diagnosed as MPP, excluding children who with a pre-admission diagnosis of sMPP, mixed infections, chronic diseases, autoimmune diseases, immunodeficiency diseases, and antiviral drug intake in the past 2 weeks. The MP infection was diagnosed by a single serum MP-specific immunoglobulin M (IgM) antibody titer of >1:160, or twice 4-fold rise in serum MP-specific immunoglobulin G (IgG) antibody titer, or a positive MP polymerase chain reaction (PCR) in a throat swab or alveolar lavage fluid (7). The participants underwent CBCs and lymphocyte subsets assays after admission. When more than one blood count was performed during a single hospitalization, only the results of the first sample were included in the analysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Review Committee of the Affiliated Hospital of Jiaxing University (No. 2024-KY-440), and individual consent for this retrospective analysis was waived.

Highlight box

Key findings

- The model formulated by age, $CD3^-CD19^+$ B cell ratio ($CD3^-CD19^+$%), and monocyte counts can be used as an early predictor of severe *Mycoplasma pneumoniae* pneumonia (sMPP) in admitted children.

What is known and what is new?

- The early clinical manifestations of sMPP are non-specific, and there is a lack of sensitive predictors for the early detection of sMPP.
- We found that the combination indicators of age + $CD3^-CD19^+$% + monocyte counts had a good diagnostic value for sMPP, especially in children aged ≤5 years.

What is the implication, and what should change now?

- The diagnosis of sMPP may be challenging given the increasing number of sMPP cases and the fact that early symptoms of sMPP are non-specific. Our findings may contribute to the early diagnosis and intervention of sMPP.

Diagnosis of MPP

The diagnosis of MPP followed the Chinese Medical Association guidelines for the treatment of pediatric CAP (8): (I) fever (>37.3 ℃) or acute respiratory symptoms, or both; (II) decreased breath sounds, dry wet rales; (III) chest radiographs demonstrating at least one of the following: speckled or patchy infiltration, interstitial changes, lobar parenchymal infiltrating shadows, and enlarged hilar lymph nodes; and (IV) a positive PCR result or ≥4-fold seroconversion of MP antibody titer. sMPP was defined as MPP with one of the following conditions: (I) poor general condition (pale or gray face, poor response to surroundings); (II) increased respiratory rate (respiratory rate >70 breaths/min in infants, and 50 breaths/min in older children), with or without dyspnea and cyanosis; (III) chest imaging (multilobar or ≥2/3 infiltrate in the lung); (IV) hypoxemia (transcutaneous oxygen saturation ≤92% on room air); and (V) extrapulmonary complications (heart failure, myocarditis, gastrointestinal bleeding, central nervous system infection, etc.).

Statistical analysis

Descriptive statistics were expressed as mean and standard deviation (SD) or median and quartiles (Q) depending on

Table 1 Clinical and laboratory characteristics of the nsMPP and sMPP patients

Parameters	All patients (n=245)	nsMPP group (n=166)	sMPP group (n=79)	P value[†]
Sex, male	131 (53.5)	95 (57.2)	36 (45.6)	0.12
Age (years)	6.0 [4.0–8.0]	6.0 [4.0–8.0]	7.0 [4.5–9.0]	0.06
CBC				
WBC ($\times10^9$/L)	6.8 [5.0–8.8]	6.3 [4.8–8.3]	7.8 [6.2–9.6]	<0.001
Neutrophil counts ($\times10^9$/L)	3.4 [2.3–5.2]	3.1 [2.0–4.9]	4.2 [2.9–5.8]	<0.001
Lymphocyte counts ($\times10^9$/L)	2.4 [1.8–3.2]	2.4 [1.8–3.1]	2.5 [1.8–3.7]	0.46
Monocyte counts ($\times10^9$/L)	0.4 [0.3–0.6]	0.3 [0.2–0.5]	0.5 [0.3–0.7]	<0.001
Platelet counts ($\times10^9$/L)	302 [246–382]	292 [237–376]	334 [261–400]	0.01
NLR	1.4 [0.9–2.3]	1.3 [0.8–2.0]	1.8 [1.0–2.6]	0.01
Lymphocyte subsets				
$CD3^+$%	67.5 [61.9–72.0]	68.2 [63.8–72.6]	66.0 [59.6–69.4]	0.005
$CD3^+CD4^+$%	36.1 [31.9–41.1]	36.4 [32.3–41.5]	35.4 [28.6–40.4]	0.14
$CD3^+CD8^+$%	25.9 [21.7–30.1]	26.6 [22.5–30.2]	24.8 [20.2–29.6]	0.03
$CD3^-CD19^+$%	17.9 [14.0–22.8]	17.3 [13.8–21.4]	19.6 [14.3–26.4]	0.005
NK (%)	10.2 [6.8–14.7]	10.4 [6.9–14.2]	10.1 [6.6–16.8]	0.94

The quantitative data were expressed by median [IQR], while qualitative data were expressed by n (%). [†], P value was a result of comparison of the nsMPP and sMPP groups. nsMPP, non-severe *Mycoplasma pneumoniae* pneumonia; sMPP, severe *Mycoplasma pneumoniae* pneumonia; CBC, complete blood cell count; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; $CD3^+$%, $CD3^+$ T cell ratio; $CD3^+CD4^+$%, $CD3^+CD4^+$ T cell ratio; $CD3^+CD8^+$%, $CD3^+CD8^+$ T cell ratio; $CD3^-CD19^+$%, $CD3^-CD19^+$ B cell ratio; NK, natural killer; IQR, interquartile range.

the distribution. For the analysis of continuous variables, we used the independent samples *t*-test in the case of normal distribution and the Mann-Whitney *U* test in the case of non-normal distribution. Qualitative variables were compared using the Chi-squared test or Fisher's exact test. A binary logistic regression analysis was performed for risk factors associated with sMPP (variable selection criteria were P<0.05). Receiver operating characteristic (ROC) curves were created and the area under the ROC curve (AUC) was calculated to evaluate the predictive value of each independent risk factor for sMPP. The statistical analysis was performed using R version 4.2.2. For the primary outcomes, P values of less than 0.05 were considered as statistically significant.

Results

Study population

The population for this study comprised 245 pediatric patients [median age, 6.0 years; interquartile range (IQR), 4.0–8.0 years; 53.5% male], divided into sMPP group and non-sMPP (nsMPP) group according to disease severity. There were 79 pediatric patients (median age, 7.0 years; IQR, 4.5–9.0 years; 45.6% male) in the sMPP group and 166 pediatric patients (median age, 6.0 years; IQR, 4.0–8.0 years; 57.2% male) in the nsMPP group. There was no significant difference in age and gender between the two groups (*Table 1*). The distribution of pediatric patients in different years is shown in *Figure 1*, predominantly located in 2023.

The association of disease severity outcomes with CBC and lymphocyte subsets

The CBC including WBC, neutrophil counts, monocyte counts, platelet counts, and neutrophil-to-lymphocyte ratio (NLR) were found to be significantly higher in sMPP group than in nsMPP group (*Table 1*). The analysis of lymphocyte subsets revealed that the $CD3^+$ T cell ratio ($CD3^+$%) and $CD3^+CD8^+$ T cell ratio ($CD3^+CD8^+$%), were lower in

the sMPP group, and the $CD3^-CD19^+$ B cell ratio ($CD3^-CD19^+$%) was higher in the sMPP group (*Table 1*).

The diagnostic value of CBC and lymphocyte subsets

The monocyte counts had best diagnostic value for the sMPP (AUC =0.646; *Table 2*), when each index was analyzed separately. The WBC had the highest sensitivity (81.0%; *Table 2*), followed by platelet (67.1%; *Table 2*). The $CD3^-CD19^+$% had the highest specificity (92.2%; *Table 2*), followed by $CD3^+$% (88.0%; *Table 2*).

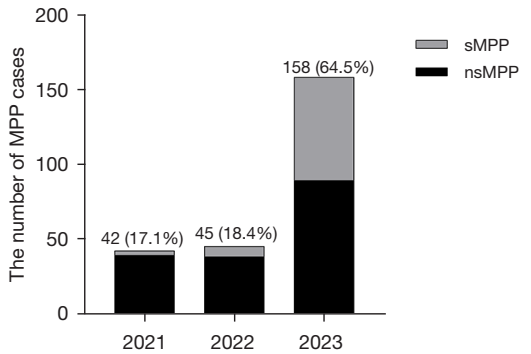

Figure 1 The number of sMPP and nsMPP cases in 2021–2023. MPP, *Mycoplasma pneumoniae* pneumonia; sMPP, severe *Mycoplasma pneumoniae* pneumonia; nsMPP, non-severe *Mycoplasma pneumoniae* pneumonia.

Because there was no index with high sensitivity and specificity, a binary logistic regression analysis, corrected for CBC, lymphocyte subsets, age, and sex, was performed. The results showed that age, $CD3^-CD19^+$%, and monocyte counts were independently associated with disease severity outcomes of pneumonia (*Table 3*). Then, we obtained a logistic regression model composed of age, $CD3^-CD19^+$%, and monocyte counts to predict sMPP. Logit(P) = 0.198 × age + 0.084 × $CD3^-CD19^+$% + 2.085 × monocyte counts – 4.583. As shown in *Figure 2A*, the model had good diagnostic value for sMPP (AUC =0.715), with sensitivity 72.2% and specificity 63.3%.

In order to evaluate the predictive value of the model in different age groups, pediatric patients were further divided into two groups: ≤5 and >5 years groups. It was worth noting that the model had a better diagnostic value for sMPP in ≤5 years group (AUC =0.823; *Figure 2B*).

Table 2 The value of each single index in the diagnosis and prediction of sMPP

Indicators	AUC (95% CI)	Sensitivity (%)	Specificity (%)
WBC	0.638 (0.565–0.712)	81.0	42.2
Neutrophil counts	0.644 (0.571–0.717)	64.6	61.4
Monocyte counts	0.646 (0.569–0.722)	59.5	69.3
Platelet counts	0.598 (0.523–0.673)	67.1	49.4
NLR	0.601 (0.524–0.677)	46.8	74.7
$CD3^+$%	0.610 (0.531–0.689)	31.6	88.0
$CD3^+CD8^+$%	0.585 (0.507–0.664)	65.8	50.6
$CD3^-CD19^+$%	0.610 (0.528–0.692)	32.9	92.2

sMPP, severe *Mycoplasma pneumoniae* pneumonia; AUC, area under the ROC curve; ROC, receiver operating characteristic; CI, confidence interval; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; $CD3^+$%, $CD3^+$ T cell ratio; $CD3^+CD8^+$%, $CD3^+CD8^+$ T cell ratio; $CD3^-CD19^+$%, $CD3^-CD19^+$ B cell ratio.

Table 3 Independent risk factors for sMPP by logistic regression analysis

Indicators	B-value	B-value standard error	Wald	OR (95% CI)	P value
Age	0.198	0.056	12.570	1.220 (1.095–1.366)	<0.001
$CD3^-CD19^+$%	0.084	0.022	14.395	1.088 (1.043–1.138)	<0.001
Monocyte counts	2.085	0.627	11.069	5.710 (2.395–28.279)	<0.001

sMPP, severe *Mycoplasma pneumoniae* pneumonia; OR, odds ratio; CI, confidence interval; $CD3^-CD19^+$%, $CD3^-CD19^+$ B cell ratio.

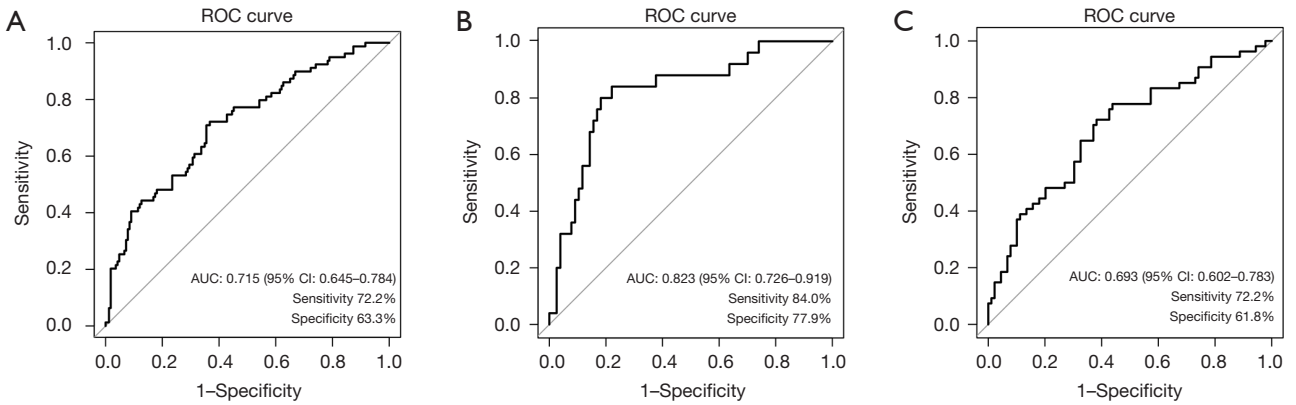

Figure 2 ROC curves of the combined index of age + $CD3^-CD19^+$% + monocyte counts for predicting sMPP. (A) ROC curves for children of all ages. The AUC was 0.715, with sensitivity 72.2% and specificity 63.3%. (B) ROC curves for children aged ≤5 years. The AUC was 0.823, with sensitivity 84.0% and specificity 77.9%. (C) ROC curves for children aged >5 years. The AUC was 0.693, with sensitivity 72.2% and specificity 61.8%. ROC, receiver operating characteristic; AUC, area under the ROC curve; CI, confidence interval; $CD3^-CD19^+$%, $CD3^-CD19^+$ B cell ratio; sMPP, severe *Mycoplasma pneumoniae* pneumonia.

However, in >5 years group, the diagnostic value of model was declined (AUC =0.693; *Figure 2C*).

Discussion

In this observational study, we evaluated the relationship between CBC and lymphocyte subsets parameters and disease severity in hospitalized children under 14 years of age with MP infection in the Jiaxing area in 2021–2023. It was found that there was a sharp increase in the total number of cases and severe cases in 2023 compared to 2021 and 2022. Compared with nsMPP, the sMPP patients showed significant changes in CBC and lymphocyte subset immune-related parameters. Our findings provide information that may improve risk assessment, facilitate early detection and intervention of disease processes in children admitted with MPP.

Results of a study on global prospective testing for MPP suggested that the MPP epidemic ended abruptly in several regions of the world after the start of the non-pharmaceutical interventions for the coronavirus disease-2019 epidemic in March 2020, until 2023, when MPP cases began to increase significantly (9). This finding is consistent with our observation of an increase in the total number of MPP cases and serious illnesses in 2023. Certainly, the relaxation of public health policies which increased personal contacts, and a concomitant increase in potential for spread of infection, was an important reason. Some studies have suggested that increased susceptibility to respiratory disease infections as a result of 3-year coronavirus disease-2019 restrictions, as well as increased antibiotic resistance in MP, were important contributors to the increase in the number of MPP cases in 2023 (10,11).

The pathogenesis of MP infection is thought to be partially attributable to an excessive immune response (12,13). Neutrophils play a central role in innate immunity and are involved in the development and progression of the inflammatory response (14). Previous studies have shown that neutrophil counts in peripheral blood and neutrophil infiltration in lung tissue are increased in children with sMPP, and that exacerbation of MPP is associated with a neutrophil-mediated immune response (13,15,16). Lower neutrophil counts were associated with less severe disease (17). NLR, as an easily measurable inflammatory marker, has been reported to predict poor prognosis in various diseases such as cancer (18-20), cardiovascular disease (21), and coronavirus disease-2019 (22,23). This was confirmed by our results, where neutrophil counts and NLR were significantly higher in the sMPP compared to the nsMPP group. In addition, WBC counts were found to be significantly higher in the sMPP group in our findings. WBC, a sensitive marker of infection and inflammation, also correlates with disease severity in MPP (24). Another study found that peripheral monocyte counts also correlated with MPP disease severity (25), and that monocyte-associated inflammatory mechanisms are involved in the pathogenesis of the disease (26,27). When pneumonia occurs, MP and its toxins, inflammatory mediators, and hypoxia can

cause endothelial damage to the vasculature, leading to platelet activation, aggregation, and overconsumption, and activation of megakaryocytes to produce more platelets. Mirsaeidi *et al.* found positive correlation between platelet count and length of hospitalization, mortality, and prognosis in pneumonia (28). And Qiu *et al.* found that platelet was a risk factor for sMPP (15). These previous studies are consistent with our findings.

In our findings, there was no significant difference in lymphocyte counts between nsMPP group and sMPP group. However, by lymphocyte subsets analysis, we found that several lymphocyte subpopulation ratios changed. The proportion of $CD3^+$ T and $CD3^+CD8^+$ T lymphocytes showed a decrease in the sMPP group, while the proportion of $CD3^-CD19^+$ B lymphocytes showed an increase. T cells play a critical role in host defense against bacterial, viral, and fungal pathogens. In general, inadequate T-cell responses during persistent infections leave the host susceptible to infection and delay pathogen clearance (29). It has been shown that $CD4^+$ T cells are involved in the immunopathologic process of MPP, with $CD4^+$ T cells determining the severity of the disease and resistance to infection, while $CD8^+$ T cells are involved in suppressing these inflammatory responses (30). Depletion of $CD8^+$ T cells *in vivo* led to a significant increase in the severity of lung disease, whereas depletion of $CD4^+$ T cells reduced its severity (30). B cells are critical for host defense against a wide range of pathogens because B cell activation produces specific immunoglobulins to neutralize pathogens (31). After initial MP respiratory infection, MP-specific IgM is detectable in serum within 1 week, and an increase in the amount of MP-specific IgG is detected at 2 weeks post-infection (32,33). Numerous studies have demonstrated the involvement of B cells in lung MP clearance (34,35). Thus, the rise in the proportion of $CD19^+$ B cells in the sMPP group may be to produce more antibodies to neutralize MP.

In this study, ROC curves were applied to assess the predictive value of immune-related markers for MPP disease severity. We found that although certain indicators differed between the sMPP group and nsMPP group, these single indicators alone were not of high value in predicting disease severity. A logistic regression analysis ultimately revealed that the combination indicators of age + $CD3^-CD19^+$% + monocyte counts had the highest combined diagnostic value (AUC =0.715). The factor of age, although not significantly different between the sMPP group and nsMPP group, was found to be an independent risk factor for disease severity in logistic regression analysis. The prevalence of sMPP increases with age, due to an excessive immune response as the immune system matures (36,37). Therefore, we divided the age into two groups, ≤5 and >5 years, to investigate the diagnostic value of the combined index of age + $CD3^-CD19^+$% + monocyte counts in different age groups. It was found that the diagnostic value of the combined indicator was significantly increased in the age group ≤5 years (AUC =0.823). In the age group >5 years, the diagnostic value of the combined indicator decreased (AUC =0.693). In summary, our study demonstrated the important value of immune-related parameters for the early prediction of sMPP. And the roles of immune-related parameters in the pathogenesis of sMPP need to be further explored.

The main limitations of the study lie in the retrospective nature of its design, there may have been a selection bias. Due to incomplete data information, the number of immune-related indicators included was relatively small and did not represent well the purpose of our study.

Conclusions

CBC and lymphocyte subsets testing can provide a good diagnosis of disease severity in MPP. Age is also an independent risk factor, with older children more likely to have sMPP. We found that the combined index of age + $CD3^-CD19^+$% + monocyte counts had good predictive value for disease severity of MPP and was better for diagnosis in children aged ≤5 years.

Acknowledgments

Funding: This study was supported by the "Venus" Talent Training of The First Hospital of Jiaxing of Zhejiang Province of China (No. 2021-QMX-20) and the Jiaxing Key Discipline of Medicine-Clinical Diagnostics (No. 2023-ZC-002).

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-172/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-172/dss

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-172/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-172/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). The study was approved by the Ethical Review Committee of the Affiliated Hospital of Jiaxing University (No. 2024-KY-440), and individual consent for this retrospective analysis was waived.

References

1. Ding G, Zhang X, Vinturache A, et al. Challenges in the treatment of pediatric Mycoplasma pneumoniae pneumonia. Eur J Pediatr 2024;183:3001-11.
2. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med 2015;372:835-45.
3. Gao LW, Yin J, Hu YH, et al. The epidemiology of paediatric Mycoplasma pneumoniae pneumonia in North China: 2006 to 2016. Epidemiol Infect 2019;147:e192.
4. Hu J, Ye Y, Chen X, et al. Insight into the Pathogenic Mechanism of Mycoplasma pneumoniae. Curr Microbiol 2022;80:14.
5. Saraya T, Kurai D, Nakagaki K, et al. Novel aspects on the pathogenesis of Mycoplasma pneumoniae pneumonia and therapeutic implications. Front Microbiol 2014;5:410.
6. Jiang Z, Li S, Zhu C, et al. Mycoplasma pneumoniae Infections: Pathogenesis and Vaccine Development. Pathogens 2021;10:119.
7. National Health Commission of the People's Republic of China, State Administration of Traditional Chinese Medicine. Guideline for diagnosis and treatment of community-acquired pneumonia in children (2019 version). Chin J Clin Infect Dis 2019;12:6-13.
8. Li J, Luu LDW, Wang X, et al. Metabolomic analysis reveals potential biomarkers and the underlying pathogenesis involved in Mycoplasma pneumoniae pneumonia. Emerg Microbes Infect 2022;11:593-605.
9. Meyer Sauteur PM, Beeton ML; European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Mycoplasma and Chlamydia Infections (ESGMAC), et al. Mycoplasma pneumoniae: delayed re-emergence after COVID-19 pandemic restrictions. Lancet Microbe 2024;5:e100-e101.
10. Conroy G. What's behind China's mysterious wave of childhood pneumonia? Nature 2023. [Epub ahead of print]. doi: 10.1038/d41586-023-03732-w.
11. Kant R, Kumar N, Malik YS, et al. Critical Insights from Recent Outbreaks of Mycoplasma pneumoniae: Decoding the Challenges and Effective Interventions Strategies. Int J Infect Dis 2024. [Epub ahead of print]. doi: 10.1016/j.ijid.2024.107200.
12. Shimizu T, Kida Y, Kuwano K. Cytoadherence-dependent induction of inflammatory responses by Mycoplasma pneumoniae. Immunology 2011;133:51-61.
13. Zhu Y, Luo Y, Li L, et al. Immune response plays a role in Mycoplasma pneumoniae pneumonia. Front Immunol 2023;14:1189647.
14. Kalafati L, Hatzioannou A, Hajishengallis G, et al. The role of neutrophils in trained immunity. Immunol Rev 2023;314:142-57.
15. Qiu J, Ge J, Cao L. D-dimer: The Risk Factor of Children's Severe Mycoplasma Pneumoniae Pneumonia. Front Pediatr 2022;10:828437.
16. Zhao Q, Zhang T, Zhu B, et al. Increasing Age Affected Polymorphonuclear Neutrophils in Prognosis of Mycoplasma pneumoniae Pneumonia. J Inflamm Res 2021;14:3933-43.
17. Mara AB, Gavitt TD, Tulman ER, et al. Vaccination with Mycoplasma pneumoniae membrane lipoproteins induces IL-17A driven neutrophilia that mediates Vaccine-Enhanced Disease. NPJ Vaccines 2022;7:86.
18. Misiewicz A, Dymicka-Piekarska V. Fashionable, but What is Their Real Clinical Usefulness? NLR, LMR, and PLR as a Promising Indicator in Colorectal Cancer Prognosis: A Systematic Review. J Inflamm Res 2023;16:69-81.
19. Winther-Larsen A, Aggerholm-Pedersen N, Sandfeld-Paulsen B. Inflammation scores as prognostic biomarkers in small cell lung cancer: a systematic review and meta-analysis. Syst Rev 2021;10:40.

20. Zhang KL, Zhou MM, Wang KH, et al. Integrated neutrophil-to-lymphocyte ratio and handgrip strength better predict survival in patients with cancer cachexia. Nutrition 2024;122:112399.
21. Angkananard T, Anothaisintawee T, Ingsathit A, et al. Mediation Effect of Neutrophil Lymphocyte Ratio on Cardiometabolic Risk Factors and Cardiovascular Events. Sci Rep 2019;9:2618.
22. Dymicka-Piekarska V, Dorf J, Milewska A, et al. Neutrophil/Lymphocyte Ratio (NLR) and Lymphocyte/Monocyte Ratio (LMR) - Risk of Death Inflammatory Biomarkers in Patients with COVID-19. J Inflamm Res 2023;16:2209-22.
23. Açıksarı G, Koçak M, Çağ Y, et al. Prognostic Value of Inflammatory Biomarkers in Patients with Severe COVID-19: A Single-Center Retrospective Study. Biomark Insights 2021;16:11772719211027022.
24. Fan F, Lv J, Yang Q, et al. Clinical characteristics and serum inflammatory markers of community-acquired mycoplasma pneumonia in children. Clin Respir J 2023;17:607-17.
25. Bi Y, Ma Y, Zhuo J, et al. Risk of Mycoplasma pneumoniae-related hepatitis in MP pneumonia pediatric patients: a predictive model construction and assessment. BMC Pediatr 2021;21:287.
26. Wang Z, Yang L, Ye J, et al. Monocyte subsets study in children with Mycoplasma pneumoniae pneumonia. Immunol Res 2019;67:373-81.
27. Wang Z, Bao H, Liu Y, et al. Interleukin-23 derived from CD16+ monocytes drives IL-17 secretion by TLR4 pathway in children with mycoplasma pneumoniae pneumonia. Life Sci 2020;258:118149.
28. Mirsaeidi M, Peyrani P, Aliberti S, et al. Thrombocytopenia and thrombocytosis at time of hospitalization predict mortality in patients with community-acquired pneumonia. Chest 2010;137:416-20.
29. Wik JA, Skålhegg BS. T Cell Metabolism in Infection. Front Immunol 2022;13:840610.
30. Jones HP, Tabor L, Sun X, et al. Depletion of CD8+ T cells exacerbates CD4+ Th cell-associated inflammatory lesions during murine mycoplasma respiratory disease. J Immunol 2002;168:3493-501.
31. Inoue T, Kurosaki T. Memory B cells. Nat Rev Immunol 2024;24:5-17.
32. Waites KB, Talkington DF. Mycoplasma pneumoniae and its role as a human pathogen. Clin Microbiol Rev 2004;17:697-728, table of contents.
33. Meyer Sauteur PM, Jacobs BC, Spuesens EB, et al. Antibody responses to Mycoplasma pneumoniae: role in pathogenesis and diagnosis of encephalitis? PLoS Pathog 2014;10:e1003983.
34. Tang L, Zheng K, Ma L, et al. Epidemiologic trends and changes in humoral immunity and lymphocyte subsets levels among hospitalized children with Mycoplasma pneumoniae infection during 2019-2023. Eur J Clin Microbiol Infect Dis 2024;43:1837-45.
35. Zhang Z, Dou H, Tu P, et al. Serum cytokine profiling reveals different immune response patterns during general and severe Mycoplasma pneumoniae pneumonia. Front Immunol 2022;13:1088725.
36. Pechous RD. With Friends Like These: The Complex Role of Neutrophils in the Progression of Severe Pneumonia. Front Cell Infect Microbiol 2017;7:160.
37. Yan C, Xue G, Zhao H, et al. Molecular and clinical characteristics of severe Mycoplasma pneumoniae pneumonia in children. Pediatr Pulmonol 2019;54:1012-21.

Cite this article as: Jiang C, Bao S, Shen W, Wang C. Predictive value of immune-related parameters in severe *Mycoplasma pneumoniae* pneumonia in children. Transl Pediatr 2024;13(9):1521-1528. doi: 10.21037/tp-24-172