Article

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Peripheral CD4+/CD8+ T-Cell Ratio Inversely Correlates With Clinical Severity in Pediatric *Mycoplasma pneumoniae* Pneumonia

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Background: *Mycoplasma pneumoniae* pneumonia (MPP) is a common cause of community-acquired pneumonia in children. Immune dysregulation, particularly involving T-cell subsets, plays a key role in its pathogenesis, but the dose-response relationship between the peripheral blood CD4+/CD8+ T cell ratio and MPP severity remains unclear. This study aimed to investigate this correlation and dose-response relationship in pediatric MPP patients.
Methods: A cohort of 237 pediatric patients diagnosed with MPP was enrolled from Zhongshan Hospital, Xiamen University between June 2022 and June 2025. Based on disease severity assessed using clinical criteria, the participants were stratified into a mild group (*n* = 181) and a severe group (*n* = 56). General information, laboratory indicators, and immune cell levels of the children were collected. Stratified regression analysis was used to analyze the relationship between the CD4+/CD8+ T cell ratio and the clinical characteristics of the children. A generalized linear model (GLM) was used to assess the association between the CD4+/CD8+ T cell ratio and the severity of the children's condition. The dose-response relationship between the two was analyzed using restricted cubic splines (RCS).
Results: The CD4+/CD8+ T cell ratio in the severe group was significantly lower than that in the mild group (0.83 ± 0.29 vs 1.36 ± 0.41, $p < 0.001$). Stratified regression analysis revealed that duration of fever, Pediatric Early Warning Score (PEWS), interleukin-10 (IL-10), lactate dehydrogenase (LDH), and ferritin all had independent negative effects on the CD4+/CD8+ T cell ratio (all $p < 0.05$). GLM analysis indicated that a lower CD4+/CD8+ T cell ratio was associated with a higher risk of disease exacerbation. After adjusting for confounding factors, children with a ratio <0.80 exhibited a 6.195-fold higher risk of disease exacerbation compared to the control group (>1.65) (95% *CI*: 2.380–16.125). RCS analysis further revealed a significant nonlinear negative dose-response relationship between the CD4+/CD8+ T cell ratio and disease severity (nonlinear $p = 0.008$).
Conclusions: The peripheral blood CD4+/CD8+ T cell ratio in children with MPP was negatively correlated with the severity of the disease, and a significant dose-response relationship was observed. This ratio can be used as a potential immunological indicator for assessing the severity of the disease in children.

Keywords: *Mycoplasma pneumoniae* pneumonia; CD4+/CD8+ T cell ratio; disease severity; dose-response relationship; restriction cubic spline

Introduction

Mycoplasma pneumoniae (MP) is one of the important pathogens of community-acquired pneumonia in children. *Mycoplasma pneumoniae* pneumonia (MPP) is prevalent globally, especially among children aged 5–15 years, with a high incidence [1–3]. Its clinical manifestations are diverse and vary in severity. Mild cases may only present with self-limiting symptoms such as cough and fever, while severe cases can rapidly develop into severe pneumonia, accompanied by multi-lobe involvement, pulmonary necrosis, pleural effusion, and even respiratory failure. Some children may also develop extrapulmonary complications, such as rash, neurological damage, and cardiovascular abnormalities, and may even progress to chronic lung disease [4–6], significantly affecting the growth, development, and quality of life of children [7,8].

The pathogenesis of MP infection is complex, involving not only the direct invasion of respiratory epithelial cells by pathogens, but more importantly, it is closely related to the abnormal response of the host immune system [9]. Studies have shown [10,11] that MP can evade host immune surveillance through mechanisms, such as surface antigen mimicry and inhibition of immune cell function, while stimulating the body to produce excessive inflammatory responses, thereby leading to cytokine storms and tissue immunopathological damage. This immune disorder drives the acute phase progression of the disease and is also closely related to the long-term prognosis [12]. T lymphocytes, especially CD4+ and CD8+ T cell subsets, play a core role in the host's anti-MP immune response [13]. CD4+ T cells are mainly involved in immune regulation and help B cells produce antibodies, while CD8+ T cells are responsible for clearing infected host cells. The balance between the two is crucial for controlling infection and preventing immunopathological damage [14]. The CD4+/CD8+ T cell ratio is a key indicator for assessing the body's immune status. Its abnormality often reflects an immune imbalance and is related to the severity and prognosis of various infectious diseases [15–17]. However, in children with MPP, the existing evidence regarding the strength of the association between the peripheral blood CD4+/CD8+ T cell ratio and disease severity, as well as the dose-response relationship, remains insufficient and lacks systematic analysis. Currently, the assessment of MPP relies heavily on clinical symptoms, imaging, and routine inflammatory markers. While these methods provide some clinical value, they are limited in their ability to precisely quantify the intrinsic link between immune status and disease severity.

Therefore, this study aims to analyze the correlation between the peripheral blood CD4+/CD8+ T cell ratio and the severity of MPP in children with the disease, and further explore whether a dose-response relationship exists between the two, in order to provide more objective laboratory evidence and theoretical foundation for early risk warning, severity assessment and immune-targeted intervention in children with MPP.

Methods

Research Subjects

The study cohort comprised 237 pediatric patients hospitalized with MPP at the Zhongshan Hospital, Xiamen University between June 2022 and June 2025. Inclusion criteria were as follow: (1) age 1–12 years; (2) meeting the diagnostic criteria for MPP [18], with the core diagnostic basis being: symptoms/signs of acute respiratory infection, plus a positive *Mycoplasma pneumoniae* nucleic acid test (from throat swab or bronchoalveolar lavage fluid), and/or a four-fold or greater increase in MP-specific antibody (e.g., immunoglobulin M [IgM]) titer between paired acute and convalescent serum samples; (3) first diagnosis and no prior systemic antibiotic or immunomodulatory therapy. Exclusion criteria were: (1) co-infection with other pathogens (such as bacteria, viruses, fungi); (2) congenital immunodeficiency, hematological diseases, malignant tumors or dysfunction of important organs; (3) recent use of immunosuppressants or glucocorticoids; (4) incomplete clinical data or loss to follow-up. The age distribution of the enrolled children was as follows: 1–3 years (toddler, $n = 75$, 31.6%), 4–6 years (preschool, $n = 98$, 41.4%), and 7–12 years (school-age, $n = 64$, 27.0%). This study was performed in compliance with the basic principles of the Declaration of Helsinki and was approved by the ethics committee of Zhongshan Hospital, Xiamen University (2025-179). Informed consent was obtained from the guardians, who provided the written informed consent.

Severity Assessment and Grouping of the Disease

The severity of MPP in children was determined according to the "Guidelines for the Management of Community-Acquired Pneumonia in Children (2024 Revision)". Based on a diagnosis of MPP, children exhibiting at least one of the following characteristics were classified as severe: refusal to feed or signs of dehydration; altered mental status; increased respiratory rate (determined according to age criteria); cyanosis; dyspnea (manifested as grunting, nasal flaring, or three-recession sign); imaging evidence of multi-lobar involvement or involvement of $\geq$2/3 of the lungs; pleural effusion; pulse oximetry (SpO_2) $\leq$0.92 without oxygen therapy; or extrapulmonary complications. Children who do not meet the above severe criteria were classified as mild.

Observation Indicators

(1) General information: gender, age, body mass index (BMI), course of illness, duration of fever, and pediatric early warning score (PEWS) upon admission were collected. (2) Laboratory indicators: Peripheral blood platelet distribution width (PDW), platelets, white blood cells, neutrophils, and red blood cells were measured using an automated hematology analyzer (Sysmex XN-series, Kobe, Japan). C-reactive protein (CRP) and procalcitonin (PCT) were determined by chemiluminescence immunoassay on a Mindray CL-6000i analyzer (Mindray, Shenzhen, China). Interleukin-10 (IL-10) levels were quantified using a commercial enzyme-linked immunosorbent assay kit (Human IL-10 ELISA Kit, Abcam, Cambridge, UK; Lot: ab130762). Lactate dehydrogenase (LDH) activity was assessed by the UV kinetic method on a Roche Cobas c702 analyzer (Roche Diagnostics, Basel, Switzerland). Ferritin levels were measured via chemiluminescence immunoassay (Abbott Architect i2000SR, Abbott Laboratories, Chicago, IL, USA). (3) Immune cells: Peripheral blood T cells, B cells, NK cells, and monocytes were quantified by flow cytometry using fluorescently labeled monoclonal antibodies (BD Multitest 6-color TBNK Reagent, BD Biosciences, San Jose, CA, USA) on a BD FACSCanto II flow cytometer (BD Biosciences). The percentages of CD4+ and CD8+ T cell subsets were obtained, and the CD4+/CD8+ T cell ratio was calculated.

Statistical Methods

Data analysis was performed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). The normality of continuous data was assessed using the Shapiro-Wilk test. Normally distributed continuous data were expressed as mean $\pm$ standard deviation, and independent samples t-tests were used for comparisons between groups. Categorical data were expressed as percentages, with comparisons con-

Table 1. Comparison of clinical data between mild and severe cases.

Variable	Mild group (n = 181)	Severe group (n = 56)	t/χ^2	p
Gender [n (%)]			0.006	0.940
Male	98 (54.14)	30 (53.57)		
Female	83 (45.86)	26 (46.43)		
Age (years)	4.31 ± 1.62	4.73 ± 2.04	1.590	0.113
BMI (kg/m^2)	16.02 ± 2.24	16.38 ± 2.42	1.031	0.304
Course of illness (days)	7.18 ± 2.13	7.47 ± 2.35	0.869	0.386
Duration of fever (days)	5.12 ± 1.82	8.35 ± 2.53	10.515	<0.001
PEWS (points)	1.24 ± 0.31	2.83 ± 0.45	29.892	<0.001
PDW (fL)	12.34 ± 1.52	14.27 ± 2.13	7.501	<0.001
Platelets (×10^9/L)	253.62 ± 67.81	314.27 ± 86.32	5.466	<0.001
White blood cells (×10^9/L)	9.76 ± 2.53	13.58 ± 4.24	8.277	<0.001
Neutrophils (%)	61.29 ± 10.46	62.12 ± 12.53	0.494	0.622
Red blood cells (×10^9/L)	4.52 ± 0.61	4.38 ± 0.73	1.430	0.154
CRP (mg/L)	18.37 ± 6.24	20.83 ± 12.75	1.953	0.052
PCT (ng/mL)	0.44 ± 0.14	0.48 ± 0.21	1.643	0.102
IL-10 (pg/mL)	12.35 ± 4.48	28.64 ± 9.83	17.284	<0.001
LDH (U/L)	215.41 ± 68.34	348.72 ± 112.50	10.781	<0.001
Ferritin (ng/mL)	212.66 ± 81.89	358.55 ± 118.21	10.406	<0.001
T cells (%)	57.26 ± 8.68	45.17 ± 10.51	8.649	<0.001
B cells (%)	14.81 ± 4.04	18.23 ± 5.54	5.041	<0.001
NK cells (%)	8.51 ± 2.91	6.67 ± 3.64	3.886	<0.001
Monocytes (%)	9.13 ± 2.53	11.63 ± 3.22	6.039	<0.001
CD4+/CD8+ T cell ratio	1.36 ± 0.41	0.83 ± 0.29	8.996	<0.001

Note: Reference ranges for pediatric laboratory indicators: White blood cells: 5.0–17.0 × 10^9/L (age-dependent); Neutrophils: 20%–60%; Lymphocytes (T+B cells): 50%–70%; Platelets: 150–400 × 10^9/L; CRP: <8 mg/L; PCT: <0.5 ng/mL; IL-10: <15 pg/mL; LDH: 120–300 U/L; Ferritin: 15–150 ng/mL. BMI, body mass index; PEWS, pediatric early warning score; PDW, platelet distribution width; CRP, C-reactive protein; PCT, procalcitonin; IL-10, interleukin-10; LDH, lactate dehydrogenase.

ducted using chi-square tests between groups. Stratified regression analysis was performed to analyze the relationship between the CD4+/CD8+ T cell ratio and the clinical characteristics of the children. Multicollinearity among independent variables in the stratified regression analysis was assessed using the variance inflation factor (VIF), with a threshold of VIF <5 considered indicative of no significant collinearity. Generalized linear model (GLM) analysis was performed to analyze the relationship between the CD4+/CD8+ T cell ratio and the disease severity in children. This model was chosen primarily to account for potential intra-group correlations and provide robust effect estimates, although the data in this study did not exhibit a complex hierarchical structure. Given that the data were collected from individual patients without a nested or longitudinal structure, no random effects were included in the model. The GLM was therefore specified with a binomial distribution and logit link function. Restricted cubic splines (RCS) analysis was used to analyze the dose-response relationship between the CD4+/CD8+ T cell ratio and the disease severity in children, with four knots placed at the 5th, 35th, 65th, and 95th percentiles of the ratio distribution, as recommended for typical sample sizes to balance model flexibility and overfitting. The model's goodness-of-fit was assessed using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), with lower values indicating better fit. A p-value < 0.05 was considered statistically significant.

Results

Comparison of Clinical Data Between Children With Mild and Severe Cases

The duration of fever was significantly longer in the severe group than in the mild group. The levels of PEWS, PDW, platelets, white blood cells, IL-10, LDH, ferritin, B cells, and monocytes were significantly higher in the severe group than in the mild group ($p < 0.05$), while the levels of T cells, NK cells, and CD4+/CD8+ T cells were significantly lower in the severe group than in the mild group ($p < 0.05$), as shown in Table 1.

Table 2. Stratified regression analysis of the relationship between the CD4+/CD8+ T cell ratio and clinical characteristics of the patients.

Layering	Project	Unstandardized coefficient		β (95% *CI*)	*t*	*p*	R^2	*F*	ΔR^2	*F*-change	*p*-change
		B	Standard error								
Layer 1	Constant	1.847	0.081		22.802	<0.001	0.182	52.336			
	Duration of fever	–0.078	0.010	–0.417 (–0.525, –0.309)	–7.800	<0.001					
Layer 2	Constant	1.915	0.112		17.098	<0.001	0.198	28.567	0.016	8.714	0.004
	Duration of fever	–0.072	0.011	–0.385 (–0.488, –0.282)	–6.545	<0.001					
	PEWS	–0.062	0.021	–0.201 (–0.334, –0.068)	–2.952	0.004					
Layer 3	Constant	2.341	0.151		15.503	<0.001	0.334	22.123	0.136	4.572	<0.001
	Duration of fever	–0.032	0.012	–0.171 (–0.281, –0.061)	–2.667	0.008					
	PEWS	–0.043	0.020	–0.140 (–0.259, –0.021)	–2.150	0.032					
	IL-10	–0.014	0.003	–0.265 (–0.360, –0.170)	–4.667	<0.001					
Layer 4	Constant	2.388	0.159		15.019	<0.001	0.365	21.224	0.031	5.820	0.017
	Duration of fever	–0.029	0.012	–0.155 (–0.259, –0.051)	–2.417	0.016					
	PEWS	–0.041	0.020	–0.133 (–0.247, –0.019)	–2.050	0.041					
	IL-10	–0.013	0.003	–0.246 (–0.339, –0.153)	–4.333	<0.001					
	LDH	–0.001	0.000	–0.168 (–0.278, –0.058)	–2.642	0.009					
Layer 5	Constant	2.512	0.168		14.952	<0.001	0.378	20.445	0.013	4.940	0.027
	Duration of fever	–0.028	0.013	–0.150 (–0.256, –0.044)	–2.154	0.032					
	PEWS	–0.039	0.012	–0.127 (–0.195, –0.059)	–3.250	0.002					
	IL-10	–0.012	0.003	–0.227 (–0.289, –0.075)	–4.002	<0.001					
	LDH	–0.001	0.000	–0.182 (–0.289, –0.075)	–2.892	0.004					
	Ferritin	–0.002	0.001	–0.134 (–0.253, –0.015)	–2.108	0.036					

Stratified Regression Analysis of the Relationship Between CD4+/CD8+ T Cell Ratio and Clinical Characteristics of Patients

Variables were entered into the hierarchical regression model in a predetermined order, guided by clinical relevance and pathophysiological considerations: duration of fever, PEWS, IL10, LDH, and ferritin. Stratified regression analysis showed that, in stratum 1, linear regression analysis with the CD4+/CD8+ T cell ratio as the dependent variable and fever duration as the independent variable showed a significant negative impact on the CD4+/CD8+ T cell ratio (t = –7.800, $p < 0.001$). In stratum 2, PEWS was included in addition to stratum 1, and the R^2 value increased from 0.182 to 0.198. Fever duration (t = –6.545, $p < 0.001$) and PEWS (t = –2.952, p = 0.004) also had significant negative impacts on the CD4+/CD8+ T cell ratio. Stratification 3: In addition to stratification 2, IL-10 was included. The duration of fever (t = –2.667, p = 0.008), PEWS score (t = –2.150, p = 0.032), and IL-10 level (t = –4.667, $p < 0.001$) had a significant negative impact on the CD4+/CD8+ T cell ratio. Stratification 4: In addition to stratification 3, LDH was included. The duration of fever (t = –2.417, p = 0.016), PEWS score (t = –2.050, p = 0.041), IL-10 (t = –4.333, $p <$ 0.001), and LDH (t = –2.642, p = 0.009) had a significant negative impact on the CD4+/CD8+ T cell ratio. Stratification 5: Ferritin was added to stratification 4. Duration of fever (t = –2.154, p = 0.032), PEWS score (t = –3.250, p = 0.002), IL-10 (t = –4.002, $p < 0.001$), LDH (t = –2.892, p = 0.004), and ferritin (t = –2.108, p = 0.036) had a significant negative impact on the CD4+/CD8+ T cell ratio. See Table 2. The VIF values for all variables in the final stratified regression model ranged from 1.12 to 1.78, indicating no significant multicollinearity and confirming the robustness of the regression estimates. The gradual increase in the R^2 value across strata indicates that the added variables (PEWS, IL-10, LDH, ferritin) provide cumulative explanatory power for the variation in the CD4+/CD8+ T cell ratio, reflecting the multifactorial nature of immune dysregulation in severe MPP.

Correlation Analysis Between the CD4+/CD8+ T Cell Ratio and Conventional Inflammatory Markers

To evaluate the relationship between the novel immune parameter (CD4+/CD8+ T cell ratio) and established inflammatory indicators, Spearman correlation analysis was performed. As shown in Fig. 1, a significant negative correlation between the CD4+/CD8+ T cell ratio and both CRP (r = –0.325, $p < 0.001$) and PCT (r = –0.287, $p <$ 0.001). This indicates that a lower CD4+/CD8+ T cell ratio, suggestive of greater immune dysregulation, is associated with higher levels of systemic inflammation measured by these conventional markers.

GLM Analysis of the Relationship Between CD4+/CD8+ T Cell Ratio and Disease Severity in Children

To quantify the association between the CD4+/CD8+ T cell ratio and disease severity, the CD4+/CD8+ T cell ratios of 237 children were divided into five quintiles (Q1–Q5): <0.80 (Q1, n = 47), 0.80–1.05 (Q2, n = 48), 1.06–1.34 (Q3, n = 48), 1.35–1.65 (Q4, n = 47), and >1.65 (Q5, n = 47), with the highest ratio (Q5) used as the reference. This quintile-based categorization ensures an approximately equal sample size across groups (each ~20% of the total), allowing for a balanced comparison of risk across the spectrum of the immune ratio while preserving the dose-response nature of the exposure. Univariate analysis showed that compared with a CD4+/CD8+ T cell ratio >1.65, children with ratios of 1.06–1.34 (β = 1.022, *OR* = 2.779, 95% *CI*: 1.171–6.594, p = 0.021), 0.80–1.05 (β = 1.609, *OR* = 4.997, 95% *CI*: 2.089–11.956, $p < 0.001$), and <0.80 (β = 2.159, *OR* = 8.667, 95% *CI*: 3.556–21.131, $p < 0.001$) had a higher risk of disease exacerbation. After adjusting for sex and age (Model 2), different CD4+/CD8+ T cell ratios were statistically associated with the severity of the children's condition. Adjustment of confounders in the multivariate model (Model 3) was based on a combination of clinical relevance and statistical criteria. Further adjustments for clinical and immunological indicators such as BMI, disease duration, fever duration, PEWS, and PDW (Model 3) showed that children with CD4+/CD8+ T cell ratios of 0.80–1.05 and <0.80 had a 1.423- to 1.824-fold higher risk of disease exacerbation compared to the control group, respectively (See Table 3).

RCS Analysis of the Dose-Response Relationship Between the CD4+/CD8+ T Cell Ratio and the Disease Severity in Children

The RCS model was used to analyze the dose-response relationship between the CD4+/CD8+ T cell ratio and the severity of the disease in children. The results showed a statistically significant overall association (Chi-Square = 29.557, $p < 0.001$) and a significant non-linear trend (Chi-Square = 9.697, p = 0.008). The model demonstrated a good fit, with an AIC of 210.5 and a BIC of 225.3. As shown in Fig. 2, the risk of severe disease increased progressively as the CD4+/CD8+ T cell ratio decreased.

Discussion

By systematically analyzing clinical and immunological profiles of 237 pediatric MPP patients, we identified the peripheral blood CD4+/CD8+ T-cell ratio as a key biomarker strongly associated with disease severity. The results showed that the CD4+/CD8+ T cell ratio in the severe group was significantly lower than that in the mild group, and this ratio was independently negatively correlated with clinical indicators such as fever duration, PEWS

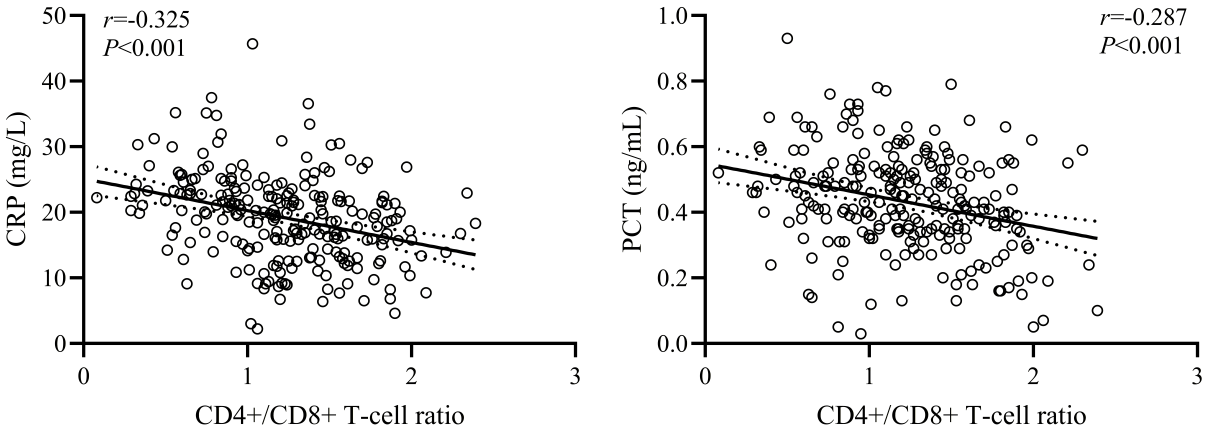

Fig. 1. Scatter plots showing the correlation between CD4+/CD8+ T cell ratio and CRP/PCT.

Table 3. GLM analysis: Relationship between CD4+/CD8+ T cell ratio and disease severity in children.

Model	CD4+/CD8+ T cell ratio	*β*	*SE*	Wald χ^2	*p*	*OR* (95% *CI*)
Model 1	>1.65 (Ref)					1.000
	1.35–1.65	0.512	0.452	1.283	0.258	1.669 (0.688–4.047)
	1.06–1.34	1.022	0.441	5.371	0.021	2.779 (1.171–6.594)
	0.80–1.05	1.609	0.445	13.074	<0.001	4.997 (2.089–11.956)
	<0.80	2.159	0.455	22.516	<0.001	8.667 (3.556–21.131)
Model 2	>1.65 (Ref)					1.000
	1.35–1.65	0.498	0.455	1.198	0.274	1.646 (0.675–4.015)
	1.06–1.34	1.001	0.444	5.083	0.024	2.721 (1.140–6.494)
	0.80–1.05	1.587	0.449	12.493	<0.001	4.890 (2.028–11.792)
	<0.80	2.131	0.460	21.461	<0.001	8.424 (3.422–20.740)
Model 3	>1.65 (Ref)					1.000
	1.35–1.65	0.441	0.469	0.884	0.347	1.554 (0.620–3.897)
	1.06–1.34	0.892	0.460	3.760	0.053	2.440 (0.990–6.013)
	0.80–1.05	1.423	0.470	9.167	0.002	4.150 (1.652–10.427)
	<0.80	1.824	0.488	13.970	<0.001	6.195 (2.380–16.125)

Note: Model 1 is a univariate model; Model 2 adjusts for gender and age; Model 3 adjusts for gender, age, BMI, disease course, duration of fever, PEWS, PDW, platelets, white blood cells, neutrophils, red blood cells, CRP, PCT, IL-10, LDH, ferritin, T cells, B cells, NK cells, and monocytes.

score, and IL-10 level. More importantly, GLM analysis indicated that as the CD4+/CD8+ T cell ratio decreased, the risk of disease exacerbation significantly increased. Even after adjusting for various confounding factors, children with a ratio <0.80 exhibited a 6.195-fold higher risk of disease progression than the control group. Restricted cubic spline analysis further revealed a significant nonlinear negative dose-response relationship between the two. These findings provide a new perspective for understanding the immunopathogenesis and clinical assessment of MPP.

The core finding of this study is that the CD4+/CD8+ T cell ratio in children with severe MPP was significantly lower than that in children with mild MPP, a phenomenon consistent with the immune imbalance commonly found in severe respiratory infections [19,20]. This decreased ratio may reflect different response patterns of CD4+ and CD8+ T cells during the pathogenesis of MPP. On the one hand, MP may preferentially activate the proliferation and differentiation of CD8+ T cells, leading to a relative increase in their numbers; on the other hand, under persistent antigenic stimulation and inflammatory conditions, CD4+ T cells may be more prone to apoptosis or functional exhaustion, resulting in a relative decrease in their numbers [21–23]. In addition, various inflammatory factors produced by the body during severe infection, such as the significantly elevated IL-10 observed in this study, may inhibit the function and survival of CD4+ T cells, further exacerbating this imbalance. This imbalance in the proportion of T cell subsets not only impairs the body's ability to effectively clear pathogens but may also contribute to immunopathological

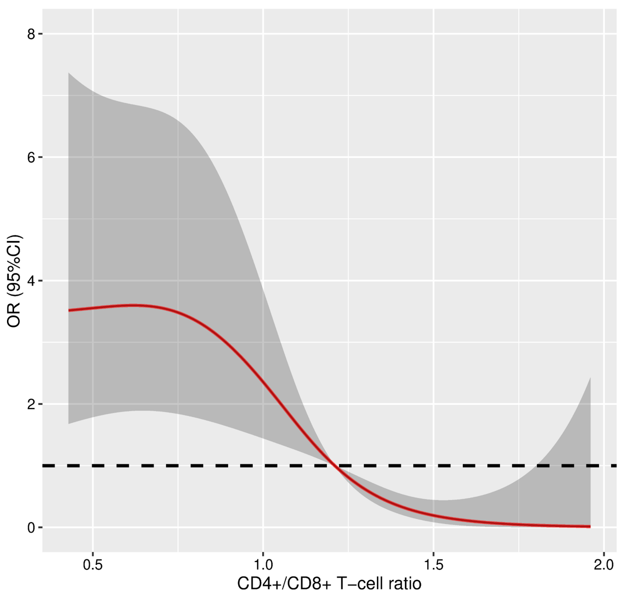

Fig. 2. Restricted cubic splines (RCS) plot of the dose-response relationship between CD4+/CD8+ T cell ratio and disease severity in children.

damage, thereby promoting the progression of the disease to a more severe state. At the molecular level, *Mycoplasma pneumoniae* may induce T cell imbalance through specific pathways. Its surface components, such as the CARDS toxin, can act as superantigens that preferentially activate CD8+ T cell clones. Simultaneously, the infection promotes a cytokine environment dominated by Th1-type responses and elevated regulatory factors like IL10, which may suppress CD4+ T cell function. Persistent antigen exposure and inflammatory signals could further lead to CD4+ T cell exhaustion or apoptosis, collectively driving the decrease in the CD4+/CD8+ ratio observed in severe MPP.

Stratified regression analysis demonstrated that duration of fever, PEWS score, IL-10, LDH, and ferritin maintained independent negative associations with the CD4+/CD8+ T-cell ratio. This result has important clinical significance. Prolonged fever often indicates persistent pathogen presence and ineffective inflammatory response, which is closely related to the sustained activation and eventual exhaustion of the immune system. The negative correlation between the PEWS score, a comprehensive indicator for assessing the severity of pulmonary infection, and the CD4+/CD8+ T cell ratio suggests an intrinsic link between the severity of local pulmonary infection and the systemic immune status. Of particular note is the independent negative correlation between IL-10 levels and the CD4+/CD8+ T cell ratio, which may reflect complex changes in the immune regulatory network during the progression of severe MPP. As an anti-inflammatory factor, elevated IL-10 levels may be a feedback mechanism to prevent excessive inflammation; however, excessive IL-10 production may also suppress T cell immune function, especially affecting the activation and proliferation of CD4+ T cells, thereby leading to a decrease in the CD4+/CD8+ T cell ratio. Furthermore, this study suggested that LDH and ferritin were also significantly negatively correlated with the CD4+/CD8+ T cell ratio. Elevated LDH levels, a marker of tissue damage, suggest that children with severe MPP may experience more extensive cellular damage and metabolic disorders. Elevated ferritin levels, as an acute-phase protein, are often associated with the intensity of the inflammatory response and the body's stress state. The negative correlation between these two indicators and the CD4+/CD8+ T cell ratio further suggests that children with severe MPP, in addition to experiencing immunosuppression, also exhibit significant tissue damage and systemic inflammatory responses, which may be one of the important factors driving disease progression towards severity.

One of the most important findings of this study was the quantification of the association strength and dose-response relationship between the CD4+/CD8+ T cell ratio and disease severity using a GLM and restricted cubic spline analysis. The results showed that as the CD4+/CD8+ T cell ratio decreased, the risk of disease exacerbation increased significantly, and this relationship remained significant after adjusting for sex, age, BMI, disease duration, various laboratory indicators, and immune cell parameters. Of particular note is the significant clinical utility of this non-linear relationship revealed by restricted cubic spline analysis. When the CD4+/CD8+ T cell ratio decreased, the risk of disease exacerbation increased significantly, with a lower ratio corresponding to a greater increase in risk. This non-linear relationship suggests that the CD4+/CD8+ T cell ratio is not a simple categorical indicator, but rather a continuous risk predictor. When its value falls below a certain range, the risk of disease exacerbation increases significantly, providing a potential, quantifiable immunological threshold for clinically identifying high-risk children and implementing intensive interventions.

From a clinical practice perspective, the findings of this study provide new insights into the assessment and risk stratification of MPP. Given the increasingly severe situation in the diagnosis and treatment of MPP, especially macrolide-resistant MPP, the search for reliable biomarkers for disease assessment is of great significance. The CD4+/CD8+ T cell ratio, as a relatively accessible immunological indicator, can complement existing clinical assessment systems by providing the perspective of immune status, enabling earlier risk identification and intervention. In the future, this indicator may be integrated into the prognostic scoring system for MPP to guide individualized treatment decisions. For example, determining whether immunomodulatory therapy should be considered in addition to standard anti-infective treatment for children with significantly low CD4+/CD8+ T cell ratios represents a promising area for further exploration.

Of course, this study also has some limitations. First, it is a single-center study with a relatively limited sample size, and the conclusions need to be validated by larger-scale, multi-center prospective studies. Second, we mainly measured immune indicators of the children upon admission, and were unable to dynamically monitor changes in the CD4+/CD8+ T cell ratio during treatment, nor its relationship with prognosis. Furthermore, this study primarily focused on changes in cell proportions and did not delve into changes in T cell functional status. Future research could combine T cell function assays and more refined subset analyses to further elucidate the specific mechanisms by which the CD4+/CD8+ T cell ratio plays a role in the pathogenesis of MPP.

It is important to note that the CD4+/CD8+ T cell ratio threshold identified in this study, although statistically significant, requires further prospective validation in larger, independent cohorts before it can be adopted as a definitive clinical cutoff. Its application should be integrated with other clinical, laboratory, and imaging findings for a comprehensive assessment of disease severity, rather than serving as an absolute, standalone diagnostic criterion.

Conclusions

In conclusion, this study confirms a significant negative correlation between the peripheral blood CD4+/CD8+ T cell ratio and disease severity in children with MPP, exhibiting a clear dose-response characteristic. As an easily accessible immunological parameter, this indicator provides an important reference for early risk stratification and disease assessment in children with MPP, highlighting its potential clinical utility.

Availability of Data and Materials

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

Author Contributions

YC and RH designed the research study. MZ and XQL performed the research. LC and RH analyzed the data. YC drafted the article. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study complies with the basic principles of the Declaration of Helsinki and has been approved by the ethics committee of Zhongshan Hospital, Xiamen University (2025-179). Informed consent was obtained from the guardians and they signed the informed consent form.

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Conflict of Interest

The authors declare no conflict of interest.

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