

RESEARCH ARTICLE

Clinical profile and risk factors for respiratory failure in children with *Mycoplasma pneumoniae* infection

Yanfei Wang ¹, Limin Huang ², Junjie Qian¹, Kelei Deng ¹, Zihao Yang³, Zhenjie Chen³, Wei Li^{4*}, and Linhua Tan ^{1*}

Mycoplasma pneumoniae (MP) is a common cause of community-acquired pneumonia (CAP) in children and can lead to severe complications, including respiratory failure. A retrospective analysis of 2084 children diagnosed with CAP and treated in our hospital from January 2022 to January 2023 was conducted. A comprehensive dataset of patient demographics, clinical symptoms, and laboratory findings was initially assembled. Subsequent statistical analyses were carried out to elucidate the clinical characteristics of MP pneumonia (MPP) in children. Additionally, the study identified high-risk factors for respiratory failure in the context of MPP. Among the hospitalized MPP cases, 15.8% progressed to respiratory failure. Statistical analysis identified D-dimer level as a significant risk factor for respiratory failure in children with MPP. A predictive model was developed using D-dimer levels, yielding an area under the curve (AUC) of 0.818 with a cutoff value of 1.015 mg/L. The model demonstrated a sensitivity of 62.4% and a specificity of 91.3%, proving effective in predicting respiratory failure caused by MPP. Respiratory failure remains a critical complication in children with MPP, and D-dimer levels serve as a key predictive risk factor. Vigilant monitoring of coagulation function, particularly D-dimer levels, is essential for the early identification of patients at risk of developing respiratory failure in MPP cases.

Keywords: *Mycoplasma pneumoniae*, MP, respiratory failure, clinical disease prediction model.

Introduction

Community-acquired pneumonia (CAP) is a common disease that can become life-threatening in severe cases. Despite significant advancements in treatment, CAP remains a leading cause of morbidity and mortality worldwide. *Mycoplasma pneumoniae* (MP) is one of the most frequent causes of CAP [1], accounting for 40% of cases in children. Compared with other pathogens, patients with CAP caused by atypical bacteria (mainly MP) often experience a longer disease course but lower severity overall [2]. The annual incidence of sporadic MP pneumonia (MPP) in children and adolescents is 3–4 per 1000 individuals, with rates increasing significantly during outbreaks, which occur every 4–7 years [3]. Additionally, 18% of pediatric MPP cases require hospitalization [4]. MP infection typically presents with mild, self-limiting symptoms. Common clinical manifestations include fever, cough, sore throat, shortness of breath, and, in some cases, dyspnea. However, patients of all ages can develop severe pulmonary or extrapulmonary complications. Pulmonary complications may include lung abscess, obliterative bronchiolitis, or respiratory failure [5], while extrapulmonary complications can involve various organ systems. For example, MP infection can lead to myocarditis in the heart, causing arrhythmias or heart failure [6]. In the liver, it can result in hepatitis, manifesting as elevated liver

enzyme levels or jaundice [7]. It can also significantly impact the nervous system (e.g., causing meningitis or encephalitis), the hematological system (e.g., hemolytic anemia), the skin and mucous membranes (e.g., rash and mucositis) [8], and the musculoskeletal system (e.g., arthritis) [9]. These diverse complications are primarily due to complex immunopathological mechanisms triggered by MP. The pathogen activates the immune response, which leads to the release of inflammatory mediators and autoantibodies. These immune reactions interact with self-antigens in various organs and tissues, ultimately causing tissue damage and functional impairment [10]. Consequently, MPP not only consumes significant medical resources but also imposes a substantial healthcare burden [11]. The increasing misuse of antibiotics has contributed to a high degree of genetic variability in MP, leading to rising macrolide resistance both domestically and internationally. This growing resistance makes treatment more difficult. Additionally, as the incidence of severe and refractory MPP increases, notable changes in its pathogenic mechanisms have been observed. MP triggers an immune response and induces cytokine release, initiating an inflammatory process characterized by the accumulation of fibrinous exudate in the alveolar cavity. This increases the likelihood of severe lung lesions, with lobar pneumonia being a prominent manifestation [12, 13]. Lobar pneumonia, a common

¹Department of Surgical ICU, Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China; ²Department of Nephrology, Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China; ³Department of Pediatric ICU, Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China; ⁴Department of Laboratory, Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China.

*Correspondence to Linhua Tan: chth@zju.edu.cn and Wei Li: liweili19860607@163.com

DOI: 10.17305/bb.2024.11641

© 2025 Wang et al. This article is available under a Creative Commons License (Attribution 4.0 International, as described at <https://creativecommons.org/licenses/by/4.0/>).

pathological form of MPP, can lead to serious complications, including atelectasis, pneumothorax, pleural effusion, and even respiratory failure [14].

Respiratory failure is a common concern in pediatric emergency departments and intensive care units. It can result from various conditions, including acute parenchymal or obstructive lung diseases, congestive heart failure, neuromuscular disorders, or diseases affecting the control of the ventilatory center [15]. Severe infection with MP is another potential trigger for respiratory failure, often leading to significant complications. Initially, children may present with symptoms, such as rapid and labored breathing. As the condition progresses, hypoxia and carbon dioxide buildup can cause tissue and organ dysfunction, potentially resulting in complications such as acidosis [1]. In severe cases, respiratory failure can increase cardiac workload and heighten the risk of cardiovascular events [9]. This condition is life-threatening and demands prompt intervention and treatment [16]. Understanding the clinical characteristics and risk factors associated with respiratory failure in children with MPP is of significant clinical importance. This study seeks to identify high-risk factors for predicting respiratory failure in these children by analyzing clinical data from MPP inpatients at our hospital in recent years. The goal is to aid clinicians in early detection, timely treatment, and improved patient outcomes.

Materials and methods

Study population

This study included patients diagnosed with MPP, admitted to the Children's Hospital of Zhejiang University School of Medicine from January 2022 to January 2023, aged 28 days to 18 years. Diagnosis was based on: (1) acute respiratory symptoms, such as fever, cough, shortness of breath and/or difficulty breathing; (2) chest X-ray or CT shows signs of inflammatory infiltration, which mainly consists of patchy shadows, lobar or segmental consolidation, and interstitial changes. In some cases, pleural effusion may be present. There may or may not be abnormal lung sounds such as wheezing or moist rales; (3) serological detection of positive MP-IgM (A single serum sample shows an MP-IgM antibody titer of $\geq 1:160$, or the antibody titer in the convalescent-phase serum has increased by four times or more) and MP RNA (The nucleic acid of MP in clinical specimens was detected by quantitative polymerase chain reaction (PCR), and the test result was positive) in nasopharyngeal swabs. Exclusion criteria included: (1) underlying diseases (malignant tumors, congenital respiratory malformations, immunodeficiency); (2) multiple pathogen infections or infection foci; (3) recovery phase of MPP (disease duration >4 weeks, stable temperature >1 week, imaging improvement) [11, 17].

Subsequently, all enrolled children were divided into two groups based on whether they experienced respiratory failure during hospitalization: the MPP with respiratory failure group and the non-respiratory failure group. Respiratory failure was diagnosed based on blood gas abnormalities, specifically a partial pressure of oxygen (PaO_2) <60 mmHg, a partial pressure of

carbon dioxide (PaCO_2) >55 mmHg, and an oxygen saturation level (SaO_2) $<90\%$ [16].

Retrospective clinical data were meticulously collected and evaluated from patient records. These data included fundamental details, such as age, gender, clinical symptoms, signs, pulmonary and extrapulmonary complications, fever duration, and length of hospital stay (LOS), along with a wide range of laboratory parameters. The laboratory parameters, continuously monitored during hospitalization, encompassed white blood cell count (WBC), neutrophil percentage, C-reactive protein (CRP), procalcitonin (PCT), lactate dehydrogenase (LDH), D-dimer, and other relevant clinical indicators. The final dataset reflected the period when each patient's condition was at its most severe. This determination was based on a comprehensive evaluation of overall trends and the most critical values of these indicators, aiming to capture the disease's most pronounced manifestations and its impact on the patient's health. Laboratory tests were conducted in the hospital's clinical laboratory. Cytokines, immunoglobulins, and D-dimer levels were measured using enzyme-linked immunosorbent assay (ELISA) kits. MP antibodies were detected via the colloidal gold method for MP antigen (manufactured by Hangzhou Genesis Biodetection & Biocontrol Co., Ltd., China). Nucleic acid detection of 13 respiratory pathogens, including MP, was performed using the fluorescence PCR-capillary electrophoresis method with the Respiratory Pathogen Multiplex Detection System (Health BioMed Co., China). PCT levels were quantified via immunofluorescence assay. Complement components were measured using immunochemical methods. Cell phenotypic analysis was conducted through flow cytometry. The erythrocyte sedimentation rate (ESR) was measured with an ESR analyzer, while complete blood counts were obtained via an automated cell counter. Coagulation profiles were assessed using an automated coagulation analyzer, and biochemical parameters were measured with an automated biochemical analyzer.

Ethical statement

This study was conducted in accordance with the Helsinki Declaration and approved by the Ethics Committee of Children's Hospital of Zhejiang University School of Medicine (2022-IRB-193). Given the retrospective nature of the study, informed consent was waived.

Statistical analysis

Data were processed using SPSS 26.0 and R version 4.4.1 (specifically, the "glmnet" and "pROC" packages). The K-S test was employed to assess the normality of the data. Quantitative data that followed a normal distribution are presented as the mean $\pm$ standard deviation ($\bar{x} \pm s$) and were compared using independent sample *t*-tests. Non-normally distributed data are shown as the median and interquartile range (median, interquartile range) and were compared using the Mann-Whitney *U* test. Count data are expressed as percentages (%) and analyzed using Fisher's exact test or chi-square test. Spearman's rank-order correlation was employed for correlation analysis. High-risk factors for respiratory failure in MPP patients were identified

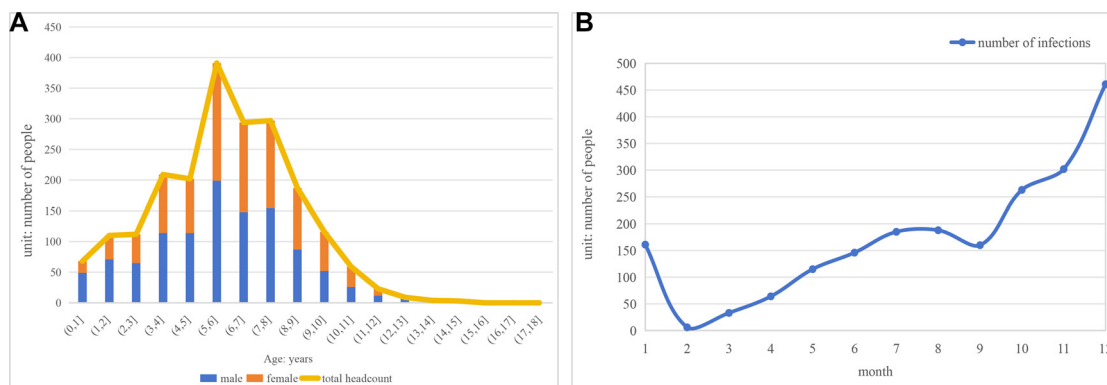


Figure 1. The overall clinical condition of children with MPP. (A) Bar chart of age and sex distribution among hospitalized children with MPP; (B) Trend chart of monthly positive cases of hospitalized children with MPP at the hospital from 2022 to 2023. MPP: Mycoplasma pneumoniae pneumonia.

through logistic regression and the Least Absolute Shrinkage and Selection Operator (Lasso) method. A clinical prediction model was constructed, and its predictive probabilities were validated using ROC curve analysis and Bootstrap resampling. An area under the curve (AUC) > 0.5 indicated predictive value. Statistical significance was set at $P < 0.05$, with a 95% confidence interval.

Results

Baseline information

In this study, 2084 children with MPP were selected from the hospital's pneumonia inpatients. The median age was six years, and 52.83% were male. MP was detected throughout 2023, with the highest MPP incidence occurring in December (Figure 1). Based on respiratory failure criteria, the children were divided into two groups: 329 (15.8%) with MPP and respiratory failure, and 1755 (84.2%) with MPP only. An analysis of clinical characteristics (Table 1) revealed that the most common symptoms among children with MPP were cough (99.5%) and fever (94.8%), followed by sputum production (88.5%). Less frequent symptoms included vomiting (7.4%) and diarrhea (2.0%). There were no significant differences between the two groups in the incidence of fever, cough, sputum production, vomiting, or diarrhea ($P < 0.05$). However, children with respiratory failure were younger, had higher peak fevers, and experienced longer durations of fever and hospital stays ($P < 0.05$). Gender distribution was not significantly different between the groups ($P > 0.05$). Treatment analysis showed that children with respiratory failure were more likely to receive steroids and combination therapy with third-line antibiotics (e.g., carbapenems) ($P < 0.05$). In contrast, macrolide antibiotics alone were more commonly used in children without respiratory failure. All children with MPP and respiratory failure received oxygen therapy: 79.94% via nasal cannula (average duration 3.9 ± 2.9 days), 20.36% via mask (2.9 ± 2.1 days), and 1.82% via mechanical ventilation (11.0 ± 11.2 days). Additionally, 5.78% required ICU admission, with an average stay of 11.3 ± 7.1 days. About 42.2% of children with respiratory failure required fiberoptic bronchoscopy, significantly higher than the 22.9% of those without respiratory failure ($P < 0.05$).

Complication statistics revealed higher incidences of pulmonary consolidation (29.22%) and pleural effusion (21.40%) in children with MPP. Extrapulmonary complications included liver function impairment (4.99%), myocardial injury (1.39%), gastrointestinal issues (18.47%), nonspecific rash (12.54%), and neurological complications (1.06%). Subgroup analysis indicated that children with MPP and respiratory failure had significantly higher rates of pulmonary consolidation, pleural effusion, liver function impairment, and myocardial injury ($P < 0.05$). Table 2 summarizes laboratory findings for both groups. Blood tests showed that children with MPP and respiratory failure had significantly higher levels of WBC, neutrophils, PLT, and CRP compared to those without respiratory failure ($P < 0.05$). Additionally, this group exhibited lower monocyte and lymphocyte percentages as well as reduced hemoglobin (HB) levels ($P < 0.05$). Elevated inflammatory and immune markers—including IL-6, IL-10, IFN- γ , IgM, IgE, PCT, and ESR—were observed in children with respiratory failure ($P < 0.05$), whereas C3 levels were significantly lower ($P < 0.05$). No significant differences were found in IL-2, IL-4, TNF- α , IgG, IgA, C4, or RBP levels ($P > 0.05$). Coagulation tests revealed increased INR, APTT, TT, and D-dimer levels in children with respiratory failure ($P < 0.05$), while Fib levels showed no significant difference ($P > 0.05$). Given the heightened risk of hepatic and myocardial injury in MPP, hepatic and cardiac function parameters were evaluated. Children with respiratory failure displayed significantly higher levels of indirect bilirubin (IBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and LDH ($P < 0.05$). However, no significant differences were observed in direct bilirubin (DBIL), total bile acid (TBA), creatine kinase (CK), or CK-MB levels ($P > 0.05$).

Risk factors of respiratory failure

Subsequently, a multivariable analysis was performed on the clinical indicators identified through univariate analysis. The Hosmer-Lemeshow test yielded a P value of 0.359, indicating good model fit and high consistency. Significant predictors of respiratory failure in children with MPP included CRP (OR = 1.013, 95% CI = 1.002-1.025), IL-10 (OR = 1.034,

Table 1. Comparison of clinical characteristics in pediatric MPP with and without respiratory failure

Characteristic	MPP with respiratory failure	MPP without respiratory failure	Chi-square value	P value
<i>Clinical features</i>				
Cough (n, %)	327 (99.4%)	1747 (99.5%)	0.134	0.714
Expectoration (n, %)	291 (88.4%)	1554 (88.5%)	0.003	0.960
Vomit (n, %)	26 (7.9%)	129 (7.4%)	0.123	0.726
Diarrhea (n, %)	9 (2.7%)	32 (1.8%)	1.195	0.274
Fever (n, %)	311 (94.5%)	1665 (94.9%)	0.066	0.797
T max, °C ^a	39.6 (39.0,40.0)	39.5 (39.0,40.0)	−2.158	0.031
Fever course, day ^a	9 (6,10)	8 (6,9)	−4.032	<0.001
Length of hospital stay, day ^a	9 (6,12)	6 (4,8)	−14.444	<0.001
Age, year ^a	5.9 (3.4,8.0)	6.0 (4.4,8.0)	−4.014	<0.001
Sex, male (n, %)	929 (52.9%)	172 (52.3%)	0.048	0.827
Steroids usage (n, %)	269 (81.76%)	842 (47.98%)	127.060	<0.001
<i>Antibiotic usage</i>				
Macrolides (n, %)	71 (21.58%)	555 (31.62%)	13.298	<0.001
Macrolides + Penicillin (n, %)	44 (13.37%)	243 (13.85%)	0.052	0.820
Macrolides + Cephalosporin (n, %)	134 (40.73%)	683 (38.92%)	0.382	0.537
Others ^b (n, %)	80 (24.32%)	274 (15.61%)	14.884	<0.001
<i>Respiratory support therapy</i>				
Nasal cannula oxygen therapy (days, %)	3.9 ± 2.9 (79.94%)	/	/	/
Mask oxygen therapy (days, %)	2.9 ± 2.1 (20.36%)	/	/	/
Mechanical ventilation therapy (days, %)	11.0 ± 11.2 (1.82%)	/	/	/
ICU length of hospital stay (days, %)	11.3 ± 7.1 (5.78%)	/	/	/
Fiber bronchoscopy (n, %)	139 (42.2%)	424 (22.9%)	54.923	<0.001
<i>Complications</i>				
Pulmonary consolidation (n, %)	149 (45.30%)	460 (26.20%)	48.756	<0.001
Pleural effusion (n, %)	141 (42.90%)	305 (17.40%)	106.920	<0.001
Liver function impairment (n, %)	42 (12.80%)	62 (3.50%)	49.817	<0.001
Myocardial injury (n, %)	7 (2.10%)	22 (0.70%)	6.394	0.011
Gastrointestinal complications (n, %)	56 (17.02%)	329 (18.75%)	0.547	0.459
Nonspecific rash (n, %)	39 (11.85%)	191 (10.88%)	0.266	0.606
Neurological complications (n, %)	10 (3.04%)	12 (0.68%)	15.007	<0.001

^aThis portion of data is continuous. In the analysis process, the Mann–Whitney *U* test is employ; ^bThe data in the last two columns represent the *Z* value and the *P* value; ^cOthers: Triple antibiotic use or use of third line antibiotics such as carbapenems. MPP: *Mycoplasma pneumoniae pneumonia*.

95% CI = 1.002–1.068), APTT (OR = 1.095, 95% CI = 1.009–1.187), D-dimer (OR = 1.287, 95% CI = 1.081–1.532), and HB (OR = 0.972, 95% CI = 0.941–0.998) ($P < 0.05$) (Figure 2A). In the analysis of complications, the Hosmer–Lemeshow test yielded a *P* value of 0.249, indicating adequate model fit. Significant predictors included pulmonary consolidation (OR = 1.635, 95% CI = 1.257–2.128), pleural effusion (OR = 2.744, 95% CI = 2.090–3.602), liver function impairment (OR = 2.396, 95% CI = 1.532–3.749), and myocardial injury (OR = 2.509, 95% CI = 0.923–6.819) ($P < 0.05$). Other indicators, such as WBC, platelets, immune markers, and liver function parameters, were not significant ($P > 0.05$) (Figure 2B). A Lasso logistic regression model was used with cross-validation to construct a risk factor classifier. Six risk factors were selected: age (coefficient = 0.955), WBC (1.026), D-dimer (1.255), IgM (1.003), pulmonary necrosis (1.056), and pleural effusion (1.794) (Figure 2C and 2D). In this study, a simple random resampling method without replacement was applied. Samples of the same size were randomly drawn 1000 times to generate bootstrap samples. These bootstrap

samples were then used to calculate statistical estimates and assess the variability and uncertainty of the results. A calibration plot based on 1000 bootstrapped resamples demonstrated high consistency between the predicted and observed probabilities of respiratory failure in children with MPP (Figure 2E).

Model validation and ROC for respiratory failure

ROC analysis of variables associated with respiratory failure complicating MPP demonstrated that CRP, IL-10, APTT, D-dimer, and HB were statistically significant predictors of respiratory failure ($P < 0.05$). Among these, the D-dimer ROC curve showed the largest AUC of 0.818, with an optimal cut-off value of 1.105 mg/L. The sensitivity and specificity for predicting respiratory failure in MPP were 62.4% and 91.3%, respectively (Figure 2F). Statistical analysis of complications identified pulmonary consolidation, atelectasis, pleural effusion, and liver function impairment as significant predictors of respiratory failure in children with MPP ($P < 0.05$). Among these, pleural effusion had the highest AUC of 0.627. Although

Table 2. Comparison of laboratory test results in pediatric MPP with and without respiratory failure

Laboratory findings	MPP with respiratory failure	MPP without respiratory failure	Z-score	P value
<i>Complete blood count</i>				
WBC, *10 ⁹ /L	9.98 (8.28)	8.09 (5.25)	−6.526	<0.001
Monocyte, %	6.60 (3.25)	7.00 (3.00)	−2.726	0.006
Neutrophil, %	66.50 (20.75)	63.40 (16.75)	−3.571	<0.001
Lymphocyte, %	24.90 (18.45)	26.90 (15.30)	−3.190	0.001
Hemoglobin, g/L	123 (13)	125 (14)	−3.695	<0.001
Platelet, *10 ⁹ /L	337 (231.5)	295 (173.25)	−3.311	0.001
C-reactive protein, mg/L	20.97 (28.58)	15.90 (19.60)	−5.030	<0.001
<i>Inflammatory immune indicators</i>				
Interleukin-2, pg/mL	1.9 (0.7)	1.9 (0.9)	−0.444	0.657
Interleukin-4, pg/mL	2.3 (1.0)	2.4 (1.0)	−0.580	0.562
Interleukin-6, pg/mL	36.7 (66.9)	28.3 (40.7)	−3.440	0.001
Interleukin-10, pg/mL	9.7 (9.4)	7.1 (4.3)	−8.065	<0.001
Interferon- α , pg/mL	2.0 (1.1)	2.0 (1.4)	−0.659	0.510
Interferon- γ , pg/mL	7.9 (19.6)	5.8 (9.1)	−3.733	<0.001
Immunoglobulin G, g/mL	9.6 (3.3)	9.8 (3.1)	−1.524	0.127
Immunoglobulin A, g/mL	1.21 (0.93)	1.29 (0.86)	0.033	0.857
Immunoglobulin M, g/mL	1.4 (0.8)	1.3 (0.7)	−2.000	0.046
Complement component 3, g/mL	1.3 (0.4)	1.3 (0.3)	−2.450	0.014
Complement component 4, g/mL	0.44 (0.21)	0.48 (0.17)	3.487	0.062
Retinol binding protein, mg/mL	17.0 (8.4)	20.1 (7.1)	−1.335	0.182
Immunoglobulin E, IU/mL	140 (358)	88 (247)	−2.88	0.004
Procalcitonin, ng/mL	0.11 (0.22)	0.09 (0.11)	−4.846	<0.001
Erythrocyte sedimentation rate, mm/H	29.88 (26.42)	27.04 (20.53)	−2.102	0.036
<i>Coagulation function indicators</i>				
International Normalized Ratio	1.06 (0.15)	1.07 (0.13)	13.382	0.337
Fibrinogen, g/L	3.98 (1.42)	4.02 (1.13)	−1.746	0.081
Activated partial thromboplastin time, s	28.9 (4.0)	28.1 (3.2)	−4.013	<0.001
Thrombin time, s	17.5 (1.7)	17.4 (1.5)	−2.407	0.016
D-dimer, mg/L	1.33 (2.42)	0.47 (0.36)	−16.264	<0.001
<i>Biochemical indicators</i>				
Direct bilirubin, Umol/L	1.4 (0.7)	1.4 (0.7)	−1.77	0.077
Indirect bilirubin, Umol/L	4.7 (2.6)	4.3 (2.2)	−3.352	0.001
Alanine aminotransferase, U/L	16 (15)	14 (8)	−5.01	<0.001
Aspartate aminotransferase, U/L	38 (30)	35 (19)	−4.476	<0.001
Total bile acids, Umol/L	5.3 (5.0)	4.9 (4.6)	−1.265	0.206
Lactate dehydrogenase, U/L	410 (319)	341 (224)	−5.797	<0.001
Creatine kinase, U/L	100 (109)	100 (77)	−0.409	0.683
Creatine kinase-MB isoenzyme, U/L	22 (25)	21 (26)	−0.085	0.932

Values are presented as median (interquartile range) as applicable. MPP: Mycoplasma pneumoniae pneumonia.

hospitalization duration and pleural effusion demonstrated predictive capabilities, their performance was inferior to that of D-dimer in predicting respiratory failure in children with MPP (Figure 2G). Internal validation of the D-dimer disease prediction model using bootstrap analysis with 100 bootstrap samples yielded similar results, with an AUC of 0.801 (95% CI: 0.769–0.832) (Figure 2H).

D-dimer and clinical indicators correlation

To clarify the role of D-dimer in MPP, and considering that the majority of clinical data in this study were not normally distributed, a Spearman rank correlation analysis was performed to evaluate the relationship between D-dimer levels and various clinical indicators. The analysis revealed that D-dimer

is positively correlated with peak fever ($r = 0.261$), duration of fever ($r = 0.269$), duration of hospitalization ($r = 0.265$), WBC ($r = 0.071$), neutrophil ratio ($r = 0.193$), CRP ($r = 0.268$), IL-6 ($r = 0.212$), IL-10 ($r = 0.265$), IFN- γ ($r = 0.241$), PCT ($r = 0.299$), ESR ($r = 0.223$), ALT ($r = 0.162$), AST ($r = 0.141$), and LDH ($r = 0.198$). In contrast, D-dimer is negatively correlated with lymphocyte ratio ($r = -0.191$) and HB ($r = -0.102$) ($P < 0.05$) (Figure 3).

Discussion

MP infection is highly prevalent and clinically significant, with disease severity ranging from mild to life-threatening.

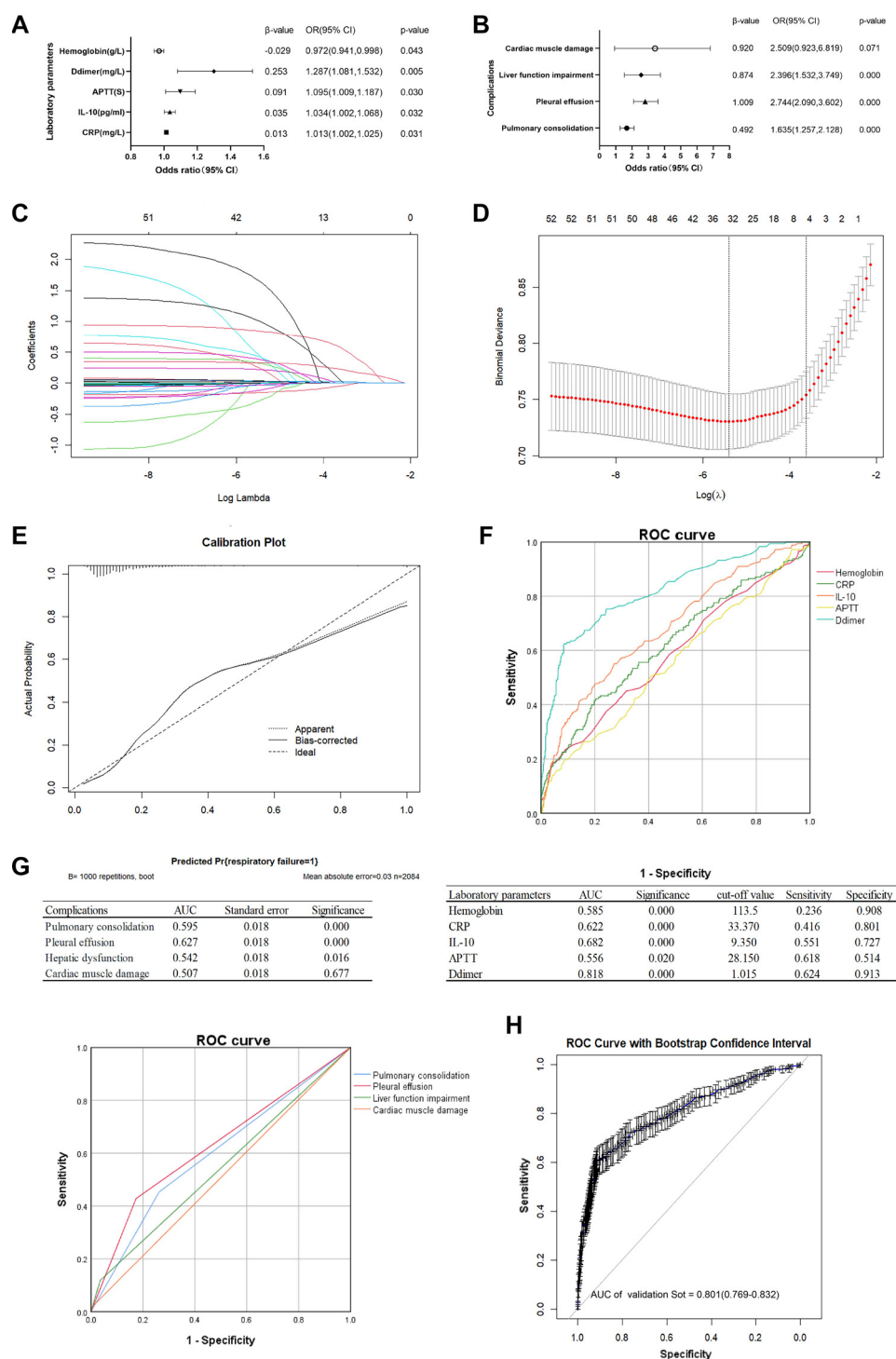


Figure 2. Identification of high-risk factors for respiratory failure in children with MPP. (A and B) Forest plot of logistic regression analysis on the association between clinical laboratory indicators and disease complications with respiratory failure in children with MPP. (C) The Lasso coefficient curves for clinical laboratory indicators and disease complications. Draw a vertical line at the value selected by 10-fold cross-validation. As the λ value decreases, the degree of model compression increases, enhancing the model's ability to select significant variables. (D) Cross-validation results. The range between the two dashed lines represents the positive and negative standard deviation of $\log(\lambda)$. The dashed line on the left indicates the value of $\log(\lambda)$ for the harmonic parameter when the model error is minimized. When $\log(\lambda) = -3.625$, four variables are selected. (E) The calibration plot represents the predicted probability and the actual incidence of respiratory failure in children with MPP. (F and G) ROC and AUC for the predictive model, clinical laboratory indicators, and disease complications. (H) Bootstrap resampling of 1000 replications for internal validity. MPP: Mycoplasma pneumoniae pneumonia; Lasso: Least Absolute Shrinkage and Selection Operator; AUC: Area under the curve.

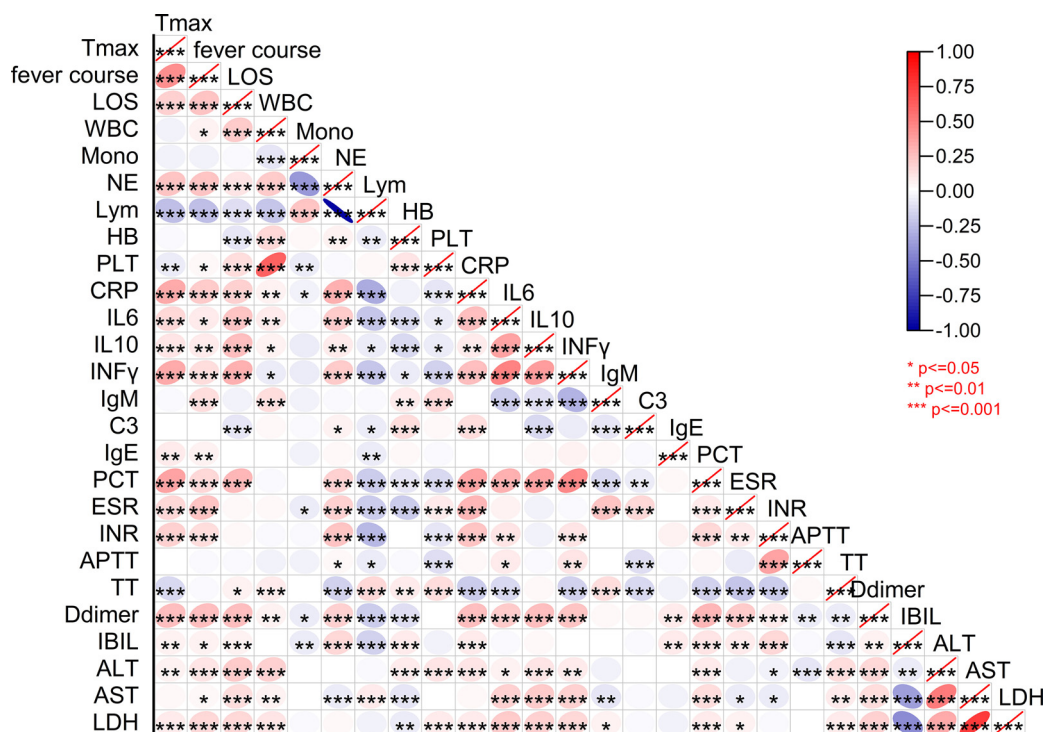


Figure 3. Heatmap analysis of the correlation between clinical symptoms and clinical indicators in children with MPP. MPP: Mycoplasma pneumoniae pneumonia; LOS: Length of hospital stay; WBC: White blood cell count; HB: Hemoglobin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; IBIL: Indirect bilirubin; ESR: Erythrocyte sedimentation rate; PCT: Procalcitonin; CRP: C-reactive protein.

Despite its often benign and self-limiting nature, MP infection is frequently underestimated [4]. Mycoplasma is primarily a mucosal pathogen that parasitizes host epithelial cells, typically targeting the respiratory or urogenital tracts. It exclusively infects humans and spreads through close contact or respiratory droplets [18]. The latency period ranges from 1 to 3 weeks. MP infections occur across all age groups worldwide, with climate, seasonality, and geographical factors generally considered insignificant. However, this study found MP infections to be more common in autumn and winter. Clinical symptoms of MP infection are diverse, with fever and cough being the most common. The cough often manifests as progressive tracheo-bronchitis and initially presents alongside upper respiratory congestion, flu-like symptoms, and pharyngitis. If the infection progresses to pneumonia, fever typically follows. In severe or fulminant cases, MP infection can be life-threatening [19]. Severe respiratory symptoms may lead to decreased blood oxygen saturation and increased work of breathing, often necessitating hospitalization [20]. Acute respiratory failure caused by MP infection is a critical condition. Post-discharge complications are common in children with acute respiratory failure and are often linked to factors experienced during their critical illness [21]. In this study, respiratory failure accounted for 15.8% of MPP cases. Respiratory failure is characterized by pulmonary mechanical or functional abnormalities, impaired gas exchange, and pulmonary circulation disorders. These issues can prevent the respiratory system from meeting the body's oxygenation, ventilation, or metabolic demands, potentially resulting in extrapulmonary organ failure, additional

complications, or even death [22]. Current consensus suggests that MP infection leading to respiratory failure involves several mechanisms. MP infection can trigger alveolar inflammation, causing lung tissue damage and impairing oxygen and carbon dioxide exchange. It may also induce airway obstruction, which hinders gas flow and results in breathing difficulties. Furthermore, MP infection can create conditions conducive to secondary infections by other bacteria or viruses [23, 24]. Children with severe cases require intensive care, aggressive respiratory support, and treatment targeting the underlying disease to improve their chances of recovery [25]. In summary, early identification of respiratory failure is crucial in children with MPP for several reasons. First, it enables the timely implementation of appropriate therapeutic measures, particularly for severe cases that may require interventions such as mechanical ventilation. Second, it aids in predicting prognosis, as respiratory failure often indicates greater disease severity. Children with severe respiratory failure typically have poorer prognoses and may require prolonged treatment and rehabilitation. Lastly, early recognition and management of respiratory failure can effectively prevent some complications, improving overall outcomes for affected children.

The treatment of respiratory failure involves airway clearance through suctioning, bronchodilator use, tracheostomy, and endotracheal intubation with respiratory support. Additionally, the management plan includes antibiotics for infections, anticoagulants for pulmonary thromboembolism, and electrolyte supplementation to address fluid imbalances [25]. In this study, children with MPP complicated by respiratory

failure showed a significantly higher frequency of steroid use, triple or third-line antibiotics, and the need for fiberoptic bronchoscopy. Respiratory failure is prevalent among pediatric patients, contributing substantially to mortality, disability, and the consumption of healthcare resources [26]. Despite growing awareness of the link between severe MPP and respiratory failure, large-scale clinical studies—particularly randomized controlled trials—remain scarce. To our knowledge, this is one of the few studies investigating the risk factors for respiratory failure in children caused by MP infection. Analysis of inflammatory markers and liver and kidney function tests in different groups of children with MPP revealed that those with respiratory failure had significantly elevated levels of white blood cells, neutrophil ratio, PCT, ESR, CRP, IL-6, IL-10, IFN- γ , ALT, AST, and LDH. Notably, children with MPP complicated by respiratory failure also experienced significantly longer hospital stays due to the need for intensive and prolonged medical interventions. This highlights a more severe inflammatory response and greater organ function damage in these patients. LDH and CRP levels, in particular, appear to correlate with respiratory function ($\text{PaO}_2/\text{FiO}_2$) and are established predictors of respiratory failure in COVID-19 patients. These markers could aid in the early identification of patients requiring closer respiratory monitoring and more aggressive treatment to improve outcomes [27]. Similarly, neutrophil ratio and IFN- γ levels may help diagnose severe MPP and predict complications in children [28, 29]. Additionally, this study identified significantly elevated platelet counts in children with respiratory failure. In COVID-19 patients with respiratory failure, enhanced platelet activation has been linked to disease severity, myocardial injury, and mortality [30]. Analysis of complications also revealed that the proportion of children with respiratory failure who developed pleural effusion was significantly higher, which may hold clinical value in predicting respiratory failure. Previous research has confirmed that pleural effusion is associated with a more severe clinical course, poorer treatment responses, and severe pneumonia based on the extent of lung lesions [31]. Further findings from our data analysis indicate that children with MPP complicated by respiratory failure exhibited higher IgE levels, consistent with prior studies. Animal experiments have shown that MP produces the Community-Acquired Respiratory Distress Syndrome (CARDS) toxin, which induces excessive mucus secretion, increased Th2 responses, eosinophilia, airway hyperresponsiveness, and elevated IgE levels. These factors contribute to exacerbated asthma symptoms and wheezing [32, 33]. Clinical research has also confirmed that patients with complications, such as necrotizing pneumonia, pneumothorax, rash, obliterative bronchiolitis, or MP-related extrapulmonary diseases exhibit relatively higher IgE levels [34]. Furthermore, MPP patients with elevated IgE levels tend to experience more severe disease, clinical symptoms, and complications [35, 36].

Based on this study, D-dimer has emerged as a crucial risk factor for predicting respiratory failure in children with MPP. D-dimer is a specific fibrin degradation product generated during fibrin monomer activation via cross-linking factors. It serves as a key marker of the fibrinolytic

system and an indicator for monitoring inflammation and severe infections [28]. In children with MPP complicated by respiratory failure, a series of pathophysiological changes are frequently observed, including local hypoxia, ischemia, and acidosis. The direct invasion of MP pathogens and their toxins triggers a cascade of events, activating the coagulation, fibrinolysis, kinin, and complement systems. This activation disrupts the body's physiological balance, leading to coagulation dysfunction [37]. A hallmark of this dysfunction is the development of a hypercoagulable state, where excessive blood clotting occurs. To counteract this, fibrin degradation intensifies, resulting in elevated D-dimer levels [38]. Moreover, MP stimulates inflammatory cells, such as macrophages and neutrophils, prompting the release of inflammatory mediators like TNF- α and IL-6 [39, 40]. These mediators can damage vascular endothelial cells, further exacerbating the condition. Damaged endothelial cells expose subendothelial collagen fibers, activating the intrinsic coagulation pathway, increasing fibrin production, and triggering fibrinolysis, which elevates D-dimer levels. Additionally, endothelial damage disrupts vascular tone and anticoagulation functions, impairing blood circulation and gas exchange in the lungs. This creates a vicious cycle that worsens respiratory function and accelerates respiratory failure progression [41, 42]. Our study also found that D-dimer correlates significantly with clinical indicators of MPP in children, particularly inflammatory markers, consistent with previous research [43]. Elevated D-dimer levels have clinical significance in predicting complications like necrotizing pneumonia [44], refractory MPP [45], and poor prognosis in children. Children with high D-dimer levels often experience complications, such as pleural effusion, myocardial damage, and liver damage [46]. They also present more severe symptoms and require longer treatment durations [43]. Notably, elevated D-dimer levels are associated with worse outcomes in respiratory diseases. Studies on patients with pneumonia and COPD have shown that higher D-dimer levels correlate with lower survival rates and an increased risk of death from respiratory failure in the general population [38]. In conclusion, D-dimer is a critical marker for assessing disease severity, predicting complications, and forecasting the prognosis of respiratory failure in children with MPP. Its role underscores the complex interplay between inflammation, coagulation, and respiratory dysfunction in these patients.

This study has several limitations. The sample source is relatively restricted, as the children were recruited from a tertiary children's hospital. This setting may overrepresent severe infection cases, which limits the generalizability of the findings to milder cases typically encountered in primary or secondary care. Pathogen detection also presents challenges: false negatives make it impossible to rule out concurrent infections with other pathogens, and the diagnostic methods employed may have overlooked some pathogens. These limitations could affect the study's ability to fully understand disease etiology and the relationships between contributing factors. Additionally, the relatively short follow-up period only permitted the observation of immediate and short-term outcomes. As a result, the study is unable to capture the long-term consequences of the

disease, which restricts a comprehensive assessment of its full impact on patients' health and development.

Conclusion

An elevated D-dimer shows a notable positive correlation with inflammatory markers, liver function, and LDH in children suffering from MPP. Serum D-dimer levels exceeding 1.015 mg/L may be associated with an increased risk of respiratory failure in these children. Therefore, during the clinical diagnosis and treatment of MPP, greater emphasis should be placed on monitoring coagulation function, with particular attention to serum D-dimer levels. For MPP patients with elevated D-dimer levels, clinicians should closely observe the child's respiratory condition and consider implementing appropriate respiratory management strategies to help reduce the risk of respiratory failure. However, due to the limitations of this study, further research is essential to validate and expand upon these findings.

Conflicts of interest: Authors declare no conflicts of interest.

Funding: Authors received no specific funding for this work.

Data availability: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Submitted: 10 November 2024

Accepted: 17 January 2024

Published online: 22 January 2025

References

- Miyashita N, Obase Y, Ouchi K, Kawasaki K, Kawai Y, Kobashi Y, et al. Clinical features of severe Mycoplasma pneumoniae pneumonia in adults admitted to an intensive care unit. *J Med Microbiol* 2007;56 (Pt 12):1625–9. <https://doi.org/10.1099/jmm.0.47119-0>.
- Otheo E, Rodriguez M, Moraleda C, Dominguez-Rodriguez S, Martin MD, Herreros ML, et al. Viruses and Mycoplasma pneumoniae are the main etiological agents of community-acquired pneumonia in hospitalized pediatric patients in Spain. *Pediatr Pulmonol* 2022;57(1):253–63. <https://doi.org/10.1002/ppul.25721>.
- Ding G, Zhang X, Vinturache A, van Rossum AMC, Yin Y, Zhang Y. Challenges in the treatment of pediatric Mycoplasma pneumoniae pneumonia. *Eur J Pediatr* 2024;183:3001–11. <https://doi.org/10.1007/s00431-024-05519-1>.
- Kumar S. Mycoplasma pneumoniae: a significant but underrated pathogen in paediatric community-acquired lower respiratory tract infections. *Indian J Med Res* 2018;147(1):23–31. https://doi.org/10.4103/ijmr.IJMR_1582_16.
- Meyer Sauter PM, Unger WWJ, van Rossum AMC, Berger C. The art and science of diagnosing Mycoplasma pneumoniae infection. *Pediatr Infect Dis J* 2018;37(11):1192–5. <https://doi.org/10.1097/INF.0000000000002171>.
- Fan Q, Meng J, Li P, Liu Z, Sun Y, Yan P. Pathogenesis and association of Mycoplasma pneumoniae infection with cardiac and hepatic damage. *Microbiol Immunol* 2015;59(7):375–80. <https://doi.org/10.1111/1348-0421.12267>.
- Poddighe D. Mycoplasma pneumoniae-related hepatitis in children. *Microb Pathog* 2020;139:103863. <https://doi.org/10.1016/j.micpath.2019.103863>.
- Brazel D, Kulp B, Bautista G, Bonwit A. Rash and mucositis associated with mycoplasma pneumoniae and chlamydia pneumoniae: a recurrence of MIRM? *J Pediatric Infect Dis Soc* 2021;10(2):220–4. <https://doi.org/10.1093/jpids/piaa028>.
- Narita M. Classification of extrapulmonary manifestations due to mycoplasma pneumoniae infection on the basis of possible pathogenesis. *Front Microbiol* 2016;7:23. <https://doi.org/10.3389/fmicb.2016.00023>.
- Poddighe D. Extra-pulmonary diseases related to Mycoplasma pneumoniae in children: recent insights into the pathogenesis. *Curr Opin Rheumatol* 2018;30(4):380–7. <https://doi.org/10.1097/BOR.0000000000000494>.
- Tsai TA, Tsai CK, Kuo KC, Yu HR. Rational stepwise approach for Mycoplasma pneumoniae pneumonia in children. *J Microbiol Immunol Infect* 2021;54(4):557–65. <https://doi.org/10.1016/j.jmii.2020.10.002>.
- Cockcroft DW, Stilwell GA. Lobar pneumonia caused by Mycoplasma pneumoniae. *Can Med Assoc J* 1981;124(11):1463–8.
- Zhao JL, Wang X, Wang YS. Relationships between Th1/Th2 cytokine profiles and chest radiographic manifestations in childhood Mycoplasma pneumoniae pneumonia. *Ther Clin Risk Manag* 2016;12:1683–92. <https://doi.org/10.2147/TCRM.S121928>.
- Xie XY, Zhou RY, Ding SA, Ma BX, Zhang X, Zhang Y. Emerging trends and concerns in Mycoplasma pneumoniae pneumonia among Chinese pediatric population. *Pediatr Res* 2024;95(6):1388–90. <https://doi.org/10.1038/s41390-024-03049-y>.
- Jose D, Parameswaran N. Advances in management of respiratory failure in children. *Indian J Pediatr* 2023;90(5):470–80. <https://doi.org/10.1007/s12098-023-04559-z>.
- Hammer J. Acute respiratory failure in children. *Paediatr Respir Rev* 2013;14(2):64–9. <https://doi.org/10.1016/j.prrv.2013.02.001>.
- Wang K, Gill P, Perera R, Thomson A, Mant D, Harnden A. Clinical symptoms and signs for the diagnosis of Mycoplasma pneumoniae in children and adolescents with community-acquired pneumonia. *Cochrane Database Syst Rev* 2012;10(10):CD009175. <https://doi.org/10.1002/14651858.CD009175.pub2>.
- Waites KB, Talkington DF. Mycoplasma pneumoniae and its role as a human pathogen. *Clin Microbiol Rev* 2004;17(4):697–728. <https://doi.org/10.1128/CMR.17.4.697-728.2004>.
- Kannan TR, Hardy RD, Coalson JJ, Cavuoti DC, Siegel JD, Cagle M, et al. Fatal outcomes in family transmission of Mycoplasma pneumoniae. *Clin Infect Dis* 2012;54(2):225–31. <https://doi.org/10.1093/cid/cir769>.
- Atkinson TP, Balish MF, Waites KB. Epidemiology, clinical manifestations, pathogenesis and laboratory detection of Mycoplasma pneumoniae infections. *FEMS Microbiol Rev* 2008;32(6):956–73. <https://doi.org/10.1111/j.1574-6976.2008.00129.x>.
- Watson RS, Asaro LA, Hutchins L, Bysani GK, Killien EY, Angus DC, et al. Risk factors for functional decline and impaired quality of life after pediatric respiratory failure. *Am J Respir Crit Care Med* 2019;200(7):900–9. <https://doi.org/10.1164/rccm.201810-1881OC>.
- Yang P, Esper AM. Acute respiratory failure: problems solved and unsolved. *Crit Care Clin* 2024;40(2):13–15. <https://doi.org/10.1016/j.ccc.2024.01.001>.
- Hu J, Ye Y, Chen X, Xiong L, Xie W, Liu P. Insight into the pathogenic mechanism of mycoplasma pneumoniae. *Curr Microbiol* 2022;80(1):14. <https://doi.org/10.1007/s00284-022-03103-0>.
- Jiang Z, Li S, Zhu C, Zhou R, Leung PHM. Mycoplasma pneumoniae infections: pathogenesis and vaccine development. *Pathogens* 2021;10(2):119. <https://doi.org/10.3390/pathogens10020119>.
- Izumikawa K, Izumikawa K, Takazono T, Kosai K, Morinaga Y, Nakamura S, et al. Clinical features, risk factors and treatment of fulminant Mycoplasma pneumoniae pneumonia: a review of the Japanese literature. *J Infect Chemother* 2014;20(3):181–5. <https://doi.org/10.1016/j.jiac.2013.09.009>.
- Hernandez-Corredor L, Plazas-Pachon R, Argote-Bolanos F, Barrera-Lopez P, Vanegas MN, Moreno-Lopez S, et al. Burden of respiratory failure in pediatric patients: analysis of a prospective multicenter cohort in Bogota, Colombia. *Health Sci Rep* 2023;6(11):e1617. <https://doi.org/10.1002/hsr2.1617>.
- Poggiali E, Zaino D, Immovali P, Rovero L, Losi G, Dacrema A, et al. Lactate dehydrogenase and C-reactive protein as predictors of respiratory failure in COVID-19 patients. *Clin Chim Acta* 2020;509:135–8. <https://doi.org/10.1016/j.cca.2020.06.012>.
- Jin X, Zhu Y, Zhang Y, Chen J, Rong L, Zhao X. Assessment of levels of D-dimer and interferon-gamma in pediatric patients with Mycoplasma pneumoniae pneumonia and its clinical implication. *Exp Ther Med* 2018;16(6):5025–30. <https://doi.org/10.3892/etm.2018.6873>.

- [29] Huang W, Xu X, Zhao W, Cheng Q. Refractory *Mycoplasma pneumoniae* in children: a systematic review and meta-analysis of laboratory features and predictors. *J Immunol Res* 2022;2022:9227838. <https://doi.org/10.1155/2022/9227838>.
- [30] Campo G, Contoli M, Fogagnolo A, Vieceli Dalla Sega F, Zucchetti O, Ronzoni L, et al. Over time relationship between platelet reactivity, myocardial injury and mortality in patients with SARS-CoV-2-associated respiratory failure. *Platelets* 2021;32(4):560–7. <https://doi.org/10.1080/09537104.2020.1852543>.
- [31] Kim SH, Lee E, Song ES, Lee YY. Clinical significance of pleural effusion in *Mycoplasma pneumoniae* pneumonia in children. *Pathogens* 2021;10(9):1075. <https://doi.org/10.3390/pathogens10091075>.
- [32] Medina JL, Brooks EG, Chaparro A, Dube PH. *Mycoplasma pneumoniae* CARDS toxin elicits a functional IgE response in Balb/c mice. *PLoS One* 2017;12(2):e0172447. <https://doi.org/10.1371/journal.pone.0172447>.
- [33] Koh YY, Park Y, Lee HJ, Kim CK. Levels of interleukin-2, interferon-gamma, and interleukin-4 in bronchoalveolar lavage fluid from patients with *Mycoplasma pneumoniae*: implication of tendency toward increased immunoglobulin E production. *Pediatrics* 2001;107(3):E39. <https://doi.org/10.1542/peds.107.3.e39>.
- [34] Poddighe D, Comi EV, Brambilla I, Licari A, Bruni P, Marseglia GL. Increased total serum immunoglobulin E in children developing *Mycoplasma pneumoniae*-related extra-pulmonary diseases. *Iran J Allergy Asthma Immunol* 2018;17(5):490–6. <https://doi.org/10.18502/ijaai.v17i5.307>.
- [35] Zhou L, Li Y, Xu Z, Peng X, Gong X, Yang L. Increased total serum immunoglobulin E is likely to cause complications of *Mycoplasma pneumoniae* pneumonia in children. *Front Cell Infect Microbiol* 2021;11:783635. <https://doi.org/10.3389/fcimb.2021.783635>.
- [36] Wang Z, Sun J, Liu Y, Wang Y. Impact of atopy on the severity and extrapulmonary manifestations of childhood *Mycoplasma pneumoniae* pneumonia. *J Clin Lab Anal* 2019;33(5):e22887. <https://doi.org/10.1002/jcla.22887>.
- [37] Hagemann L, Grundel A, Jacobs E, Dumke R. The surface-displayed chaperones GroEL and DnaK of *Mycoplasma pneumoniae* interact with human plasminogen and components of the extracellular matrix. *Pathog Dis* 2017;75(3). <https://doi.org/10.1093/femspd/ftx017>.
- [38] Kobayashi M, Shibata Y, Inoue S, Igarashi A, Sato K, Sato M, et al. Predictors for mortality from respiratory failure in a general population. *Sci Rep* 2016;6:26053. <https://doi.org/10.1038/srep26053>.
- [39] Lian H, Cai H, Wang X, Zhang H, Gao Y, Zhang S, et al. Inflammation-Associated coagulation reactions are associated with the prognosis in critically ill very old patients (VOPs) with infection. *J Inflamm Res* 2024;17:9335–46. <https://doi.org/10.2147/JIR.S474990>.
- [40] Park YJ, Acosta D, Vassell R, Tang J, Khurana S, Weiss CD, et al. D-dimer and CoV-2 spike-immune complexes contribute to the production of PGE2 and proinflammatory cytokines in monocytes. *PLoS Pathog* 2022;18(4):e1010468. <https://doi.org/10.1371/journal.ppat.1010468>.
- [41] Zheng B, Zhao J, Cao L. The clinical characteristics and risk factors for necrotizing pneumonia caused by *Mycoplasma pneumoniae* in children. *BMC Infect Dis* 2020;20(1):391. <https://doi.org/10.1186/s12879-020-05110-7>.
- [42] Luo Y, Wang Y. Risk prediction model for necrotizing pneumonia in children with *Mycoplasma pneumoniae* pneumonia. *J Inflamm Res* 2023;16:2079–87. <https://doi.org/10.2147/JIR.S413161>.
- [43] Zheng Y, Hua L, Zhao Q, Li M, Huang M, Zhou Y, et al. The level of D-dimer is positively correlated with the severity of *Mycoplasma pneumoniae* pneumonia in children. *Front Cell Infect Microbiol* 2021;11:687391. <https://doi.org/10.3389/fcimb.2021.687391>.
- [44] Li YT, Zhang J, Wang MZ, Ma YM, Zhi K, Dai FL, et al. Changes in coagulation markers in children with *Mycoplasma pneumoniae* pneumonia and their predictive value for *Mycoplasma* severity. *Ital J Pediatr* 2023;49(1):143. <https://doi.org/10.1186/s13052-023-01545-1>.
- [45] Huang X, Li D, Liu F, Zhao D, Zhu Y, Tang H. Clinical significance of D-dimer levels in refractory *Mycoplasma pneumoniae* pneumonia. *BMC Infect Dis* 2021;21(1):14. <https://doi.org/10.1186/s12879-020-05700-5>.
- [46] Qiu J, Ge J, Cao L. D-dimer: the risk factor of children's severe *Mycoplasma pneumoniae* pneumonia. *Front Pediatr* 2022;10:828437. <https://doi.org/10.3389/fped.2022.828437>.

Related articles

1. Epidemiology, pathogenicity, risk factors, and management of *Helicobacter pylori* infection in Saudi Arabia

Mutasim E. Ibrahim, *Biomol Biomed*, 2023

2. Predominance of OXA-48 carbapenemase-producing *Klebsiella pneumoniae* strains in tertiary hospital in Sarajevo, Bosnia and Herzegovina

Amela Dedeić Ljubović et al., *Biomol Biomed*, 2024