

A nomogram for predicting severe *Mycoplasma pneumoniae* pneumonia in children undergoing bronchoscopy: a retrospective study

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Abstract

Objective

To analyze risk factors for progression from *Mycoplasma pneumoniae* pneumonia (MPP) to severe MPP (SMPP) in children and establish a predictive nomogram.

Methods

A retrospective cohort of 255 children diagnosed with MPP from April 2023 to June 2024 was randomly split into a training cohort (n = 174, 109 mild MPP, 65 SMPP) and a validation cohort (n = 81) at a 7:3 ratio. Univariate analysis and Lasso regression screened candidate predictors, followed by multivariate logistic regression to identify independent risk factors. A nomogram was built using R software. Receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA) were used to evaluate model performance.

Results

D-dimer, plasma interleukin (IL)-5, plasma IL-6, and bronchoalveolar lavage fluid (BALF) IL-8 were independent predictors of SMPP (all $P < 0.05$). The nomogram yielded an area under the ROC curve (AUC) of 0.935 (95% CI: 0.901–0.969) in the training set (specificity = 0.853, sensitivity = 0.862 at the maximum Youden index) and 0.928 (95% CI: 0.871–0.985) in the validation set (specificity = 0.765, sensitivity = 0.967). Calibration curves showed favorable agreement between predicted and observed SMPP risks, and DCA confirmed its clinical utility.

Conclusion

The nomogram based on D-dimer, plasma IL-5, plasma IL-6, and BALF IL-8 reliably predicts SMPP risk in children who undergo bronchoscopy, demonstrating strong predictive performance.

1 Introduction

Mycoplasma pneumoniae (MP) is a common pathogen responsible for community-acquired pneumonia in children and adolescents¹. Although *mycoplasma pneumoniae* pneumonia (MPP) is typically self-limiting, with most cases involving mild symptoms and favorable treatment outcomes, the increasing resistance displayed by its causal pathogen to macrolide antibiotics in recent years has significantly increased the incidence of severe MPP (SMPP). Indeed, around 12% of hospitalized children with MPP are at risk of progressing to SMPP, with the latter being characterized by serious complications, such as pleural effusion, pulmonary atelectasis, and necrotizing pneumonia¹. In certain critical cases, SMPP can

even lead to respiratory failure and hypoxemia, requiring mechanical ventilation and extracorporeal membrane oxygenation (ECMO). Additionally, SMPP may be associated with severe extrapulmonary complications which, in some cases, can be fatal^{2,3}.

Emerging evidence has highlighted the critical role of immune dysfunction in the progression of SMPP. MP invades the respiratory tract where it adheres to the surface of respiratory epithelial cells and proliferates within these cells. This results in the release of reactive oxygen species and toxins that not only damage the epithelial cells and their functions but also induce the release of pro-inflammatory cytokines in the airway mucosa, thereby triggering cellular inflammatory responses. Consequently, cytokines have become a focal point of interest in understanding the pathogenesis of SMPP. However, most studies have primarily focused on monitoring plasma cytokines. To address this gap, the current study included 255 children with MPP who underwent fiberoptic bronchoscopy. Their clinical characteristics, laboratory test results, cytokine levels and cytological findings were then collected and analyzed to develop a predictive nomogram model aimed at assisting in the early identification and treatment of SMPP in view of improving prognosis for affected children.

2 Materials and methods

2.1 Study participants

A total of 301 children who met the diagnostic criteria for MPP and underwent bronchoscopy were initially collected. However, exclusions were made for those with incomplete data (n = 22), coexisting bronchial asthma (n = 19), tuberculosis (n = 2), and immune deficiencies (n = 3), resulting in a final study cohort of 255 patients. The dataset was randomly split into a training cohort (n = 174) and a validation cohort (n = 81) in a 7:3 ratio. The training cohort was divided into two groups, namely the GMPP (n = 109) and the SMPP (n = 65) groups, based on the presence of severe manifestations. Participants were included if 1) they met the diagnostic criteria for MPP (i.e., a single serum MP-IgM antibody titer of $\geq 1:160$ as well as nasopharyngeal secretions or alveolar lavages that were positive for MP-DNA/RNA); 2) they underwent bronchoscopy and provided bronchoalveolar lavage fluid (BALF) samples for cytokine, cytology and etiology testing and 3) their age was between 29 days and 17 years (inclusive). In addition, the following exclusion criteria were applied: 1) those suffering from underlying conditions, such as chronic cardiopulmonary diseases, rheumatic diseases, immunodeficiency diseases, severe hematologic diseases or chromosomal diseases; 2) those with respiratory disorders, such as bronchial asthma, bronchiectasis and tuberculosis, amongst others and 3) those who did not have bronchoscopy and were unable to provide BALF for cytokine, cytology and etiology testing.

This retrospective study was approved by the Medical Ethics Committee of Jinhua Maternal and Child Health Care Hospital (Approval No. 2024KY083). The ethics committee waived the requirement for written informed consent because only anonymized historical routine clinical data were retrospectively analysed. All procedures were performed in accordance with the Declaration of Helsinki.

2.2 Grouping criteria

Children diagnosed with SMPP met the diagnostic criteria for MPP and also fulfilled at least one of the following conditions: (1) persistent high fever exceeding 39°C for at least five days or a fever lasting at least seven days with no significant reduction in peak body temperature; (2) presence of one or more symptoms, such as wheezing, shortness of breath, breathing difficulty, chest pain or hemoptysis which reflect the disease's severity and may suggest complications like pulmonary embolism, asthma exacerbations, pleural effusion or other severe conditions; (3) oxygen saturation of $\leq 93\%$ at rest during inhalation as measured by pulse oximetry; (4) specific imaging findings that indicate $\geq$ uniform high-density consolidation involving $\geq 2/3$ of a single lung lobe or high-density consolidation in two or more lung lobes, potentially accompanied by moderate to large pleural effusion or localized bronchiolitis; $\geq$ widespread bronchiolitis affecting one lung or $\geq 4/5$ of the lobes bilaterally, often associated with bronchitis and the formation of mucus plugs that result in atelectasis; (5) progressively worsening clinical symptoms, with imaging showing over 50% increase in lesion size within 24 to 48 hours. On the other hand, the general MPP(GMPP) group included children that met the diagnostic criteria for MPP but did not exhibit any of the manifestations associated with SMPP. All aforementioned data were based on objective clinical records from medical charts. Imaging assessments relied on formal reports by radiologists rather than subjective evaluations by researchers.

2.3 Bronchoscopy and bronchoalveolar lavage

In this study, Bronchoscopy was performed within 3 days of hospital admission. The procedure primarily aimed to assess airway mucosal damage, clear mucus plugs to prevent atelectasis, and obtain BALF samples. All interventions adhered to the Chinese Guidelines for Flexible Bronchoscopy Surgery in Pediatrics (2018 Edition)⁴ and the Official American Thoracic Society technical standards: flexible airway endoscopy in children⁵. Patients undergoing bronchoscopy met at least one of the following criteria: unexplained stridor, unexplained wheeze, chronic cough, recurrent pneumonia, suspected aspiration, suspected structural anomalies, suspected endobronchial lesion, radiographic abnormality, hemoptysis and pulmonary hemorrhage, and monitoring of the artificial airway. Before the procedure, informed consent for fiberoptic bronchoscopy was obtained from the parents or legal guardians. A comprehensive preoperative assessment, including adherence to fasting and water restriction protocols, was then conducted. The bronchoscopy was performed starting with the healthy lung side, followed by the affected side. At the segmental bronchus opening, 10 mL of saline at 37°C was used for quantitative irrigation before collecting the first sample of BALF. Routine bronchoalveolar lavage was then performed to observe airway secretions, with additional BALF samples subsequently collected for analyzing respiratory pathogens. Throughout the procedure, if mucus plugs (i.e., thick secretions or obstructions that were resistant to negative pressure suction) were encountered, sterile brushes and/or sterile forceps were used for removal. BALF specimens were considered to be valid if there were no signs of blood contamination in the first tube of quantitative lavage, and the samples were stored at room temperature for less than 4 hours or at 0–4°C for no more than 12 hours.

2.4 Collection of clinical data

The clinical data of participants included demographic characteristics, such as age, sex and maximum body temperature, as well as laboratory investigations which encompassed blood count, C-reactive protein (CRP), albumin (ALB), alanine aminotransferase (ALT), creatine kinase (CK), creatine kinase isoenzyme (CK-MB), blood urea nitrogen (BUN), lactate dehydrogenase (LDH), fibrinogen (FIB), prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer and the plasma and BALF levels of 12 cytokines. All laboratory parameters were collected within 24 hours of admission. In addition, imaging studies were included to assess the presence of pleural effusion, while fiberoptic bronchoscopic findings were focused on bronchial mucosal erosions, mucus plug formation, and bronchial stenosis.

2.5 Statistical analysis

All results were statistically analyzed in SPSS version 27.0. Specifically, categorical data were presented as frequencies (n) and percentages (%), with group comparisons subsequently performed using the chi-square (χ^2) test. In addition, normally distributed measurements were expressed as mean $\pm$ standard deviation (SD) before using the independent sample t-test to assess the significance of group differences, while in the case of non-normally distributed data, the results were expressed as median (interquartile range) [P50 (P25, P75)] and compared with the Mann-Whitney U test. Furthermore, potential predictors of SMPP were identified through univariate analysis and LASSO regression, with the independent risk factors subsequently determined using multivariate logistic regression analysis. Based on the latter's results, a nomogram was then constructed with the RMS package in R before evaluating the model's performance on both training and validation sets. In this case, the predictive ability of the model was also assessed using receiver operating characteristic (ROC) curves, while internal validation and calibration were performed using the bootstrap resampling method to ensure reliability. Finally, to assess the clinical utility of the nomogram, a decision curve analysis (DCA) was conducted. For all analyses, statistically significant differences were indicated by p-values of < 0.05 .

3 Results

3.1 Differences in clinical data between the GMPP and SMPP groups

A total of 255 children who met the diagnostic criteria for MPP and underwent bronchoscopy were recruited for this study. These patients were then randomized into a training cohort (n = 174) and a validation cohort (n = 81) in a 7:3 ratio, with their clinical characteristics summarized in Table 1. For the MPP cohort, the children in the training and validation cohorts had median ages of 6 and 7 years, respectively, with the proportion of males being 44.3% and 48.1%, respectively. However, the clinical features were not significantly different between the two groups ($P > 0.05$), thus indicating successful randomization. Univariate analysis of the training cohort further revealed that the SMPP group had higher percentages of neutrophils, CRP, D-dimer, plasma cytokines (including IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, TNF α , γ -IFN and α -IFN), lavage cytokines (IL-1 β , IL-5, IL-6, IL-8, IL-10, IL-17, TNF α and γ -IFN) and lavage cytology (nucleated cell count) compared with the GMPP group, while the percentages

of lymphocytes and monocytes as well as levels of albumin and urea nitrogen were lower. In addition, the incidence of plastic bronchitis and pleural effusion was significantly higher in the SMPP group ($P < 0.05$) (Table 2).

Table 1
Baseline characteristics for the training and validation cohorts [n (%), M (P25, P75)].

Male (%)	Validation Cohort (81)	Training Cohort (174)	x2 /t/Z	P
	39 (48.1%)	77 (44.3%)	0.338	0.561
Age (year)	6 (5, 8.5)	7 (5, 8.25)	-0.702	0.483
Max Temp (°C)	39.4 (38.85, 39.95)	39.2 (38.9, 39.8)	-0.105	0.916
WBC (×10 ⁹ /L)	8.07 (6.63, 9.86)	7.32 (5.96, 9.28)	-1.629	0.103
NE (%)	65.72 ± 10.37	63.62 ± 11.97	-1.364	0.174
MONO (%)	7.3 (5.95, 8.8)	7.2 (5.7, 8.93)	-0.577	0.564
LY (%)	23.7 (18.2, 32.65)	25.85 (18.88, 34.98)	-1.125	0.260
Hb (g/L)	124 (118, 129)	125 (119, 130)	-1.110	0.267
PLT (×10 ⁹ /L)	271 (213, 361.5)	270 (216.5, 334.25)	-0.411	0.681
CRP (mg/L)	11.66 (6.49, 24.2)	12.55 (5.87, 24.03)	-0.138	0.890
ALB (g/L)	41.94 ± 3.24	41.82 ± 3.19	-0.272	0.786
ALT (U/L)	15 (13, 19)	16 (12, 21)	-0.606	0.545
CK (U/L)	64 (50.5, 99)	76 (53.75, 97.5)	-1.003	0.316
CK-MB (U/L)	20.5 (15.95, 27.4)	19.8 (16.08, 24)	-1.089	0.276
BUN mmol/L	3.7 ± 1.12	3.82 ± 1.04	0.790	0.430
LDH(U/L)	287 (233.5, 360.5)	275 (238.75, 329.25)	-1.045	0.296
FIB (g/L)	5 (4.4, 5.71)	5 (4.3, 5.87)	-0.212	0.832
APTT (S)	36.6 (33.75, 41.15)	36.5 (34.18, 40.73)	-0.616	0.538
PT (S)	12.9 (12.3, 13.7)	12.8 (12.1, 13.2)	-1.617	0.106
D-dimer (ug/L)	540 (410, 740)	565 (460, 730)	-0.452	0.651
IL-1β(pg/mL)	3.84 (2.38, 9.45)	3.69 (2.08, 7.07)	-0.889	0.374
IL-2 (pg/mL)	2.86 (1.67, 4.38)	2.51 (1.55, 3.53)	-0.969	0.333
IL-4 (pg/mL)	2.46 (1.35, 4.13)	2.68 (0.96, 3.8)	-0.739	0.460
IL-5 (pg/mL)	1.52 (0.94, 2.41)	1.33 (0.87, 2)	-1.273	0.203
IL-6 (pg/mL)	19.09 (11.96, 34.01)	17.33 (10.74, 39.92)	-0.072	0.943
IL-8 (pg/mL)	18.13 (12.6, 31.29)	20.06 (14.38, 30.97)	-1.091	0.275

Male (%)	Validation Cohort (81)	Training Cohort (174)	x2 /t/Z	P
	39 (48.1%)	77 (44.3%)	0.338	0.561
IL-10 (pg/mL)	12.04 (6.69, 16.23)	11.21 (7.32, 15.16)	-0.256	0.798
IL-12 (pg/mL)	4.87 (3.16, 7.63)	5.02 (2.76, 7.89)	-0.115	0.909
IL-17 (pg/mL)	17.23 (9.95, 32.29)	19.69 (9.98, 35.11)	-0.523	0.601
TNFα (pg/mL)	2.58 (1.82, 5.06)	2.71 (1.63, 4.65)	-0.005	0.996
γ-IFN (pg/mL)	5.16 (3.33, 9.38)	5.65 (3.91, 9.91)	-1.296	0.195
α-IFN (pg/mL)	4.95 (3.07, 9.92)	5.41 (3.06, 8.66)	-0.522	0.602
BALF IL-1β (pg/mL)	188.36 (54.8, 709.27)	164.75 (47.4, 627.93)	-0.074	0.941
BALF IL-2 (pg/mL)	7.45 (4, 12.57)	7.16 (3.87, 10.61)	-0.501	0.617
BALF IL-4 (pg/mL)	0.15 (0, 1.85)	0 (0, 0.82)	-1.802	0.072
BALF IL-5 (pg/mL)	0.01 (0, 0.39)	0 (0, 0.25)	-1.052	0.293
BALF IL-6 (pg/mL)	0.07 (0.02, 0.24)	0.08 (0.03, 0.22)	-0.964	0.335
BALF IL-8 (pg/L)	1.24 (0.63, 3.35)	1.26 (0.64, 3)	-0.357	0.721
BALF IL-10 (pg/mL)	1.84 (0.14, 3.78)	1.22 (0, 4.42)	-0.002	0.999
BALF IL-12 (pg/mL)	0 (0, 1.45)	0 (0, 0.93)	-0.818	0.413
BALF IL-17 (pg/mL)	10.01 (0, 24.26)	9.3 (0, 21.53)	-0.057	0.955
BALF TNFα (pg/mL)	0.82 (0, 2.37)	0.53 (0, 2.2)	-0.937	0.349
BALF γ-IFN (pg/mL)	3.86 (1.72, 7.98)	3.89 (1.63, 9.93)	-0.554	0.579
BALF α-IFN (pg/mL)	1.62 (0.62, 5.27)	1.38 (0.72, 3.77)	-0.735	0.462
BALF Nucleated cell (n/uL)	1571 (824.5, 3286.5)	1633 (879, 3169)	-0.500	0.617
BALF NE (%)	76 (67.5, 86)	78 (67.75, 85)	-0.307	0.759
BALF LY (%)	7 (4, 11)	7 (4, 11)	-0.200	0.841
BALF MONO (%)	12 (6.5, 17)	12 (7, 16)	-0.338	0.736
Plastic bronchitis (%)	11 (13.6%)	25 (14.4%)	0.280	0.866
Pleural effusion (%)	8 (9.9%)	18 (10.3%)	0.013	0.908

Max Temp (maximum body temperature), WBC (white blood cell count), NE (neutrophil percentage), MONO (monocyte percentage), LY (lymphocyte percentage), HB (hemoglobin), PLT (platelet count), CRP (c-reactive protein), ALB (albumin), ALT (alanine aminotransferase), CK (creatinine kinase), CK-MB

(creatine kinase-MB isoenzyme), BUN (blood urea nitrogen), LDH (lactate dehydrogenase), FIB (fibrinogen), APTT (activated partial thromboplastin time), IL (interleukin), TNF α (tumor Necrosis Factor Alpha), γ -IFN (gamma Interferon), α -IFN (alpha Interferon), BALF (bronchoalveolar lavage fluid).

Table 2

Characteristics and univariate statistics of GMPP and SMPP in the training cohort. [n (%), M (P25, P75)].

Male (%)	GMPP	SMPP	x2 /t/Z	p
	47 (43.1%)	30 (46.2%)		
Age (year)	7 (5, 8.5)	7 (5, 8.5)	-0.094	0.925
Max Temp (°C)	39.2 (38.9, 39.8)	39.2 (38.9, 39.8)	-0.372	0.71
WBC (×10 ⁹ /L)	7.05 (5.83, 9.03)	7.66 (6.18, 10.51)	-1.633	0.102
NE (%)	60.53 ± 11.86	68.80 ± 10.32	4.665	< 0.01
MONO (%)	7.3 (6, 9.25)	6.5 (5.2, 8.1)	-2.021	0.043
LY (%)	30.65 ± 11.43	21.76 ± 9.41	-5.29	< 0.01
Hb (g/L)	125 (119, 130)	125 (120, 129.5)	-0.072	0.943
PLT (×10 ⁹ /L)	272 (217.5, 333)	259 (211.5, 351.5)	-0.037	0.97
CRP (mg/L)	10.47 (5.5, 20.48)	15.26 (6.14, 33.57)	-2.031	0.042
ALB (g/L)	42.21 ± 3.23	41.17 ± 3.04	-2.083	0.039
ALT(U/L)	16 (11.5, 21)	16 (13, 21)	-1.002	0.316
CK (U/L)	72 (53.5, 95.5)	78 (53, 108)	-0.254	0.8
CK-MB (U/L)	20 (16.15, 24.2)	19 (16.05, 24)	-0.94	0.347
BUN mmol/L	3.96 ± 1.04	3.58 ± 1.02	-2.295	0.023
LDH(U/L)	274 (233, 308.5)	278 (244.5, 340.5)	-1.422	0.155
FIB (g/L)	4.96 (4.28, 5.66)	5.09 (4.49, 6.23)	-1.518	0.129
APTT (S)	36.6 (33.75, 40.15)	36.5 (34.3, 41.2)	-0.94	0.347
PT (S)	12.6 (12.05, 13.2)	13 (12.3, 13.7)	-1.885	0.059
D-dimer (ug/L)	510 (425, 620)	690 (520, 930)	-5.433	< 0.01
IL-1 (pg/mL)	3.18 (1.87, 5.96)	4.83 (2.38, 8.75)	-2.844	0.004
IL-2 (pg/mL)	2.2 (1.41, 3.45)	2.86 (2.12, 4.22)	-2.593	0.01
IL-4 (pg/mL)	2.3 (0.67, 3.51)	3.33 (1.59, 4.73)	-2.887	0.004
IL-5 (pg/mL)	1.09 (0.61, 1.51)	1.98 (1.3, 4.88)	-6.296	< 0.01
IL-6 (pg/mL)	13.51 (9.9, 26.94)	35.08 (15.18, 68.13)	-4.898	< 0.01
IL-8 (pg/mL)	18.99 (13.44, 26.06)	27.21 (17.15, 37.24)	-3.125	0.002

Male (%)	GMPP	SMPP	x2 /t/Z	p
	47 (43.1%)	30 (46.2%)	0.152	0.697
IL-10 (pg/mL)	9.87 (7.02, 14.2)	13.9 (9.39, 17.44)	-3.246	0.001
IL-12 (pg/mL)	4.53 (2.28, 7.05)	5.92 (4.1, 9)	-2.891	0.004
IL-17 (pg/mL)	17.94 (8.8, 30.75)	22.84 (13.3, 41.06)	-2.048	0.041
TNFα (pg/mL)	2.32 (1.41, 4.11)	3.27 (2.26, 5.89)	-3.125	0.002
γ-IFN (pg/mL)	5.34 (3.49, 8.66)	7.04 (4.92, 11.99)	-2.82	0.005
α-IFN (pg/mL)	4.34 (2.81, 7.24)	7.09 (4.34, 11.82)	-3.721	< 0.01
BALF IL-1β (pg/mL)	90.35 (31.03, 390.55)	526.09 (109.09, 1185.26)	-4.835	< 0.01
BALF IL-2 (pg/mL)	7.94 (4.84, 11.37)	6.23 (3.21, 9.59)	-1.867	0.062
BALF IL-4 (pg/mL)	0 (0, 0.75)	0 (0, 1.67)	-0.933	0.351
BALF IL-5 (pg/mL)	0 (0, 0.17)	0.09 (0, 0.45)	-2.325	0.02
BALF IL-6 (pg/mL)	0.05 (0.03, 0.16)	0.16 (0.06, 0.48)	-4.718	< 0.01
BALF IL-8 (pg/L)	0.93 (0.52, 2.08)	3 (1.26, 5.26)	-5.762	< 0.01
BALF IL-10 (pg/mL)	0.75 (0, 2.73)	3.4 (0.68, 16.54)	-4.245	< 0.01
BALF IL-12 (pg/mL)	0 (0, 0.93)	0 (0, 1.07)	-0.723	0.47
BALF IL-17 (pg/mL)	7.63 (0, 16.92)	16.37 (1.73, 37.08)	-3.169	0.002
BALF TNFα (pg/mL)	0 (0, 1.37)	2.07 (0, 5.76)	-5.046	< 0.01
BALF γ-IFN (pg/mL)	3.36 (1.38, 6.15)	6.81 (2.46, 23.2)	-3.881	< 0.01
BALF α-IFN (pg/mL)	1.24 (0.72, 2.77)	1.44 (0.65, 7.02)	-1.023	0.306
BALF Nucleated cell (n/uL)	1404 (792, 2841)	2123 (1061, 3870.5)	-3.016	0.003
BALF NE (%)	78 (67.5, 85.5)	78 (68, 84)	-0.342	0.732
BALF LY (%)	7 (4, 11)	7 (4.5, 11.5)	-0.09	0.928
BALF MONO (%)	12 (7, 16)	12 (7, 17.5)	-0.674	0.5
Plastic bronchitis (%)	5 (4.6%)	20 (30.8%)	22.687	< 0.01
Pleural effusion (%)	4 (3.7%)	14 (21.5%)	14.018	< 0.01

Next, a LASSO regression model was developed to identify potential predictive factors from the training cohort (Fig. 1a), and the changes in regression coefficients for each independent variable at different λ values were subsequently visualized (Fig. 1b). Based on the results of LASSO regression, the following

variables were then excluded: CRP, plasma cytokines (IL-1 β , IL-2, IL-4, IL-8, IL-10, IL-12, IL-17, TNF α , γ -IFN, α -IFN), lavage cytokines (IL-5, IL-6, IL-10, TNF α , γ -IFN) and lavage cytology (nucleated cell count). The remaining variables, namely monocyte percentage, albumin, urea nitrogen, pleural effusion, lymphocyte percentage, D-dimer, plasma cytokines (IL-5, IL-6), lavage cytokines (IL-1 β , IL-8, IL-17) and plastic bronchitis bronchiolitis, were subsequently retained for further analysis using multifactorial logistic regression.

3.2 Identification of independent risk factors for SMPP

Multivariate logistic regression analysis revealed that D-dimer (OR = 1.003; 95% CI = 1.001–1.006; P = 0.003), IL-5 (OR = 3.654; 95% CI = 1.851–7.213; P < 0.01), IL-6 (OR = 1.029; 95% CI = 1.002–1.056; P = 0.032) and BALF levels of IL-8 (OR = 1.876; 95% CI = 1.309–2.69; P = 0.001) were significant independent risk factors associated with the development of SMPP (Table 3).

Table 3
Multivariate analysis of risk factors for SMPP in the training cohort.

Plastic bronchitis	P	OR	95%CI
	0.164	3.205	0.622–16.51
LY (%)	0.058	0.944	0.890–1.002
D-dimer (ug/L)	0.003	1.003	1.001–1.006
IL-5 (pg/mL)	< 0.001	3.654	1.851–7.213
IL-6 (pg/mL)	0.032	1.029	1.002–1.056
BALF IL-1 β (pg/mL)	0.165	1.001	1.000-1.002
BALF IL-8 (pg/L)	< 0.001	1.876	1.309–2.690
BALF IL-17 (pg/mL)	0.280	1.013	0.989–1.038
Constant	< 0.001	0.002	

3.3 Development and validation of SMPP’s predictive nomogram model

The nomogram prediction model for SMPP was developed using D-dimer, plasma levels of IL-5 and IL-6 as well as BALF levels of IL-8 as biomarkers (Fig. 2). The results of the ROC curve analysis were then found to be as follows: for the training set, the area under the curve (AUC) was 0.935 (95% CI: 0.901–0.969), while the sensitivity and specificity at the maximal Youden's index were 0.862 and 0.853, respectively (Fig. 3a). Similarly, for the validation set, the AUC was 0.928 (95% CI: 0.871–0.985), while the sensitivity and specificity at the maximal Youden's index were 0.967 and 0.765, respectively. For example, in a child with confirmed MPP, the following biomarker levels were recorded: a D-dimer level of

1,330 µg/L, plasma IL-5 and IL-6 levels of 1.39 pg/mL and 96.95 pg/mL, respectively as well as IL-8 levels of 0.615 pg/L in BALF samples. Furthermore, using the nomogram prediction model analysis, the assigned points for each risk factor were as follows: D-dimer (17 points), plasma IL-5 (7 points), plasma IL-6 (15 points), and BALF IL-8 (2 points). This resulted in a total score of 41 points which corresponded to an approximate probability of SMPP of 94.3%. Internal validation of the model was then performed using the bootstrap resampling method, and in this case, the calibration curves for the training (Fig. 3b) sets demonstrated strong agreement between the predicted probabilities and the actual outcomes, thus indicating high predictive accuracy. Additionally, the model's clinical utility was assessed using DCA. In this case, when the risk threshold in the training set ranged from 0% to 96%, the net benefit of the model's SMPP risk prediction was greater than that of both the non-intervention and full intervention strategies (Fig. 3c). Similarly, in the validation set, the model's predicted net benefit exceeded those of the non-intervention and full intervention methods when the threshold ranged from 0% to 90% (Fig. 3d). These results suggest that the nomogram prediction model exhibits robust predictive capability and clinical utility for assessing SMPP risk.

4 Discussion

In recent years, there has been a significant rise in the isolation of macrolide-resistant strains of MP, with the reported average prevalence rates of macrolide resistance reaching as high as 63% in Asia⁶. This increasing resistance complicates MPP management, thus placing more children at risk of progressing to SMPP. Consequently, early diagnosis and timely intervention are crucial for reducing the incidence of SMPP-related complications and lowering its associated mortality. In this study, a nomogram prediction model, developed based on D-dimer, plasma levels of IL-5 and IL-6 as well as BALF levels of IL-8, could effectively predict the occurrence of SMPP. As a result, this model may facilitate the early identification of high-risk patients and enhance timely adjustment of personalized treatment strategies.

In particular, the findings revealed that the GMPP and SMPP groups, for which the median ages ranged from 6 to 7 years, were not significantly different in terms of age, sex, and maximum body temperature. This aligns with the well-documented high prevalence of MPP in this particular age group⁷.

D-dimer, a specific degradation product of fibrin monomers cross-linked by activated factor XIII and subsequently hydrolyzed by plasmin, serves as a reliable marker of fibrinolysis. In addition, it is an important indicator for monitoring inflammation and severe infections⁸. The progression of MPP is often associated with coagulation system abnormalities, which are closely linked to disease outcomes⁹. Although the precise mechanism of MPP remains unclear, it is hypothesized that MP triggers the synthesis and secretion of various cytokines, leading to vascular endothelial cell damage as well as the accumulation of metabolites, such as D-dimer, which eventually lead to vascular obstructions¹⁰. A study by Liu et al. identified D-dimer levels exceeding 11.1 mg/L – and even those above 5.0 mg/L – as indicators for the early diagnosis of thrombosis in children with refractory MPP¹¹. Similarly, research by Li et al. noted a positive correlation between elevated levels of D-dimer and fibrin degradation products

and the severity of MPP. Specifically, D-dimer levels above 3.705 mg/L were identified as independent predictors of MPP complicated by necrotizing pneumonia in children¹². Additional evidence further supports the role of D-dimer as a reliable predictor of SMPP, with one study showing that it could exhibit greater sensitivity compared with N%, PLT, CRP and LDH. Indeed, when D-dimer levels exceeded 403 mg/L, the risk of MPP progressing to SMPP increased sevenfold compared with children having normal levels. Furthermore, elevated D-dimer levels were also strongly associated with a higher likelihood of developing pleural effusion as well as myocardial and hepatic damage in children with MPP¹³. Consistent with the above findings, multifactorial logistic regression analysis identified D-dimer levels as a significant risk factor for predicting SMPP. However, no significant correlations were observed with fibrinogen (FIB) and prothrombin time (PT). Altogether, these results underscore the importance of prompt coagulation testing in hospitalized children with MPP to monitor disease severity. Additionally, the early implementation of combination therapy involving anticoagulants should be considered for critically ill children as such measures may proactively prevent microthrombosis and reduce the risk of severe complications.

MP infection triggers the release of pro-inflammatory cytokines and chemokines in the respiratory tract, activating a diverse array of immune cells. MP primarily targets the lower respiratory tract of humans, adhering to host cell membranes via specialized apical structures. However, its membrane lipoproteins are recognized by toll-like receptors (TLRs) on alveolar macrophages, which, through a MyD88-dependent pathway, activate NF- κ B transcription factors. This activation subsequently leads to the production of various cytokines and chemokines, resulting in damage to airway mucosal epithelial cells and ultimately causing various complications^{14,15}. In this study, significantly elevated plasma cytokine levels (IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, TNF α , γ -IFN and α -IFN) were noted in the SMPP group compared with the GMPP group. Among these, plasma IL-5 and IL-6 emerged as key indicators for predicting progression to SMPP. Furthermore, IL-5 and IL-6, secreted by T helper 2 (Th2) cells, function as soluble pro-inflammatory and immunomodulatory factors. Indeed, IL-5 was shown to not only influence eosinophils but also to enhance their bactericidal capacities by promoting the formation of extracellular traps *in vitro*. As such, it plays a critical role in the early stages of infection response¹⁶. Additionally, IL-5 impacts structural cells, such as airway epithelial cells and fibroblasts, which are pivotal in airway remodeling¹⁷. In this context, research by Esposito et al. reported that, among MPP patients, those experiencing wheezing symptoms had significantly elevated levels of IL-5¹⁸. MPP infection can also increase the gene expression and protein secretion of IL-6¹⁹, which can serve as an early indicator for assessing MPP's severity^{20–22}. In fact, reports suggest that elevated IL-6 levels tend to be particularly notable in MPP patients with pulmonary necrosis²³. The current findings align with these observations, suggesting that plasma levels of IL-5 and IL-6 are critical for understanding the pathogenesis of MP infection. Furthermore, these cytokines may represent significant targets for managing SMPP progression.

While predicting SMPP using plasma cytokines is more clinically convenient, lavage cytokines often provide a more accurate reflection of local inflammation. In this context, Deng et al. reported

significantly higher levels of IL-6, IL-10 and TNF- α in the BALF of severe MPP cases compared with mild MPP cases²⁴. The results further demonstrated significantly elevated levels of IL-1 β , IL-5, IL-6, IL-8, IL-10, IL-17, TNF- α , γ -IFN and nucleated cell counts in SMPP patients compared with the GMMP group. However, BALF levels of IL-8 exhibited the most significant differences between the two groups, thus suggesting it as a valuable biomarker for the early diagnosis and assessment of SMPP. One major pathological feature of MPP is the perivascular infiltration of plasma-rich lymphocytes in the lungs, along with large numbers of macrophages, neutrophils and lymphocytes in the alveolar spaces²⁵. IL-8, produced by macrophages, acts as a chemokine for neutrophils¹⁴. Indeed, elevated IL-8 levels in lavage fluid enhance neutrophil infiltration, thereby promoting further recruitment through the activation and chemotaxis of polymorphonuclear leukocytes. Overall, this neutrophil accumulation may contribute to the progression and severity of SMPP.

In China, flexible bronchoscopy with BAL has been increasingly utilized in the management of children with MPP, particularly in tertiary referral centers. At our institution, bronchoscopy is routinely performed in cases suspected of progressing to SMPP, those refractory to empirical antibiotic therapy, or when complications such as atelectasis, necrotizing pneumonia, or airway obstruction are present. BAL enables direct sampling of the lower respiratory tract, allowing accurate pathogen identification and quantification of local inflammatory responses that may not be fully reflected by peripheral blood markers. Accordingly, biomarkers derived from BAL fluid, such as cytokines, may offer unique insights into the severity of pulmonary inflammation and facilitate early risk stratification. Nevertheless, it must be acknowledged that bronchoscopy is an invasive procedure requiring specialized equipment and expertise; it is not universally performed for all children with MPP, especially in resource-limited settings or regions where less invasive diagnostic approaches are preferred. Therefore, although models incorporating BAL-derived parameters may demonstrate high predictive accuracy in selected populations, their generalizability to broader clinical contexts remains limited.

The nomogram prediction model developed in this study is simple, intuitive, and scientifically valid. It effectively quantifies individual clinical risk by integrating multiple factors and demonstrates satisfactory discriminative ability and accuracy. However, this study has several limitations. First, a major practical challenge in applying our nomogram clinically is the difficulty of obtaining BALF specimens, as BALF IL-8—a key biomarker in the model—requires collection via an invasive procedure such as bronchoscopy. To address this limitation and improve real-world applicability, we propose a hierarchical early warning strategy that prioritizes serum-based screening and uses BALF-based validation as a complementary step. Specifically, upon hospital admission, serum D-dimer, IL-5, and IL-6 are routinely measured within 24 hours of enrollment, enabling risk score calculation using only serum indicators. For most cases, BALF IL-8 is not mandatory for initial screening; rather, it serves as an adjunctive verification tool for patients who already meet clinical indications for bronchoscopy (e.g., those with suspected severe airway involvement). This approach enhances clinical operability while preserving the model's predictive sensitivity, thereby securing a critical time window for timely interventions such as anticoagulation and immunomodulation. For high-risk patients at risk of progressing to severe pneumonia, we recommend

implementing proactive therapeutic strategies. These include performing drug resistance gene analysis to guide the selection of targeted antibiotics, with timely escalation of antimicrobial therapy when indicated. Early immunomodulatory interventions should be initiated, such as glucocorticoid administration (e.g., methylprednisolone), to mitigate cytokine storm. Close and dynamic monitoring of key laboratory parameters—including inflammatory markers and oxygenation status—is essential. If clinical deterioration persists or the response to initial therapy is inadequate, treatment should be intensified with methylprednisolone pulse therapy, supplemented by intravenous immunoglobulin (IVIG) if clinically warranted. Additionally, the possibility of undetected mixed infections in some cases cannot be excluded. To overcome these limitations, future research should focus on long-term, multicenter, large-sample prospective studies that could provide a robust theoretical basis for the early identification, diagnosis, and intervention of SMPP in clinical practice.

5 Conclusion

In conclusion, the nomogram prediction model developed in this study can effectively estimate the probability of SMPP occurrence using biomarkers including D-dimer, plasma IL-5, plasma IL-6, and BALF IL-8. The model demonstrated strong predictive performance in both the training and validation sets: in the training set, the AUC was 0.935 (95% CI: 0.901–0.969), with a sensitivity of 0.862 and specificity of 0.853 at the maximal Youden index; in the validation set, the AUC was 0.928 (95% CI: 0.871–0.985), with a sensitivity of 0.967 and specificity of 0.765 at the maximal Youden index. These findings highlight the model's excellent discriminatory power and accuracy, underscoring its clinical applicability in children who undergo bronchoscopy. For high-risk SMPP patients, clinicians are encouraged to dynamically monitor changes in clinical status, promptly assess severity, and implement early interventions to reduce the risks of sequelae and mortality.

Declarations

Author Contributions

Shuang-Shuang Guo: conceptualization, supervision, writing – original draft, writing – review and editing; Da-Yan Wang: methodology, software, investigation, validation; Pan-Jian Lai: methodology, software, formal analysis; Peng Lou: methodology, software, formal analysis, visualization; Xiao-Bin Li: investigation, validation, visualization, project administration, writing – review and editing; Jie-Jie Guo: investigation, formal analysis, validation; Dao-Quan Fang: investigation, data curation, resources; Peng-Fei Yu: methodology, validation, visualization, resources.

Ethical Declaration

His retrospective observational study was approved by the **Medical Ethics Committee of Jinhua Maternal and Child Health Care Hospital**, Approval No. 2024KY083. The cohort consisted of children diagnosed with MPP between April 2023 and June 2024 whose data were reviewed after routine clinical care had been completed. No prospective enrolment, intervention allocation, or additional research

sampling was performed. Written guardian consent had been obtained for clinically indicated bronchoscopy and bronchoalveolar lavage. The ethics committee waived additional written informed consent for the retrospective analysis of routine clinical data. The whole research was conducted in strict accordance with the Declaration of Helsinki. Human Ethics declaration: applicable; Consent to Participate declaration: waived by the institutional ethics committee for this retrospective study of existing routine clinical data.

Funding Declaration

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Data Availability Statement

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

Conflicts of Interest

The authors declare no conflicts of interest.

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Figures

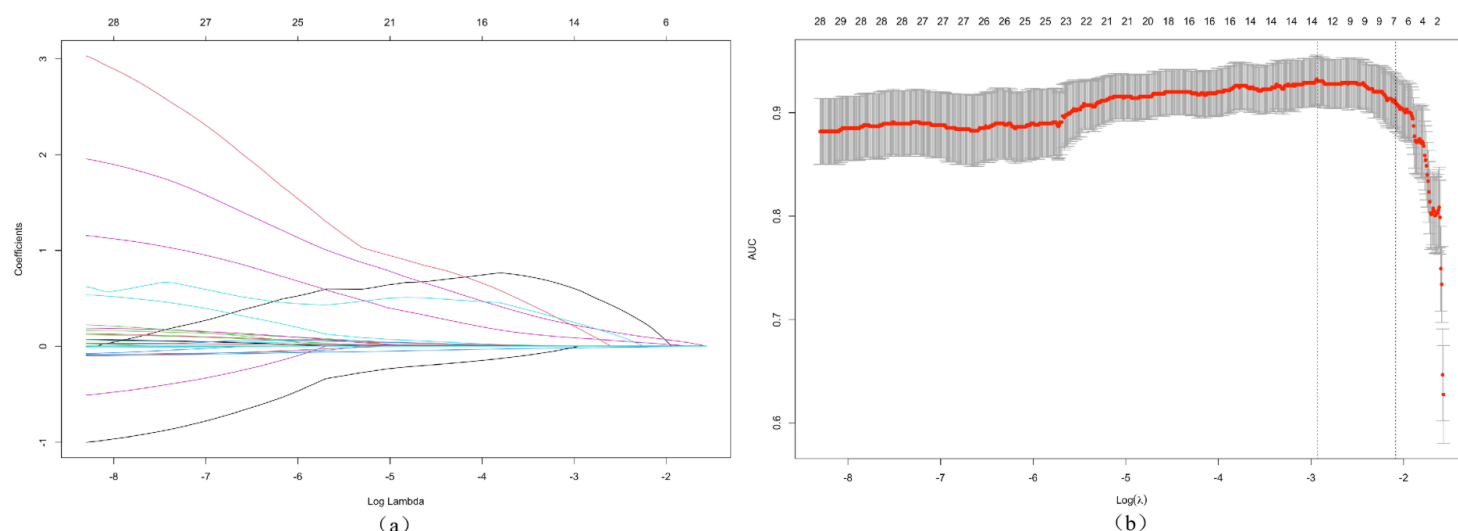


Figure 1

LASSO regression for screening predictive risk factors. (a) Screening of candidate predictive risk factors using LASSO regression analysis. (b) LASSO coefficient profiles plotted against $\log(\lambda)$. Partial

likelihood deviance is displayed, and the vertical dashed line at the minimum log (lambda) marks the optimal lambda value for variable selection.

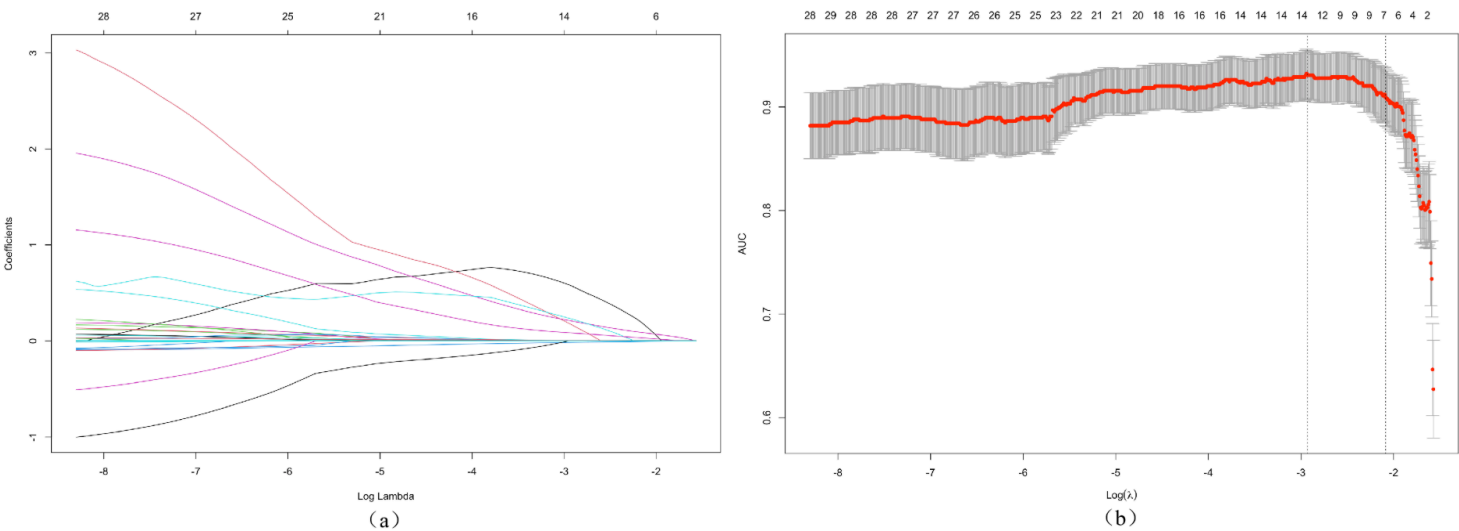


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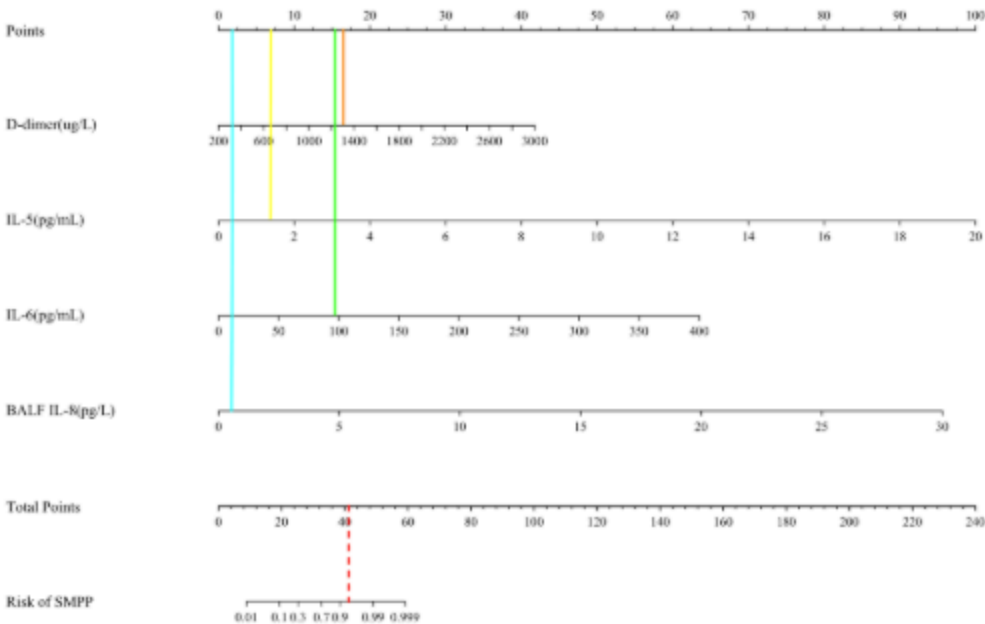


Figure 2

A nomogram prediction model of SMPP in children. D-dimer, plasma levels of IL-5 and IL-6, as well as BALF levels of IL-8 represent the measured values. The variable scores were summed to obtain a total score for the probability of SMPP.

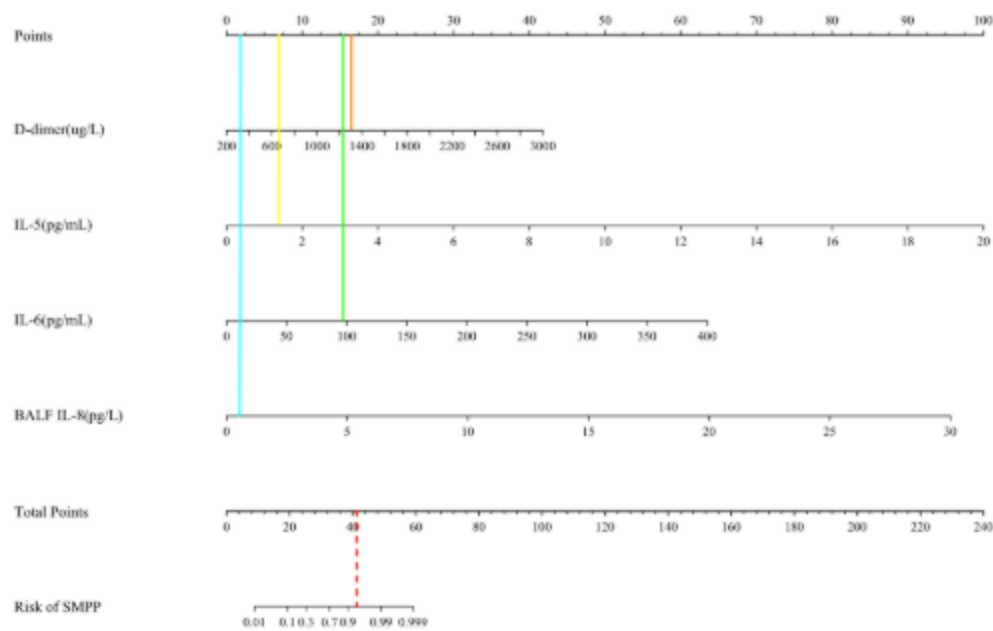


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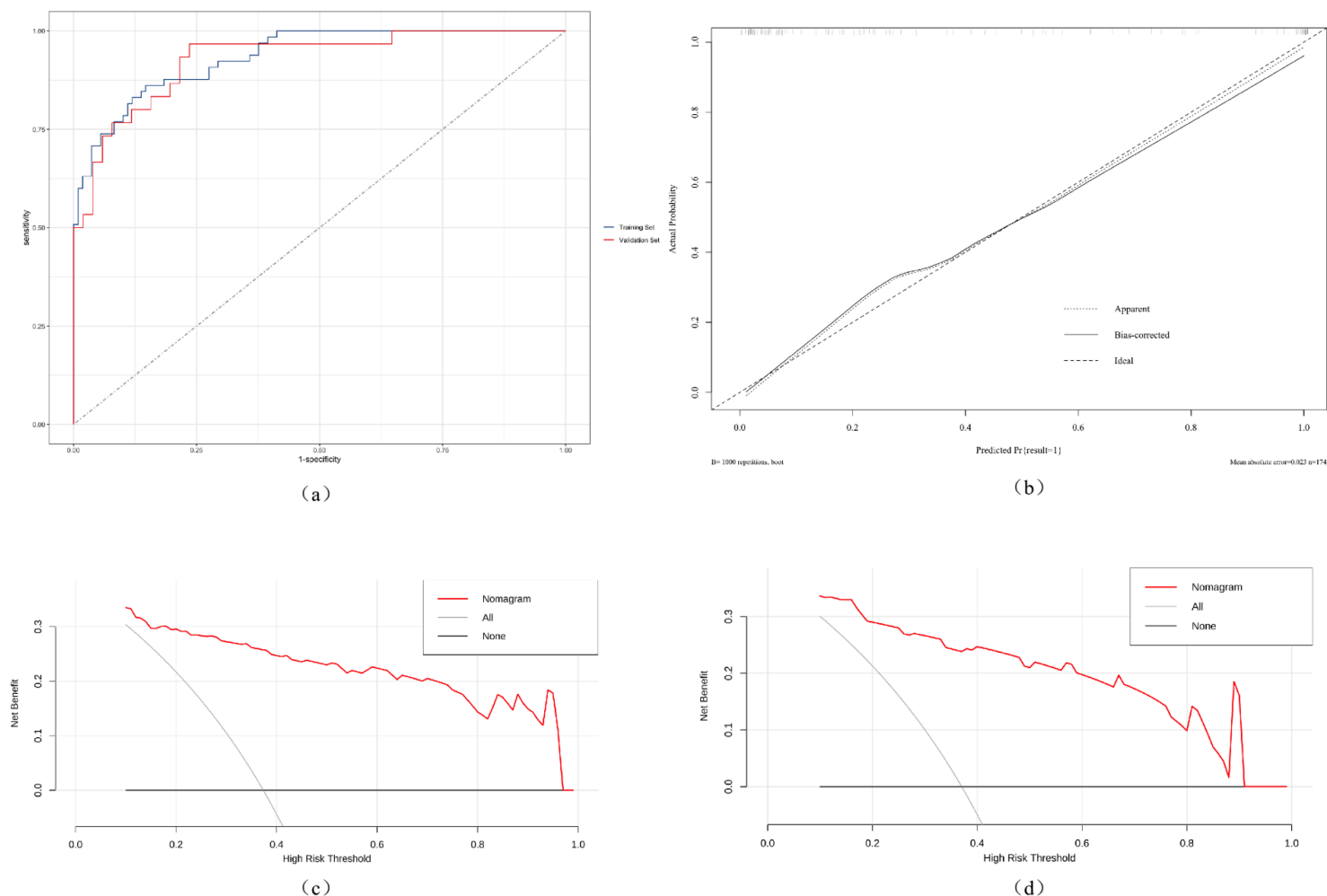


Figure 3

Performance evaluation of the predictive nomogram for children with severe Mycoplasma pneumoniae pneumonia (SMPP). (a) Nomogram prediction model; the AUC was 0.935 in the training set and 0.928 in the validation set, indicating good discriminative ability. (b) Calibration curve of the nomogram in the training set. The “Ideal” line represents perfect prediction; “Apparent” shows the original prediction curve of the nomogram; “Bias-corrected Apparent” is the curve adjusted for raw bias; “Bias-corrected” is the curve further corrected for overfitting. Prediction accuracy improves when the curve is closer to the Ideal line. (c) Decision curve analysis (DCA) of the nomogram in the training set. The “Nomogram” curve presents the net benefit of the model; “All” represents the net benefit of intervening all patients; “None” represents no intervention. (d) DCA of the nomogram in the validation set.

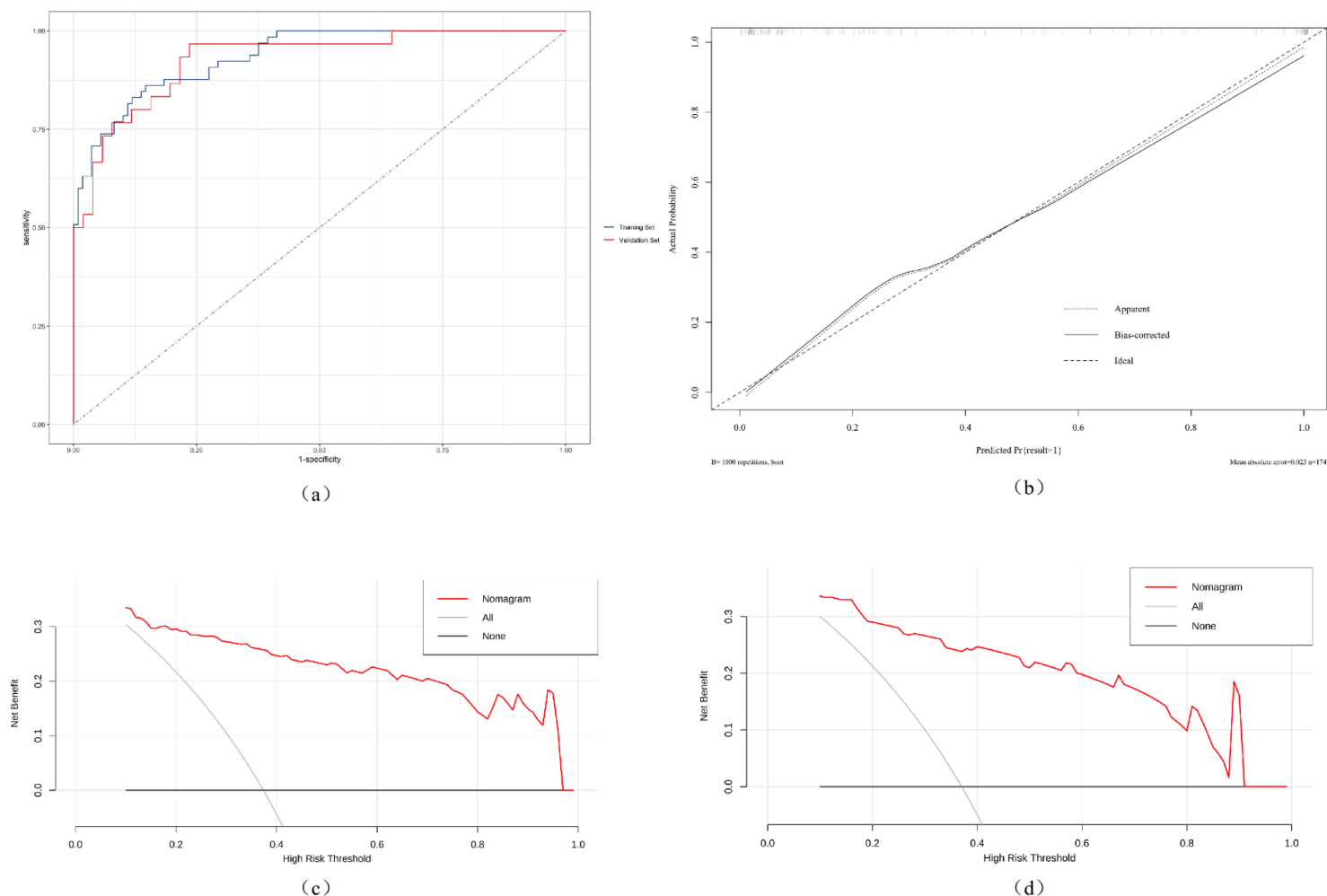


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