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Original Article

Construction and Validation of an Early Identification Model for Refractory *Mycoplasma pneumoniae*-Positive Lobar Pneumonia

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Abstract

Objective This study analyzed the relationship between clinical parameters and prognosis in children with *Mycoplasma pneumoniae* (MP)-positive lobar pneumonia and developed an early identification model.

Methods Relevant clinical parameters were collected. Patients were then categorized into two groups based on their length of hospital stay: 116 cases in the refractory group ($\geq$10 days) and 94 cases in the non-refractory group ($<$10 days). A univariate analysis of variance and binary logistic regression were utilized to develop a predictive model, accompanied by the construction of a nomogram. The model's performance was assessed using receiver operating characteristic (ROC) curves, diagnostic calibration curves, and decision curve analysis (DCA) curves. Furthermore, clinical data from 100 additional cases of MP-positive lobar pneumonia in children treated at other centers were gathered for external validation of the model.

Results Binary logistic regression analysis identified four independent risk factors for prolonged disease duration in children with MP-positive lobar pneumonia: erythrocyte sedimentation rate (ESR), globulin, lactate dehydrogenase (LDH), and SF. We constructed a nomogram model based on these risk factors. In the training set, the area under the curve (AUC) was 0.869 (95% CI: 0.822–0.917), with a sensitivity of 68.54% and a specificity of 82.61%. For the test set, the AUC increased to 0.918 (95% CI: 0.866–0.971), demonstrating a sensitivity of 91.67% and a specificity of 78.69%. The DeLong test results indicated that the difference in AUC between the two datasets was not statistically significant ($D = -1.724$, $p = 0.086$). Calibration curve analysis confirmed that the nomogram model exhibited a good fit in both the training set (Hosmer–Lemeshow test, $\chi^2 = 8.120$, $p = 0.421$) and the validation set (Hosmer–Lemeshow test, $\chi^2 = 14.601$, $p = 0.067$). DCA further demonstrated that the model performed significantly across a range of threshold probabilities.

Conclusion The nomogram model developed for predicting refractory MP-positive lobar pneumonia in children has significant clinical value and can guide personalized treatment strategies.

Keywords
- model
- MP
- refractory
- lobar pneumonia
- pediatric

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Introduction

Mycoplasma pneumoniae pneumonia (MPP) is the most common type of community-acquired pneumonia in children aged 5 and older in China. It typically occurs every 3 to 5 years and has shown an increasing trend in recent years.[1,2] Notably, the outbreak of MPP in 2023 occurred for the first time after the coronavirus disease 2019 (COVID-19) pandemic. During the pandemic, prolonged home isolation may have weakened children's immunity. Additionally, the administration of COVID-19 vaccines has altered their immune status to some extent.[3] This current cohort of MPP patients shows a clear trend toward younger age groups, with a significant increase in severe cases, including MPP infections in children under 5 years and *M. pneumoniae* (MP)-positive lobar pneumonia. Besides causing symptoms like fever and cough, MPP can affect multiple systems, including the nervous, circulatory, integumentary, hematologic, urinary, and digestive, leading to damage in these organs. Drug resistance in *Mycoplasma* and severe MP present significant challenges for pediatricians.[4,5]

According to the pathological morphology of pneumonia caused by MP infection, it can be classified into lobar pneumonia, interstitial pneumonia, and bronchopneumonia. Lobar pneumonia involves inflammation accumulating in one lobe or segment of the lung. Studies have found that children with MP-positive lobar pneumonia present with acute onset and severe symptoms. Even after treatment with macrolide antibiotics, their condition may progress to refractory MPP, with the possibility of resulting in permanent lung atelectasis.[6] Given the significant increase in lobar pneumonia cases during this outbreak of MP, early identification of children with refractory or prolonged lobar pneumonia is crucial for improving their prognosis through targeted treatment. Currently, there is limited research on the early assessment of MP-positive lobar pneumonia. Therefore, this study aimed to collect and analyze relevant clinical data of children with MP-positive lobar pneumonia treated in our department, using binary logistic regression to establish a risk prediction model, thereby providing scientific evidence for early clinical identification and intervention.

Materials and Methods

We collected clinical data from 210 children with MP-positive lobar pneumonia treated at our center from April 1, 2023, to December 31, 2023, along with data from another center involving 100 cases. We based our diagnostic and treatment criteria on the 2023 edition of the Guidelines for the Diagnosis and Treatment of *Mycoplasma pneumoniae* Pneumonia in Children.[7,8] The 210 children from our center formed the training group, while the 100 children from the other center formed the validation group.

We collected samples using a sterile throat swab from both sides of the tonsils and the pharyngeal wall. These samples were then placed in a sterile tube containing normal saline. The tube was securely sealed and promptly sent to the laboratory for analysis. PCR amplification was conducted according to the manufacturer's instructions, with a positive result for MP determined by a Ct value exceeding the threshold for the target gene. Additionally, all children underwent chest X-rays or CT scans upon admission to evaluate for lobar pneumonia radiographically. Exclusion criteria included (1) the presence of chronic lung diseases, bronchiectasis, bronchiolitis obliterans, pulmonary tuberculosis, liver or kidney diseases, cardiovascular diseases, or primary or secondary immunodeficiency; (2) prior treatment with glucocorticoids before admission; and (3) incomplete clinical data or unfinished treatment course. We divided the enrolled children into two groups based on their hospital stay: a refractory group with 116 cases ($\geq$10 days) and a non-refractory group with 94 cases ($<$10 days).

This study obtained approval from the Ethics Review Committee of Suzhou Hospital Affiliated with Anhui Medical University with informed consent from the guardians of the children.

We systematically collected clinical data, including age, gender, duration of hospitalization, and the location of pneumonia lesions. Additionally, we noted concurrent infections with other pathogens and recorded the performance of bronchoalveolar lavage using bronchoscopy. We measured various laboratory parameters, including hemoglobin (Hb), white blood cell count (WBC), lymphocyte count, monocyte count, neutrophil count, and platelet count. Other parameters included high-sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), procalcitonin, alanine transaminase, aspartate transaminase, globulin, albumin, lactate dehydrogenase (LDH), serum ferritin (SF), activated partial thromboplastin time, prothrombin time, fibrinogen, D-dimer (D-D), and fibrin degradation products.

We used a standardized method with throat swabs to test all children for co-infections with several pathogens, including respiratory syncytial virus, adenovirus, Coxsackievirus B, parainfluenza virus, influenza A virus, influenza B virus, and human rhinovirus. In the refractory group ($n = 116$), we identified the following infections: one adenovirus, one influenza A, five influenza B, four Coxsackievirus B, two parainfluenza, one human rhinovirus, and one respiratory syncytial virus. In the non-refractory group ($n = 94$), we found one adenovirus, two influenza A, three parainfluenza, four influenza B, five Coxsackievirus B, one human rhinovirus, and one respiratory syncytial virus. There was no significant difference in co-infection rates between the two groups ($p > 0.05$; ►**Supplementary Table S1** [available in the online version only]).

Statistical analyses for this study were conducted using R version 4.2.1. Normally distributed continuous data are presented as mean $\pm$ standard deviation. Intergroup differences were analyzed using the independent samples *t*-tests. Non-normally distributed data are reported as M (P25, P75), and intergroup differences were evaluated using the Wilcoxon rank-sum test. Categorical data were expressed as counts (%), and intergroup differences were assessed using the chi-square test. Initially, we conducted a univariate logistic regression analysis. Significant variables were then included in a multivariable logistic regression model using

stepwise regression to identify independent influencing factors. The rms package in R was employed to develop a nomogram prediction model, and the area under the receiver operating characteristic curve (AUC) was calculated to assess the model's performance. Calibration plots were generated to evaluate model fit, and decision curve analysis (DCA) was performed to determine its clinical utility. A *p*-value of less than 0.05 was deemed statistically significant.

Results

This study included 210 cases of MP-positive lobar pneumonia in children, comprising 111 males and 99 females. The children's ages ranged from 8 months to 13 years, with a median age of 6.0 years (interquartile range: 4.0–7.0 years). Hospitalization duration varied from 4 to 20 days, with a mean of 10.0 days (range: 8.0–12.0 days). Additionally, the validation group consisted of 100 cases of MP-positive lobar pneumonia, including 56 males and 44 females. The ages of these children ranged from 8 months to 13 years, with a mean age of 5.0 years (interquartile range: 3.3–7.8 years).

Patients in the refractory group were younger than those in the non-refractory group, and this difference was statistically significant ($p < 0.05$). Additionally, they had a lower proportion of bronchoalveolar lavage via bronchoscopy, lower levels of HB and globulin, and higher levels of hs-CRP, ESR, LDH, and SF, all of which were statistically significant ($p < 0.05$; ►**Table 1**).

We conducted an additional analysis by including the significant variables identified in the univariate logistic regression in a multivariate logistic regression model. The results indicated that ESR, globulin, LDH, and SF were independent risk factors affecting the length of hospitalization in children with MP-positive lobar pneumonia ($p < 0.05$; ►**Table 2**).

Four independent factors were identified through multivariate logistic regression analysis of the training set. These factors were used to create a nomogram model for differential diagnosis (►**Fig. 1**). Each influencing factor was assigned a score based on its contribution to the multivariate logistic regression model. The individual scores were summed to obtain a total score. This total score was then used to calculate the predicted risk probability for the children.

The nomogram model (►**Fig. 1**) indicates that children with low globulin levels and high ESR, LDH, and SF levels are at increased risk for prolonged treatment duration.

Receiver operating characteristic (ROC) curve analysis was conducted using the identified independent risk factors to predict refractory MP-positive lobar pneumonia. The results showed the following AUC values: ESR was 0.616 (95% CI: 0.540–0.692), globulin was 0.775 (95% CI: 0.712–0.839), LDH was 0.649 (95% CI: 0.574–0.724), and SF was 0.727 (95% CI: 0.659–0.795; ►**Fig. 2A**). The AUC for the nomogram predictive model in the training set was 0.869 (95% CI: 0.822–0.917), with a sensitivity of 68.54% and a specificity of 82.61%. Similarly, in the test set, the AUC was 0.918 (95% CI: 0.866–0.971), which indicated a sensitivity of 91.67% and a specificity of 78.69%. The DeLong test showed no significant difference in diagnostic performance between the two datasets ($D = -1.724$, $p = 0.086 > 0.05$). This indicates that the model performed robustly in both the training and test sets (►**Fig. 2B**).

The accuracy of the predictive model was assessed using calibration curves. The goodness-of-fit analysis for the nomogram indicated a strong correlation between predicted risks and actual outcomes in the training set (Hosmer–Lemeshow test: $\chi^2 = 8.120$, $p = 0.421 > 0.05$; ►**Fig. 3A**). In the test set, the model also demonstrated a good fit, as indicated by the Hosmer–Lemeshow test results, which showed a satisfactory correlation between predicted risks and actual outcomes ($\chi^2 = 14.601$, $p = 0.067 > 0.05$; ►**Fig. 3B**).

We analyzed the nomogram predictive model using the DCA curve. The results showed that setting the probability threshold (Pt) at ≥5% gradually increased the net benefit for patients compared with conducting additional tests on all children. In clinical practice, when Pt is set at 5%, the predictive model can identify an additional five cases of refractory MP-positive lobar pneumonia for every 100 individuals screened, without increasing the rate of false positives (►**Fig. 4A, B**).

Discussion

MPP is common among preschool and school-aged children. The peak of MPP in 2023 marked the first occurrence after the COVID-19 pandemic, bringing forth new epidemiological features. Notable changes include an increase in cases among infants and toddlers aged 1 to 3 years, a higher prevalence of macrolide-resistant cases, and a rise in children with extensive pulmonary consolidation. These developments put patients at risk for severe illness, resulting in longer hospital stays and higher medical costs, which create new challenges for clinical management.[5] Lobar pneumonia is an acute inflammation of the lungs that affects one or more segments of lung tissue. It is mainly characterized by the presence of diffuse alveolar exudation. Recently, the incidence of MP-positive lobar pneumonia in children has significantly increased. This increase was especially notable in 2023. Some patients experienced longer treatment durations and developed multiorgan damage, along with persistent pulmonary atelectasis, leading to poorer prognoses. Early recognition and targeted treatment of children with MP-positive lobar pneumonia who require extended treatment durations are crucial for improving disease outcomes.[9]

The causes of pediatric MPP are still not well understood. Some studies indicate that the disease's onset and progression are linked to abnormal immune system activation.[10] The inflammatory response is closely associated with the occurrence and development of pediatric MPP. Both ESR and LDH are widely recognized clinical indicators for assessing infection and inflammation, with their elevations positively correlating with the severity of the inflammatory response. In our predictive model, these factors were identified as independent risk factors for refractory lobar pneumonia in children with positive MP tests. While ESR exhibits high sensitivity, it has low specificity. Infection caused by MP

Table 1 Comparison of clinical data between the two groups

Features	Category	Total	Duration of hospitalization		Statistics	*p*-Value
			≥10 days	<10 days		
All		210	116	94		
Gender					0.0557	0.455
	Male	99	52	47		
	Female	111	52	47		
Location					1.466	0.480
	Left	75	38	37		
	Right	110	62	48		
	Both	25	16	9		
Other pathogens					1.068	0.301
	Yes	32	15	17		
	No	178	101	77		
BAL					4.220	0.040
	Yes	62	41	21		
	No	148	75	73		
ALL		210	116	94		
Age (years)			5 (5, 6.8)	6 (4, 8)	6,856.0	<0.001
HB (g/L)			124 (117, 132)	128 (121, 132)	2,083.0	0.039
WBC ($\times 10^9$/L)			8.2 (6.1, 10.9)	8.1 (6.6, 9.9)	5,262.0	0.865
Lymphocyte ($\times 10^9$/L)			2.4 (1.7, 3.1)	2.1 (1.7, 3.0)	4,785.0	0.355
Monocyte ($\times 10^9$/L)			0.61 (0.41, 0.86)	0.59 (0.49, 0.8)	5,316.0	0.739
Neutrophil ($\times 10^9$/L)			5.0 (3.5, 7.0)	5.2 (3.8, 6.9)	5,270.5	0.822
Platelet ($\times 10^9$/L)			285 (230, 353)	301 (265, 366)	6,140.0	0.062
Hs-CRP (mg/L)			14.5 (6.8, 30)	9.6 (4.8, 15.8)	3,767.0	0.000
ESR (mm/h)			21.5 (14, 28)	18 (13.8, 22)	−2.826	0.005
PCT (μg/L)			0.13 (0.08, 0.28)	0.11 (0.06, 0.18)	3,612.5	0.063
ALT (U/L)			18 (16, 24)	19 (16, 22)	5,198.0	0.936
AST (U/L)			35 (29, 39.7)	32 (28, 40)	4,419.5	0.056
Globulin (g/L)			27.3 (25, 29.3)	28.4 (25.7, 32.1)	8,184.0	0.000
Albumin (g/L)			42.2 (40.1, 45)	43.7 (41.6, 45.5)	6,022.5	0.063
LDH (U/L)			306 (269, 355)	277 (245, 316)	3,674.5	0.000
SF			238 (191, 278)	184 (148, 224)	−6.104	0.000
APTT			38.1 (33.7, 42.3)	36.8 (34.3, 38.9)	1,980.5	0.274
PT			13.5 (12.7, 14.4)	13.3 (12.3, 14.0)	1,941.5	0.205
FIB			4.5 (3.9, 5.1)	4.3 (3.7, 5.0)	2,037.5	0.401
D-D			0.8 (0.6, 1.2)	0.9 (0.7, 1.2)	2,366.0	0.541
FDP			2.8 (2.0, 3.8)	2.7 (2.3, 3.4)	2,177.0	0.824

Abbreviations: ALT, alanine transaminase; APTT, activated partial thromboplastin time; AST, aspartate transaminase; D-D, D-dimer; ESR, erythrocyte sedimentation rate; FDP, fibrin degradation product; FIB, fibrinogen; HB, hemoglobin; hs-CRP, high-sensitivity C-reactive protein; LDH, lactate dehydrogenase; PCT, procalcitonin; PT, prothrombin time; SF, serum ferritin; WBC, white blood cell count.

leads to the release of inflammatory mediators, which speed up red blood cell sedimentation.[11] Prolonged and excessive inflammation in the lungs can damage tissues and cause cell death. This process subsequently releases LDH into the bloodstream.[12] Extensive research has been conducted on the ESR and LDH in relation to severe MPP (SMPP). Fan et al reported significant increases in hs-CRP, ESR, and LDH levels in children with resistant MPP.[13] Additionally, Jing and Lu demonstrated that CRP and LDH are independent risk factors for SMPP in children, which aligns with our findings.[14]

Table 2 Univariate and multivariate logistic regression analyses

Characteristics	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
ESR	0.952 (0.917–0.986)	0.008	0.941 (0.893–0.991)	0.014
Globulin	1.329 (1.219–1.463)	0.000	1.326 (1.200–1.487)	0.000
LDH	0.993 (0.988–0.997)	0.001	0.93 (0.988–0.998)	0.002
SF	0.985 (0.979–0.990)	0.000	0.983 (0.975–0.990)	0.000

Abbreviations: ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; SF, serum ferritin.

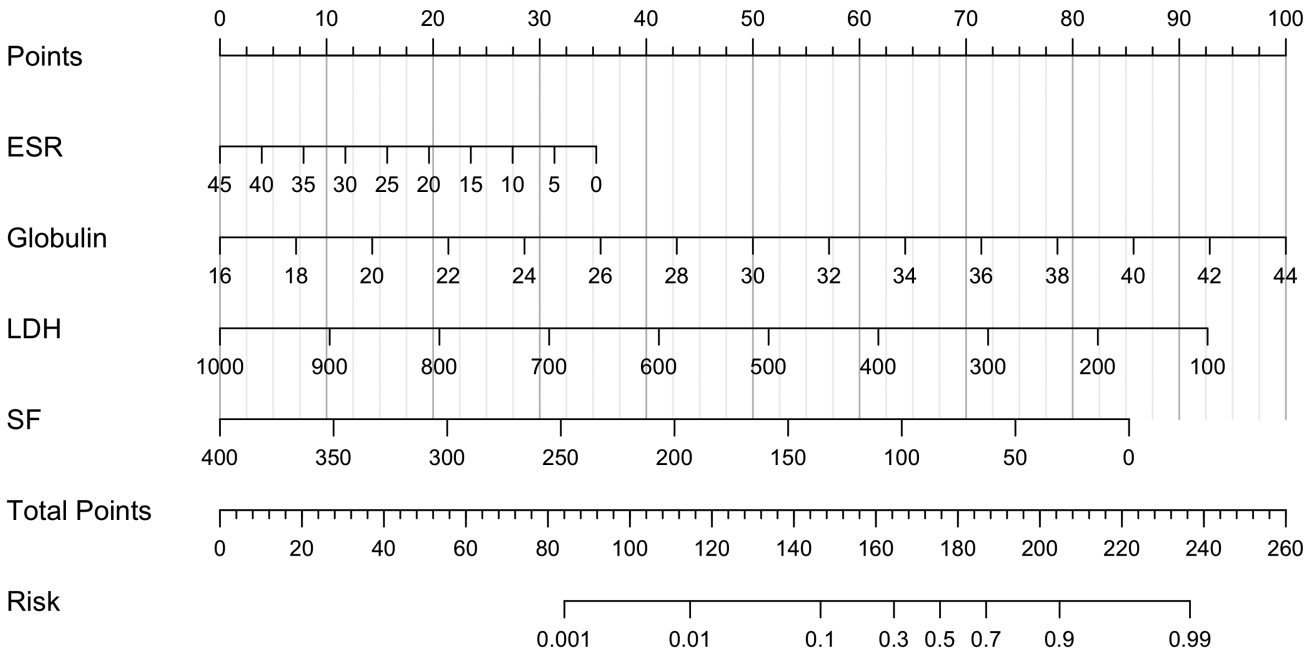

Fig. 1 A nomogram model for predicting refractory cases. A nomogram model to predict MP-positive lobar pneumonia was constructed based on the following four independent factors: ESR, globulin, LDH, and SF level. ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; MP, SF, serum ferritin.

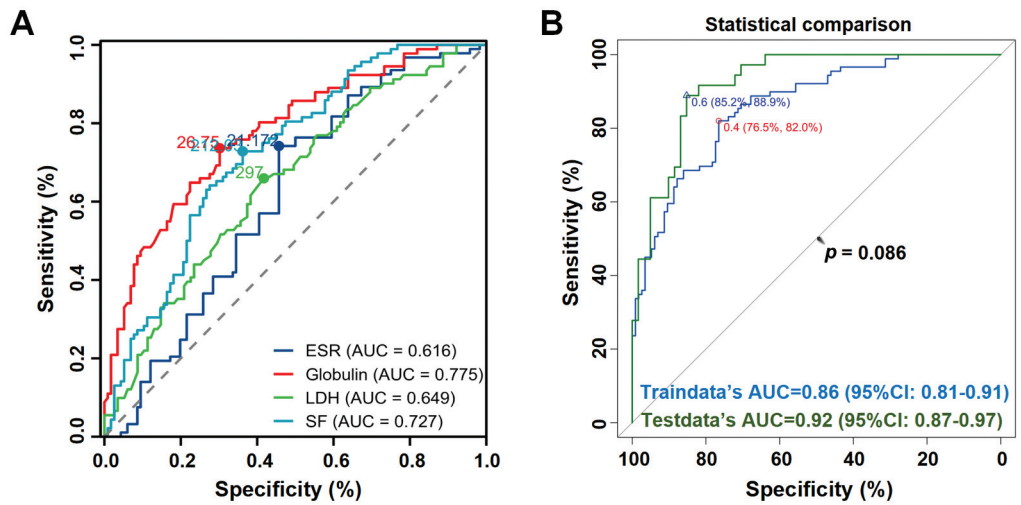

Fig. 2 ROC curve analysis results. (**A**) ROC curves illustrate the prediction of refractory *Mycoplasma pneumonia* in children based on ESR, globulin, LDH, and SF levels. (**B**) Assessment of the discriminative ability of the predictive model using ROC curves. AUC, area under the curve; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; MP; ROC, receiver operating characteristic (ROC); SF; serum ferritin.

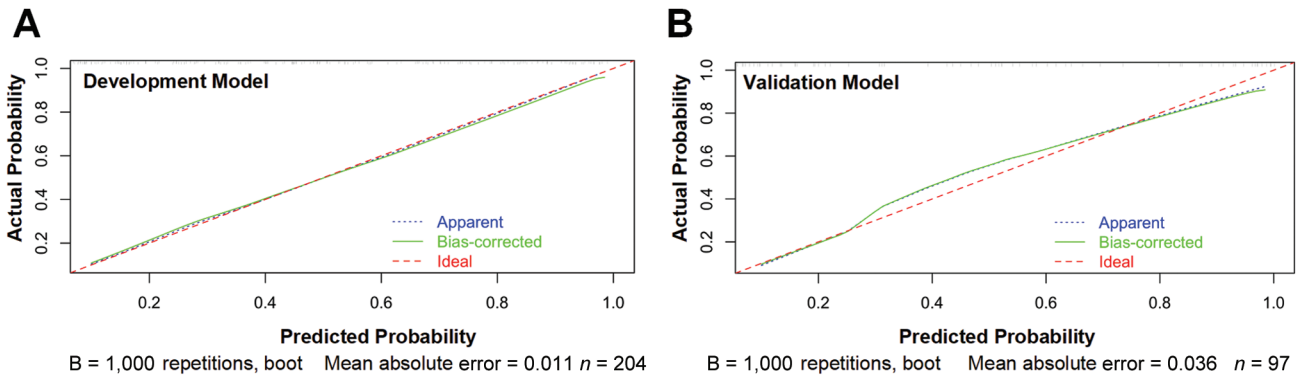

Fig. 3 Calibration curve evaluating the accuracy of the predictive model. (**A**) Development model. (**B**) Validation model.

There is currently a significant gap in research on early prediction models for refractory MP-positive lobar pneumonia in children. Most studies on refractory MPP have focused on developing predictive models using serum inflammatory markers, such as hs-CRP, ESR, and LDH. For instance, Chen et al developed an early prediction model incorporating D-D, hs-CRP, and LDH, while Liu et al included pleural effusion, LDH, and hs-CRP in their own predictive model for refractory MPP in children.[6,15] Along with these commonly used infection indicators, our model incorporates SF and globulin as predictive factors. SF is an acute-phase reactant protein that is synthesized and released in response to cytokines produced during inflammation. It plays a significant role in immune regulation.[16] Zhang et al reported that ferritin levels were significantly elevated in patients with SMPP compared with those with milder cases. Furthermore, studies have indicated a positive correlation between SF levels and both LDH and CRP in patients with SMPP, reinforcing the potential of SF as a valuable clinical predictor.[17–19] Globulin also serves as a critical predictive factor in our model. Humoral immunity primarily relies on immunoglobulins; when pathogens invade the body, B cells proliferate and differentiate into plasma cells upon antigenic stimulation, subsequently secreting large quantities of immunoglobulins to neutralize and eliminate the pathogens. The levels of immunoglobulins reflect the state of humoral immune function. MP infection can stimulate B cells to produce specific antibodies, which may exhibit partial antigenic overlap with various organs, including the heart, lungs, kidneys, and smooth muscle tissues. This overlap can lead to immune complex formation, resulting in damage to both the lungs and other organs, while dysregulated inflammatory factors may worsen the condition.[20,21] Wang et al found that IgG and IgA levels significantly increased in children with MPP following treatment, and these changes correlated with improvements in clinical symptoms. Additionally, miR-155 and miR-492 have been shown to regulate immune responses by enhancing immunoglobulin expression, thereby improving the patient's resistance to infection.[22–24] Our model further indicates that high immunoglobulin expression serves as a protective factor for children with refractory MP-positive lobar pneumonia, consistent with these research findings.

In conclusion, we created and validated a model to identify refractory MP-positive lobar pneumonia in children, based on four common clinical laboratory indicators. Additionally, we found that including a nomogram made the model more user-friendly. This model shows high discriminative ability, sensitivity, and specificity. It is applicable, accurate, and reliable in distinguishing between refractory and non-refractory MP-positive lobar pneumonia patients. However, our study has limitations, including a relatively small sample size for establishing the predictive model. Furthermore, prior studies have investigated the expression and clinical significance of non-coding RNAs,[22] cytokines,[4] and chemokines[25] in MPP. These findings encourage us to explore additional potential biomarkers and increase our sample size in future research. Our goal is to refine the predictive model and apply it to different pediatric subgroups, such as varying ages and underlying conditions, to improve its applicability and specificity.

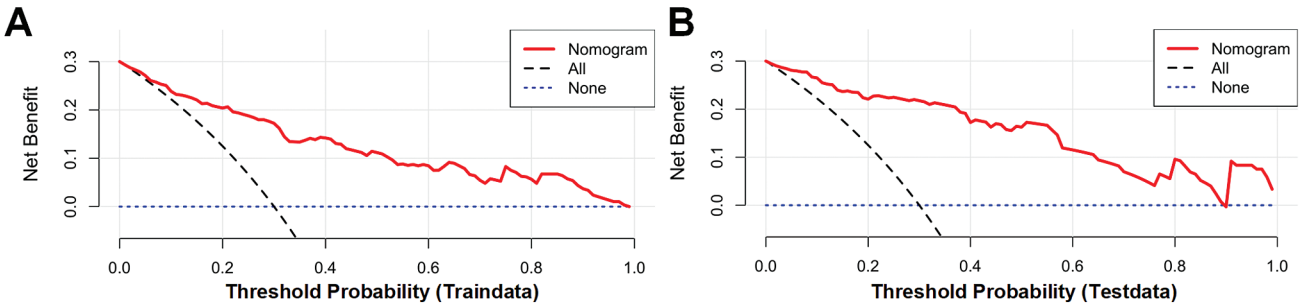

Fig. 4 DCA results (**A, B**). DCA assesses the predictive performance of the model in the validation and training cohorts. DCA, decision curve analysis.

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Conflict of Interest
None declared.

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