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ORIGINAL RESEARCH

Risk Prediction Model for Necrotizing Pneumonia in Children with *Mycoplasma pneumoniae* Pneumonia

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Objective: To analyze the predictive factors for necrotizing pneumonia (NP) in children with *Mycoplasma pneumoniae* pneumonia (MPP) and construct a prediction model.

Methods: The clinical data with MPP at the Children's Hospital of Kunming Medical University from January 2014 to November 2022 were retrospectively analyzed. Eighty-four children with MPP who developed NP were divided into the necrotizing group, and 168 children who did not develop NP were divided into the non-necrotizing group by propensity-score matching. LASSO regression was used to select the optimal factors, and multivariate logistic regression analysis was used to establish a clinical prediction model. The receiver operating characteristic (ROC) curve and calibration curve were used to evaluate the discrimination and calibration of the nomogram. Clinical decision curve analysis was used to evaluate the clinical predictive value.

Results: LASSO regression analysis showed that bacterial co-infection, chest pain, LDH, CRP, duration of fever, and D-dimer were the influencing factors for NP in children with MPP ($P < 0.05$). The results of ROC analysis showed that the AUC of the prediction model established in this study for predicting necrotizing MPP was 0.870 (95% CI: 0.813–0.927, $P < 0.001$) in the training set and 0.843 (95% CI: 0.757–0.930, $P < 0.001$) in the validation set. The Bootstrap repeated sampling for 1000 times was used for internal validation, and the calibration curve showed that the model had good consistency. The Hosmer-Lemeshow test showed that the predicted probability of the model had a good fit with the actual probability in the training set and the validation set (P values of 0.366 and 0.667, respectively). The clinical decision curve showed that the model had good clinical application value.

Conclusion: The prediction model based on bacterial co-infection, chest pain, LDH, CRP, fever duration, and D-dimer has a good predictive value for necrotizing MPP.

Keywords: mycoplasma pneumonia, necrotizing pneumonia, nomogram, children

Introduction

Mycoplasma pneumoniae pneumonia (MPP) is a common childhood respiratory disease caused by *Mycoplasma pneumoniae* (MP) infection.[1] Most children are mild and have a good prognosis.[2] However, some cases still develop into refractory *Mycoplasma pneumoniae* pneumonia (RMPP) complicated by serious intrapulmonary and extrapulmonary complications.[3] Necrotizing pneumonia (NP) is a serious and not uncommon intrapulmonary complication of MPP. At present, there is no completely unified definition of NP, and most scholars[4–6] believe that NP is an imaging diagnosis. Chest CT examination is the gold standard for diagnosing NP, which is characterized by multiple low-density, thin-walled cavities based on lung consolidation. However, it takes a long time to diagnose NP clinically through chest CT. It has been reported that the average time for finding NP is 17 days,[7] which may lead to delayed diagnosis and missed optimal treatment time. Therefore, many scholars have explored the predictive indicators of NP in children with MPP for early identification. Many studies[8–11] have found that WBC, CRP, INF-α, and other markers may be risk factors for NP. However, the clinical practicability of using these single indicators to predict NP is not high, and there is still a lack of a simple and practical prediction

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model. The clinical prediction nomogram has been widely used in the prediction of the outcome of MPP because of its good interpretation and visualization. Cheng et al[12] developed an early prediction model for the development of MPP to bronchiolitis obliterans with good predictive accuracy. Our previous research[13] has also explored predictive models used to predict the severity of NP. Considering the above reasons, the purpose of this study is to analyze the clinical characteristics, laboratory examination, imaging, and treatment of NP in children with MPP, in order to construct a clinically practical predictive nomogram, so as to provide more reference for clinicians in the early diagnosis and treatment of necrotizing *Mycoplasma pneumoniae* pneumonia (NMPP).

Materials and Methods

Study Population

In this study, the clinical data of 3872 children with MMP were collected from the Children's Hospital of Kunming Medical University from January 2014 to November 2022. This study complied with the Declaration of Helsinki and was approved by the Ethics Review Committee of the Children's Hospital affiliated with Kunming Medical University. Written informed consent was obtained from the guardian of each patient.

Inclusion criteria: 1) meeting the clinical diagnostic criteria for pneumonia; 2) a single serum MP antibody titer greater than 1:160 or a positive MP DNA-PCR in nasopharyngeal aspirate, alveolar lavage fluid, or pleural effusion.[14] Exclusion criteria include: 1) patients with a history of chronic lung disease, immunodeficiency disease, connective tissue disease, or hematological disease; 2) hospitalized patients with pneumonia during the recovery period. 3) cavitary lung diseases, including congenital lung diseases with infection, tuberculosis, lung abscess, etc.

A total of 84 children with MPP who were diagnosed with NP were enrolled in the necrotizing group. The propensity-score method was used to match the remaining 3788 children with MPP in a ratio of 1:2, that is, each case in the necrotizing group was matched with the two cases in the non-necrotizing group with the most similar propensity score value based on age, sex, and weight. Finally, 168 children were included in the non-necrosis group.

Data Extraction

The clinical data included baseline information (sex, weight, age), symptoms and signs (cough, duration of fever, peak body temperature, hemoptysis, chest pain, wheezing, shortness of breath, cyanosis, rales), complications (digestive system, circulatory system, urinary system, blood system, nervous system, endocrine system), laboratory tests (WBC, Hb, neutrophil percentage, PLT, CPR, PCT, AST, ALT, LDH, Alb, CKMB, D-dimer, bacterial co-infection, viral co-infection), imaging examinations (pulmonary consolidation, atelectasis, pleural effusion, skin lesions), treatment (glucocorticoid, IVIG, surgery), outcome (length of stay, ICU admission, Death).

Statistical Analysis

Software R 4.2.2 and SPSS 25 were used for statistical analysis. The continuous variables of a normal distribution were compared by *t*-test and expressed as X ±standard deviation, while the continuous variables of a non-normal distribution were compared by Mann–Whitney test and expressed as the median of quartile [M (P25, p75)]. Categorical variables were analyzed by χ^2 test or Fisher's exact test and expressed as numbers (n) and percentages (%). All samples were randomly divided into training and validation sets at a ratio of 7:3 using the "caret" package of R software. Subsequently, to avoid model overfitting, a LASSO regression model was used to filter the independent variables on the training set. The training set was used to construct the logistic risk model, and the validation set was used as the internal validation cohort to evaluate the model, and a nomogram was drawn to visualize the model. The ROC curve, calibration curve, and decision curve analysis (DCA) were used to verify the reliability of the model. $P<0.05$ was regarded as statistically significant.

Outcome

Clinical Characteristics

A total of 252 children with MPP were included, including 123 boys (48.8%) and 129 girls (51.2%). The mean age was 6.10±2.93 months in the non-necrotizing group and 5.90 ±4.17 months in the necrotizing group. The average weight of

the non-necrotizing group was 20.21±6.74 kg and that of the necrotizing group was 18.71±10.21 kg. Cough was present in all cases. The digestive system complications were most common, including gastrointestinal dysfunction (n = 10), liver damage (n = 23), hypoproteinemia (n = 25) and electrolyte disturbance (n = 21). Four (1.6%) patients were transferred to the ICU due to severe condition. 5 (2%) patients underwent necrotic lobectomy and pleural decortication. The median length of hospital stay was 5.50 (4.00, 7.00) days in the non-necrotizing group and 10.50 (8.00, 16.00) days in the necrotizing group. All patients were discharged after improvement or recovery, and no patient died (see Table 1).

Table 1 The Clinical Characteristic and Laboratory Tests in Non-Necrotizing Group and Necrotizing Group

	Overall (n=252)	**Non-Necrotizing Pneumonia (n=168)**	**Necrotizing Pneumonia (n=84)**	**p**
Baseline information				
Age (mean (SD)), y	6.03 (3.39)	6.10 (2.93)	5.90 (4.17)	0.656
Weight (mean (SD)), kg	19.71 (8.07)	20.21 (6.74)	18.71 (10.21)	0.164
Sex (boy/girl), n	123/129	83/85	40/44	0.789
Clinical feature				
Cough, n (%)	252 (100.0)	168 (100.0)	84 (100.0)	
Hemoptysis, n (%)	2 (0.8)	0 (0.0)	2 (2.4)	0.209
Chest pain, n (%)	10 (4.0)	2 (1.2)	8 (9.5)	0.004
Wheeze, n (%)	13 (5.2)	3 (1.8)	10 (11.9)	0.002
Shortness of breath, n (%)	15 (6.0)	5 (3.0)	10 (11.9)	0.011
Cyanosis, n (%)	3 (1.2)	1 (0.6)	2 (2.4)	0.538
Rales, n (%)	71 (28.2)	43 (25.6)	28 (33.3)	0.055
Duration of fever (median [IQR]), d	7.00 [5.00, 10.00]	7.00 [4.00, 9.00]	9.00 [7.00, 12.00]	<0.001
Peak body temperature (median [IQR]),°C	39.30 [39.00, 40.00]	39.22 [38.77, 40.00]	39.50 [39.00, 40.00]	0.007
Radiological features				
Lobar consolidation, n (%)	118 (46.8)	76 (45.2)	42 (50.0)	0.562
Pleural effusion, n (%)	73 (29.0)	43 (25.6)	30 (35.7)	0.128
Atelectasis, n (%)	9(3.6)	7(4.2)	2(2.4)	0.471
Complications				
Digestive system, n (%)	62 (24.6)	36 (21.4)	26 (31.0)	0.134
Nervous system, n (%)	5 (2.0)	3 (1.8)	2 (2.4)	1
Urinary tract system, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Circulatory system, n (%)	13 (5.2)	5 (3.0)	8 (9.5)	0.056
Endocrine system, n (%)	8 (3.2)	4 (2.4)	4 (4.8)	0.525
Blood system, n (%)	29 (11.5)	12 (7.1)	17 (20.2)	0.004
Skin damage, n (%)	12 (4.8)	9 (5.4)	3 (3.6)	0.754

(*Continued*)

Table 1 (Continued).

	Overall (n=252)	Non-Necrotizing Pneumonia (n=168)	Necrotizing Pneumonia (n=84)	p
Laboratory values				
WBC, (median [IQR]), 10^9/L	7.63 [6.05, 11.42]	7.61 [6.23, 10.34]	8.28 [5.38, 14.90]	0.406
Hb (median [IQR]), g/L	127.50 [117.00, 130.00]	129.00 [120.00, 129.45]	121.00 [106.00, 133.00]	0.112
N% (median [IQR])	0.60 [0.53, 0.70]	0.60 [0.52, 0.66]	0.64 [0.53, 0.73]	0.017
PLT (median [IQR]), 10^9/L	380.41 [287.75, 456.50]	380.41 [303.75, 426.25]	380.41 [279.00, 504.00]	0.402
CRP (median [IQR]), mg/L	9.00 [4.00, 22.94]	4.00 [4.00, 15.00]	20.98 [6.01, 34.79]	<0.001
PCT (median [IQR]), ng/mL	0.21 [0.08, 0.44]	0.10 [0.05, 0.21]	0.47 [0.25, 0.90]	<0.001
AST (median [IQR]), U/L	19.15 [12.00, 30.60]	21.00 [13.00, 30.60]	17.00 [11.00, 30.60]	0.283
ALT (median [IQR]), U/L	34.00 [26.00, 42.62]	34.35 [26.00, 42.62]	31.00 [26.00, 46.00]	0.78
LDH (median [IQR]), U/L	322.50 [272.00, 388.50]	316.00 [271.75, 365.50]	336.00 [274.00, 412.00]	<0.001
Alb (median [IQR]), g/L	34.32 [31.82, 37.04]	34.25 [32.57, 37.03]	34.36 [29.00, 37.30]	0.221
CKMB (median [IQR]), U/L	7.60 [1.02, 9.00]	1.38 [0.74, 7.60]	14.00 [9.00, 20.00]	<0.001
D-dimer (median [IQR]), mg/L	1.92 [0.98, 2.70]	1.76 [0.83, 2.52]	2.36 [1.19, 3.28]	0.001
Bacterial co-infection, (%)	65 (25.8)	32 (19.0)	33 (39.3)	0.001
Viral co-infection, n (%)	46 (18.3)	30 (17.9)	16 (19.0)	0.954
Treatment				
Glucocorticoid, n (%)	81 (32.1)	33 (19.6)	48 (57.1)	<0.001
IVIG, n (%)	15 (6.0)	8 (4.8)	7 (8.3)	0.397
Surgery, n (%)	5 (2.0)	0 (0.0)	5 (6.0)	0.007
Outcome				
Length of stay (median [IQR]), d	7.00 [5.00, 9.00]	5.50 [4.00, 7.00]	10.50 [8.00, 16.00]	<0.001
ICU admission, n (%)	4 (1.6)	0 (0.0)	4 (4.8)	0.021
Death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	

Abbreviations: WBC, white blood cell; Hb, hemoglobin; N%, Percentage of neutrophils; PLT, platelet; CRP, C -reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; AST, alanine aminotransferase; ALB, albumin; CK-MB, Creatine kinase isoenzyme; LDH, lactate dehydrogenase; IVIG, intravenous immune globulin; ICU, intensive care unit.

Variable Selection

A total of 17 variables in univariate analysis showed significant statistical differences between the two groups ($P < 0.05$) (Table 1). Since the aim of this study was to construct a model for early prediction of NMPP, four variables (length of stay, ICU admission, glucocorticoid, and surgery) representing the severity of the disease were excluded. Finally, 13 variables, including chest pain, wheezing, shortness of breath, duration of fever, peak body temperature, bacterial co-infection, blood system complications, neutrophil percentage, CRP, PCT, LDH, D-dimer, and CKMB, were selected as candidate predictors. For linear models, complexity is directly related to the number of variables in the model. The more variables, the higher the complexity of the model. If the traditional binary logistic regression is used to select variables, overfitting and multicollinearity are likely to occur. Therefore, we chose the LASSO algorithm for variable selection,

which can effectively avoid the above problems.The LASSO regression showed that bacterial co-infection, chest pain, LDH, CRP, duration of fever, and D-dimer were the risk factors for NMPP (see Figure 1).

Development of Nomogram

A predictive nomogram containing six independent predictors (bacterial co-infection, chest pain, LDH, CRP, fever duration and D-dimer) was established by logistic regression (Figure 2). The logistic regression equation was logit(P)= $-5.072 + 1.387X_{\text{bacterial co-infection}} - 2.319X_{\text{chest pain}} + 0.002X_{\text{LDH}} + 0.221X_{\text{Duration of fever}} + 0.019X_{\text{CRP}} + 0.339X_{\text{D-dimer}}$. For example, a patient with MPP had no chest pain symptom, no bacterial co-infection, fever lasting for 6 days, serum LDH level was 180U/L, CRP was 192mg/L, and D-dimer was 2.9mg/L, with a total point of 212(21+21+28+31+31+80). The predicted risk is 0.821.

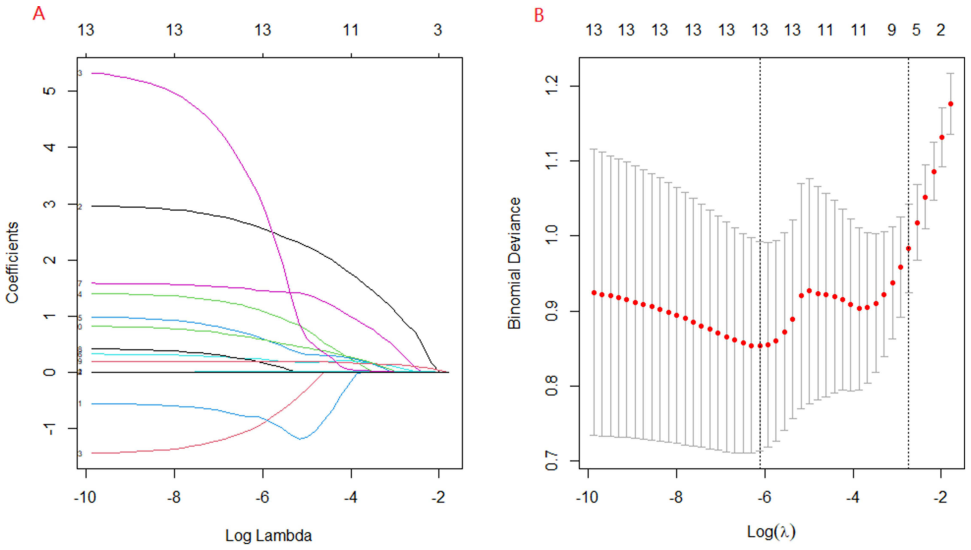

Figure 1 Predictors' selection using LASSO regression method. (**A**) LASSO coefficient profiles of the 13 variables. The coefficient profile plot was produced against the log (λ) sequence. (**B**) The best penalty coefficient lambda was selected using a tenfold cross-validation and minimization criterion. By verifying the optimal parameter (λ) in the LASSO model, the binomial deviance curve was plotted versus log(λ) and dotted vertical lines were drawn based on 1 standard error criteria. 6 variables with nonzero coefficients were selected by 1 standard error criteria.

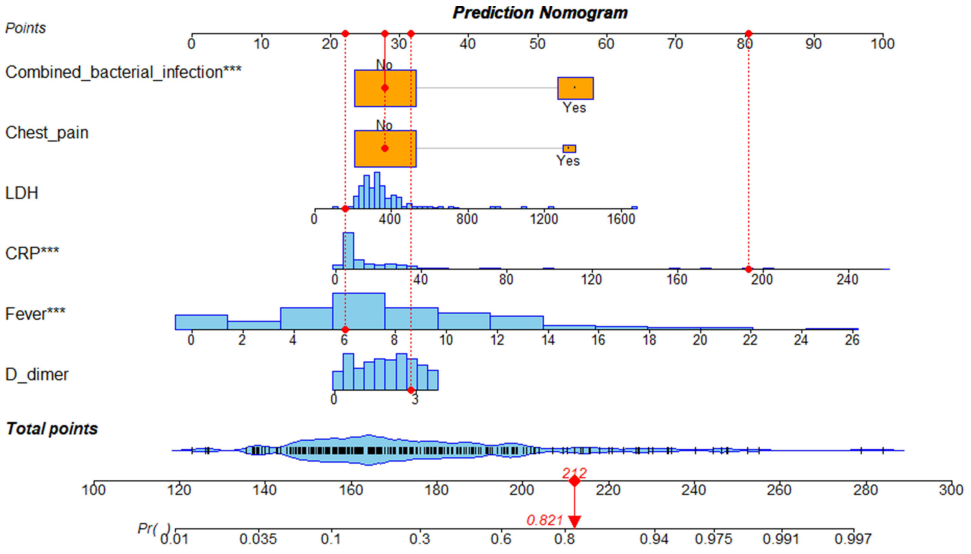

Figure 2 Nomogram was plotted based on six optimal predictors (bacterial co-infection, chest pain, LDH, CRP, fever duration and D-dimer) for necrotizing *Mycoplasma pneumoniae* pneumonia. ***Indicates that this predictor has the most significant statistical significance by logistics regression analysis.
Abbreviations: LDH, lactate dehydrogenase; CRP, C-reactive protein.

Validation and Evaluation of the Nomogram

The 1000 bootstrap analysis was performed for the internal validation of the nomogram. The calibration curve of the training set (Figure 3A) and the validation set (Figure 3B) shows that, ideally, the calibration curve of the disease risk predicted by the prediction model is close to 45°diagonal. The Hosmer-Lemeshow test showed good probability consistency between the predicted and actual probability in the training set and validation set (P=0.366 and P=0.667, respectively). The ROC curve in the training set showed an AUC of 0.870 (95% CI: 0.813–0.927, P < 0.001) (Figure 4A) and the ROC curve in the validation set showed an AUC of 0.843 (95% CI: 0.757–0.930, P < 0.001) (Figure 4B). The DCA curve was drawn with the net benefit rate as the ordinate and the high-risk threshold as the abscissa, and the high-risk threshold was set as (0, 1). Figure 5A and B showed that when the high-risk threshold was 0.2 to 1.0, the net benefit rate of the training set and the validation set was greater than 0 and clinically significant, suggesting that the prediction model has important clinical value in predicting NMPP. The clinical impact curve analysis (Figure 6A and B) showed

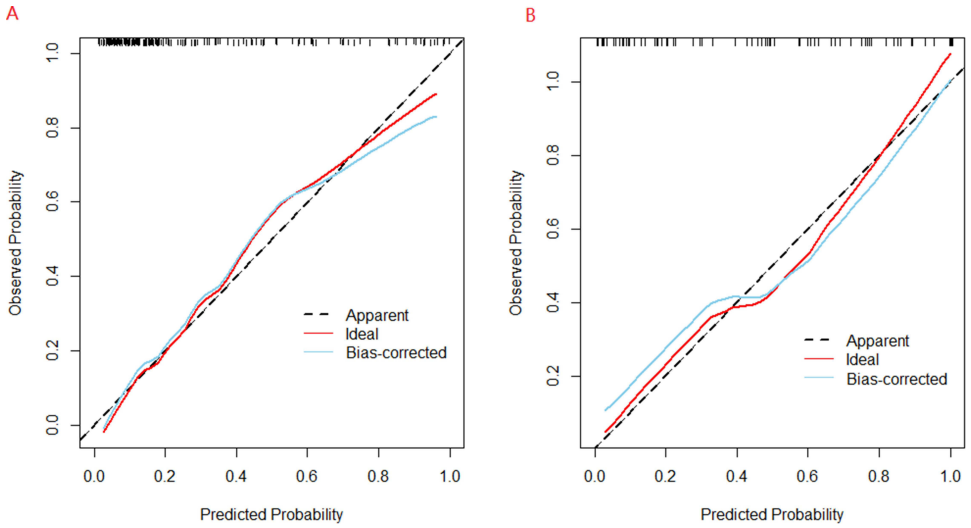

Figure 3 Calibration plots of the nomogram in (**A**) the training set and (**B**) the validating set.

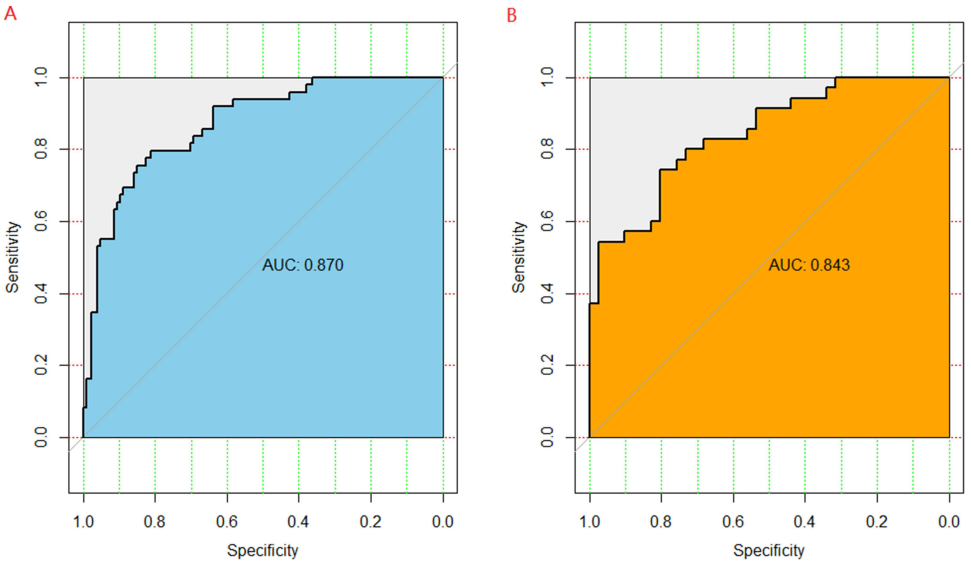

Figure 4 ROC curve of predictive nomogram in (**A**) the training set and (**B**) the validating set.

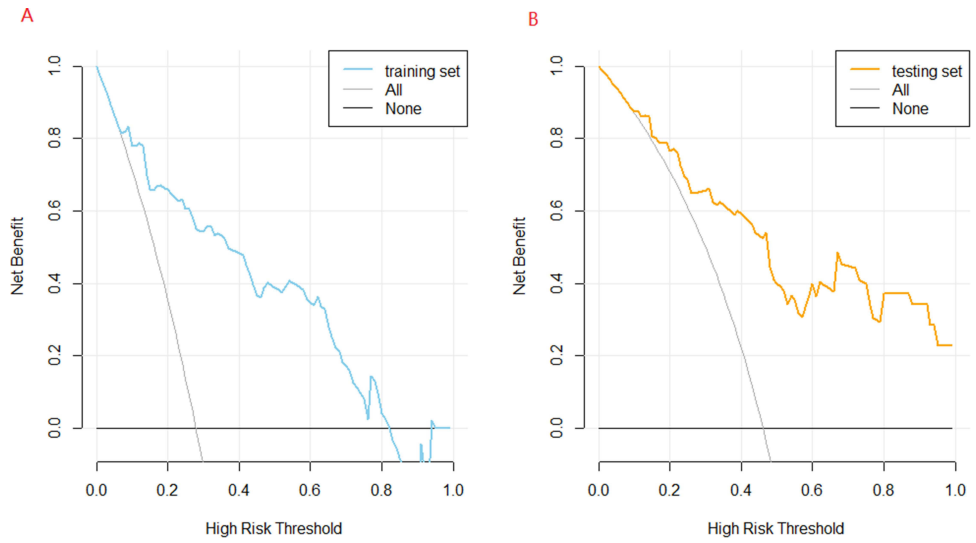

Figure 5 Decision curve analysis (DCA) for the predictive model. (**A**) The training set. (**B**) The validating set.

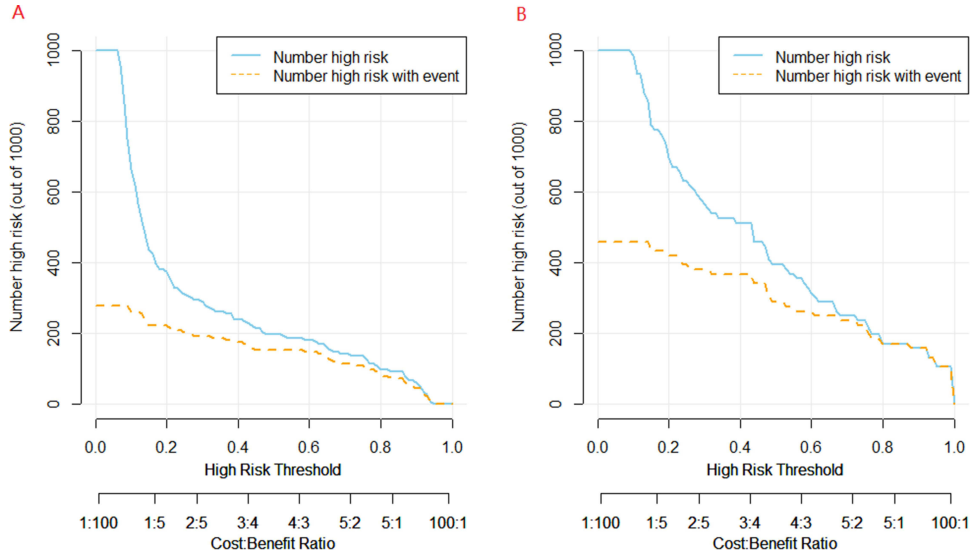

Figure 6 Clinical impact curves for the predictive model. (**A**) The training set. (**B**) The validating set.

that the predicted number of patients was close to the actual number of patients when the high-risk threshold was greater than 0.4 using 1000 patients for prediction.

Discussion

The aim of this study is to identify the factors that can predict NMPP and establish a prediction model. We found that the nomogram established by regression combined with bacterial co-infection, chest pain, LDH, CRP, duration of fever, and D-dimer can conveniently and effectively predict whether MPP will develop into NP. To the best of our knowledge, this study is the first study to date on a predictive model for NP in children.

NP is defined as the liquefaction and necrosis of the lung tissue involved with the progress of the disease on the basis of lung consolidation, resulting in the formation of multiple cysts or cavities.[4] The clinical diagnosis is mainly based on imaging examinations. Although it has been found that the proportion of NP caused by MP is rising in recent years,[7] it is still believed that *Streptococcus pneumoniae* and *Staphylococcus aureus* are the main pathogens of NP.[4,15] This study

also found that *Streptococcus pneumoniae* and *Staphylococcus aureus* were the main bacteria in co-infection of NMPP, and the combined bacterial infection also increased the possibility of NMPP. It suggests that when we choose drugs for MPP complicated with bacterial infection, in addition to macrolides, the addition of β-lactam antibiotics is also indispensable.

In this study, we found that the duration of fever was an important predictor of NMPP. The pathogenesis of NMPP is not only the direct damage to lung tissue caused by pathogens and toxins, but also related to the secondary injury caused by the release of a large number of inflammatory factors caused by the host immune inflammatory response. The stronger the immune response, the more serious the organ damage. The immune response of the host determines the prognosis of MPP. Persistent fever is one of the important clinical manifestations of MPP. It is generally believed that persistent fever is related to excessive inflammatory reaction caused by MP infection. A meta-analysis compared the duration of fever between MPP and RMPP and found that prolonged fever was a risk factor for RMPP in children.[16] CRP is an acute inflammatory marker that increases with a strong immune inflammatory response, which can be used to quickly judge the severity of the disease. Zhou et al[8] found that the CRP of NMPP was significantly higher than that of non-necrotizing MPP group. A large number of retrospective studies[17–19] have suggested that the higher the CRP, the more serious the condition. LDH exists in the cytoplasm of all tissue cells in the body. When the cell dissolves or the cell membrane is damaged, LDH is released into the blood, so it can be used as a biomarker of tissue injury.[20] A number of previous studies[17,18,21–23] have suggested the important predictive value of LDH in the poor prognosis of MPP. In our prediction model, CRP and LDH were also selected as predictors, suggesting that the immune response plays an important role in the pathogenesis of NP.

This study found that the increase of D-dimer is a risk factor for NMPP. It has been found that D-dimer is a predictor of RMPP and has high predictive accuracy (AUC=0.923).[24] Zheng et al[9] found that the level of D-dimer > 1367.5ng/mL is an independent risk factor for pulmonary necrosis in MPP. MP can stimulate inflammatory cells to release a variety of inflammatory transmitters, resulting in vascular endothelial cell damage and a significant increase in the level of D-dimer. Therefore, D-dimer is also a marker of inflammation. In addition, D-dimer is a specific fibrin degradation product activated by cross-linking of fibrin monomers with activating factors, it is a specific marker of the fibrinolytic system, and its high level implies a hypercoagulable state. In this hypercoagulable state, the lungs are prone to thrombus and vascular occlusion, which affect the blood supply and further develop into NP.

The symptom of chest pain was often ignored in previous studies on MPP, and our study revealed a close relationship between chest pain and NP for the first time. It suggests that clinicians should consider the possibility of NP once hearing of chest discomfort in patients with MPP.

Due to the low incidence of NP, the sample size of previous studies on NMPP is relatively small, often only 30–40 cases. In addition, previous studies often explored the predictive value of a single predictive index for NP, but the clinical practice is not high. This study summarized all the clinical data about NMPP since the establishment of the medical record system in our hospital, and constructed a simple and practical clinical predictive nomogram, which shows good clinical practicability through the validation of the model, which may be a very suitable tool for clinical diagnosis and treatment of NP.

There are some limitations, and selection bias is possible due to the retrospective study. In addition, the establishment of the prediction model should be validated by an external cohort, but there is a lack of external validation data. We look forward to future prospective clinical studies with multi-center and larger sample sizes to verify the accuracy of the conclusions of this study.

Conclusion

The prediction model based on bacterial co-infection, chest pain, LDH, CRP, fever duration, and D-dimer has a good predictive value for necrotizing MPP.

Disclosure

The authors report no conflicts of interest in this work.

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