Original Article

Construction of a nomogram for early diagnosis of refractory *Mycoplasma pneumoniae* pneumonia in children

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Background: Refractory *Mycoplasma pneumoniae* pneumonia (RMPP) has a serious, rapid progression that can easily cause a variety of extra-pulmonary complications. Therefore, the early identification of RMPP is crucial. This study aimed to construct and validate a risk prediction model based on clinical manifestations, laboratory blood indicators, and radiological findings to help clinicians identify patients who are at high risk of RMPP.

Methods: We retrospectively analyzed the medical records of 369 children with *Mycoplasma pneumoniae* pneumonia (MPP) admitted to Xi'an Children's Hospital, China. The demographics, clinical features, laboratory data, and radiological findings between the RMPP group and the general *Mycoplasma pneumoniae* pneumonia (GMPP) group were compared and subjected to univariate and multivariate logistic regression analyses.

Results: The fever peak and duration of the children in the RMPP group (n=86) were higher and longer compared with those in the GMPP group (n=283) (P<0.05). There was a significant difference in the incidence of lobar pneumonia and pleural effusion in pulmonary imaging between the two groups (P<0.05). Laboratory tests showed that the children with RMPP had lower serum uric acid (SUA) and albumin (ALB) as compared with the GMPP group (P<0.05). White blood cells (WBCs), neutrophil count (NEP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), C-reactive protein (CRP), and neutrophil-to-lymphocyte ratio (NLR) were higher in the RMPP group (P<0.05). Binary logistic regression analysis showed that the fever duration, pleural effusion, WBC, NEP, lactate dehydrogenase (LDH), CRP, NLR, and SUA levels were independent predictors of RMPP (P<0.05). The receiver operator characteristic (ROC) curve results showed fever duration, WBC, NEP, CRP, LDH, SUA, and NLR had good predictive value. The areas under the curve (AUCs) were 0.861, 0.730, 0.758, 0.837, 0.868, 0.744, and 0.713 and the best cutoff values were 10.50, 10.13, 6.43, 29.45, 370.50, 170.50, and 3.47, respectively. Finally, fever duration of more than 10.5 days, pleural effusion, WBC >10.13×10^9/L, NEP >6.43×10^9/L, CRP >29.45 mg/L, LDH >370.50 U/L, NLR >3.47, and SUA <170.5 μmol/mL constructed a prediction model of RMPP. According to internal validation, the mean AUC of the nomogram based on the development dataset was 0.956 [95% confidence interval (CI): 0.937–0.974] with good discrimination ability for predicting RMPP patients. The calibration plot and Hosmer-Lemeshow test (P=0.70) of the prediction model showed good consistency between the predicted probability and actual probability. Decision curve analysis (DCA) showed that the nomogram is clinically useful.

Conclusions: The simple and easy-to-use nomogram can help clinicians, especially primary doctors, to make early diagnoses of RMPP.

Keywords: *Mycoplasma pneumoniae* (MP); serum uric acid (SUA); children; diagnosis; refractory

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Introduction

Mycoplasma pneumoniae (MP) is an important pathogenic bacterium which can cause community-acquired pneumonia in children. MP pneumonia (MPP) is responsible for 10–40% of hospitalizations among children with community-acquired pneumonia (1). Most children with MPP have a mild condition and a self-limiting process. Refractory *Mycoplasma pneumoniae* pneumonia (RMPP) has a serious, rapid progression that can easily cause a variety of extra-pulmonary complications, leading to poor efficacy of conventional drugs; the condition is susceptible to delayed treatment, seriously threatening children's physical and mental health and safety (2). Therefore, searching for early warning indicators of RMPP has important clinical implications. At present, there are many clinical studies on RMPP and the more recommended indicators are lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin (FER), and D-dimer (3-5). Shen *et al.* (3) reported that CRP, LDH, and D-dimer were predictive factors for RMPP, with an area under the receiver operating characteristic (ROC) curve (AUC) of the nomogram of 0.881. However, the clinical specificity of the above indicators is not high. In recent years, studies have also confirmed that cytokine imbalance can serve as a key factor in predicting RMPP. Studies have shown that interleukin (IL)-6, IL-10, IL-17, IL-8, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and CXCL10/IP-10 may be potential biomarkers of RMPP (6,7). The study found that the soluble B7-DC (sB7-DC) and IL-17 levels of children with RMPP were significantly increased. The sensitivity of IL-17 to RMPP prediction was 83.3% and the specificity was 62.9%. The sensitivity and specificity of sB7-DC to RMPP were 86.7% and 62.9%, respectively, and sB7-DC had a higher predictive value than IL-17 for RMPP (8). Zhu *et al.* (9) reported that the AUC of CCL2 in bronchoalveolar lavage fluid (BALF) predicting RMPP was 0.94, the cut-off value was 0.645 ng/mL, the sensitivity was 85%, and the specificity was 94%. However, the prediction role of these cytokines has not achieved a wide consensus, and these indicators are difficult to obtain clinically, especially in primary hospitals. Therefore, the discovery of a safe, accurate, efficient, easy to obtain, and quantifiable diagnostic tool to predict RMPP is an urgent need.

Serum uric acid (SUA) is an end product of purine metabolism in the body (10,11). Studies have shown that abnormal uric acid levels are a risk factor for cardiovascular, neurological, and metabolic diseases. However, studies of uric acid levels in respiratory tract infections are rare; there are few studies on the prediction of SUA levels in RMPP. Neutrophil-to-lymphocyte ratio (NLR) represents an essential cellular component of human host defense. Neutrophils (NEP) are the first cells in the line of defense against infection in the non-specific immune system. They induce and activate an inflammatory response, whereas lymphocytes play a role in adaptive immunity. It has been reported that the NLR could better predict the clinical outcomes of patients with systemic inflammation (12). The clinical significance of the NLR for the early diagnosis of RMPP is currently unclear. This study aimed to establish and validate a risk prediction model based on clinical manifestations, laboratory blood indicators, and radiological findings to help clinicians identify patients who are at high risk of RMPP. We present this article in accordance with the TRIPOD reporting checklist (available at https://

Highlight box

Key findings

- Fever duration of more than 10.5 days, pleural effusion, white blood cells >10.13×10^9/L, neutrophil count >6.43×10^9/L, C-reactive protein >29.45 mg/L, lactate dehydrogenase >370.50 U/L, neutrophil-to-lymphocyte ratio (NLR) >3.47, and serum uric acid (SUA) <170.5 μmol/mL was an early predictive model of refractory *Mycoplasma pneumoniae* pneumonia (RMPP).

What is known and what is new?

- Although nomograms for RMPP had been established in previous studies, the clinical specificity of them is not very high or they do not fully apply to primary doctors.
- We found that the SUA and NLR are a widely available and low-cost predictive index with good clinical value. SUA and NLR indicators were added to the nomogram, which could more comprehensively help clinicians to predict RMPP, especially in primary care hospitals.

What is the implication, and what should change now?

- The simple and easy-to-use nomogram can help clinicians, especially primary doctors, to make early diagnoses of RMPP.

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Methods

Participants and inclusion and exclusion criteria

This retrospective study was a single-center clinical data analysis. We retrospectively analyzed the medical records of 369 children with MPP admitted to Xi'an Children's Hospital between January 2022 and January 2023. Patient-related information, including demographics, clinical and laboratory findings, and imaging data were extracted from the medical records. The inclusion criteria were as follows: (I) MPP: consistent with the clinical presentation and imaging changes of pneumonia; (II) cephalexin and penicillin antibiotics were not effective; (III) the diagnosis of MP infection was based on the positive serologic test results (MP IgM positive and antibody titer 1:160) combined with positive results for MP polymerase chain reaction (PCR) tests of nasopharyngeal secretions. General *Mycoplasma pneumoniae* pneumonia (GMPP): MPP was treated with macrolide antibiotics for 5–7 days and improved significantly. RMPP: MPP has been regularly treated with macrolide antibiotics for 7 days, with aggravated clinical signs, persistent fever, and worse pulmonary imaging symptoms. The exclusion criteria were as follows: congenital heart disease, genetic and metabolic diseases, neurological diseases, congenital bronchopulmonary dysplasia, immune deficiency, and long-term use of immunosuppressants, tuberculosis, asthma, and bronchial foreign bodies was excluded. All cases of MPP were reviewed by a final diagnosis committee composed of two specialist pediatricians (with experience in pediatric respiratory medicine) and a radiologist in cases of pneumonia. The cases were divided into GMPP and RMPP groups according to the diagnostic criteria. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Medical Ethics Committee of Xi'an Children's Hospital (reference number: 20230004) and informed consent was provided by the parents or legal guardians of the children.

Data collection

The study collected the case data of children, including general details (age, sex), clinical data (fever duration, fever peak, wheezing), laboratory examination results [white blood cells (WBCs), NEP, lymphocytes (LYM), platelets (PLT), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), CRP, LDH, lymphocyte/leukocyte ratio, NLR, platelet/lymphocyte ratio], and imaging data (consolidation, lung atelectasis, pleural effusion). Values for the abovementioned laboratory indictors were determined using an automatic blood analyzer and automatic biochemical analyzer at Xi'an Children's Hospital. The radiological reports were performed by a radiologist. All laboratory examinations were completed within 24 hours of hospital admission. Patients with incomplete data and information were excluded.

Statistical analysis

Variable selection and model construction

Statistical analysis was performed using the software SPSS 25.0 (IBM Corp., Armonk, NY, USA). Measurement data were non-normally distributed. Non-normally distributed continuous variables were summarized as medians and interquartile ranges (IQRs), and the rank-sum test was used to assess the significance of differences between groups. Categorical data were expressed as n (%), and a chi-square test was used for the comparison between groups. A single factor analysis was used to screen the indicators with significant differences. Those variables with P value of 0.2 and below in univariable analysis were entered into a binary logistic regression. The independent risk factors for RMPP were analyzed by binary logistic regression analysis and were considered statistically significant with $P<0.05$. ROC analysis was used to determine the cut-off value for each index and to evaluate the predictive value of the relevant indicators in the RMPP. Multiple linear regression analysis was used to find the correlation between the independent risk factors.

Model performance evaluation

Statistical analysis was carried out using R software (version 4.0.5; The R Foundation for Statistical Computing, Vienna, Austria) to create all of the graphics. A 2-sided α less than 0.05 was considered statistically significant. The performance of the prediction model was evaluated from discrimination ability, calibration ability, and clinical value. The discrimination ability was evaluated through ROC analysis with AUC, and the calibration plot accompanied with the Hosmer-Lemeshow test was applied to assess the calibration ability. A P value >0.05 in the model calibration test (Hosmer-Lemeshow test) indicated acceptable model calibration. The closer the AUCs were to 1.0, the higher the authenticity of the detection method. The higher the

sensitivity, the higher the diagnostic accuracy, and the higher the specificity, the lower the misdiagnosis rate. The usual performance measurements for risk prediction models (discrimination and calibration) were unable to address the question of how beneficial the produced nomogram would be in clinical practice. As a result, decision curve analysis (DCA) was performed with the intention of developing a more clinically interpretable risk prediction model. The model was validated using a bootstrap method with 1,000 resamples to quantify any overfitting.

Statistical analyses were performed separately by two researchers to ensure the reliability of the findings.

Results

A total of 369 children with MPP were included after excluding 8 cases with incomplete data, including 86 cases of RMPP and 283 cases of GMPP 283.

Clinical characteristics of children with RMPP and GMPP

There were no statistically significant differences in sex and age between the children in the RMPP group and those in the GMPP group. Baseline data were comparable between both groups. The results showed that the fever peak and duration of the children in the RMPP group were higher and longer compared with the GMPP group. The wheezing symptom was not significantly different between the RMPP and GMPP groups, as shown in *Table 1*. There was a significant difference in the incidence of lobar pneumonia and pleural effusion in pulmonary imaging between the two groups, but there were no statistically significant differences in the incidence of atelectasis (*Table 1*). Laboratory tests showed that WBC, NEP, CRP, ESR, PCT, SUA, albumin (ALB), LDH, lymphocyte-to-white blood cell ratio (LWR) and NLR were statistically different between the two groups.

Results of the RMPP binary logistic regression analysis

The above meaningful indicators were subjected to binary logistic regression analysis. Fever duration, pleural effusion, WBC, NEP, LDH, CRP, NLR, and SUA levels were identified as independent predictors of RMPP, as shown in *Table 2*.

ROC curve analysis

The ROC curve results showed that fever duration, WBC, NEP, CRP, LDH, NLR, and SUA had good predictive value. The AUC values were 0.861, 0.730, 0.758, 0.837, 0.868, 0.713, and 0.744 and the best cutoff values were 10.50, 10.13, 6.43, 29.45, 370.50, 3.47, and 170.50, respectively. The best predictor of the above laboratory indicators was the LDH, with a sensitivity and specificity of 0.837 and 0.837, respectively. The newly discovered indicator was the SUA levels. When the cutoff values of SUA were 170.50, the sensitivity and specificity were 0.651 and 0.742, respectively (*Table 3*).

Multiple linear regression analysis

A multivariate linear regression analysis was carried out for the independent risk factors obtained by logistic regression analysis. The fever duration was selected as the dependent variable, SUA, CRP, LDH, and NLR as the independent variables. Multivariate linear regression model analysis showed the R^2 was 0.328, indicating that the four indicators of SUA, CRP, LDH, and NLR could explain 32.8% of the fever duration variability. The Durbin-Watson index of 1.77, which is used to detect the presence of autocorrelation in the residuals of a regression, indicated a slight non-independence (*Table 4*). However, there was little effect on the accuracy of the regression results. The results of multiple linear regression analysis showed a positive linear relationship between CRP, LDH, NLR, and fever duration, and a negative linear relationship between SUA and fever duration, as shown in *Table 5*.

Nomogram of the final model

The eight selected variables were applied to establish a logistic regression model and presented with a nomogram. These eight variables included fever duration, pleural effusion, WBC, NEP, CRP, LDH, NLR, and SUA. The final predictive model incorporating the eight factors is shown as a nomogram in *Figure 1A*. Total points based on the sum of the points for each predictor in this nomogram were associated with the risk of RMPP.

Performance of the nomogram

By internal bootstrap validation with 1,000 resamples, the mean AUC of the nomogram based on the development dataset was 0.956 [95% confidence interval (CI): 0.937–0.974], the sensitivity, and specificity of the nomogram model were 0.848, and 0.953, respectively (see *Figure 1B*),

Table 1 Clinical characteristics of children with GMPP and RMPP

Variables	GMPP (n=283)	RMPP (n=86)	Z/χ^2	P value
Baseline characteristics				
Age (years)	6.75 (5.160–8.16)	6.91 (5.500–8.43)	–1.383	0.167
Sex, male	157 (55.5)	45 (52.3)	0.264	0.607
Clinical characteristics				
Fever peak (℃)	39.6 (39.2–40)	40.0 (40–40.525)	–7.339	<0.001*
Fever duration (days)	9 (7–11)	13.5 (12–17)	–10.168	<0.001*
Wheezing	18 (6.4)	7 (8.1)	0.331	0.565
Pulmonary imaging characteristics				
Lobar pneumonia	247 (87.3)	85 (98.8)	9.767	0.002*
Atelectasis	8 (2.8)	3 (3.5)	0.100	0.752
Pleural effusion	72 (25.4)	67 (77.9)	77.324	<0.001*
Laboratory characteristic				
WBC ($\times10^9$/L)	7.88 (5.94–9.61)	11.07 (7.92–13.35)	–6.473	<0.001*
NEP ($\times10^9$/L)	4.98 (3.56–6.48)	7.55 (5.47–10.26)	–7.260	<0.001*
LYM ($\times10^9$/L)	1.90 (1.48–2.38)	2.00 (1.50–2.62)	–1.004	0.315
PLT ($\times10^9$/L)	294.00 (229.00–351.00)	265.50 (206.75–393)	–0.761	0.446
CRP (mg/L)	11.25 (0.00–25.95)	59.27 (24.71–118)	–9.515	<0.001*
ESR (mm/h)	38.00 (30.00–60.00)	50.50 (32.75–80.00)	–3.249	0.001*
PCT (ng/mL)	0.07 (0.00–1.40)	0.22 (0.10–0.745)	–7.822	<0.001*
SUA (μmol/mL)	203.00 (168.00–250.00)	150.00 (124.50–184.50)	–6.854	<0.001*
ALB (g/L)	37.90 (34.90–39.90)	31.95 (28.55–35.23)	–9.304	<0.001*
LDH (U/L)	268.00 (224.00–339.00)	473.00 (389.75–622.00)	–10.340	<0.001*
LWR	0.25 (0.19–0.31)	0.19 (0.15–0.26)	–5.682	<0.001*
NLR	2.56 (1.78–3.63)	3.77 (2.67–5.26)	–5.987	<0.001*
PLR	150.00 (118.50–195.10)	140.60 (104.60–196.20)	–1.186	0.236

All continuous variables are non-normally distributed and presented as median (interquartile range). Categorical variables are presented as n (%).*, P<0.05, compared with children with GMPP and RMPP. GMPP, general Mycoplasma pneumoniae pneumonia; RMPP, refractory *Mycoplasma pneumoniae* pneumonia; WBC, white blood cell; NEP, neutrophil count; LYM, lymphocyte count; PLT, platelet count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; SUA, serum uric acid; ALB, albumin; LDH, lactate dehydrogenase; LWR, lymphocyte-to-white blood cell ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

with good discrimination ability for predicting RMPP patients. Furthermore, the calibration plot and Hosmer-Lemeshow test (P=0.70) of the prediction model showed good consistency between the predicted probability and actual probability, as shown in *Figure 1C,1D*. The DCA showed that the nomogram model can bring clinical benefit to patients within a large threshold range (see *Figure 1E,1F*).

Discussion

RMPP disease progresses rapidly, the symptoms are relatively intense, and the conventional treatment effect is poor. RMPP often causes various intrapulmonary complications, such as bronchial mucus plug formation, necrotizing pneumonia, bronchiolitis obliterans,

Table 2 Binary logistic regression analysis

Factors	B	S.E.	Wald	P value	OR	95% CI
Fever duration	0.287	0.067	18.299	<0.001	1.332	1.168–1.520
Fever peak	0.811	0.433	3.498	0.061	2.249	0.962–5.260
Lobar pneumonia	0.549	1.350	0.166	0.684	1.732	0.123–24.430
Pleural effusion	1.060	0.435	5.944	0.015	2.885	1.231–6.764
WBC	–1.149	0.416	7.615	0.006	0.317	0.140–0.717
NEP	1.695	0.567	8.927	0.003	5.447	1.792–16.562
ESR	–0.014	0.009	2.615	0.106	0.986	0.969–1.003
PCT	0.202	0.196	1.060	0.303	1.224	0.833–1.797
CRP	0.021	0.006	12.575	<0.001	1.021	1.009–1.033
SUA	–0.012	0.005	5.417	0.020	0.989	0.979–0.998
ALB	0.079	0.070	1.266	0.261	1.082	0.943–1.240
LDH	0.007	0.002	17.099	<0.001	1.007	1.004–1.011
LWR	–7.912	4.454	3.155	0.076	0.000	0.000–2.266
NLR	–0.910	0.328	7.700	0.006	0.403	0.212–0.765
Constant	–36.887	17.892	4.251	0.039	0.000	–

WBC, white blood cell; NEP, neutrophil count; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; CRP, C-reactive protein; SUA, serum uric acid; ALB, albumin; LDH, lactate dehydrogenase; LWR, lymphocyte-to-white blood cell ratio; NLR, neutrophil-to-lymphocyte ratio; B, β value; S.E., standard error; OR, odds ratio; CI, confidence interval.

Table 3 Predictive value of independent factors in patients with RMPP

Factors	AUC	P value	Cut off	Sensitivity	Specificity
Fever duration	0.861	<0.001	10.50	0.895	0.728
WBC	0.730	<0.001	10.13	0.616	0.809
NEP	0.758	<0.001	6.43	0.674	0.742
CRP	0.837	<0.001	29.45	0.733	0.774
LDH	0.868	<0.001	370.50	0.837	0.837
NLR	0.713	<0.001	3.47	0.605	0.731
SUA	0.744	<0.001	170.50	0.651	0.742

RMPP, refractory *Mycoplasma pneumoniae* pneumonia; WBC, white blood cell; NEP, neutrophil count; CRP, C-reactive protein; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; SUA, serum uric acid.

and bronchiectasis. It can also cause extrapulmonary complications, involving multiple systems, such as myocarditis, nephritis, encephalitis, hepatitis, arthritis, Steven-Johnson syndrome, and others, and even lead to multi-system, multi-organ involvement and death (13,14). Therefore, actively exploring the early warning indicators of RMPP and initiating timely intervention can reduce the occurrence of RMPP complications and reduce the mortality rate. This study was aimed at developing a risk prediction nomogram for prediction of RMPP patients.

The results of this study showed no statistically significant differences between sex and age in the RMPP and GMPP groups. Compared with the GMPP group, the RMPP group had longer thermal duration, higher

thermal peak, higher incidence of consolidation, and pleural effusion. This is consistent with the research results of Shen *et al.* (3), who uncovered significant differences in WBC, NEP, PCT, CRP, LDH, ALB, and SUA between the two groups. The logistic regression analysis found that the fever duration, pleural effusion, WBC, NEP, CRP, LDH, NLR, and SUA were independent predictors of RMPP. The fever duration and laboratory indicators (WBC, NEP, CRP, LDH, NLR, and SUA) were included to draw the ROC curves. The AUC values were 0.861, 0.730, 0.758, 0.837, 0.868, 0.713, and 0.744 and the best cutoff values were 10.50, 10.13, 6.43, 29.45, 370.50, 3.47, and 170.50 respectively. The best predictor of the above laboratory indicators was the LDH, with a sensitivity and specificity of 0.837 and 0.837, respectively. The newly discovered indicator was the SUA levels. When the cutoff value of SUA was 170.50, the sensitivity and specificity were 0.651 and 0.742, respectively.

The nomogram model can evaluate the prognosis intuitively, concisely, and accurately, which helps medical staff make better clinical decisions. In this study, we screened the predictive variables for RMPP through logistic regression analysis to build a nomogram. Finally, fever duration, pleural effusion, WBC, NEP, CRP, LDH, NLR, and SUA were entered into the predictive model. The results of this study show that the prediction model has good prediction effect and calibration degree, and the internal validation results confirm that the model has good performance. The DCA showed that the nomogram model can bring clinical benefit to patients within a large threshold range. Cheng *et al.* (15) used LASSO regression analysis to screen for risk factors for RMPP and found that high fever, ALB, LDH, and the neutrophil ratio were 4 independent risk factors; the AUC of the nomogram was greater than 0.8 in both the training and validation groups. Bi *et al.* (16) took six indicators, including age, fever days, CRP, alanine aminotransferase (ALT), LDH, and chest imaging score, and developed a predictive nomogram for RMPP with a sensitivity of 78.3% and a specificity of 86.2%. The AUC of the predictive scale was 0.871. The clinical predictive model included in this study showed an AUC of 0.956, which was significantly higher than the above two study models. The results of this study were similar to the model predictive power of the study conducted by Liu *et al.* (17). The results of their study showed that consolidation size/body surface area (BSA), pleural effusion, CRP, and LDH were significant indicators of RMPP development, and were subsequently used to develop a nomogram prediction tool. The AUC for the predictive nomogram was 0.955 in the training cohort and 0.916 in the validation cohort.

The results of this study showed that the sensitivity and specificity of LDH were 0.837 and 0.837, respectively, which were better predictors. LDH is a non-specific inflammatory marker, mainly involved in anaerobic glucose metabolism. LDH catalyzes the interconversion of lactate and pyruvate, and that of nicotinamide adenine dinucleotides and nicotinamide adenine dinucleotides. LDH is present in the cytoplasm of cells in all tissues, released to the extracellular matrix upon cell membrane damage or cell lysis, and is a

Table 4 Linear regression model

Model	Values
R	0.572[a]
R^2	0.328
Adjusted R^2	0.32
S.E. of the estimate	3.835
Durbin-Watson	1.77

[a], predictors: (Constant), SUA, CRP, LDH, NLR. S.E., standard error. ; SUA, serum uric acid; CRP, C-reactive protein; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio

Table 5 Results of the multiple linear regression analysis

Model	Coefficients[a]		t	P value	Capacity	VIF
	Unstandardized coefficients (β)	Standardized coefficients (β)				
SUA	−0.010	−0.130	−2.851	0.005	0.889	1.125
CRP	0.022	0.203	4.047	<0.001	0.731	1.369
LDH	0.006	0.256	5.349	<0.001	0.808	1.237
NLR	0.587	0.241	5.098	<0.001	0.830	1.205

[a], dependent variable: fever duration. SUA, serum uric acid; CRP, C-reactive protein; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; VIF, variance inflation factor.

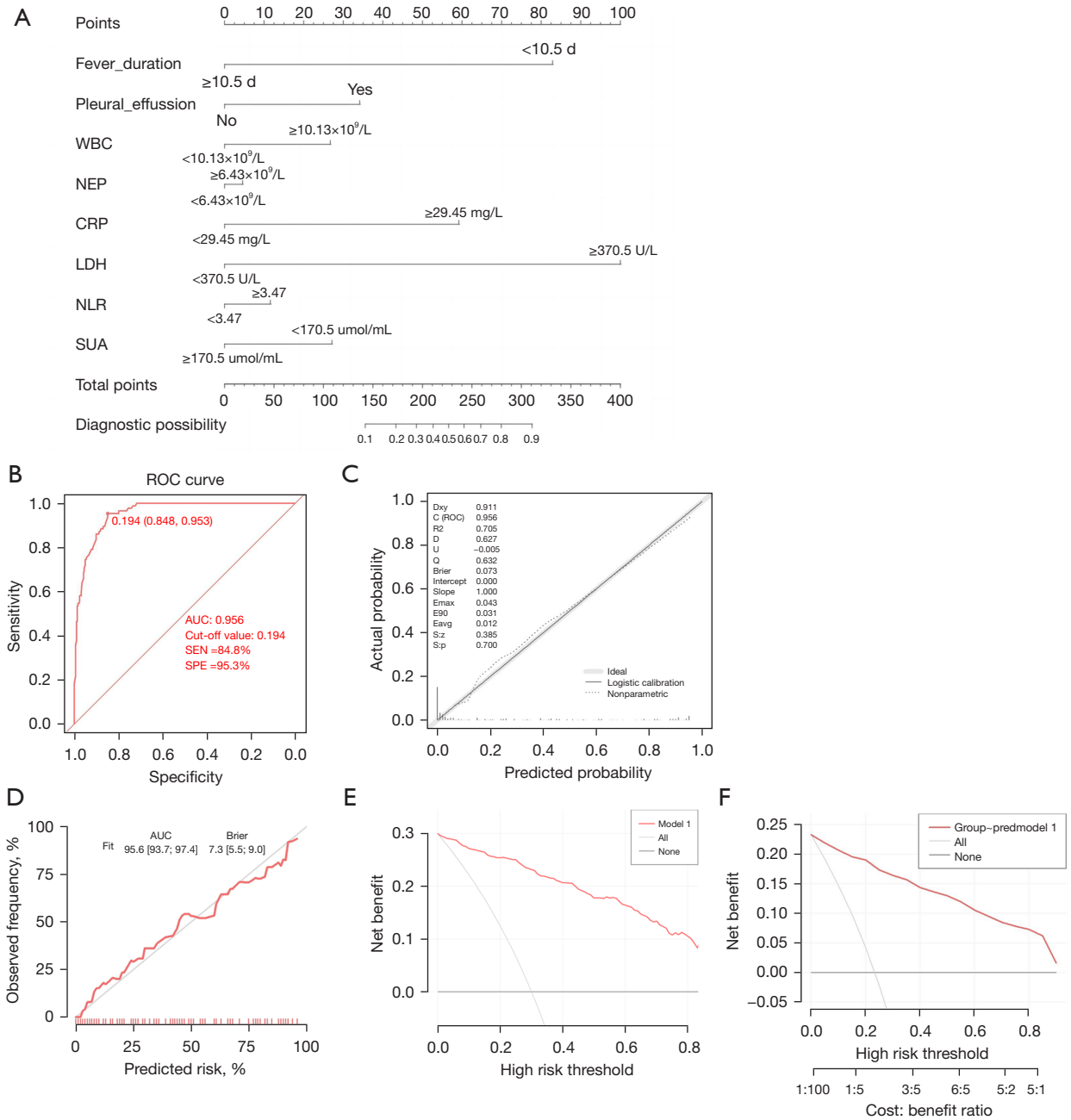

Figure 1 Establishment and validation of the risk nomogram model for early diagnosis of RMPP in children. (A) Nomogram to predict RMPP children was constructed based on 8 independent predictors, which is applied as follows: mark the value of these included factors on the corresponding axis. Draw a vertical line from the value to the top lines and get corresponding points. Then, sum the points from each variable value. Locate the sum on the total points scale and project it vertically on the bottom axis to obtain an RMPP risk. (B) The ROC curves of the prediction model. (C) Calibration plot of the prediction model. The ideal outcome (gray thick line), the logistic calibration (solid line) and the nonparametric outcome (dashed line) are depicted; (D) Calibration plot of the model after internal validation using the bootstrapping method. (E) DCA for the prediction model. The y-axis measured the net benefit. The black solid line represented the assumption that all patients had no RMPP. The gray solid line represented the assumption that all patients had RMPP. (F) DCA of the model after internal validation using the bootstrapping method. RMPP, refractory *Mycoplasma pneumoniae* pneumonia; WBC, white blood cell; NEP, neutrophil count; CRP, C-reactive protein; LDH, lactate dehydrogenase; NLR, neutrophil/lymphocyte ratio; SUA, serum uric acid; ROC, receiver operating characteristic; AUC, area under the curve; DCA, decision curve analysis.

surrogate marker for tissue damage. The results of many Chinese and international studies suggest that LDH and CRP have an important role in the early identification of RMPP and the utility time of glucocorticoid (18-21), but large sample studies are still needed to determine their value. Huang *et al.* showed that LDH greater than 339.0 U/L was an independent risk factor for predicting RMPP (5). Another result suggested that the best cut-off value of LDH for predicting RMPP was 384.5 U/L and the sensitivity and specificity were 78.1% and 80.8%, respectively, which is more consistent with the best cut-off value of this study (370.50 U/L) (22).

SUA is produced in the liver by xanthine oxidase oxidation, and it is the end-product of purine metabolism in the human body. It exists in the blood and is excreted with urine, and the kidneys play an important role in the regulation of uric acid level in the body, accounting for 60–70% of uric acid excretion (23). Therefore, renal function impairment or purine metabolism disorders cause changes in the body's uric acid levels (24). Uric acid has a variety of biological effects in the human body, which can promote the inflammatory response, and can also serve as an antioxidant and endogenous free radical scavenger; it is also closely related to adult chronic obstructive pulmonary disease. In addition to chronic obstructive pulmonary disease, respiratory diseases are also closely associated with pulmonary interstitial fibrosis, asthma, obstructive sleep apnea, and hypoventilation syndrome, lung cancer, and pneumonia. Meanwhile, uric acid is also present in the occurrence and development of diabetes, and liver, kidney, cardiovascular, cerebrovascular, and other systemic diseases (25,26). The majority of patients in the intensive care unit usually experience a variety of pathogenic processes, such as ischemia–reperfusion injury, inflammation, and coagulopathy. Uric acid may be a factor involved in the aforementioned pathogenic processes and may be of potential value for assessing changes in clinical conditions and disease outcomes. The results of this study suggest that a decreased SUA level may be a predictor of RMPP. The AUC was 0.744; the best cutoff value was 170.5 μmol/mL; the sensitivity was 0.651; and the specificity was 0.742. Although SUA is not the best predictor, the SUA level is a widely available and low-cost predictive RMPP index, which has certain clinical value. In addition, the results of multiple linear regression analysis showed a positive linear relationship between CRP, LDH, and NLR and the duration of the fever, suggesting that CRP, LDH, and NLR increased with the delay of fever duration. There is a negative linear relationship between SUA and the duration of the fever, suggesting that the SUA level decreases with the extension of fever duration, and whether it is of great significance for the pathogenesis, treatment, and prognosis of RMPP needs further study.

The mechanism of the reduced SUA levels in RMPP patients is unknown. The study found that the concentration of uric acid in respiratory epithelial tissue fluid was high, and the uric acid of respiratory epithelial lining fluid played an antioxidant effect together with other endogenous antioxidants and ascorbic acid (27). Uric acid was found to act as an endogenous modulator of innate immunity, so it is tempting to speculate that low levels of SUA may exacerbate the cytokine storm during coronavirus disease 2019 (COVID-19) (28,29). Recent evidence suggests that acute and severe hypouricemia induced in healthy individuals causes endothelial cell dysfunction (30). Recently, researchers have focused on SUA levels in COVID-19, believing that hyperuricemia in COVID-19 patients may lead to acute kidney injury and adverse outcome (31). A most recent clinical study showed that SUA exhibits protective effects in the pediatric MPP process, with an anti-inflammatory effect (32). All the above suggest that reduced SUA level is a risk factor for disease, but the specific mechanism needs further study.

Limitations and strengths

This study showed that SUA level and NLR are a widely available and low-cost predictive index with good clinical value. SUA levels and NLR indicators were added to the nomogram, which could more comprehensively and fully help clinicians to predict RMPP, especially in primary care hospitals. Moreover, this study is retrospective, and there may have been bias in case selection, which requires further validation by large sample prospective studies.

Conclusions

Fever duration of more than 10.5 days, pleural effusion, WBC >10.13×10^9/L, NEP >6.43×10^9/L, CRP >29.45 mg/L, LDH >370.50 U/L, NLR >3.47 and SUA <170.5 μmol/mL are early predictors of RMPP. This study shows that SUA and NLR are a widely available and cost-effective predictor with certain clinical value, and can provide a reference for clinicians, especially primary hospitals to diagnose RMPP. The developed nomogram, which has a satisfactory level of accuracy and good calibration, can be utilized to predict

RMPP patients. The model has been found to be useful in clinical practice and is clinically interpretable. In addition, the study found that the SUA level decreased with the extension of the fever duration, and whether this is of great significance to the pathogenesis, treatment, and prognosis of RMPP needs to be further studied. However, as this study was conducted retrospectively, there may have been bias in case selection, thus further validation is required via large sample prospective studies.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-16/rc

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-16/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Medical Ethics Committee of Xi'an Children's Hospital (reference number: 20230004) and informed consent was provided by the parents or legal guardians of the children.

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