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Construction of an early prediction model for exacerbation of pneumonia caused by *Mycoplasma pneumoniae* in children: an incremental value study based on dynamic changes in C-reactive protein and IgG subclasses

Konstrukcija modela za rano predviđanje egzacerbacije pneumonije izazvane *Mycoplasmom pneumoniae* kod dece: studija inkrementalne vrednosti zasnovana na dinamičkim promenama C-reaktivnog proteina i potklasa IgG

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Abstract

Background/Aim. Exacerbation of *Mycoplasma pneumoniae* pneumonia (MPP) in children commonly manifests as severe or refractory disease. The aim of this study was to evaluate the predictive value of the dynamic percentage change in C-reactive protein – CRP (ΔCRP%) and immunoglobulin (Ig) G1 subclass for the exacerbation of MPP in children, and to determine whether their incorporation into the basic prediction model improves the prediction of disease exacerbation. **Methods.** This retrospective study included hospitalized pediatric patients diagnosed with MPP between 2020 and 2023, who were enrolled and stratified according to the occurrence of MPP exacerbation. Baseline clinical characteristics, laboratory parameters, serial CRP measurements (at 0 and 72 hrs), and IgG1–IgG4 subclass levels were collected. According to the predicted probabilities generated by the enhanced model, patients were categorized into three risk groups: low-risk (< 0.20), medium-risk (0.20–0.35), and high-risk (≥ 0.35). **Results.** Among the 512 pediatric patients, 110 (21.5%) experienced MPP exacerbation. Multivariate analysis identified fever duration, bilateral lung involvement, decreased lymphocyte percentage, elevated lactate dehydrogenase, increased D-dimer, higher ΔCRP% (*per* 10 percentage-point increase), and low IgG1 levels as independent predictors ($p < 0.05$). The enhanced model demonstrated superior discriminative performance, with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.873, significantly higher than that of the basic model (0.792; $p = 0.004$). Risk stratification analysis showed a progressive increase in the observed exacerbation rate across the low-, medium-, and high-risk groups (approximately 10%, 30%, and 50%, respectively). **Conclusion.** Both ΔCRP% and low IgG1 levels are independent predictors of MPP exacerbation in children. The incorporation of these markers significantly improves the model's discrimination, calibration, and clinical utility for predicting the risk of disease progression.

Keywords:
biomarkers; c-reactive protein; disease progression; immunoglobulin g; models, statistical; mycoplasma pneumoniae; pneumonia, mycoplasma; prognosis.

Apstrakt

Uvod/Cilj. Egzacerbacija (pogoršanje) pneumonije izazvane *Mycoplasmom pneumoniae* (*Mycoplasma pneumoniae* pneumonija – MPP) kod dece obično se manifestuje kao teška ili refraktorna bolest. Cilj rada bio je da se proceni prediktivna vrednost dinamičke procentualne promene C-reaktivnog proteina – CRP (ΔCRP%) i potklase imunoglobulina (Ig) G1 za pogoršanje MPP kod dece kao i da se utvrdi da li njihovo uključivanje u osnovni prediktivni model poboljšava predviđanje pogoršanja bolesti. **Metode.** Ovom retrospektivnom studijom obuhvaćeni su pedijatrijski

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bolesnici sa dijagnozom MPP u periodu između 2020. i 2023. godine, koji su uključeni u studiju i svrstani u grupe prema pojavi pogoršanja MPP. Prikupljeni su početni klinički podaci, laboratorijski parametri, rezultati serijskih merenja CRP-a (u 0. i 72. satu), kao i nivoi potklasa IgG1–IgG4. Prema predviđenim verovatnoćama koje je generisao unapređeni model, bolesnici su podeljeni u tri grupe rizika: nizak rizik (< 0,20), srednji rizik (0,20–0,35) i visok rizik (≥ 0,35). **Rezultati.** Od 512 pedijatrijskih bolesnika, kod njih 110 (21,5%) zabeleženo je pogoršanje MPP. Multivarijantnom analizom kao nezavisni prediktori identifikovani su trajanje groznice, obostrana zahvaćenost pluća, snižen procenat limfocita, povišena laktat dehidrogenaza, povišen D-dimer, viši ΔCRP% (po povećanju od 10 procentnih poena) i niski nivoi IgG1 ($p < 0,05$). Unapređeni model je pokazao bolju diskriminativnu sposobnost, sa vrednošću površine ispod *receiver operating characteristic* (ROC) krive (*area under the curve* – AUC) od 0,873, što je značajno više nego kod osnovnog modela (0,792; $p = 0,004$). Analizom stratifikacije rizika pokazano je progresivno povećanje stope primećenih egzacerbacija u grupama niskog, srednjeg i visokog rizika (približno 10%, 30% i 50%, redom). **Zaključak.** I ΔCRP% i niski nivoi IgG1 nezavisni su prediktori egzacerbacije MPP kod dece. Uključivanje tih markera značajno poboljšava diskriminativnu sposobnost, kalibraciju i kliničku korisnost modela za predviđanje rizika od progresije bolesti.

Ključne reči:
biomarkeri; c-reaktivni protein; bolest, progresija; imunoglobulin g; modeli, statistički; mycoplasma pneumoniae; pneumonija, mikoplazma; prognoza.

Introduction

Mycoplasma pneumoniae (MP) is one of the most common pathogens responsible for community-acquired pneumonia in children, accounting for approximately 10–40% of cases among hospitalized pediatric patients [1]. Although most children experience mild disease with favorable outcomes, the incidence rate of MP pneumonia (MPP) exacerbation has increased in recent years. For example, a 2024 study involving 526 pediatric patients with MPP reported that approximately 12% developed severe disease [2]. These severe cases are characterized by a higher incidence of lung consolidation, progressive lung injury, and even respiratory failure compared with non-severe cases, resulting in prolonged hospitalization, increased treatment complexity, and a greater burden on healthcare resources. Although the pathogenesis of MPP remains incompletely understood, accumulating evidence suggests that a dysregulated inflammatory response, an immune dysfunction, and pathogen virulence are key contributing factors [3].

Currently, early identification of MPP exacerbation remains a major challenge in clinical practice. Most existing studies focus on risk assessment based on single inflammatory markers, imaging findings, or routine clinical variables at admission [4]. However, these methods may not adequately capture disease progression, as they rely on static measurements and fail to reflect the dynamic nature of the inflammatory response. For instance, C-reactive protein (CRP) is a commonly used inflammatory biomarker, but its predictive value based on a single measurement is limited by substantial inter-individual variability [5]. Emerging evidence indicates that CRP is not only a marker of inflammation but may also contribute to lung epithelial cell injury by activating p38 mitogen-activated protein kinase and mitochondrial apoptotic pathways, thereby being associated with worse clinical outcomes [6]. Moreover, immune function plays a critical role in MPP progression [7]. A previous study has shown that children with MPP exacerbation exhibit impaired activation of T cells, an imbalance in $CD4^+/CD8^+$ T-cell subsets, and reduced anti-inflammatory capacity [8]. Despite these findings, the role of immunoglobulin (Ig) G subclasses, such as IgG1, in the exacerbation of MPP remains insufficiently explored. Moreover, the relationship between humoral immune reserve indicators (such as IgG subclasses) and the risk of disease exacerbation has not been systematically investigated.

Therefore, the aim of this study was to evaluate the predictive value of the dynamic percentage change in CRP (ΔCRP%) and IgG subclasses for MPP exacerbation in children, integrating both inflammatory dynamics and humoral immune status by using the basic model (BM) and enhanced model (EM). This integrated approach aims to provide a practical tool for early risk stratification and individualized management of MPP exacerbation in children.

Methods

Study design and sample size estimation

A single-center retrospective cohort design was adopted in this study. According to the events *per* variable principle for prediction modeling, at least 10 outcome events are required *per* variable independent principle. Based on a planned inclusion of 12–15 candidate predictors, a minimum of 120 severe events was required. Considering the previously reported incidence of MPP exacerbation in children (approximately 20–25%), the estimated total sample size ranged from 480 to 600 cases. All consecutive patients meeting the inclusion criteria during the study period were screened, and only those with complete data for key variables, including CRP measurements at both 0 and 72 hrs and IgG subclass levels, were included in the final analysis. No cases with missing data for these variables were retained, and a complete-case analysis was performed. A total of 512 pediatric patients were ultimately enrolled, including 110 (21.5%) cases of MPP exacerbation, thereby meeting the predefined sample size requirements and ensuring adequate statistical power.

Subjects and eligibility criteria

Children diagnosed with MPP and hospitalized between January 2020 and December 2023 were consecutively en-

rolled. Complete clinical data, laboratory results, IgG subclass measurements, and follow-up information were available for all included patients. The study was approved by the Ethics Committee of the People's Hospital of Cangnan, China (from January 02, 2020), and all procedures complied with relevant ethical standards.

Inclusion criteria were as follows: age 1 to 16 years; meeting at least one of the following clinical and etiological diagnostic criteria for MPP [9]: a positive MP polymerase chain reaction (PCR) result from throat swabs or respiratory secretions, an MP-specific IgM antibody titer ≥ 1 : 160 or a ≥ 4-fold increase in paired sera, and completion of CRP measurements at 0 and 72 hrs after admission.

The exclusion criteria were the following: diagnosed immunodeficiency or ongoing long-term immunosuppressive therapy; co-infection with other pathogens (such as influenza virus, adenovirus, or *Streptococcus* (*S.*) *pneumoniae*, etc.) or mixed infections, and presence of severe underlying diseases (such as congenital heart disease, neuromuscular disease, or chronic lung disease).

Etiological confirmation

Respiratory specimens were collected to detect MP deoxyribonucleic acid – DNA using real-time fluorescence quantitative PCR, which served as a primary basis for confirming the diagnosis of MPP. Commercial nucleic acid amplification kits (Daan Gene, Guangzhou, China) were used according to the manufacturer's instructions, with a cycle threshold value < 35 considered positive. To exclude mixed infections, all patients were concurrently screened for common respiratory viruses and bacterial pathogens, such as influenza virus, adenovirus, respiratory syncytial virus, and *S. pneumoniae*. Only patients with confirmed single MP infection were included in the subsequent modeling and analysis.

Collection of clinical data

Baseline data, including age, gender, previous illnesses, fever duration prior to admission, presence of wheezing, extent of radiological involvement (unilateral or bilateral), and use of glucocorticoid during hospitalization, were collected.

All imaging findings were independently reviewed by two experienced pediatric radiologists in a double-blind manner. In cases of disagreement, a third senior radiologist adjudicated the final interpretation to ensure consistency. Bilateral lung involvement was defined as the presence of consolidation, infiltrates, or reticular patterns in both lungs.

The primary outcome of this study was defined as MPP exacerbation, operationalized as a composite endpoint occurring during hospitalization. Specifically, MPP exacerbation was defined as the occurrence of at least one of the following criteria: the requirement for non-invasive or invasive mechanical ventilation; a significant decrease in the PaO_2/FiO_2 ratio indicating respiratory impairment; the development of imaging-confirmed pleural effusion or the rapid progression of lung consolidation on serial imaging. These criteria were considered clinically relevant indicators of disease exacerbation, and fulfillment of any single criterion was deemed sufficient to classify a case as having experienced exacerbation (such as an "or" composite definition), without applying a hierarchical weighting scheme.

Outcome ascertainment was performed retrospectively based on a comprehensive review of electronic medical records, including clinical notes, laboratory data, and imaging reports throughout hospitalization. To enhance the reliability of outcome classification, two independent senior pediatric clinicians, blinded to model variables, reviewed all cases. In cases of disagreement, a third senior clinician adjudicated the final classification. The same double-blind principle applied to imaging interpretation was extended to outcome assessment to ensure consistency.

Detection of laboratory indicators

All routine laboratory tests were performed within 24 hrs after admission, and key biochemical parameters were reassessed at 72 hrs to evaluate dynamic changes in inflammatory status. Hematological parameters, including white blood cell (WBC) count and lymphocyte percentage, were measured using a Sysmex XN-series automated hematology analyzer (Sysmex Corporation, Kobe, Japan). Biochemical markers, including lactate dehydrogenase (LDH) and D-dimer, were measured using an AU5800 full-automatic biochemistry analyzer (Beckman Coulter Inc., Brea, CA, USA). All assays were conducted using serum or plasma as appropriate for each test, and standard quality control and calibration procedures were strictly followed to ensure the accuracy and reliability of the measurements. Detailed age-specific reference ranges for laboratory parameters used in the present study are provided in Supplementary Table 1.

Measurement of the inflammatory marker C-reactive protein

CRP levels were measured using immunoturbidimetry on AU-series full-automatic biochemistry analyzers (Beckman Coulter Inc., Brea, CA, USA). To assess dynamic changes in the inflammatory response, CRP was measured at admission (CRP_{0hrs}) and approximately 72 hrs after admission (CRP_{72hrs}). ΔCRP% was calculated as a percentage change in CRP levels using the following formula: $\Delta CRP\% = (CRP_{72hrs} - CRP_{0hrs}) / CRP_{0hrs} \times 100\%$. Thus, ΔCRP% represents the percentage-point change in CRP over 72 hrs. For regression analyses, ΔCRP% was scaled *per* 10 percentage-point increase to improve interpretability of effect estimates. A positive ΔCRP% indicates persistence or an increase of inflammation, whereas a negative value reflects a decline.

Detection of immunoglobulin G subclasses as immunological indicators

Serum IgG subclasses (IgG1, IgG2, IgG3, and IgG4) were measured using immunonephelometry on a BN-series nephelometer (Mindray® Bio-Medical Electronics Co., Ltd., Shenzhen, China). The testing results were evaluated against

age-stratified reference intervals provided by the manufacturer for the BN-series system, which are routinely applied in clinical laboratory practice. Specifically, age-specific lower limits of normal were used for each IgG subclass, and patients were classified as having "low" levels if their measured values fell below the corresponding age-adjusted threshold. Given the wide age range of the study population (1–16 years), the detailed age-stratified reference intervals used for classification are provided in Supplementary Table 2 to ensure transparency and reproducibility. A low IgG1 level was considered an important marker of impaired humoral immunity reserve and was incorporated as a key immunological predictor in EM. Measurement of IgG subclasses facilitates assessment of immune function in pediatric patients and enables exploration of their potential associations with the risk of disease exacerbation.

Construction of logistic regression prediction models

Prediction models for the risk of MPP exacerbation in children were developed using a logistic regression framework, including BM and EM. Prior to model construction, the linearity assumption between continuous predictors and the logit of the outcome was evaluated using the Box-Tidwell test and visual inspection of locally weighted scatterplot smoothing (locally estimated scatterplot smoothing – LOESS) curves. The results indicated that most continuous variables, including lymphocyte percentage, LDH, and D-dimer, approximately satisfied the linearity assumption. For ΔCRP%, although mild deviation from strict linearity was suggested by exploratory analysis and SHapley Additive exPlanations (SHAP) plots, the relationship was considered approximately linear within the main data range; therefore, it was retained as a continuous variable in the logistic regression model for interpretability. No variables required transformation using restricted cubic splines or categorization. Given the potential for nonlinearity, ΔCRP% was additionally scaled *per* 10 percentage-point increase to improve model stability and interpretability of the regression coefficients. Moreover, the variables with significant multicollinearity (variance inflation factor > 5) were excluded or combined.

BM included routine clinical and laboratory variables, including age, fever duration, WBC count, lymphocyte percentage, LDH, D-dimer levels, and extent of imaging involvement (unilateral/bilateral). Based on this model, two additional predictors, namely ΔCRP% and IgG1_low (0/1), were incorporated to construct EM. EM was developed to assess the incremental predictive value of dynamic inflammatory changes and humoral immune reserve in estimating the risk of MPP exacerbation. Model performance was comprehensively assessed in terms of discrimination, calibration, and clinical utility. Furthermore, to explore potential nonlinear effects and interactions among predictors, the eXtreme Gradient Boosting (XGBoost) algorithm combined with SHAP was employed to enhance interpretability and validate the robustness of the findings. Model performance was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC), sensitivity, and specificity were calculated and compared between the two models. Differences in AUC were assessed using the DeLong test.

Goodness-of-fit and calibration performance of the logistic regression model

Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit (HL test). Calibration performance was evaluated using calibration curves, calibration slopes, and intercepts to examine the agreement between predicted probabilities and observed event rates.

Decision curve analysis

Decision curve analysis (DCA) was performed to evaluate the clinical net benefit of the models across a range of threshold probabilities. The performance of EM, BM, and "Treat All"/"Treat None" strategies was compared to assess their clinical utility. Models demonstrating higher net benefit across a broader range of thresholds were considered to have greater clinical applicability.

Internal validation of the enhanced model

The stability and generalization ability of EM were evaluated using bootstrap resampling (1,000 resamples). For each resampling, the model was reconstructed, and the AUC was calculated, generating an empirical distribution of AUC values and enabling estimation of a bootstrap-corrected AUC. This procedure was applied to reduce optimism bias and mitigate the impact of overfitting on performance estimates. Model calibration was further assessed using the Brier score as a measure of overall prediction error, with lower values indicating better calibration and more accurate probability estimates.

Risk stratification analysis of the enhanced model

Patients were categorized into three risk groups according to the predicted probabilities generated by EM: low-risk (< 0.20), medium-risk (0.20–0.35), and high-risk (≥ 0.35). Observed incidence rates of MPP exacerbation were compared across these groups to evaluate the model's risk stratification performance and clinical interpretability. A progressive increase in event rates across risk categories was considered indicative of effective risk discrimination, supporting the use of the model for risk-adapted clinical management.

Establishment of a nonlinear model and analysis of interpretability (XGBoost + SHAP)

In the present study, an XGBoost-based nonlinear prediction model was developed to validate the robustness of incremental indicators (ΔCRP% and IgG1_low) and to explore potential nonlinear effects. Model hyperparameters were optimized using 5-fold cross-validation, so as to enhance generalizability. Following model training, the SHAP framework was applied to quantify the contribution and im-

portance of individual features. SHAP summary plots were generated to illustrate the global ranking of feature importance. In addition, SHAP dependence plots were used to evaluate the marginal effects of key variables (such as ΔCRP% and IgG1_low) at different values and to explore their interactions with other predictors, such as lymphocyte percentage and LDH. This approach complements the logistic regression model by capturing complex nonlinear relationships and interaction patterns, thereby improving model interpretability and supporting the biological plausibility of the identified predictors.

Statistical analysis

All statistical analyses were performed using SPSS version 26.0 and Python version 3.10. The distribution of continuous variables was assessed using the Shapiro-Wilk normality test. Normally distributed variables are presented as mean ± standard deviation and were compared using the independent-samples *t*-test. Non-normally distributed variables are expressed as median (interquartile range – IQR) and were compared using the Mann-Whitney *U* test. Categorical variables are presented as frequencies (percentages) and were compared using the χ^2 test or Fisher's exact test, as appropriate. Variables with $p < 0.10$ in univariate analysis were entered into multivariate logistic regression analysis. Independent predictors were identified using a bidirectional stepwise selection procedure. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Comparison of clinical baseline characteristics and laboratory features in pediatric patients

A total of 512 pediatric patients with confirmed MPP were included in this study, of whom 110 (21.5%) experienced exacerbation. Compared with the non-exacerbation group, patients in the exacerbation group were younger, had a longer duration of fever, and exhibited a higher proportion of bilateral lung involvement ($p < 0.05$). Laboratory findings showed that WBC count, LDH, and D-dimer levels were elevated, whereas lymphocyte percentage was lowered in the exacerbation group. A significant difference in the magnitude of CRP dynamic percentage change (ΔCRP%) was observed ($p < 0.001$), indicating that a persistent inflammatory response is closely associated with disease exacerbation. Disease immunological indicators, low IgG1 and IgG4 levels, were more frequently observed in the exacerbation group ($p < 0.01$), whereas no significant differences were found for IgG2 and IgG3 levels. Moreover, patients in the exacerbation group had longer hospital stays and a higher rate of corticosteroid use ($p < 0.001$) (Table 1). Overall, age, duration of fever, extent of radiological involvement, dynamic changes in CRP, and abnormalities in IgG subclasses were significantly associated with MPP exacerbation and were, therefore, considered candidate predictors for subsequent model development.

Table 1

Baseline features of enrolled children

Variable	Groups		Statistical value	*p*-value
	non-exacerbation (n = 402)	exacerbation (n = 110)		
Age, years	6.6 ± 2.7	5.7 ± 3.1	$t = 2.54$	0.012
Male	218 (54.2)	66 (60.0)	$\chi^2 = 1.16$	0.28
Duration of fever before admission, days	6.1 ± 2.0	7.1 ± 2.6	$t = 3.81$	< 0.001
Bilateral lung involvement	104 (25.9)	60 (54.5)	$\chi^2 = 32.7$	< 0.001
History of wheezing	61 (15.2)	15 (13.6)	$\chi^2 = 0.17$	0.68
WBC count, $\times 10^9$/L	8.4 ± 3.4	9.8 ± 4.0	$t = 2.97$	0.003
Lymphocyte, %	33.9 ± 12.8	27.3 ± 12.5	$t = 4.11$	< 0.001
LDH, U/L	345 (275–416)	427 (360–512)	$Z = 4.55$	< 0.001
D-dimer, mg/L	0.55 (0.35–0.88)	0.97 (0.63–1.65)	$Z = 4.27$	< 0.001
CRP_{0hrs}, mg/L	43.2 ± 26.5	63.5 ± 30.4	$t = 6.05$	< 0.001
ΔCRP%	-33.8 ± 38.9	+8.9 ± 47.1	$t = 7.71$	< 0.001
Low levels, g/L				
IgG1	47 (11.7)	31 (28.2)	$\chi^2 = 15.6$	< 0.001
IgG2	38 (9.5)	18 (16.4)	$\chi^2 = 3.99$	0.046
IgG3	27 (6.7)	7 (6.4)	$\chi^2 = 0.01$	0.91
IgG4	26 (6.5)	16 (14.5)	$\chi^2 = 7.62$	0.006
Glucocorticoid use	60 (14.9)	44 (40.0)	$\chi^2 = 33.3$	< 0.001
Length of hospital stay, days	7 (6–9)	11 (9–15)	$Z = 7.92$	< 0.001

WBC – white blood cell; LDH – lactate dehydrogenase; CRP – C-reactive protein; IgG – immunoglobulin G; n – number of patients.

Values are given as numbers (percentages) or mean ± standard deviation, except for length of hospital stay, LDH, and D-dimer, which are expressed as median (interquartile range).

***Note*: Reference ranges for D-dimer and CRP for all pediatric ages: < 0.5 mg/L, < 8 mg/L, respectively. Other reference ranges are shown in Supplementary Table 1.**

Results of univariate and multivariate logistic regression analyses

All continuous variables were assessed for linearity with the logit prior to modeling. Most variables approximately satisfied the linearity assumption. Although ΔCRP% showed mild deviation from strict linearity, it was considered approximately linear within the main data range and was, therefore, retained as a continuous variable. Univariate analysis showed that age, duration of fever, bilateral lung involvement, WBC count, lymphocyte percentage, LDH, D-dimer, ΔCRP%, and low IgG1 and IgG4 levels were significantly associated with MPP exacerbation ($p < 0.05$). Variables with $p < 0.10$ in univariate analysis were entered into multivariate logistic regression. Duration of fever [odds ratio (OR) = 1.18, 95% confidence interval (CI): 1.05–1.34, $p = 0.007$], bilateral lung involvement (OR = 2.41, 95% CI: 1.45–4.01, $p = 0.001$), lymphocyte percentage (OR = 0.97, 95% CI: 0.95–0.99, $p = 0.008$), LDH (OR = 1.003, 95% CI: 1.001–1.006, $p = 0.012$), D-dimer (OR = 1.79, 95% CI: 1.05–3.06, $p = 0.032$), ΔCRP% (*per* 10 percentage-point increase) (OR = 1.22, 95% CI: 1.08–1.38, $p = 0.001$), and low IgG1 (OR = 2.15, 95% CI: 1.18–3.94, $p = 0.012$) were identified as independent predictors of MPP exacerbation in children (Table 2).

Glucocorticoid use, as an intervention-related variable, was excluded from the primary prediction model because corticosteroid administration was a post-admission treatment decision potentially influenced by early clinical severity assessment. To evaluate potential confounding by indication, sensitivity analyses were additionally performed. After further adjustment for glucocorticoid use as a covariate, ΔCRP% (adjusted OR = 1.19, 95% CI: 1.05–1.35, $p = 0.006$) and low IgG1 status (adjusted OR = 2.02, 95% CI: 1.10–3.73, $p = 0.024$) remained independently associated with MPP exacerbation. Similar findings were observed after excluding patients who received glucocorticoid therapy during hospitalization, with no material changes in model discrimination or effect estimates, supporting the robustness of the primary model.

Discriminating performance of logistic regression models

To evaluate model discrimination, BM and EM were constructed for comparison. BM incorporated routine clinical variables, such as age, duration of fever, WBC count, lymphocyte percentage, LDH, D-dimer, and extent of radiological involvement. EM further incorporated ΔCRP% and low IgG1 status (IgG1_low). ROC analysis showed that both models demonstrated good discriminative performance for predicting MPP exacerbation in children. BM achieved an AUC of 0.792 (95% CI: 0.743–0.838), sensitivity of 73.6%, and specificity of 71.2%. EM showed improved performance, with an AUC of 0.873 (95% CI: 0.835–0.908), sensitivity of 82.7%, and specificity of 80.4% (Figure 1). The difference in AUC between the two models was 0.083 ($p = 0.004$), indicating that the inclusion of ΔCRP% and low IgG1 significantly improved model discrimination. These findings suggest that dynamic inflammatory changes and humoral immune dysfunction provide additional predictive value for MPP exacerbation in children.

Goodness-of-fit and calibration performance of logistic regression models

To further evaluate the agreement between predicted probabilities and observed event rates, the HL test and calibration curves were applied. EM yielded an HL test *p*-value of 0.72, indicating adequate model fitting. Similarly, BM

Table 2

Results of univariate and multivariate logistic regression analyses for MPP exacerbation in children

Variable	OR of univariate analysis (95% CI)	*p*-value	OR of multivariate analysis (95% CI)	*p*-value
Age, years	0.89 (0.82–0.96)	0.003	0.92 (0.84–1.01)	0.074
Duration of fever, days	1.32 (1.17–1.49)	< 0.001	1.18 (1.05–1.34)	0.007
Bilateral lung involvement	3.49 (2.25–5.40)	< 0.001	2.41 (1.45–4.01)	0.001
WBC count, $\times 10^9$/L	1.09 (1.03–1.16)	0.004	1.05 (0.98–1.13)	0.165
Lymphocyte, %	0.95 (0.93–0.97)	< 0.001	0.97 (0.95–0.99)	0.008
LDH, U/L	1.006 (1.004–1.009)	< 0.001	1.003 (1.001–1.006)	0.012
D-dimer, mg/L	2.84 (1.83–4.41)	< 0.001	1.79 (1.05–3.06)	0.032
Initial CRP level, mg/L	1.02 (1.01–1.03)	< 0.001	–	–
ΔCRP% (*per* 10 percentage-point increase)	1.31 (1.19–1.45)	< 0.001	1.22 (1.08–1.38)	0.001
Low levels, g/L				
IgG1	2.96 (1.72–5.08)	< 0.001	2.15 (1.18–3.94)	0.012
IgG4	2.44 (1.19–4.98)	0.015	1.89 (0.92–3.87)	0.083
Glucocorticoid use	3.91 (2.44–6.27)	< 0.001	–*	–*

MPP – *Mycoplasma pneumoniae* pneumonia; OR – odds ratio; CI – confidence interval; WBC – white blood cell; LDH – lactate dehydrogenase; CRP – C-reactive protein; IgG – immunoglobulin G.

***Note*: *Glucocorticoid use as an intervention-related variable was excluded from the prediction model. The multivariate model was constructed using bidirectional stepwise regression, incorporating variables with $p < 0.10$ identified in univariate analysis. For reference ranges for laboratory parameters, see Table 1 and Supplementary Table 1.**

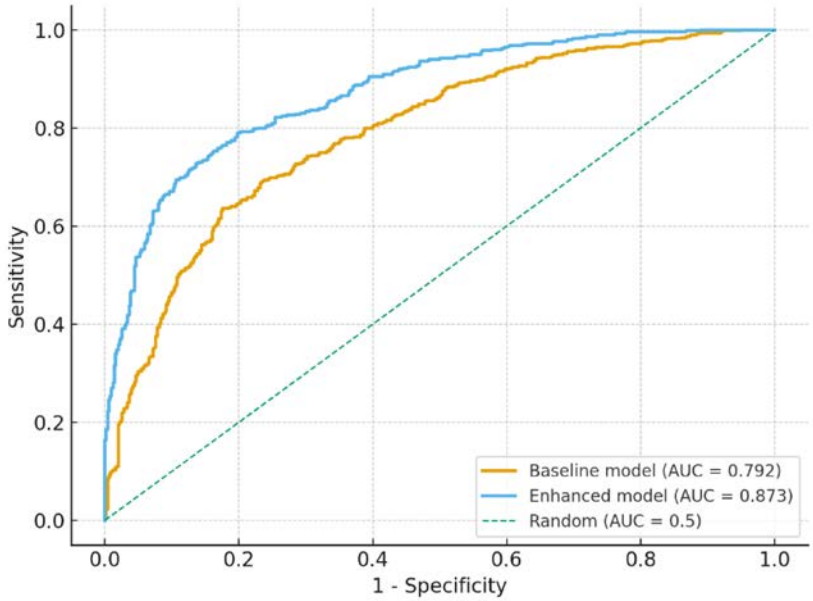

Fig. 1 – Comparison of receiver operating characteristic curves for the discriminating performance of logistic regression models.
AUC – area under the curve.

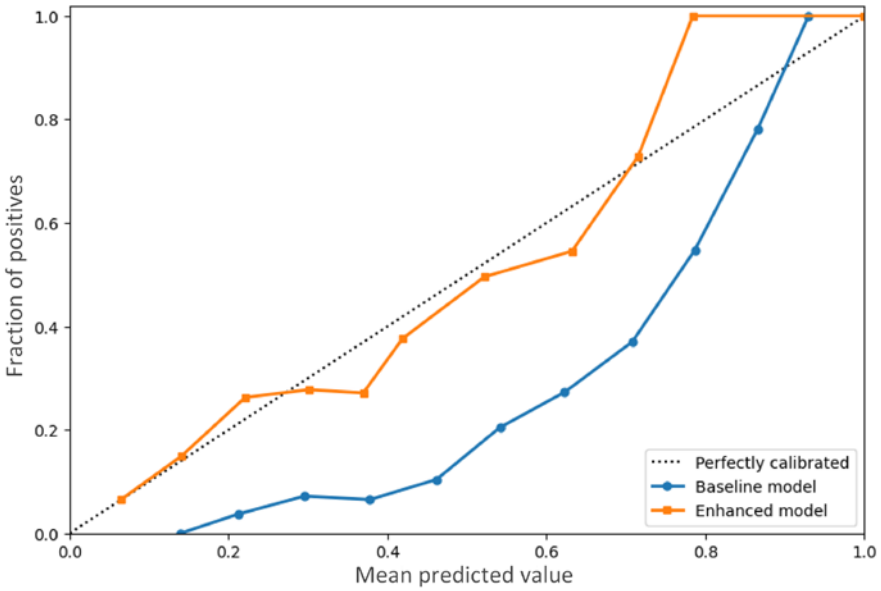

Fig. 2 – Comparison of calibration curves of logistic regression models.

showed a *p*-value of 0.41, which also indicates acceptable calibration with no evidence of poor fit. In both models, predicted probabilities generally increased with higher observed risk of severe disease. However, the calibration curve of EM was closer to the ideal reference line, indicating better agreement between predicted and observed outcomes. By contrast, BM demonstrated a tendency to underestimate risk in the medium-to-high probability range. Compared with BM, EM demonstrated improved calibration performance, as reflected by a calibration slope closer to 1 and an intercept closer to 0, indicating better agreement between predicted and observed risks across the full range of probabilities. Overall, although both models demonstrated acceptable calibration based on the HL test, EM showed superior calibration characteristics based on graphical assessment and calibration metrics, supporting its greater reliability for early risk stratification in clinical practice (Figure 2).

Decision curve analysis results of logistic regression models

DCA was performed to evaluate the clinical net benefit of the prediction models across a range of threshold probabilities. Within the threshold probability range of 0.1–0.7, EM consistently demonstrated higher net benefits than BM as well as the "Treat All" and "Treat None" strategies, indi-

cating superior clinical utility across a broad range of decision thresholds. Notably, EM showed the greatest improvement in net benefit within the 0.2–0.5 threshold range, suggesting that the inclusion of ΔCRP% and IgG1_low substantially enhances the model's clinical applicability (Figure 3). Overall, EM not only improved discriminative performance but also reduced potential clinical harm associated with overtreatment and missed diagnoses, thereby providing more practical support for risk stratification and individualized management of MPP exacerbation in children.

Results of internal validation of the enhanced model

Internal validation of EM was performed with 1,000 bootstrap resamples. The median bootstrap-corrected AUC was 0.823 (95% CI: 0.785–0.865), which was consistent with the apparent AUC, indicating a low risk of overfitting (Figure 4A). Calibration curves demonstrated excellent agreement between predicted probabilities and observed event rates. The model showed strong calibration in the low- and medium-risk ranges, with a slight overestimation in the high-risk group. However, the overall trend remained close to the ideal reference line (Figure 4B). The Brier score of the model was 0.114, further confirming good calibration performance and overall predictive accuracy.

Stratification results of the enhanced model-predicted risks

Applying the stratification into three groups according to model-predicted probabilities, the observed incidence of MPP exacerbation was approximately 10% in the low-risk

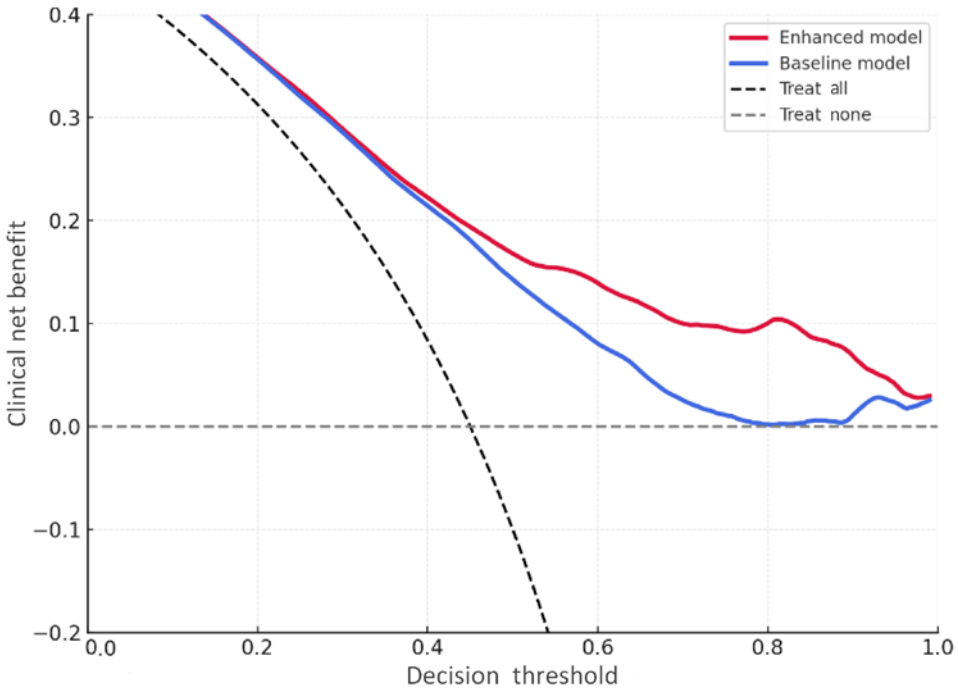

Fig. 3 – Decision curve analysis results of logistic regression models.

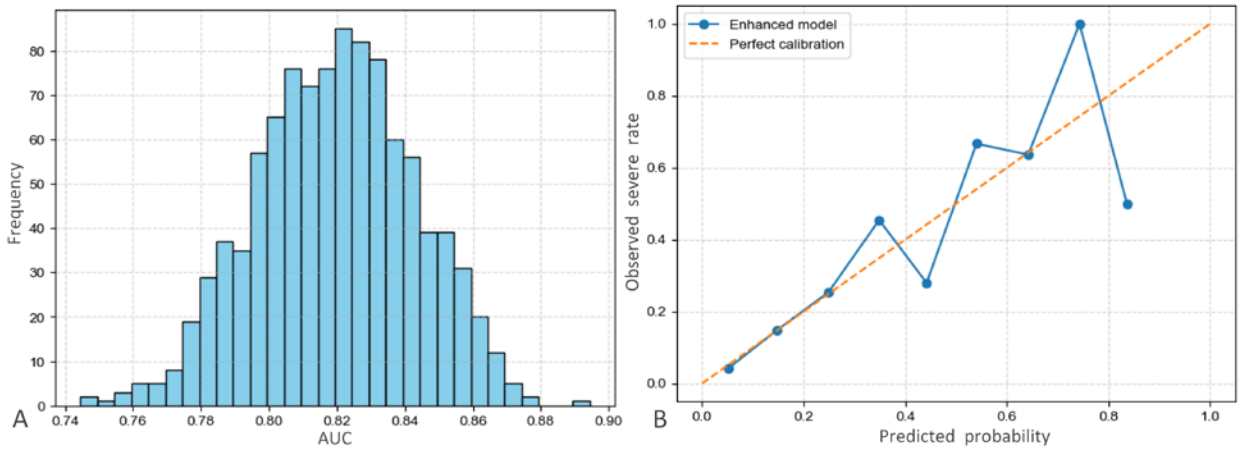

Fig. 4 – Results of internal validation of enhanced model: A) bootstrap distribution of area under curve (AUC) (1,000 resamples); B) calibration curve.

group, which was substantially lower than the overall rate. The incidence increased to approximately 30% in the medium-risk group and further increased to around 50% in the high-risk group, consistent with the model-predicted trends. A clear stepwise increase in event rates was observed across the three risk groups, indicating good discriminatory ability of the model for identifying patients at different levels of exacerbation risk. Notably, the high-risk group exhibited an exacerbation rate of nearly 50%, highlighting its clinical relevance for identifying patients who may benefit from early intervention or closer monitoring. In contrast, the low-risk group showed a markedly lower risk, supporting the potential to reduce unnecessary treatments or imaging examinations in this population (Figure 5).

Nonlinear XGBoost model and SHAP interpretability analysis

To further examine the robustness of key predictors and enhance model interpretability, a nonlinear classification model based on XGBoost was developed using the same feature set as the enhanced logistic model. The XGBoost algorithm can automatically capture nonlinear relationships and higher-order interactions among variables, thereby complementing the limitations of linear logistic regression models in modeling complex feature contributions. SHAP analysis was subsequently applied to interpret the model. The XGBoost model exhibited good predictive performance during 5-fold cross-validation, with a mean AUC of 0.851 (95% CI: 0.823–0.884), sensitivity of 80.2%, and specificity of 77.5% (Supplementary Figure 1). These findings indicated acceptable out-of-sample discrimination and supported the reliability of subsequent SHAP-based interpretability analyses.

The SHAP summary plot of the XGBoost model (Figure 6A) was largely consistent with the results of the logistic regression model, identifying lymphocyte percentage, duration of fever, bilateral lung involvement, ΔCRP%, and low IgG1 as key contributors to the prediction of MPP exacerbation. Notably, ΔCRP% and low IgG1 demonstrated more pronounced contributions in the nonlinear model, suggesting that these variables may exert complex, interaction-dependent effects beyond simple linear associations.

SHAP dependency plots further elucidated potential interaction patterns among variables. For ΔCRP%, SHAP values increased markedly in the case of “insufficient decline” or “re-escalation”, indicating that persistent inflammatory activity is strongly associated with a higher risk of exacerbation. This effect was further amplified in the presence of lymphopenia, reflecting a combined effect of increased inflammatory burden and impaired immune response (Figure 6B). For low IgG1 status, SHAP values were consistently higher when IgG1_low = 1, indicating that reduced humoral immune reserve is an important risk factor. This effect was more pronounced in patients with elevated LDH, suggesting a potential synergistic interaction between immune dysfunction and tissue injury (Figure 6C).

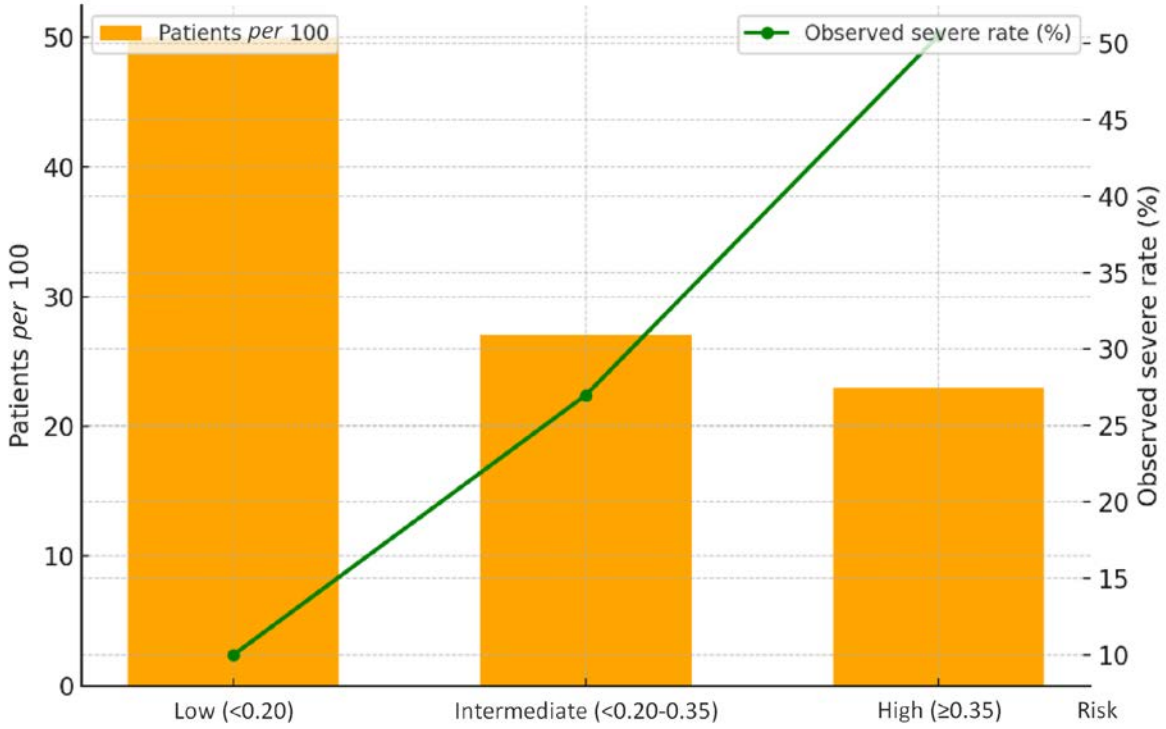

Fig. 5 – Stratification results of the enhanced model-predicted risks.

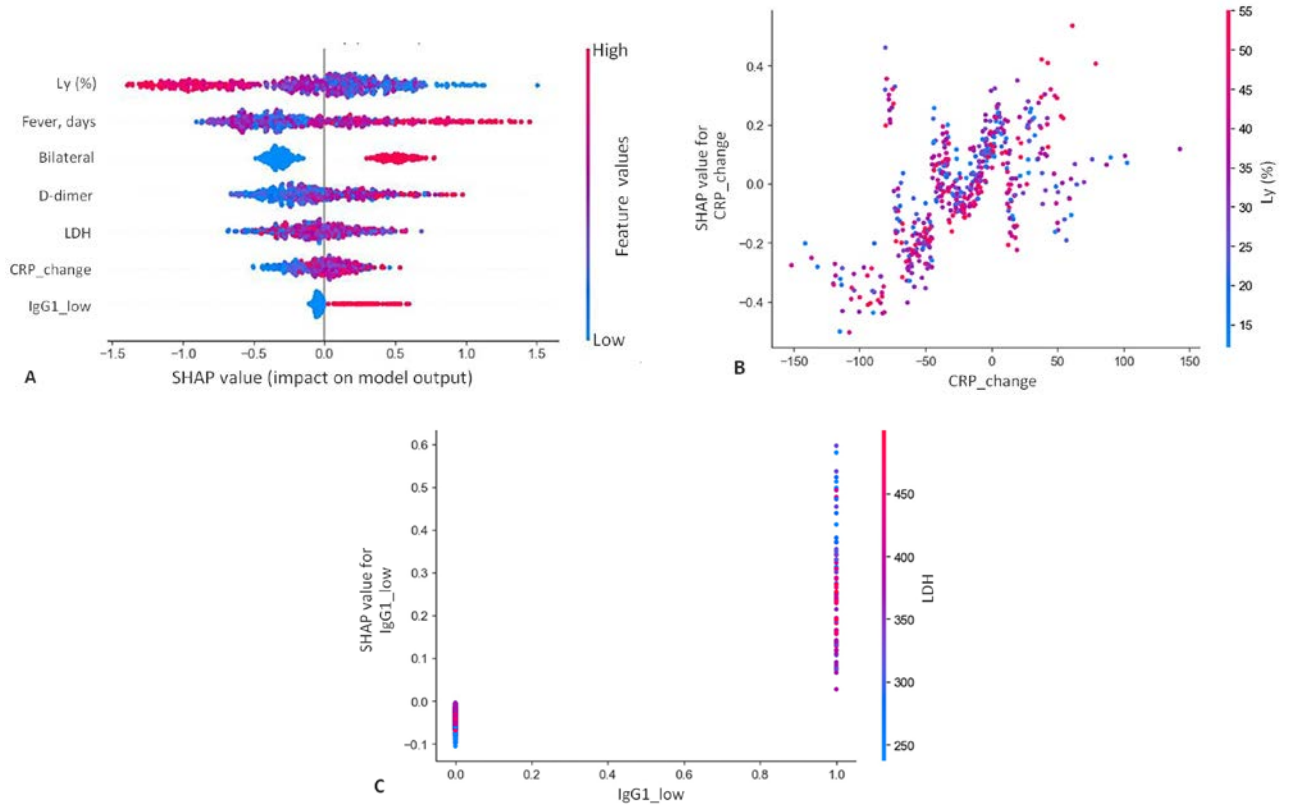

Fig. 6 – Nonlinear XGBoost model and SHAP interpretability analysis results: A) SHAP summary plot of the XGBoost model; B) SHAP dependence plot of CRP change (ΔCRP%); C) SHAP dependence plot of IgG1 low status. XGBoost – eXtreme Gradient Boosting; SHAP – SHapley Additive exPlanations; CRP – C-reactive protein; IgG – immunoglobulin G; Ly – lymphocyte; LDH – lactate dehydrogenase.

Discussion

In the present study, we systematically evaluated the predictive value of ΔCRP% and low IgG1 for disease exacerbation using clinical data from 512 pediatric patients with MPP. Both BM and EM were developed and compared. EM, incorporating ΔCRP% and IgG1_low, demonstrated superior predictive performance compared with BM (AUC = 0.083), along with good model calibration and effective risk stratification.

CRP is a crucial marker of inflammatory response, and its dynamic change (ΔCRP%) may better reflect the persistence and intensity of inflammation than a single measurement [10]. In this study, ΔCRP% made a substantial contribution to EM and showed interactions with lymphocyte percentage and LDH. These findings are consistent with previous research results. For example, Zhang et al. [11] reported that the combined detection of CRP and LDH could serve as a marker of disease severity in pediatric MPP. Besides, Reccardini et al. [12] also uncovered an association between ΔCRP% and disease progression, supporting the relevance of CRP changes in predicting clinical deterioration. The predictive value of ΔCRP% likely lies in its ability to capture the temporal evolution of inflammatory responses, whereas static CRP measurements may not fully reflect the trajectory of disease progression.

IgG1 is a major component of humoral immunity, and reduced levels may impair pathogen clearance and host defense [13]. In our study, low IgG1 was identified as an important contributor to EM and interacted with lymphocyte percentage. Lee et al. [14] reported a 1-year mortality rate of 56% in patients with IgG1 deficiency compared with deficiencies in other IgG subclasses, suggesting its potential prognostic relevance. Moreover, IgG1 deficiency has been associated with increased susceptibility to infections and immune dysregulation [15]. Taken together, these findings suggest that reduced IgG1 levels may contribute to persistent infection and sustained inflammatory responses, thereby increasing the risk of disease exacerbation.

The results of the XGBoost model were largely consistent with those of the enhanced logistic regression model, while additionally revealing nonlinear and interaction effects that cannot be captured by the latter. These findings further support the critical roles of dynamic CRP changes and low IgG1 in the MPP exacerbation in children. The complementary use of these modeling approaches strengthens the robustness of model interpretation and provides mechanistic insight into the clinical significance of persistent inflammation and impaired immune reserve.

EM demonstrated improved discriminative performance and satisfactory calibration, indicating that the inclusion of ΔCRP% and IgG1_low provides incremental predictive val-

ue. This finding is consistent with previous studies emphasizing the advantages of multiparametric models in MPP risk assessment. For instance, Chen et al. [5] showed that composite indicators, such as CRP-neutrophil to lymphocyte ratio (C-NLR) and lymphocyte-CRP ratio (LCR), improved the prediction of refractory MPP. Furthermore, the XGBoost + SHAP analysis in our study revealed potential interactions between ΔCRP%, IgG1_low, and other variables (such as lymphocyte percentage and LDH), suggesting that these factors may jointly influence disease progression. For instance, reduced lymphocyte percentage may reflect immune suppression, while elevated LDH may indicate tissue injury. Their combined effects with ΔCRP% and IgG1_low may contribute to a higher risk of exacerbation [16].

Risk stratification analysis further demonstrated that the observed incidence of severe disease increased from approximately 10% in the low-risk group to nearly 50% in the high-risk group, highlighting the clinical relevance of the model. These findings support the potential utility of early risk identification in guiding clinical management. Jiang et al. [17] reported that early recognition of high-risk patients enables timely adjustment of treatment strategies, such as the use of immunomodulatory therapy or intensified supportive care, thereby improving outcomes. In addition, previous studies have shown that inflammatory biomarkers (such as CRP and IgM) can help predict the complications of MPP, including pleural effusion [18, 19]. Building on this evidence, our study suggests that ΔCRP% and IgG1_low may provide additional value in predicting overall exacerbation risk.

Limitation of the study

Nevertheless, several limitations should be acknowledged. Firstly, this was a single-center retrospective study, and although internal validation using bootstrap resampling (1,000 iterations) was performed, no external validation was conducted. Therefore, the generalizability of the model remains uncertain. Notably, ΔCRP% and IgG1 measurements depend on specific analytical platforms (such as Beckman Coulter AU-series and Mindray® BN-series), and inter-laboratory variability may introduce systematic differences, potentially affecting model performance in other settings. This suggests a moderate risk of limited transportability. Future studies should prioritize external validation in independent multicenter cohorts. In addition, temporal validation (such as training on 2020–2022 data and testing on 2023 data) may provide a more robust assessment of model stability. Standardization of laboratory measurements may further improve model applicability. Secondly, although ΔCRP% and low IgG1 were identified as key predictors, IgG subclass testing is not routinely performed in many pediatric settings, which may limit clinical applicability. Future studies are warranted to explore alternative markers and validate these findings in larger populations.

Conclusion

Ultimately, we developed a prediction model for pediatric *Mycoplasma pneumoniae* pneumonia that demonstrated good discriminative performance, calibration, and risk stratification, with the dynamic percentage change in C-reactive protein and immunoglobulin G1 as key predictors. These findings provide additional insight into the early identification of *Mycoplasma pneumoniae* pneumonia exacerbation and suggest a potential framework for risk assessment integrating inflammatory dynamics and immune status in clinical practice.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary Table 1

Age-specific reference ranges for laboratory parameters used in the present study

Age group, years	WBC, $\times 10^9$/L	Lymphocyte, %	LDH, U/L	IgG1, g/L	IgG2, g/L	IgG3, g/L	IgG4, g/L
1–3	6.0–17.0	50–70	150–450	2.3–6.3	0.4–1.5	0.2–1.2	0.01–0.5
4–6	5.5–15.5	40–60	140–400	3.0–8.0	0.5–2.0	0.3–1.5	0.02–0.8
7–12	4.5–13.5	30–50	120–350	4.0–10.5	0.7–3.0	0.4–1.8	0.03–1.0
13–16	4.0–11.0	20–45	100–300	5.0–12.0	1.0–4.0	0.5–2.0	0.05–1.5

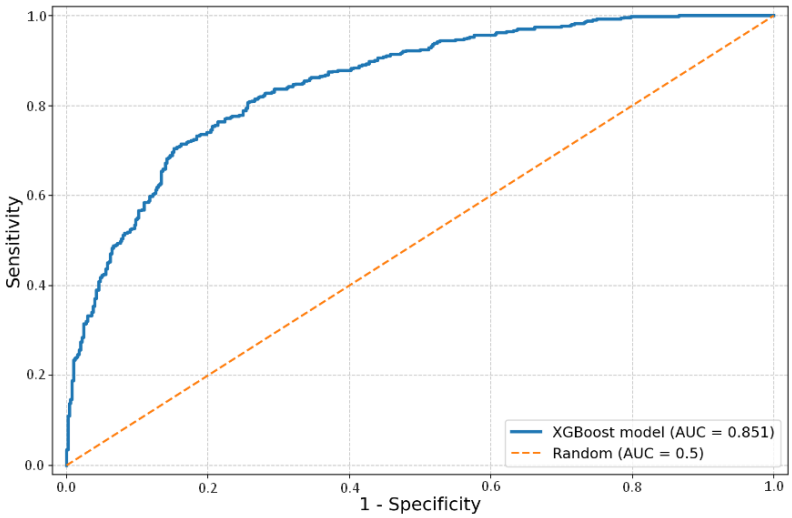
WBC – white blood cell; LDH – lactate dehydrogenase; IgG – immunoglobulin G.

Supplementary Table 2

Age-stratified reference intervals used for classification

Age group, years	IgG1	IgG2	IgG3	IgG4
1–3	2.3–6.3	0.4–1.5	0.2–1.2	0.01–0.5
4–6	3.0–8.0	0.5–2.0	0.3–1.5	0.02–0.8
7–12	4.0–10.5	0.7–3.0	0.4–1.8	0.03–1.0
13–16	5.0–12.0	1.0–4.0	0.5–2.0	0.05–1.5

IgG – immunoglobulin G.
Values are expressed as lower and upper limits of normal for each age group and given as g/L. IgG subclass levels below the lower limit of the corresponding age-specific interval were classified as "low".
Note: **Reference intervals were based on the manufacturer's instructions for the BN-series nephelometer (Mindray® Bio-Medical Electronics Co., Ltd., Shenzhen, China) and were cross-referenced with published pediatric immunoglobulin standards.**



Supplementary Fig. 1 – Receiver operating characteristic curve of the eXtreme Gradient Boosting (XGBoost) model.
AUC – area under the curve.