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Epidemiological characteristics and early predict model of children *Mycoplasma Pneumoniae* Pneumonia outbreaks after the COVID-19 in Shandong

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Since October 2023, a significant outbreak of *Mycoplasma Pneumoniae* Pneumonia (MPP) has been observed in children in northern China. Chinese health authorities have attributed this epidemiological to immune debt resulting from the relaxation of coronavirus disease 2019 (COVID-19) control measures. This study described the epidemiological features of *Mycoplasma pneumoniae* (MP) prevalence in children and developed a straightforward prediction model to differentiate between MPP and viral pneumonia in children. The infection rate of MP in children notably increased from 8.12 in 2022 to 14.94% in 2023, peaking between October and November, especially among school-age children. Logistic regression screening identified four key indicators: Age, D-Dimer levels, erythrocyte sedimentation rate, and gender. The developed nomogram exhibited a receiver operator characteristic curve-area under the curve (ROC-AUC) of 0.858, with external validation confirming an ROC-AUC of 0.794. This study examined the epidemiological characteristics of MPP prevalence in children in Shandong Province during and after the COVID-19 pandemic. An early predict model was developed and validated to differentiate between *Mycoplasma Pneumoniae* and viral infections.

Keywords *Mycoplasma Pneumoniae* Pneumonia, Nomogram, Outbreak, Epidemiology, COVID-19

In October and November 2023, hospitals in major cities in northern China reported a surge in childhood pneumonia cases, leading to overwhelmed pediatric emergency care facilities[1,2]. Chinese health authorities attributed this increase to a seasonal spike in respiratory infections following the lifting of the coronavirus disease 2019 (COVID-19) pandemic restrictions, similar to outbreaks seen in the United States and Europe in late 2022[2,5]. While there were differences in the presentation of these recent cases, the underlying reasons were yet to be determined.

Recent studies on childhood pneumonia have highlighted *Mycoplasma pneumoniae* (MP) as a significant factor, either alone or in combination with respiratory syncytial virus (RSV), SARS-CoV or influenza virus[3,4]. *Mycoplasma Pneumoniae* Pneumonia (MPP) is an atypical pneumonia characterized by interstitial lung disease, which can damage other organs through local respiratory infections. The global incidence of MPP has notably increased in recent years, now accounting for 10–40% of cases of children's community-acquired pneumonia (CAP)[6]. Therefore, MPP is very common in pediatrics. The infection rate of children over 5 years old could reach up to 50% occurring throughout all seasons, mainly with atypical symptoms such as fever, cough, asthma, and difficulty breathing[7–9]. Due to these atypical symptoms, distinguishing CAP caused by MP from viral origins can be challenging when MPP is co-epidemic with viral pneumonia[10].

Currently, there is limited information regarding the epidemiological characteristics of MPP outbreaks in children in northern China. To enhance our understanding of these characteristics, we collected data on hospitalized patients infected with *Mycoplasma pneumoniae* at our hospital before and after the COVID-19 outbreak in 2022 and 2023. We analyzed various factors, including gender, age, and season, to develop a clinical predictive

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model aimed at distinguishing MPP from viral pneumonia. This model is intended to facilitate the early detection and treatment of MPP, thereby preventing severe cases and mitigating MPP outbreaks.

Methods

Study population

Epidemiological characteristics of MP

To gain more detailed insight into the current MP epidemiology, we conducted data in Children's Hospital Affiliated to Shandong University from January 2022 to December 2023, which was the largest tertiary children's hospital in Shandong, China. We collected basic information on all children who underwent MP testing due to respiratory symptoms, utilizing data from the hospital information system. Our hospital currently employed four distinct MP testing methods. The selection of the method for each child was determined by the attending physician, based on the specific characteristics of the child's condition. The specific flow chart was illustrated in Fig. 1.

Nomogram to predicting MPP

This retrospective study received approval from the Ethical Board of Children's Hospital Affiliated to Shandong University (Ethical approval number: SDFE-IRB/P-2023015). Research was performed in accordance with the Declaration of Helsinki. To differentiate MPP from viral pneumonia, we screened the individuals mentioned above who were suspected of MP infection. The criteria for enrolling children were as follows: (1) Hospitalized children with signs and symptoms of CAP in 2023, including fever, cough, abnormal lung auscultation, and new infiltrates on chest radiograph; (2) samples were collected from children who did not receive treatment after admission; (3) MP group: had positive results of MP by multiple polymerase chain reaction (PCR) combined with next generation sequencing technology (PCR-NGS) in nasopharyngeal secretions; Virus group: Children whose nasopharyngeal secretions tested positive for viruses by PCR-NGS were matched to the MP testing time and randomly enrolled (including influenza virus, respiratory syncytial virus, coronavirus and other common viruses in children). Exclusion criteria were the follows: (1) co-infection with other pathogens; (2) history of chronic diseases, autoimmune disease, malignancy, etc.; (3) had incomplete medical records.

Validation set

Independent data was used for external validation, with the case group consisting of children who were hospitalized in 2022 for PCR-NGS testing for MP infection due to pneumonia. The control group included children who underwent PCR-NGS testing for virus infection during the same period and for the same reason. In order to address the small sample size of the case group, data from children who tested positive for MP-IgM antibodies twice within a 10-day period were also included.

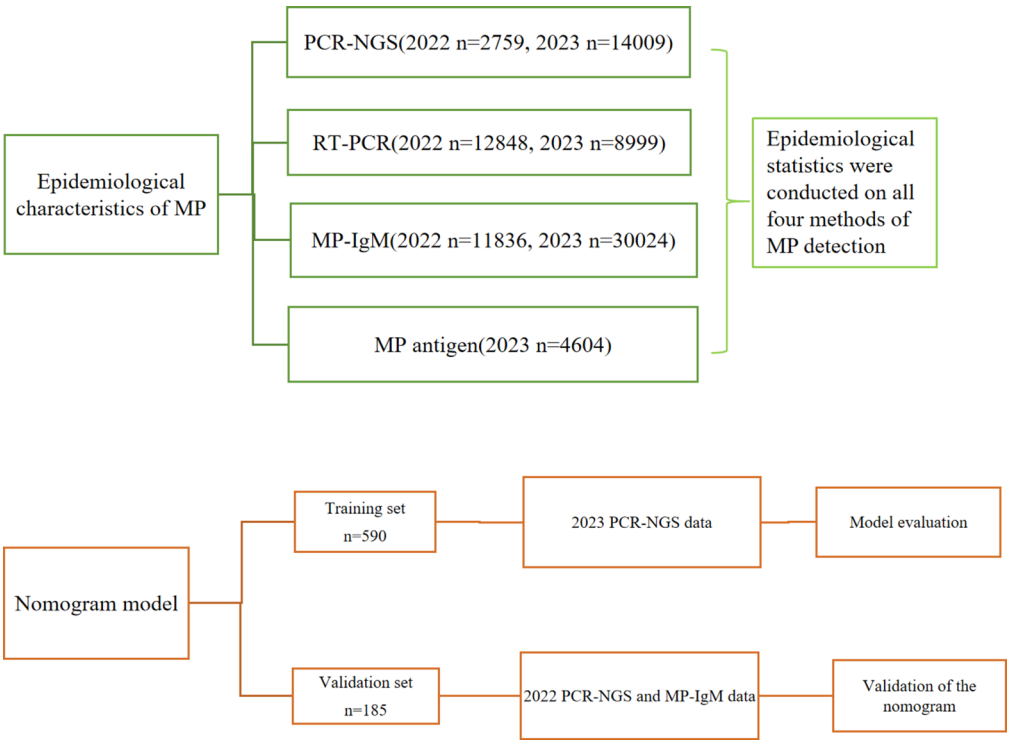

Fig. 1. Flow Chart.

MP Detection methods

Nucleic acid detection of MP was conducted using multiple PCR combined with next generation sequencing technology (PCR-NGS) (KingCreate Biotechnology, Guangzhou, China) or reverse transcription polymerase chain reaction (RT-PCR) (SANSURE BIOTECH, Hunan, China) on nasopharyngeal aspirate/swab specimens. MP-IgM was assessed through chemiluminescence or immunocolloidal gold assay on peripheral blood samples (YHLO Biotech, Shenzhen, China). MP antigen detection was carried out using the immunocolloidal gold technique on throat swab samples (Innovita Biological Technology, Beijing, China). All procedures were executed following the manufacturer's instructions.

Predictor selection

Demographic and clinical information, along with laboratory data including white blood cell count (WBC), platelet count (PLT), neutrophil count (NEU), lymphocyte count (LYM), monocyte count (MON), and derived ratios such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), were retrospectively collected from all children by reviewing their electronic medical records. Additionally, procalcitonin (PCT), D-dimer (DD), fibrinogen (Fg), and erythrocyte sedimentation rate (ESR) were included based on their clinical importance and predictive value.

Statistical analysis

SPSS 17.0 was utilized for statistical analysis with continuous data presented as median (25th–75th percentile). and compared between groups using the Wilcoxon rank sum test. Qualitative data were displayed as example (n/n), and inter-group comparison was conducted using Chi-square test. Statistical significance was defined as $P < 0.05$.

Subsequently, R software was used to perform univariate analysis and multivariate logistic regression analysis to determine the risk factors for MPP. In the logistic regression model, independent variables of age < 60 month, ESR < 15 mm/h and DD < 0.55 mg/L were considered as the reference group. For the MP positive group, the virus positive group was chosen as the reference group.

We established a nomogram model involving the risk factors in the multivariate logistic analysis to distinguish MPP from viral pneumonia. Area under the curve (AUC) was used to evaluate recognition ability and the calibration capability was evaluated by calibration curve test. In addition, decision curve analysis (DCA) was performed to evaluate the clinical utility of the nomogram. Whatmore, data from 2022 were used for external validation of the model.

Ethics approval

The study was approved by the Ethical Board of Children's Hospital Affiliated to Shandong University (Ethical approval number: SDFE-IRB/P-2023015). This study was a retrospective study, the use of anonymized information data for research complied with relevant regulations and ethical principles, Informed consent was waived by the Ethical Board of Children's Hospital Affiliated to Shandong University.

Results

Infection rate of MP in 2022–2023

The total number of MP tests in 2023 is 57,636. As shown in Supplementary Table 1, among the four methods, the MP-IgM method exhibited the highest positive rate at 21.16%, followed by PCR-NGS at 14.94%, the MP antigen method at 3.69%, and PCR with the lowest detection rate at 2.71%. We observed a steep rise in MP infection starting in October especially in the PCR-NGS and PCR methods, which remained high positive rate in November and began to decline in December, as shown in Fig. 2.

In 2022, a total of 27,443 children were enrolled for MP testing. Figure 2 illustrated that the MP-IgM method yielded the highest positive rate at 38.93%, followed by PCR-NGS at 8.12%, while PCR demonstrated the lowest detection rate of 3.99%. The peak incidence of MP infection was observed in January, with no significant increase noted from October to November 2022, as depicted in Fig. 2.

Seasonal distribution of MP

The PCR-NGS and PCR methods indicate that the epidemic season of MP occurs in autumn and winter; however, the MP antibody method could not be accurately determined due to the limitations of the method, as depicted in Fig. 2.

Age distribution of MP

As shown in Fig. 3, our data showed that the peak of MP infection occurred in children after 5 years of age. Furthermore, when categorizing children into age groups (infancy: 0- < 3 years, pre-school: 3- < 6 years, and school age: ≥ 6 years), the positive rate of MP infection in school age was higher than that in infancy and pre-school ($P < 0.001$).

Patient characteristics and hematological parameters in two groups

This study recruited 590 hospitalized children with pneumonia eventually and divided them into MP positive group and Virus positive group based on the results of PCR-NGS and their basic information and hematological parameters was shown in Table 1.

There were significant differences in age distribution, gender composition and oxygen inhalation. There were significantly different in all other indicators between the two groups, except for WBC count, MON count and

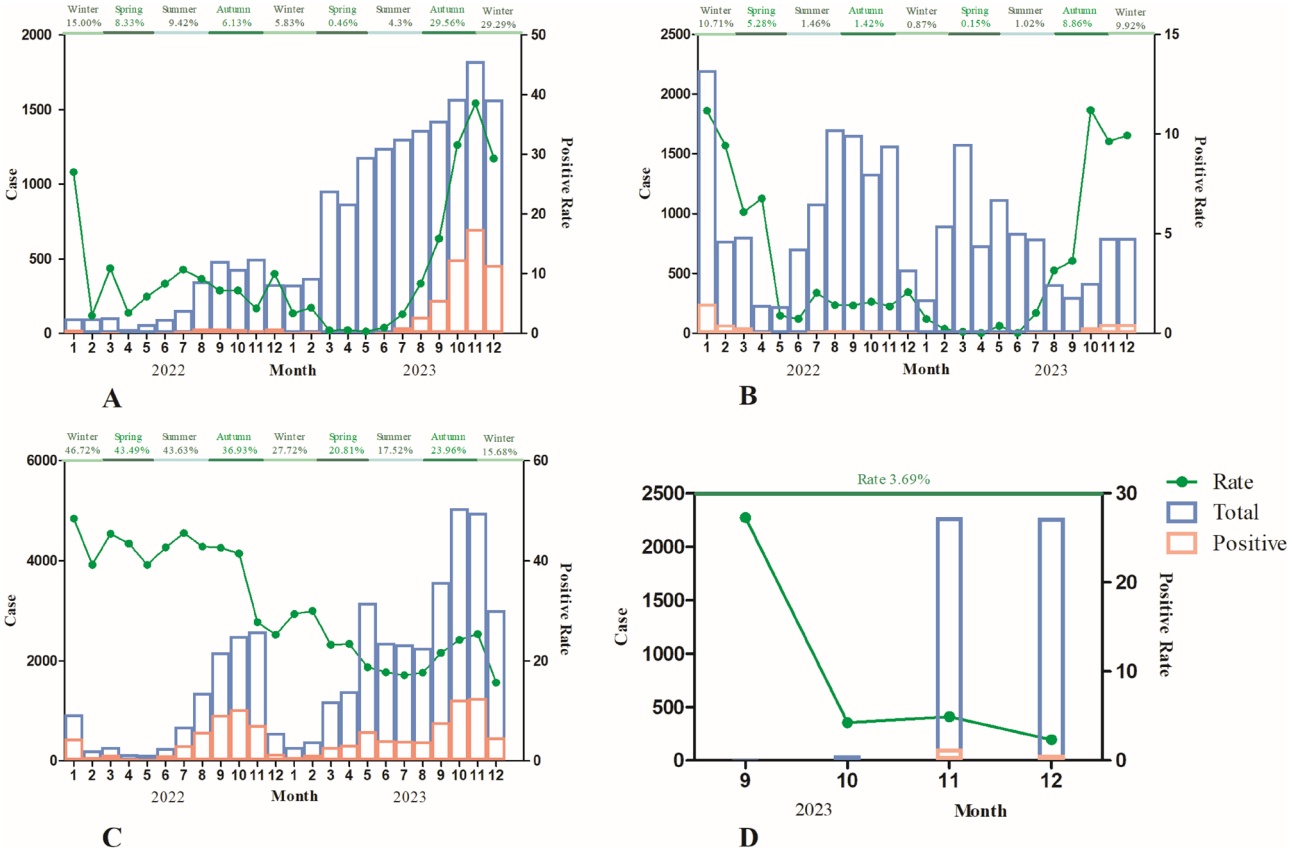

Fig. 2. Seasonal distribution of MP infection in 2022–2023. (**A**) PCR-NGS; (**B**) PCR; (**C**) MP-IgM; (**D**) Antigen.

PLT count. Compared with the Virus group, the MP group had higher DD, Fg, ESR, NEU count, NLR and PLR values, and lower PCT, LYM count and LMR values.

Selecting predictive factors by logistic regression

The clinical variables related to MPP were assessed according to clinical importance and predictors identified and the indicators with statistically significant differences were selected from Table 1 as the included variables. Variable selection was performed using multivariate logistic regression. Finally, older Age [OR = 0.09 (95% CI 0.06–0.14), $P < 0.001$], higher ESR [OR = 0.38 (95% CI 0.22–0.64), $P < 0.001$], and higher DD [OR = 0.59 (95% CI 0.37–0.94), $P = 0.026$, Sex(girls) [OR = 0.55 (95% CI 0.35–0.85)] were selected as four predictive factors for MPP (Table 2).

Nomogram model to predict the incidence of MPP

The nomogram for the prediction model with MPP was developed based on the selected variables, allowing for visualization and accurate quantification (Fig. 4). The cumulative scores of Age, ESR, DD, and Sex in the nomogram were indicative of an increased risk of MPP. By utilizing this nomogram, it was possible to calculate a child's pneumonia risk by considering their age, ESR, DD, and Sex, summing up the corresponding points to obtain a total score. For example, a 6-year-old boy with pneumonia, having a DD test result of 1.0 and an ESR of 20, would accumulate scores of 100, 0, 18, and 40, totaling 158 and corresponding to a risk of MP > 0.80. He was considered to have a relatively high risk of MPP.

The receiver operator characteristic curve-area under curve (ROC-AUC) of the nomogram based on the training dataset was 0.858 (95% CI 0.827–0.888) (Fig. 5A), with good ability to distinguish between patients with MPP and viral pneumonia. Furthermore, the standardized graph (Supplementary Fig. 1A) showed the nonparametric curve fit well with the ideal line indicating good consistency between the predicted probability and actual probability. The DCA curve for the predictive nomogram is presented in Supplementary Fig. 2A, showing clear net benefits associated with using the nomogram for prediction.

Validation of nomogram

A comparison of the data from children in the training set and the validation set is presented in Supplementary Table 3, revealing no significant differences between the two datasets ($P > 0.05$). The calibration curves of the nomogram demonstrated good consistency between predicted probabilities and observed outcomes. Furthermore, the ROC-AUC of the probability of MPP was 0.794 (95% CI 0.729–0.859) in the validation cohort, as shown in Fig. 5B.

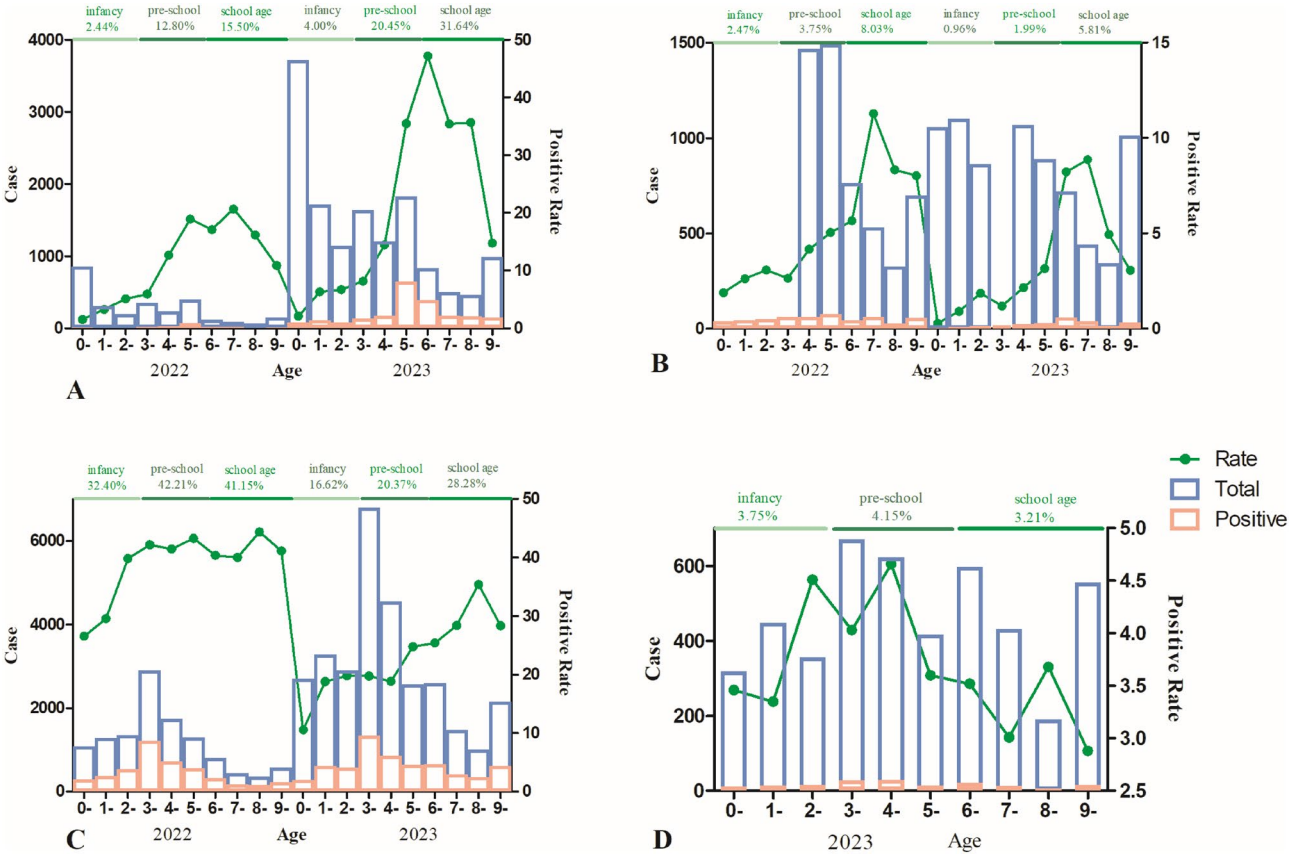

Fig. 3. Age distribution of MP infection in 2022–2023. (**A**) PCR-NGS; (**B**) PCR; (**C**) MP-IgM; (**D**) Antigen.

Variables M (Q_1, Q_3)	Total (n = 590)	MP (n = 299)	Virus (n = 291)	*P*
AGE (m)	62.50 (26.25, 84.00)	72.00 (67.00, 96.00)	31.00 (11.50, 53.50)	< .001
DD (mg/L)	0.44 (0.30, 0.87)	0.56 (0.36, 1.44)	0.38 (0.25, 0.67)	< .001
Fg (g/L)	3.13 (2.53, 3.83)	3.40 (2.89, 3.99)	2.77 (2.09, 3.36)	< .001
ESR (mm/h)	20.00 (11.00, 33.00)	25.00 (15.50, 35.00)	14.00 (5.00, 26.00)	< .001
PCT (ng/ml)	0.09 (0.06, 0.15)	0.08 (0.05, 0.13)	0.09 (0.06, 0.18)	< .001
WBC (10^9/L)	8.68 (6.72, 11.79)	8.95 (6.94, 11.74)	8.15 (6.45, 12.09)	0.210
MON (10^9/L)	0.59 (0.41, 0.83)	0.59 (0.44, 0.80)	0.60 (0.39, 0.90)	0.819
NEU (10^9/L)	4.54 (2.75, 6.98)	5.60 (4.00, 7.33)	3.44 (1.83, 6.46)	< .001
LYM (10^9/L)	2.96 (2.04, 4.54)	2.54 (1.75, 3.83)	3.81 (2.44, 5.22)	< .001
PLT (10^9/L)	341.00 (279.00, 425.75)	340.00 (280.00, 431.00)	342.00 (277.50, 417.00)	0.984
NLR	1.59 (0.70, 2.94)	2.22 (1.36, 3.29)	0.89 (0.43, 2.03)	< .001
PLR	115.29 (81.23, 165.68)	129.66 (97.28, 179.49)	96.54 (64.36, 147.99)	< .001
LMR	5.15 (3.36, 7.88)	4.41 (3.07, 6.35)	6.02 (3.82, 9.07)	< .001
SEX, n (%)				< .001
1(Boys)	325 (55.08)	140 (46.82)	185 (63.57)	
2(Girls)	265 (44.92)	159 (53.18)	106 (36.43)	
Admission to ICU,n(%)	6(1.02%)	1(0.33%)	5(1.72%)	0.216
Oxygen Inhalation,n(%)	311(52.71%)	215(71.91%)	96(32.99%)	< .001

Table 1. Basic information of patients in modeling data. DD:D-dimer; Fg:fibrinogen; ESR:erythrocyte sedimentation rate; PCT:procalcitonin; WBC:white blood cell count; MON:monocyte count; NEU:neutrophil count; LYM:lymphocyte count; PLT:platelet count; NLR:neutrophil-to-lymphocyte ratio; PLR:platelet-to-lymphocyte ratio; LMR:lymphocyte-to-monocyte ratio.

Variables (n = 590)	Beta	S.E	Z	*P*	OR (95% CI)
PCT (ng/ml)*	− 1.06	0.50	− 2.14	0.032	0.35 (0.13–0.91)
Fg (g/L)	0.04	0.14	0.28	0.779	1.04 (0.79–1.36)
NEU (10^9/L)	0.06	0.05	1.24	0.214	1.07 (0.96–1.18)
LYM (10^9/L)	− 0.19	0.08	− 2.28	0.023	0.83 (0.71–0.97)
NLR	− 0.20	0.10	− 1.99	0.047	0.82 (0.67–0.99)
PLR	0.00	0.00	0.56	0.577	1.00 (1.00–1.01)
LMR	− 0.05	0.04	− 1.38	0.168	0.95 (0.89–1.02)
AGE_group					
2 ≥ 60 m					1.00 (Reference)
1 < 60 m	− 2.42	0.23	− 10.34	< .001	0.09 (0.06–0.14)
ESR_group					
2 ≥ 15 mm/h					1.00 (Reference)
1 < 15 mm/h	− 0.97	0.27	− 3.62	< .001	0.38 (0.22–0.64)
DD_group					
2 ≥ 0.55 mg/L					1.00 (Reference)
1 < 0.55 mg/L	− 0.53	0.24	− 2.22	0.026	0.59 (0.37–0.94)
SEX					
2(Girls)					1.00 (Reference)
1(Boys)	− 0.60	0.22	− 2.68	0.007	0.55 (0.35–0.85)

Table 2. Multiple logistic regression of the risk factors for MPP. DD:D-dimer; Fg:fibrinogen; ESR:erythrocyte sedimentation rate; PCT:procalcitonin; WBC:white blood cell count; MON:monocyte count; NEU:neutrophil count; LYM:lymphocyte count; PLT:platelet count; NLR:neutrophil-to-lymphocyte ratio; PLR:platelet-to-lymphocyte ratio; LMR:lymphocyte-to-monocyte ratio. *The reason why PCT was not included in the model was due to incomplete data in the validation group.

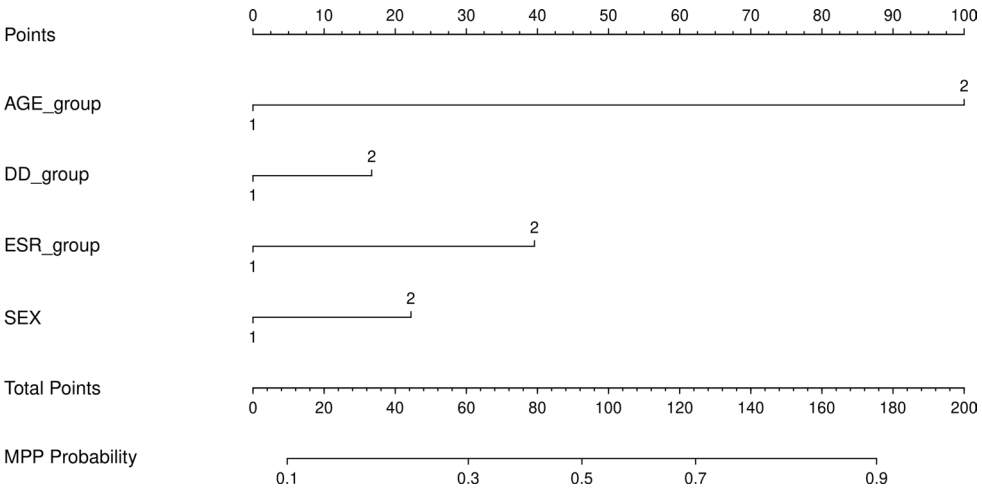

Fig. 4. Nomogram model to predict the incidence of MPP. AGE_group: 1 < 60 m, 2 ≥ 60 m; ESR_group: 1 < 15 mm/h, 2 ≥ 15 mm/h; DD_group: 1 < 0.55 mg/L, 2 ≥ 0.55 mg/L; SEX: 1(Boys), 2(Girls).

Discussion

On November 13th, the National Health Commission reported a rise in respiratory diseases among children nationwide, particularly in the northern regions. Investigations revealed that this increase was primarily attributed to the relaxation of COVID-19 control measures coinciding with the onset of the cold season[11–13]. Following the end of the epidemic, many children who had not been exposed to these pathogens for an extended period became vulnerable[14,15]. As previously common respiratory pathogens reemerged, widespread non-seasonal outbreaks ensued. Recent reports of respiratory illnesses, particularly the increase in childhood pneumonia cases, were primarily attributed to a combination of MP and viral infections.

The incidence rate of MP confirmed by direct detection across all age groups worldwide was 8.61% from 2017 to 2020. However, during the COVID-19 pandemic, this rate dropped to 1.69% between 2020 and 2021, likely due to nonpharmaceutical interventions[12,16]. Our own research findings align with this trend, showing a detection rate of MP using the PCR NGS method at 8.12% in 2022, which then increased to 14.96% in 2023.

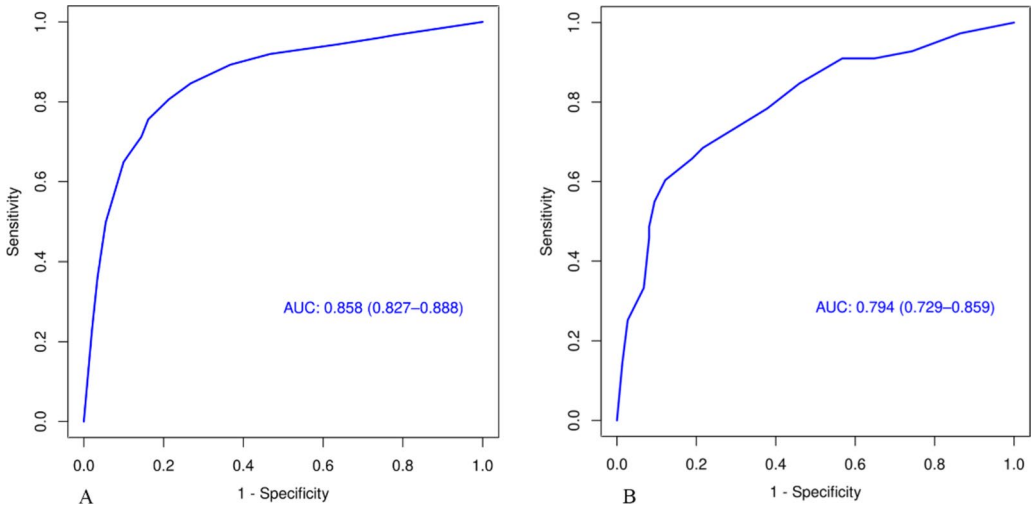

Fig. 5. The ROC-AUC of the training and validation groups. (**A**) training group; (**B**) validation group.

This study compared data from four MP detection methods, with the MP-IgM antibody detection method yielding the highest detection rate at 21.16%. This high rate can be attributed to the inherent limitations of antibody detection. While antibodies typically appear 4–5 days after MP infection, their prolonged presence can lead to false positives. Interestingly, all three methods (PCR-NGS, RT-PCR, MP-IgM) exhibited a peak in detection between October and November in 2023, aligning with the seasonal epidemic pattern observed in northern China. The introduction of the antigen detection method in September and its full implementation in October resulted in a detection rate that differed from the other methods, offering limited comparative value.

In terms of seasonal epidemics, MPP demonstrated a significant epidemic peak during the autumn and winter of 2023, a phenomenon not observed in the corresponding seasons of 2022. This increase is attributed to the "immunity debt" resulting from the relaxation of COVID-19 pandemic restrictions. Furthermore, an outbreak of MP occurred in early 2022 (the winter of 2021), which aligns with existing research findings[17,18]. This pattern highlights the seasonal characteristics of MP epidemics.

In terms of age distribution, all three methods, except for antigen testing, indicated a higher incidence of MP infection in school-age children compared to infants and preschoolers, aligning with previous research ($P < 0.001$)[19–22]. Notably, antigen testing methods demonstrated a higher incidence in preschoolers, possibly due to the smaller sample size of antigen testing cases.

The symptoms of MPP were atypical and easily confused with viral pneumonia, particularly during the widespread outbreak of MPP in children. To improve early and accurate identification of MPP, facilitate early treatment, reduce children's discomfort, and prevent severe complications, this study developed a nomogram to assist clinical doctors in effectively differentiating between MPP and viral pneumonia.

Easily accessible clinical and laboratory data of pediatric patients were extracted and analyzed to compare differences in various indicators. Our findings revealed that the MP group exhibited higher values for DD, Fg, ESR, NEU count, NLR, and PLR, while presenting lower values for PCT, LYM count, and LMR compared to the Virus group, which aligns with existing literature[23]. Subsequently, logistic regression identified age, DD, erythrocyte sedimentation rate, and gender as the four variables used to construct the nomogram.

In this study, we initially included C-reactive protein (CRP) and serum amyloid A (SAA) as indicators, as they were commonly used pediatric inflammatory markers in laboratory settings[24]. However, the results proved to be unreliable due to an excessive number of out-of-limit data points, such as values below 0.5. After conducting a thorough statistical analysis, we ultimately decided against using CRP and SAA as differentiating indicators. Although there was a statistically significant difference in oxygen inhalation between the two groups, the primary objective of our study was to differentiate MPP from viral pneumonia at an early stage. The indicators included in our analysis could be readily obtained upon the children's admission to the hospital; therefore, it was not incorporated into subsequent models.

MP was more common in children over 5 years old, which had been confirmed in a large number of literatures; D-dimer is considered a specific degradation product of fibrin, which can reflect the coagulation function and fiber activity of the body[20]. However, current research had found that immune cells release different types of inflammatory mediators after infection with MP, which exacerbated damage to endothelial cells and leaded to an increase in D-dimer levels[25,26]. As a marker of infection and inflammation, ESR is also elevated during MP infection[20,27].

We validated this nomogram not only in discrimination ability and calibration ability but also in clinical value. Compared with previous research results, the AUC value of this prediction model had similar results to the nomogram established by Huixian Guo, but their model had 6 parameters, which was more complex than ours[23]. Considering the result of this curve and the ease to obtain these variables at admission, the model could help to make contribution to timely intervention and appropriate treatment for MP children.

Nevertheless, we identified several limitations in our research. Firstly, this study was based on patient data from single medical center. Although we had conducted external validation on data from the same medical center in different years, our conclusions and nomogram utility should be carefully validated in future multicenter studies. Secondly, the modal diagram was based on retrospective research and excluded individuals with incomplete data, which might lead to selection bias.

Conclusion

This study examined the current epidemiological characteristics of *Mycoplasma pneumoniae* (MP) prevalence among children in Shandong, China. Since the onset of autumn this year, there has been a slight increase in MP infections among children, significantly higher than the previous year. This has led to a rise in emergency cases in hospitals across various provinces and cities, although it has not triggered a large-scale epidemic. Additionally, the MP infections observed were accompanied by a co-infection of other viruses such as influenza, adenovirus, and respiratory syncytial virus. To differentiate between mixed cases of MP pneumonia and viral pneumonia, a predictive model was developed and validated. This model, based on four commonly used variables at admission (Age, DD, ESR and Sex), demonstrated good performance in terms of discrimination, calibration, and clinical utility. It shows promise in early identification of MP pneumonia, facilitating timely intervention and appropriate treatment.

Data availability

The data sets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Author contributions

Q.Z. contributed to data curation, methodology, formal analysis, validation, writing of the original draft and editing. Y.R.L. contributed to investigation, methodology, formal analysis and reviewing. Y.Y.Y. and MW contributed to investigation and data curation. C.Y. and X.L. contributed to conceptualization and revising it critically for important intellectual content.

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Competing interests

The authors declare no competing interests.

Additional information

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