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ORIGINAL RESEARCH

Construction and Validation of a Nomogram Model to Predict the Severity of *Mycoplasma pneumoniae* Pneumonia in Children

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Background: This study aimed to develop a nomogram model for early prediction of the severe *Mycoplasma pneumoniae* pneumonia (MPP) in children.

Methods: A retrospective analysis was conducted on children with MPP, classifying them into severe and general MPP groups. The risk factors for severe MPP were identified using Logistic Stepwise Regression Analysis, followed by Multivariate Regression Analysis to construct the nomogram model. The model's discrimination was evaluated using a receiver operating characteristic curve, its calibration with a calibration curve, and the results were visualized using the Hosmer–Lemeshow goodness-of-fit test.

Results: Univariate analysis revealed that age, duration of fever, length of hospital-stay, decreased sounds of breathing, respiratory rate, hypokalemia, and incidence of co-infection were significantly different between severe and general MPP. Significant differences ($p < 0.05$) were also observed in C-reactive protein, procalcitonin, peripheral blood lymphocyte count, neutrophil-to-lymphocyte ratio, ferritin, lactate dehydrogenase, alanine aminotransferase, interleukin-6, immunoglobulin A, and CD4^{+} T cells between the two groups. Logistic Stepwise Regression Analysis showed that age, decreased sounds of breathing, respiratory rate, duration of fever (OR = 1.131; 95% CI: 1.060–1.207), length of hospital-stay (OR = 1.415; 95% CI: 1.287–1.555), incidence of co-infection (OR = 1.480; 95% CI: 1.001–2.189), ferritin level (OR = 1.003; 95% CI: 1.001–1.006), and LDH level (OR = 1.003; 95% CI: 1.001–1.005) were identified as risk factors for the development of severe MPP ($p < 0.05$ in all). The above factors were applied in constructing a nomogram model that was subsequently tested with 0.862 of the area under the ROC curve.

Conclusion: Age, decreased sound of breathing, respiratory rate, duration of fever, length of hospital-stay, co-infection with other pathogen(s), ferritin level, and LDH level were the significant contributors for the establishment of a nomogram model to predict the severity of MPP in children.

Keywords: *Mycoplasma pneumoniae* pneumonia, nomogram, severity prediction

Introduction

Mycoplasma pneumoniae pneumonia (MPP) is a common community-acquired pneumonia in children, primarily caused by airway infection with *Mycoplasma pneumoniae*.[1] Although MPP usually presents with mild symptoms and carries a favorable prognosis, once it develops into severe MPP, it can be accompanied by a variety of complications and sequelae, such as pleural effusion, lung abscess, atelectasis, necrotizing pneumonia, and bronchiolitis obliterans, all of which can significantly impair the daily life and wellbeing of infected children.[2]

In recent years, the incidence of severe MPP has been steadily rising. Studies have demonstrated that severe MPP can not only trigger extrapulmonary complications such as myocarditis, nephritis, encephalitis, and hemolytic anemia but also present a risk to life,[3,4] thus emphasizing the importance of early detection of severe MPP as well as shortening its course to reduce

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comorbidity and mortality is necessary. Consequently, precise prediction and identification of severe MMP in clinical practice is of importance to reduce mortality and complications and to improve the prognosis of severe MPP. However, a unified scale or tool to evaluate and analyze the condition of children with MPP is currently unavailable in clinic, and thus, it is imperative to develop a scoring model that can promptly predict the severity of MPP so that development of severe MPP can be prevented. The current study was, therefore, designed to retrospectively analyze the risk factors related to the development of severe MPP in children, and based on the findings of the analysis, to construct and validate a nomogram model that could be applied in early identification and intervention of severe MPP.

Methods

Study Population and Data Collection

Cases of children with MPP who visited the Tianjin Children's Hospital from January 2021 to December 2021 were retrospectively analyzed. Clinical data and results of laboratory tests for the children with MMP were collected through the electronic medical record system stored in the database of The Tianjin Children's Hospital. Specifically, the following clinical data were collected: (1). The basic demographic information of the children including age, gender, past medical history, comorbidities, clinical symptoms, date of starting to have airway symptoms of *Mycoplasma pneumoniae* infection, length of hospital-stay, incidence and type of pathogen(s) of co-infection, as well as treatment and outcome. (2). Findings of physical examination including respiratory rate, heart rate, and sounds of breathing. (3). Results of routine blood test, blood biochemical panels, liver and kidney function, panels of immune function and coagulation function, and pathogenic test.

Inclusion criteria: (1). Patients under 18 years old and hospitalized with a diagnosis of MPP. (2). MPP was diagnosed by the criteria defined by The Chinese National Health Commission (Expert consensus on the diagnosis and treatment of *Mycoplasma pneumoniae* pneumonia in children, version 2023),[5] that is, in addition to the clinical symptoms and signs, the patients had positive results from either one of the following laboratory tests: 1. MP-DNA or MP-RNA by nucleic acid amplification test. 2. Either anti-MP antibody titer in a single test was ≥1:160, or at least fourfold increase in antibody titer during illness period by serum particle agglutination test for MP antibody. (3). Patients' clinical data and laboratory test results were completely recorded and fully available.

Exclusion criteria: (1). Children had history of recurrent respiratory infection. (2). Because children with immuno-deficiency are prone to develop into severe conditions and their laboratory test results might be different from that of children with normal immunity, children with comorbidity of severe diseases including congenital immunodeficiency were excluded.

Criteria for defining severe MPP: Severity of MPP was determined using previously published criteria.[6] The MPP cases were categorized as severe MPP if the patients had any of the followings: (1). Poor general condition. (2). Disturbance of consciousness, cyanosis, and tachypnea (respiratory rate ≥ 70 times/min for an infant, or ≥ 50 times/min for children over 1 year old). (3). Assisted respiration (moaning, nasal fan, three concave sign), intermittent apnea, and oxygen saturation ≤ 92%. (4). Had extremely high fever that lasted for more than 5 days. (5). Dehydration and food refusal. (6). Chest X-ray or CT scan showed ≥2/3 unilateral lung infiltration, multi-lobar lung infiltration, pleural effusion, pneumothorax, atelectasis, lung necrosis, and lung abscess. (7). Extrapulmonary complications including complications of the neurological systems (encephalitis, acute disseminated encephalomyelitis; transverse myelitis; Guillain-Barre syndrome; or cerebral infarction); cardiovascular systems (blood clots in the heart, septic shock; myocarditis; pericarditis; Kawasaki disease; arterial or venous embolism); blood systems (immune thrombocytopenia; autoimmune hemolytic anemia; hemophagocytic syndrome; disseminated intravascular coagulation); skin and mucous membranes (urticaria; allergic purpura; erythema multiforme; Stevens-Johnson syndrome; toxic necrotic epidermolysis; mycoplasma pneumoniae-induced rash and mucositis); and others including glomerulus nephritis complicated with severe congestion or hypertensive crisis, acute kidney injury, liver function failure, acute pancreatitis, arthritis, or rhabdomyolysis syndrome.

Statistical Analysis

The data were analyzed using SPSS (version 27.0) statistical software. For continuously distributed data, normally distributed data were expressed as mean ± standard deviation (SD) and non-normally distributed data were expressed as median (interquartile range, IQR). Comparisons between groups were conducted using t-tests or rank-sum tests. Categorical data were presented as percentages (%), and discrepancies between groups were compared using the chi-square test. Factors showing significant differences were included in the logistic multivariate regression model to identify independent risk factors for severe MPP. The MPP-independent risk factors obtained from the multifactor regression analyses were used to construct nomogram models through the rms package (version 4.2.2) of the R software. The discriminatory power of the model was assessed by plotting the ROC curve and calculating the area under the ROC curve (AUC), which was equivalent to the C-statistic, using the AUC function in the R software. Meanwhile, internal validation was performed using bootstrapping with 1000 resamples. The calibration of the model was assessed using the calibration curve, and the Hosmer–Lemeshow goodness-of-fit test results were visualized. A significance level of $p < 0.05$ was considered statistically significant.

Results

Demographic Feature of the Enrolled Patients

A total of 1332 patients were enrolled in this study. Of them, 346 cases met the diagnostic criteria of severe MMP with a median age of 6 (4, 8) years old, and the rest 986 cases were categorized as general MPP with a median age of 4 (3,7) years old. Significance of demographic factors or clinical manifestations was examined by univariate analysis and the results are shown in Table 1. In addition to the gender ratio, factors including age, incidence of decreased sounds of breathing, incidence of hypokalemia, respiratory rate, days of fever lasted, days of hospitalstay, and incidence of co-infection with other

Table 1 Comparison of the Demographic, Clinical, and Laboratory Examination Factors*

	GMPP (N = 986)	SMPP (N = 346)	p value
Gender			
Male	493	171 (49.4%)	0.853
Female	493	172 (50.6%)	
Age (year)	4 (3, 7)	6 (4, 8)	< 0.001
Decreased breath sounds	52 (5.3%)	98 (28.3%)	< 0.001
Hypokalemia	26 (2.6%).	18 (5.2%).	0.022
Respiratory rate (bpm)	29 (27, 31)	31 (28, 35)	< 0.001
Fever duration (day)	5 (3, 8)	8 (6, 10)	< 0.001
Days of hospital-stay (day)	5 (4, 7)	7 (6, 9)	< 0.001
Co-infection	216 (21.9%)	104 (30.1%)	0.002
CRP (mg/L)	12.6 (5.25, 27.59)	22.37 (10.68, 44.30)	< 0.001
PCT (μg/L)	0.10 (0.06, 0.19)	0.12 (0.08, 0.27)	< 0.001
L (%)	2.29 (1.71, 3.10)	1.99 (1.44, 2.73)	< 0.001
NLR	2.32 (1.42, 3.57)	2.77 (1.85, 4.09)	< 0.001
Ferritin (ng/mL)	93.62 (64.48, 133.33)	127.65 (84.86, 197.55)	< 0.001
LDH (U/L)	316.00 (277.00, 370.00)	352.50 (288.25, 439.50)	< 0.001
ALT (U/L)	12.00 (10.00, 15.00)	13.00 (10.00, 18.00)	0.001
IL-6 (pg/mL)	16.92 (8.95, 30.07)	24.30 (14.53, 38.63)	< 0.001
IgA (g/L)	1.07 (0.70, 1.61)	1.24 (0.79, 1.73)	0.006
CD_4^+ T (cells/mm^3)	991.70 (744.00, 1363.02)	886.00 (626.00, 1112.00)	< 0.001

Notes: *Univariate analysis was used for the comparison.
Abbreviations: GMPP, general *mycoplasma pneumoniae* pneumonia; SMPP, severe *mycoplasma pneumoniae* pneumonia; bpm, breaths per minute; CRP, C-reactive protein; PCT, procalcitonin; L, percent of peripheral lymphocytes; NLR, neutrophil to lymphocyte ratio; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; IL-6, interleukin-6; IgA, immunoglobulin A; CD_4^+ T, CD_4 positive T cells.

pathogen(s) were significantly higher or longer in children with severe MMP compared to those of children with general MMP ($p < 0.05$, Table 1).

Next, selected factors of the laboratory tests were examined by Univariate Analysis and the factors that statistically differ between the two groups are listed in Table 1. Of the examined parameters, numbers of peripheral blood lymphocyte and CD_4^+ T cells were significantly lower in the severe MPP than that in the general MPP ($p < 0.05$), while the rest of the listed parameters including C-reactive protein (CRP), procalcitonin (PCT), neutrophil-to-lymphocyte ratio (NLR), ferritin, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), IL-6, and immunoglobulin A (IgA) were significantly higher in the severe MPP compared to the general MPP group ($p < 0.05$, Table 1).

Selection of the Predictive Factors by Stepwise Regression

Taking severe and non-severe (general) as the dependent variables, statistically significant factors in the univariate analysis were selected for Logistic Regression Collinearity Analysis. The factors for classification included in the final binary logistic were assigned values including decreased sounds of breathing (no = 0, yes = 1) and severe pneumonia (no = 0, yes = 1), as well as the continuous variables that were input with their values. It was found that age, decreased sounds of breathing, respiratory rate, duration of fever, length of hospital-stay, incidence of co-infection, blood ferritin level, and serum lactate dehydrogenase (LDH) level were the factors that could possibly predict the severity of MPP (all $p < 0.05$, Table 2).

Establishment and Validation of the Nomogram Model

A nomogram model for severe MPP was constructed based on the screening results of the Logistic Regression. As shown in Figure 1, total 8 independent variables including age, decreased sounds of breathing, ferritin concentration, lactate dehydrogenase (LDH) concentration, incidence of co-infection, respiratory rate, days of having fever, and days of hospital-stay, were applied for the construction of the model. Internal validation for the nomogram model was then performed, and the results showed that the confidence interval (CI) of the area under the ROC curve of the model for predicting severe MPP was 0.862 (95% CI: 0.839, 0.886, Figure 2). Furthermore, as shown in Figure 3, this calibrated curve of the nomogram model in predicting prognosis for the children with severe MPP was close to the ideal curve. In addition, an excellent consistency of this nomogram model in predicting the risk of death in children with severe MPP was confirmed by the Hosmer–Lemeshow goodness-of-fit test ($\chi^2 = 9.28$, $p = 0.3192$).

Discussion

In recent years, prevalence of MPP has been on the rise, with annual increase of the severity rate, reaching as high as 42.6% in 2016 in Suzhou, China.[7] In the current study, we identified several characteristic clinical factors that might be associated with the development of severe MPP in children. These factors include age, decreased sounds of breathing, respiratory rate, fever duration, length of hospital-stay, co-infection with other pathogen(s), ferritin level, and LDH level. These independent risk factors presented in a score form to predict the severity of MPP with an area under the ROC

Table 2 Results of Multivariate Regression Analysis

Variables	ß	SE	χ^2	p	OR	95% CI
Age (year)	0.196	0.041	23.139	< 0.001	1.216	1.123–1.318
Decreased sounds of breathing	1.400	0.250	21.268	< 0.001	4.056	2.483–6.626
Respiratory rate (bpm)	0.121	0.019	39.342	< 0.001	1.128	1.087–1.172
Days of fever (day)	0.123	0.033	13.965	< 0.001	1.131	1.060–1.207
Days of hospital-stay (day)	0.347	0.048	51.949	< 0.001	1.415	1.287–1.555
Co-infection	0.392	0.200	3.859	0.049	1.480	1.001–2.189
Ferritin (ng/mL)	0.003	0.001	5.791	0.016	1.003	1.001–1.006
LDH (U/L)	0.003	0.001	12.737	< 0.001	1.003	1.001–1.005

Abbreviations: ß, ß coefficient; SE, standard error; OR, odds ratio; 95% CI, 95% confidence interval; bpm, breaths per minute; LDH, lactate dehydrogenase.
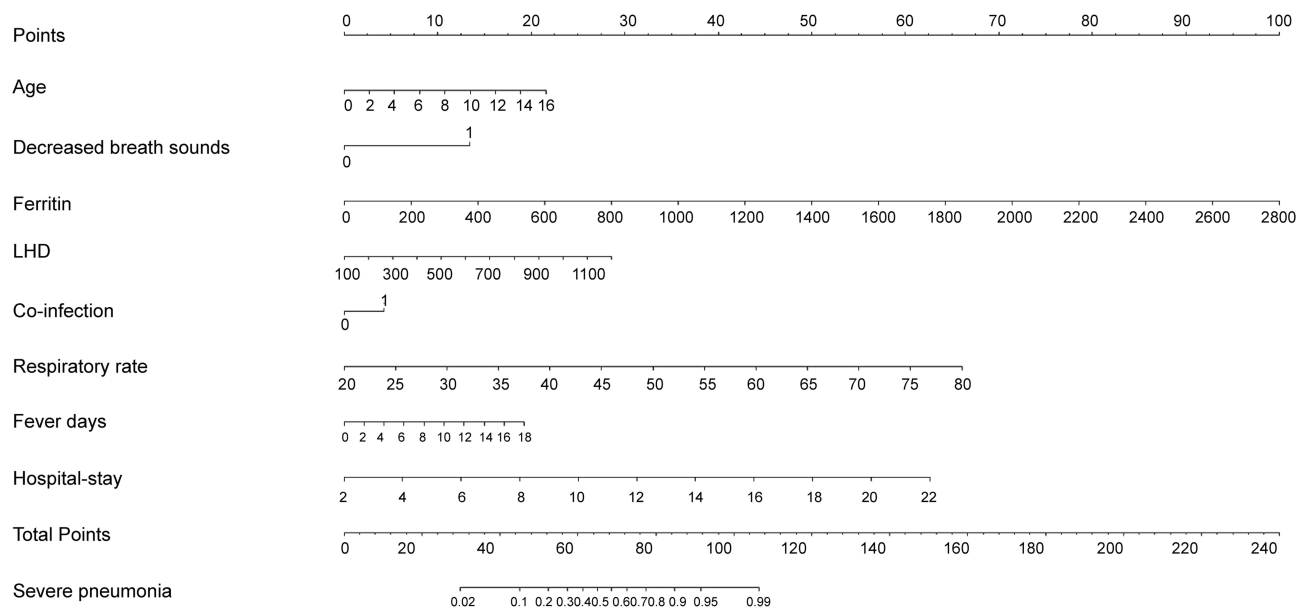
Figure 1 A nomogram model for predicting severe *Mycoplasma pneumoniae* pneumonia (MPP). A nomogram model to predict severe MPP was constructed based on the following 8 independent factors: age, decreased sounds of breathing, respiratory rate, fever duration, length of hospital-stay, incidence of co-infection with other pathogen, levels of ferritin, and serum LDH level.
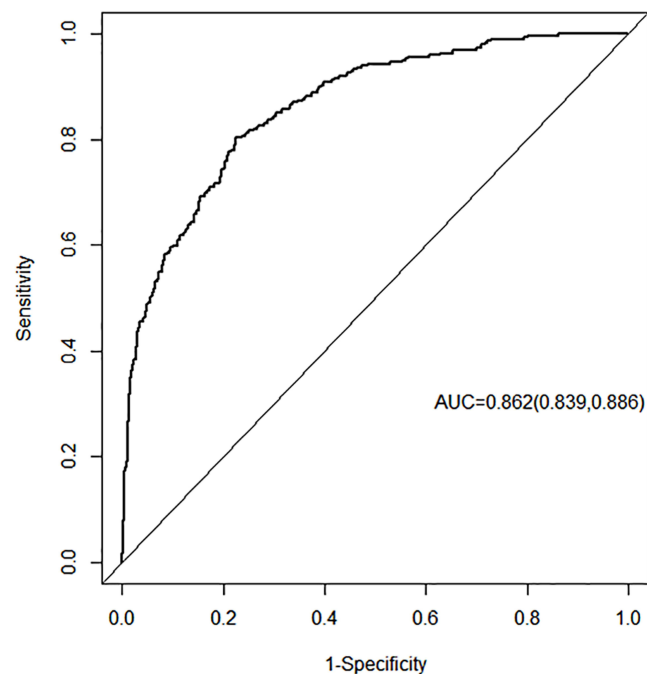
Figure 2 ROC curve of the nomogram model. The 8 independent risk factors presented with an area under the ROC curve (AUC) of 0.862 (95% CI: 0.839, 0.886).

curve of 0.862 (95% CI: 0.839, 0.886). Furthermore, internal validation showed that the calibration curve had a good fit with the standard curve, which was confirmed by Hosmer–Lemeshow test with high consistency, indicating that the nomogram model established in this study is highly accurate in predicting the severity of MPP.

The incidence of severe MPP increased with age in children due to an excessive immune response with the maturity of immunity.[8–10] Decreased sounds of breathing, tachypnea, and persistent fever are common clinical features of severe airway infections, which could result in longer stays in the hospital. Consistently, the current study found that age,
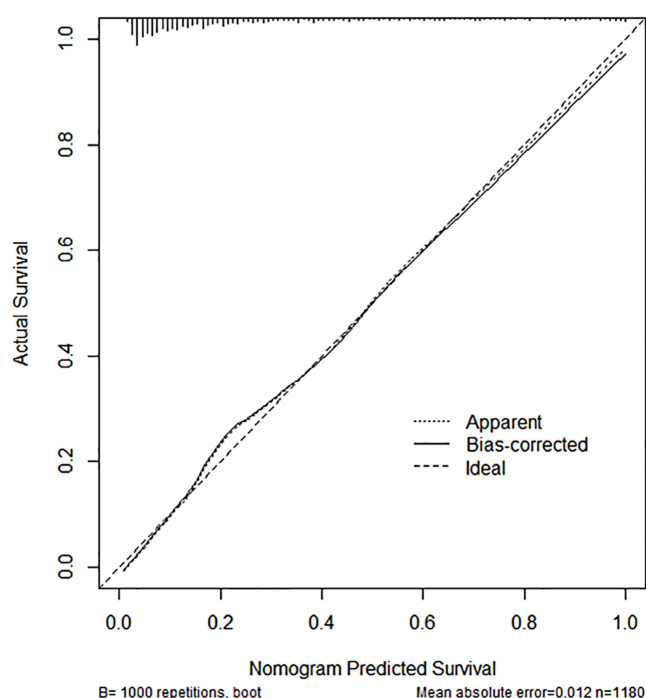
Figure 3 Calibration curve of the nomogram model. The observed apparent outcome (dotted line), the bias-corrected outcome (solid line), and the ideal outcome (dashed line) were presented.

decreased sounds breathing, respiratory rate, days of fever lasted, and days of hospital stay were the factors that significantly contributed to the formation of a nomogram model for predicting severity of MPP.

Mycoplasma pneumoniae is a common pathogen that causes community-acquired pneumonia in children.[11] Previous studies have reported that the co-infection rate of *Mycoplasma pneumoniae* and other pathogens ranged from 10% to 56.1%.[12–14] *Streptococcus pneumoniae*, Epstein–Barr virus, parainfluenza virus, and respiratory syncytial virus are the most common pathogens that are co-infected with *Mycoplasma pneumoniae* in children. Co-infection of *Mycoplasma pneumoniae* with virus or bacteria could not only influence the progress of MPP but also increase the chance of extrapulmonary complications including complications of neurological systems such as encephalitis, acute disseminated encephalomyelitis; transverse myelitis; Guillain-Barre syndrome; or cerebral infarction; cardiovascular systems such as blood clots in the heart, septic shock; myocarditis; pericarditis; Kawasaki disease; arterial or venous embolism; blood systems such as immune thrombocytopenia; autoimmune hemolytic anemia; hemophagocytic syndrome; disseminated intravascular coagulation; skin and mucous membranes such as urticaria; allergic purpura; erythema multiforme; Stevens-Johnson syndrome; toxic necrotic epidermolysis; mycoplasma pneumoniae-induced rash and mucositis and others including glomerulus nephritis complicated with severe congestion or hypertensive crisis, acute kidney injury, liver function failure, acute pancreatitis, arthritis, or rhabdomyolysis syndrome. The current study found that co-infection was also a risk factor for the development of severe MPP, which is consistent with previous reports.[9,14,15]

The pathogenesis of severe MPP is mainly caused by the following two aspects: the virulence of the *Mycoplasma pneumoniae* pathogen itself, and the host immune response to defense against *Mycoplasma pneumoniae* infection.[16] Inflammatory mediators such as reactive oxygen species and cytokines (IL-18) were produced by human host cells in response to the infection of *Mycoplasma pneumoniae* and released into circulation.[17] These inflammatory mediators are responsible for the development of severe MPP by causing cellular death, tissue damage, and organ dysfunction. In addition, indirect interaction of immunological or allergic reaction of the host cells to *Mycoplasma pneumoniae* infection leads to the progress of severe MPP. In this regard, it has been reported that a positive correlation between IL-18 and LDH levels exists in severe MPP cases and that serum LDH levels were significantly higher in the cases of severe MPP compared to the control group.[18–21] Consistently, we found that LDH level was one of the factors that could predict the

development of severe MPP, suggesting airway cell damage caused by an excessive host-cellular response to *Mycoplasma pneumoniae* infection may play a critical role in the development of severe status.

Persistent fever is one of the important clinical manifestations of severe infection including severe MPP, which often indicates that the body has generated an excessively intense immuno-inflammatory response. Long-term fever may cause systemic immune dysfunction, resulting in difficulty to fight off infections and to control inflammation, which leads further to an extended fever and longer hospital-stays. Severe or refractory MPP with manifestations of pulmonary consolidation, pleural effusion, and atelectasis may be developed if systemic immune dysfunction and excessive inflammatory reaction were not resolved.[3,10,22,23] As anticipated, days of fever was also one of the significant contributors to the formation of a nomogram model constructed in this study.

Procalcitonin (PCT), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are often used as indicators of systemic inflammation. However, limited studies on the application of ferritin in monitoring inflammatory reactions have been reported.[24,25] In response to pro-inflammatory cytokines such as IL-1ß and TNF-α, hepatocytes could release a large amount of ferritin. High concentrations of ferritin could further promote the release of pro-inflammatory mediators and aggravate the inflammatory response by binding to T cells. Therefore, elevation of ferritin level can be an indicator of excessive inflammatory response.[26,27] Here, we report that ferritin level could be one of the factors that predicts the development of severe MPP in children.

Persistent and excessive inflammatory reaction in the lung could also cause tissue damage and cell death, which results in release of LDH into the blood.[16,28] As a non-specific marker of tissue damage and cellular death, LDH is often used as one of the indicators for judging the severity of the disease and prognosis. Consistent with previous reports,[4,19,21] the current study found that LDH was significantly increased in severe MPP patients compared to patients with general MPP and that LDH was one of the factors significantly associated with the severity of MPP.

There are several limitations with our study. First, this was a retrospective study carried out in a single institute. Although the confidence interval of the area under the ROC curve in this retrospective study reached 0.862, a prospective cohort study is necessary to confirm that the predictive scale of the factors selected in this study can accurately distinguish between severe MPP and general MPP. Second, patients with incomplete clinical data were excluded from this study, which may cause selection bias. Third, only internal validation was used to evaluate the model in this study in that there was no external data available for us. A more effective and stronger external validation from cohort studies with other institutes remains to be conducted to confirm the findings of this study. While a larger scale and multi-center prospective study is needed to confirm the accuracy and adaptability of the current model, the clinical indicators included in this study are easy to obtain, and thus, accuracy of the nomogram model constructed in this study could be easily tested in future clinical work.

Conclusion

The current study found that age, decreased sounds of breathing, respiratory rate, fever duration, days of hospitalization, incidence of co-infection, and levels of ferritin and LDH were independent factors that significantly contributed to the construction and validation of a nomogram model for predicting the severity of MPP. This nomogram model could be a reliable tool for clinicians to make prediction on the progress of MPP so that a timely diagnosis and treatment for severe MPP could be applied in clinical work.

Data Sharing Statement

The original data included in this study are presented in this article. Further inquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

This study was approved by the Ethic Committee of the Tianjin Children's Hospital (No. 022-LXKY-004). All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from individual participants and their legal guardians.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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