Prediction Model for Severe Mycoplasma Pneumoniae Pneumonia in Pediatric Patients by Admission Laboratory Indicators

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Research Article

Keywords: severe mycoplasma pneumoniae pneumonia, pediatric patients, prediction model, admission laboratory indicators

Posted Date: April 26th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-403591/v1>

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Abstract

Objective

The purpose of this study was to develop a model for predicting severe mycoplasma pneumoniae pneumonia (SMMP) in pediatric patients with MMP on admission by laboratory indicators.

Methods

Pediatric patients with MMP from January 2019 to December 2020 in our hospital were enrolled in this study. SMMP was diagnosed according to guideline for diagnosis and treatment of community acquired pneumonia in children (2019 version). Prediction model was developed according to the admission laboratory indicators. ROC curve and Goodness of fit test were analyzed for the predictive value.

Results

A total of 233 MMP patients were included in the study, with 121 males and 112 females, aged 4.541 (1–14) years. Among them, 84 (36.1%, 95% CI 29.9%-42.6%) pediatric patients were diagnosed as SMPP. Some admission laboratory indicators (IgM, eosinophil proportion, eosinophil count, hemoglobin, ESR, total protein, albumin and prealbumin) were found statistically different ($P < 0.05$) between non-SMMP group and SMMP group. Logistic regress analysis showed IgM, eosinophil proportion, eosinophil count, ESR, and prealbumin were independent risk factors for SMMP. According to these five admission laboratory indicators, Nomograph prediction model was developed. The AUC of the Nomograph prediction model was 0.777, and the goodness of fit test showed that the predicted incidence of the model was consistent with the actual incidence ($\chi^2 = 244.51$, $P = 0.203$).

Conclusion

We developed a model for predicting SMMP in pediatric patients by admission laboratory indicators. This model has good discrimination and calibration, which provides a basis for the early identification SMMP on admission.

Introduction

Mycoplasma pneumoniae pneumonia (MMP) is a common respiratory infection in children. In recent years, MMP accounts for 10%-40% of community acquired pneumonia (CAP) in children, especially in Asia [1]. If the host cannot effectively clear the pathogen of mycoplasma pneumoniae, immune response will continuously damage of the respiratory epithelium and cilia [2, 3]. In addition, drug resistant MP strains are more and more common. In China, more than 85% of MP strains among pediatric patients have been reported as macrolide-resistant [4]. In Taiwan, the rate of macrolide-resistant strains in the

pediatric population was 23.6% [5]. Therefore, severe mycoplasma pneumoniae pneumonia (SMMP) has become a significant issue all around the world. SMMP cases will give rise to numerous complications, such as organ dysfunction, pleural effusion, capillary leak syndrome, and plastic bronchitis [6, 7]. Furthermore, cardiovascular dysfunction, liver injury, or multiple organ dysfunction syndrome were associated with longer mechanical ventilation duration, delayed PICU discharge, and high hospital mortality [6]. Therefore, early identification and prevention of the occurrence of SMMP is very important.

Risk assessment is the first step for early identification and prevention of SMMP. Some studies have assessed the risk factors of the SMMP. Shin JE et al found pediatric patients with atopic sensitization (OR, 3.83; 95% CI, 1.55–9.47) and history of asthma (OR, 5.40; 95% CI, 1.67–17.45) showed a higher association with refractory MP requiring steroid therapy after controlling for age and sex [8]. Bao YX et al reported atopy may be a risk factor for the presence and severity of refractory MP pneumonia due to the high pathogen load in airway [9]. A recent meta-analysis showed that fever for more than 10 days (OR 3.965, 95% CI 2.109–7.456), pleural effusion (OR 6.922, 95% CI 2.058–23.282), extra-pulmonary complications (OR 17.762, 95% CI 11.146–28.305), pulmonary X-ray consolidation $\geq 2/3$ (OR 8.245, 95% CI 1.990–34.153), CRP > 40 mg/L (OR 4.975, 95% CI 2.116–11.697) were significantly related to the risk of SMPP [10]. However, these studies only provided individual risk factors for SMPP. It is still difficult to predict the occurrence of SMMP accurately.

Some studies also have found laboratory indicators were also related with SMMP in pediatric patients. Huang X et al reported C-reactive protein (CRP), lactate dehydrogenase (LDH) and D-dimer (D-D) as independent risk factors for SMMP, and D-D had the highest predictive power ($P < 0.01$) [11]. Wang M et al found that the serum concentrations of tumor necrosis factor alpha (median 114.5 pg/ml, range 49.1–897.9 pg/ml) and interferon gamma (median 376.9 pg/ml, range 221.4–1997.6 pg/ml) were significantly higher in children with SMMP [12]. Laboratory indicators are easy to obtain for each hospitalized pediatric patients. In this study, we aim to develop a model for predicting SMMP in pediatric patients by admission laboratory indicators.

Patients And Methods

Patients

Pediatric patients with MPP from January 2019 to December 2020 in our hospital were enrolled in this study.

Selection criteria: pediatric patients with MPP should meet the following three conditions: (1) clinical manifestations of cough with or without fever; (2) imaging findings of lobar infiltration, lobular patchy infiltration or interstitial changes in the lung; (3) laboratory evidence of the titer of single MP antibody was $\geq 1:160$.

Exclusion criteria: (1) pediatric patients with immunodeficiency; (2) pediatric patients with underlying lung diseases (tuberculosis, tracheomalacia, etc.); (3) pediatric patients with other pathogenic infections.

Informed consent was obtained from their parents or legal guardians.

SMPPdiagnostic criteria

SMMP was diagnosed according to the guideline for diagnosis and treatment of community acquired pneumonia in children (2019 version)[13]. Any of the following manifestations is considered as SMPP: (1) disturbance of consciousness; (2) hypoxemia, shown as: rapid breathing, $RR \geq 70$ / min (infant), $RR \geq 50$ / min (over 1 year old); assisted breathing (groan, nasal fan, three concave sign); intermittent apnea; oxygen saturation $< 92\%$; (3) persistent high fever for more than 5 days; (4) dehydration; (5) chest X-ray showed that multiple lobes were involved or complicated with pleural effusion; (6) with serious extrapulmonary complications.

Admission Laboratory examination

Within 24 hours after admission, venous blood was collected and sent to the laboratory. MP-IgM and MP-IgG were detected by enzyme linked immunosorbent assay (ELISA). White blood cell (WBC) count, neutrophil proportion, neutrophil count, eosinophil proportion, eosinophil count, hemoglobin, and platelet were detected by automatic blood cell analyzer. Lactate dehydrogenase (LDH), total protein, albumin, and pre-albumin were detected by automatic biochemical analyzer. Hypersensitive C-reactive protein (HsCRP) were detected by automatic chemiluminescence instrument. Erythrocyte sedimentation rate (ESR) was detected by automatic ESR analyzer.

Statistical analysis

The count data were expressed by the number of cases and percentage, chi square test was used for comparison. The normal distribution of the admission laboratory data was expressed by the mean $\pm$ standard deviation, and the t test was used for comparison.

Prediction model was developed according the following steps: first, all the admission laboratory indicators were analyzed by logistic stepwise regression analysis using forward likelihood ratio method (the inclusion and exclusion criteria were 0.20); then, Nomograph prediction model was constructed based on logistic regression; finally, the predictive value of the model was evaluated by discrimination and calibration (discrimination was described by ROC and AUC, calibration was described by goodness of fit test).

All analyses were conducted using Stata 14.0. Statistical significance was defined as $P < 0.05$ in the tests.

Results

Study population

A total of 233 MMP pediatric patients were included in the study, with 121 males and 112 females, aged 4.541 (1-14) years. Among them, 84 pediatric patients were diagnosed as SMPP, with the incidence of 36.1% (95% CI 29.9%-42.6%). No significant difference was found in the distribution of gender among two groups (74/75 in the non-SMPP group Vs. 47/37 in the SMPP group, $\chi^2=0.851$, $P=0.356$), and no significant difference in the age (4.346 ± 2.685 in the non-SMPP group Vs. 4.833 ± 0.297 in the SMPP group, $t=1.243$, $P=0.215$).

Admission laboratory indicators difference between non-SMPP and SMPP groups

MP-IgM, MP-IgG, WBC, neutrophil proportion, neutrophil count, eosinophil proportion, eosinophil count, hemoglobin, platelet, LDH, total protein, albumin, pre-albumin, HsCRP and ESR were detected in all pediatric patients within 24 hours after admission.

There was no significant difference in IgG, WBC, neutrophil proportion, neutrophil count, platelet, HsCRP, LDH ($P>0.05$) between non-SMPP group and SMPP group; but significant differences were found in IgM, eosinophil proportion, eosinophil count, hemoglobin, ESR, total protein, albumin and prealbumin ($P<0.05$) between non-SMPP group and SMPP group. Companion of admission laboratory indicators between two groups was shown in the Tab1.

Logistic regression analysis

In the Model 1, IgM, WBC, neutrophil proportion, eosinophil proportion, eosinophil count, hemoglobin, platelet, HsCRP, ESR, total protein, albumin, prealbumin, and LDH were included. The Model 1 was statistically significant, with LR χ^2 63.04, Prob 0.000, and Pseudo R^2 0.2069.

In the Model 2, IgM, eosinophil proportion, eosinophil count, hemoglobin, ESR, prealbumin, and LDH were included. The Model 2 was statistically significant, with LR χ^2 55.67, Prob 0.000, and Pseudo R^2 0.1828.

In the Model 3, IgM, eosinophil proportion, eosinophil count, ESR, and prealbumin were included. The Model 3 was statistically significant, with LR χ^2 53.97, Prob 0.000, and Pseudo R^2 0.1772.

The Model 1, Mode2, and Model 3 were listed in the Tab. 2-4.

Prediction model development

Based on 5 laboratory indicators in the Model 3, the Nomograph prediction model was developed, which was shown in the Fig.1. The AUC of the Nomograph prediction model was 0.777, and the ROC was shown in the Fig.2. The goodness of fit test showed that the predicted incidence of the model was consistent with the actual incidence ($\chi^2=244.51$, $P=0.203$).

Discussion

In this study, we developed a Nomograph prediction model based on 5 laboratory indicators of IgM, eosinophil proportion, eosinophil count, ESR, and prealbumin on admission. This model showed a good discrimination and calibration. Zhang J et al developed a prediction model of bronchial mucus plugs in children with MPP, the ROC curve analysis showed that children with MPP had $PA \leq 144.5$ mg/L, had used corticosteroids during the course of the illness of ≥ 4.5 days, $CRP \geq 12.27$ mg/L, an $LDH \geq 462.65$ U/L, and there was a possibility of intra-airway mucus formation [14]. Although bronchial mucus plugs in children with MPP was not different with SMMP, their predictive model has similar characteristics to our model, and both included many laboratory indicators.

In our prediction model, IgM was recognized as an important laboratory indicator for SMMP. MP-IgM is the firstly produced antibody after the onset MP infection, followed by specific IgG antibodies in the early stage of MPP, and many MP-IgM showed unchanged higher titers during subsequent course of the disease [15]. MP-IgM was a sensitive indicator of MP infection in children with a high consistency and correlation with the reference positive standard of PA titer $\geq 1:160$, and a 4-fold increase in MP-IgG could be the supplementary diagnosis method [16]. In our study, we found MP-IgM was important indicator for SMMP, but MP-IgG was not.

In our study, we found eosinophil was related with SMMP, not only eosinophil proportion, but also eosinophil count. Kim JH et al reported in pediatric patients with MPP, serum eosinophil cationic protein (ECP) levels were significantly higher in atopic patients at all three time points tested, and eosinophil counts were higher in the clinical recovery and follow-up phases [17]. Bao YX believed atopy was a risk factor for the presence and SMMP due to the high pathogen load in airway, they found more children in the high-MP-load group presented with increased serum IgE and ECP ($P < 0.05$). Their views are the same as ours. We included eosinophil proportion and eosinophil count for the model predicting SMMP [9].

ESR and prealbumin were also enrolled in our prediction model. As an important indicator of SMMP, ESR has been confirmed by many studies. Huang X et al found ESR was significantly higher in the SMPP group than those in the general MPP group ($P < 0.05$) [11]. Lu A et al reported that age, LDH, and ESR were the significant factors in predicting refractory *M. pneumoniae* pneumonia by logistic regression [18]. Prealbumin was also an important indicator for SMMP. In Zhang J's study, they found prealbumin levels were lower in the mucous group of children with MPP [14]. Zhang Y et al reported the levels of prealbumin were lower than that in SMPP group than those in the general MPP group ($P < 0.01$) [19].

Limitation

There are some limitations in our study. First, we only included 233 MPP pediatric patients. The sample is small, and we can't do external validation in other patient cohorts. Second, the patients were come from a medical center. The prediction effect of the model needs to be further verified by other medical centers.

Conclusion

We developed a model for predicting SMMP in pediatric patients by admission laboratory indicators. This model has good discrimination and calibration, which provides a basis for the early identification SMMP on admission.

Declarations

Ethics approval and consent to participate: Ethical approval was granted from Ethical Committee of Wuxi No.8 People's Hospital and Wuxi Occupational Disease Hospital.

Consent for publication: Not applicable.

Availability of data and materials: Data for this article can be accessed by contacting the corresponding author.

Competing interests: The authors had no conflicts of interest to declare in relation to this article.

Funding: Scientific research projects of health committee of Wuxi city in 2019.

Authors' contributions: Qing Chang, concept designer, data analysis; Hong-Lin Chen, writing support, statistical analysis; Neng-Shun Wu, Yan-Min Gao, Rong Yu, Wei-Min Zhu, data gathering, data interpretation and clinical data analysis. All authors have read and approved the manuscript.

Acknowledgements: None

All experimental protocols were approved by Wuxi No.8 People's Hospital and Wuxi Occupational Disease Hospital.

All methods were carried out in accordance with regulations.

Informed consent was obtained from all participants.

We agree share raw data.

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Tables

Tab1 Companion of laboratory indicators between non-SMPP and SMPP groups

Laboratory Indicators	non-SMPP group (N=149)	SMPP group (N=84)	t	P
IgM (mg/dL)	3.910±2.809	4.880±2.957	2.482	0.014*
IgG (mg/dL)	230.825±93.456	239.218±83.269	0.684	0.495
WBC (10 ⁹ /L)	9.769±5.711	8.460±4.392	-1.819	0.070*
Neutrophil Proportion (%)	55.713±15.655	58.695±16.022	1.384	0.168*
Neutrophil Count (10 ⁹ /L)	6.092±6.657	5.479±4.014	-0.768	0.443
Eosinophil Proportion (%)	1.622±2.1145	0.941±1.387	-2.963	0.003*
Eosinophil Count (10 ⁹ /L)	0.167±.21371	0.079±0.117	-4.099	0.000*
Hemoglobin (g/L)	127.260±12.547	123.120±9.178	-2.887	0.004*
Platelet (10 ⁹ /L)	250.280±86.000	228.130±96.914	-1.802	0.073*
HsCRP (mg/L)	11.817±24.097	19.898±42.851	1.844	0.066*
ESR (mm/h)	24.725±15.776	35.635±26.590	3.435	0.001*
Total Protein (g/L)	66.995±3.791	65.396±5.390	-2.404	0.018*
Albumin (g/L)	42.206±2.957	40.122±3.061	-5.101	0.000*
Prealbumin (mg/L)	136.624±32.860	112.496±30.173	-5.540	0.000*
LDH (U/L)	361.404±169.022	392.002±177.049	1.304	0.193*

* P<0.20

Tab2 Results for Logistic regression analysis of SMPP related influencing factors (Model 1)

Laboratory Indicators	Odds Ratio	Std. Err.	z	P>z	[95% Conf. Interval]
IgM (mg/dL)	1.087177	.0597774	1.52	0.128*	.9761077-1.210884
WBC (10 ⁹ /L)	.9702647	.0505076	-0.58	0.562	.8761542-1.074484
Neutrophil Proportion (%)	1.008905	.0118566	0.75	0.451	.9859317-1.032413
Eosinophil Proportion (%)	1.423446	.325009	1.55	0.122*	.9098925-2.226856
Eosinophil Count (10 ⁹ /L)	.0010825	.0029772	-2.48	0.013*	4.93e-06-.2374588
Hemoglobin (g/L)	.980695	.0148777	-1.28	0.199*	.9519646-1.010293
Platelet (10 ⁹ /L)	.9980204	.0021028	-0.94	0.347	.9939074-1.00215
HsCRP (mg/L)	.9973154	.006431	-0.42	0.677	.9847901-1.01
ESR (mm/h)	1.024273	.0110801	2.22	0.027*	1.002785-1.046221
Total Protein (g/L)	.9590784	.0493472	-0.81	0.417	.8670766-1.060842
Albumin (g/L)	.9283569	.0696269	-0.99	0.322	.8014468-1.075363
Prealbumin (mg/L)	.9857628	.0070449	-2.01	0.045*	.9720513-.9996677
LDH (U/L)	1.001344	.0010253	1.31	0.190*	.9993362-1.003355
_cons	4671.292	15092.18	2.62	0.009*	8.305067-2627428

* P<0.20

Tab3 Results for Logistic regression analysis of SMPP related influencing factors (Model 2)

Laboratory Indicators	Odds Ratio	Std. Err.	z	P>z	[95% Conf. Interval]
IgM (mg/dL)	1.095334	.0576964	1.73	0.084*	.987893-1.214461
Eosinophil Proportion (%)	1.414326	.2967639	1.65	0.099*	.9374422-2.133805
Eosinophil Count (10 ⁹ /L)	.0007146	.0018193	-2.85	0.004*	4.87e-06-.104974
Hemoglobin (g/L)	.9828942	.0142274	-1.19	0.233	.9554008-1.011179
ESR (mm/h)	1.017831	.0081296	2.21	0.027*	1.002021-1.03389
Prealbumin (mg/L)	.9784627	.0059771	-3.56	0.000*	.9668178-.990248
LDH (U/L)	1.000651	.000946	0.69	0.491	.9987987-1.002507
_cons	31.9945	59.23192	1.87	0.061*	.8496354-1204.809

* P<0.20

Tab4 Results for Logistic regression analysis of SMPP related influencing factors (Model 3)

Laboratory Indicators	Odds Ratio	Std. Err.	z	P>z	[95% Conf. Interval]
IgM (mg/dL)	1.079541	.0553107	1.49	0.135*	.9763992-1.193578
Eosinophil Proportion (%)	1.403339	.2938067	1.62	0.106*	.9310071-2.115302
Eosinophil Count (10 ⁹ /L)	.0007718	.0019572	-2.83	0.005*	5.36e-06-.1111867
ESR (mm/h)	1.019056	.0080448	2.39	0.017*	1.003409-1.034946
Prealbumin (mg/L)	.9764974	.0058074	-4.00	0.000*	.9651811-.9879463
_cons	6.238631	5.263401	2.17	0.030*	1.193847-32.60093

* P<0.20

Figures

Figure 1

Nomograph prediction model for SMPP in pediatric patients according to admission laboratory indicators

Figure 2

ROC for Nomograph prediction model for SMPP in pediatric patients