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ORIGINAL ARTICLE

Correlations of Different Serological Parameters with the Severity and Prognosis of Pneumonia in Children Infected with *Mycoplasma Pneumoniae*

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SUMMARY

Background: **As a common pediatric respiratory disease, *Mycoplasma pneumoniae* pneumonia (MPP) accounts for 20 - 30% of acquired pneumonia in children, with a rising morbidity rate annually. We aimed to explore the correlations of different serological parameters with the severity and prognosis of MPP children.**
Methods: **A total of 108 MPP children were divided into severe group (n = 58) and mild group (n = 50). The serum levels of triglycerides, HDL-C, LDL-C, erythrocyte sedimentation rate (ESR), D-dimer (DD), lactate dehydrogenase (LDH), interleukin-6 (IL-6), galectin-3 (Gal-3), homocysteine (Hcy), and procalcitonin (PCT) were measured. Receiver operating characteristic (ROC) curves were plotted to analyze their predictive values for poor prognosis. They were followed up for 6 months and assigned into good and poor prognosis groups. Multivariate logistic regression analysis was performed to explore the serological parameters affecting prognosis. A prediction model was established.**
Results: **In acute and recovery phases, the levels of ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT in the severe group were significantly higher than those in the mild group ($p < 0.05$). Prediction combining various serological parameters had the highest value for poor prognosis. ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT levels were independent risk factors. The concordance index of the nomogram model established using these factors was 0.745 (95% CI: 0.684 - 0.830). The area under the ROC curve was 0.726 (95% CI: 0.701 - 0.815). The predicted probability of the model was consistent with the actual one, showing high accuracy.**
Conclusions: **Serum levels of ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT are closely correlated with the severity and prognosis of MPP children, which provide references for prognostic evaluation. Prediction combining these indices is more valuable than that using a single index.**
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KEYWORDS

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INTRODUCTION

As a common pediatric respiratory disease, *Mycoplasma pneumoniae* pneumonia (MPP) accounts for 20 - 30% of acquired pneumonia in children, with a rising morbidity rate annually [1]. About 3 - 10% of cases with MP-induced upper respiratory tract infection develop into MPP [2]. The pathogenesis of MPP is complex. Specifically, a considerable amount of cytokines released in the early stage of MP infection destroy the balance between coagulation and plasminogen activation, leading to abnormal immune responses and hypercoagulable states [3-6]. The majority of MPP children have good prognosis, but some of them may suffer from severe extrapulmonary complications and other complications such as bronchiectasis and bronchiolitis obliterans, seriously threatening the health and life safety. Bronchiectasis is a chronic respiratory disease manifested as damage, deformation, and dilation of the bronchial wall due to long-term repeated infection and secretion obstruction. It is an irreversible change [7]. Bronchiolitis obliterans is a chronic airflow obstruction syndrome that mainly involves small and medium bronchi, being associated with fibrous tissue hyperplasia. It is primarily manifested as atelectasis and lobar collapse. Sub-segmental and sub-subsegmental distal occlusions can be observed by fiberoptic bronchoscopy, partly accompanied by proximal mucosal atrophy and lumen dilation [8].

Therefore, the early prognostic evaluation of MPP children and screening of high-risk factors for poor prognosis are of great significance to the preparation of effective treatment protocols and improvement of prognosis. The levels of erythrocyte sedimentation rate (ESR), D-dimer (DD), lactate dehydrogenase (LDH), interleukin-6 (IL-6), galectin-3 (Gal-3), homocysteine (Hcy), and procalcitonin (PCT) in the serum are abnormally elevated upon the onset of MPP, which are reference values for early diagnosis, but their relationships with the prognosis of MPP children have not been clarified yet [9]. In the present study, the serum ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT levels in MPP children were detected, and their correlations with the severity and prognosis were investigated, which are conducive to early intervention and prognosis improvement in clinical practice.

MATERIALS AND METHODS

Clinical data

This study has been approved by the ethic committee of our hospital. The family members of children were informed of the study and agreed to participate in the study. Our hospital is a first-class tertiary hospital in Changzhou, Jiangsu Province, China, with a reputable pediatric section. At present, the number of outpatient and emergency visits in the pediatric section has reached over 460,000 throughout the year. A total of 108 MMP children treated from October 2019 to March 2021 were selected as the subjects for observation group, including 59 boys and 49 girls aged 3 - 12 years old, 7.48 ± 2.61 years on average. The children with the following symptoms at the same time were allocated into severe group (n = 58): 1) those with positive MP-IgM antibody in the serum, persistent high fever for more than 7 days, and serious cough or intrapulmonary and extrapulmonary complications, and 2) those with systemic inflammatory responses and large patchy shadows occupying 1 or more pulmonary lobes according to imaging examination (chest X-ray; GE Healthcare, LLC, Waukesha, WI, USA). Otherwise, the children were included into mild group (n = 50). In addition, 40 healthy children receiving physical examination in the same period were enrolled into control group. There were 18 boys and 22 girls aged 3 - 11 years old, with an average of 7.12 ± 2.66 years. The two groups had similar gender ratio and age ($p > 0.05$).

Inclusion and exclusion criteria

Inclusion criteria: 1) Children meeting the diagnostic and treatment criteria of MPP [10] and with a single MP antibody titer ≥ 1:160, 2) those aged 3 - 12 years old, 3) those receiving conventional treatment and with good compliance, and 4) those with complete clinical data. Exclusion criteria: 1) Children with recurrent respiratory tract infection, pulmonary tuberculosis, tracheomalacia, bronchial asthma or other underlying pulmonary diseases, 2) those complicated with other acute or chronic pathogen infection, 3) those with congenital heart disease, pulmonary hypoplasia or immune deficiency, 4) those with severe hepatic or renal dysfunction or malignant tumors, 5) those complicated with abnormal cognitive development or serious trauma, or 6) those who took immunosuppressants or anticoagulants within 3 months.

Grouping

The 7th - 10th day after onset was regarded as the acute phase. From the 10th day after onset, the children were in the recovery phase if their body temperature returned to normal and cough was relieved remarkably. The blood was collected from control group at enrollment and 14 days later for detection to compare the indices with those of severe and mild groups in acute and recovery phases, respectively.

Methods

Fasting venous blood (3 mL) was collected in the morning after hospitalization or at the time of visit (for healthy children), placed at room temperature for 10 - 20 minutes for spontaneous coagulation, and centrifuged at 3,000 r/minute for 10 minutes (Thermo Fisher

Scientific, Waltham, MA, USA; centrifugal radius: 10 cm). Then the upper-layer serum was obtained and frozen in a freezer at -80°C for later tests. Next, ESR, DD, and LDH of the two groups in acute and recovery phases were examined. The levels of serum IL-6, Gal-3, and Hcy were detected by enzyme-linked immunosorbent assay kits (Beijing Bio-Lab Technology Co. Ltd., China). PCT was determined using sandwich chemiluminescence immunoassay kits provided by Wuhan EasyDiagnosis Biomedicine Co. Ltd. (China), with the positive threshold of ≥ 0.5 ng/mL. Additionally, the levels of the above serological parameters in the control group were measured. All specimens were tested by personnel in the Department of Clinical Laboratory in strict accordance with the instructions.

The clinical pulmonary infection score (CPIS) at admission was recorded, involving body temperature, white blood cell count, airway secretion, oxygenation, chest X-ray, pulmonary infiltrates, and endotracheal aspirate culture. The total score is 12 points, and a higher score means more severe disease.

Follow-up

All the MPP children were followed up by telephone interview, home visit or outpatient appointment for 6 months, during which their conditions were recorded. Then they were assigned into good and poor prognosis groups based on the prognosis according to the symptoms and chest X-ray examination results. Good prognosis: The clinical symptoms and signs were relieved or eliminated, the chest X-ray examination returned to normal or most foci were absorbed, and serological parameters were basically restored to normal levels. Poor prognosis: The clinical symptoms and signs were alleviated inconspicuously or aggravated, and minor changes and even deterioration of chest X-ray examination and laboratory indices were observed.

Statistical analysis

SPSS 21.0 software (IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA) was used for statistical analysis. The normally distributed measurement data were represented as ($\bar{x}$ ± s), analysis of variance was conducted for comparison among multiple groups, and *t*-test was used for comparison between two groups. Pearson's analysis was employed to explore the correlations of CPIS with various serological parameters. Receiver operating characteristic (ROC) curve was plotted to investigate the values of the serological parameters for evaluating the prognosis of MPP children. The influencing factors for prognosis were explored through multivariate logistic regression analysis. Two-tailed $p < 0.05$ indicated that a difference was statistically significant.

RESULTS

In the acute phase, the severe group had significantly higher levels of serum ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT as well as CPIS than those of the mild group ($p < 0.05$), and both severe and mild groups had significantly increased serological parameter levels and CPIS compared with those of the control group ($p < 0.05$). The levels of triglycerides, HDL-C and LDL-C were similar ($p > 0.05$) (Table 1).

In the recovery phase, the levels of serum ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT as well as CPIS were significantly higher in the severe group than those in the mild group ($p < 0.05$), and they increased significantly in severe and mild groups compared with those in the control group ($p < 0.05$) (Table 2).

The levels of serum ESR ($r = 0.314$), DD ($r = 0.329$), LDH ($r = 0.356$), IL-6 ($r = 0.374$), Gal-3 ($r = 0.331$), Hcy ($r = 0.382$), and PCT ($r = 0.307$) were significantly positively correlated with CPIS of MPP children ($p < 0.05$).

After 6 months of follow-up, 28 of the 108 MPP children had poor prognosis (25.93%), while the remaining 80 had good prognosis. Besides, the levels of serum ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT were significantly raised in the poor prognosis group in comparison with those in the good prognosis group ($p < 0.05$) (Table 3).

The ROC curves of serum ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT levels and their combination for predicting the poor prognosis of MPP children were analyzed (Figure 1). As for predicting poor prognosis, the combination of ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT was more valuable than a single index (Table 4).

Multivariate logistic regression analysis was performed with poor prognosis as a dependent variable and serum levels of ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT as independent variables. The results revealed that the levels of serum ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT were independent influencing factors for the prognosis of MPP children ($p < 0.05$) (Table 5).

The risk prediction model was established using the influencing factors for poor prognosis and the statistical software based on R Language. The total score was the sum of the score of each index on corresponding scale bar, and the numerical value on the axis of poor prognosis risk indicated the risk of poor prognosis (Figure 2).

Harrell's concordance index (C-index) analysis and ROC curves were employed to evaluate the discrimination of prediction model for poor prognosis. The calculated C-index was 0.745 (95% CI: 0.684 - 0.830), and the area under the ROC curve (AUC) was 0.726 (95% CI: 0.701 - 0.815), with favorable discrimination (Figure 3).

The Bootstrap repeated sampling method was used for internal validation of the model. The calibration curve results exhibited that the incidence rate of poor prognosis predicted by the nomogram model was highly

Table 1. Levels of serological parameters and CPIS in acute phase ($\bar{x} \pm s$).

Item	Severe group (n = 58)	Mild group (n = 50)	Control group (n = 40)	F	p
ESR (mm/h)	33.86 ± 8.21 *#	21.15 ± 6.14	5.74 ± 3.25 *	7.678	0.016
DD (mg/L)	2.16 ± 0.57 *#	1.24 ± 0.74	0.64 ± 0.06 *	4.791	0.024
LDH (IU/L)	483.52 ± 159.72 *#	316.12 ± 100.58	236.21 ± 87.46 *	32.231	0.019
IL-6 (pg/mL)	49.54 ± 8.43 *#	22.79 ± 5.02	5.64 ± 1.27 *	4.097	0.007
Gal-3 (μg/mL)	52.82 ± 12.18 *#	33.15 ± 5.16	9.64 ± 2.36 *	9.286	0.015
Hcy (μmol/L)	32.41 ± 3.17 *#	18.49 ± 4.24	5.69 ± 1.76 *	3.691	0.028
PCT (ng/L)	1.25 ± 0.21 *#	0.12 ± 0.09	0.05 ± 0.02 *	9.419	0.022
CPIS (point)	8.13 ± 1.46 *#	6.04 ± 0.42	3.23 ± 1.08 *	5.437	0.003
Triglycerides (mM)	0.69 ± 0.11	0.71 ± 0.11	0.68 ± 0.11	0.892	0.103
HDL-C (mM)	1.51 ± 0.68	1.52 ± 0.68	1.53 ± 0.68	0.278	0.75
LDL-C (mM)	2.49 ± 0.35	2.46 ± 0.35	2.46 ± 0.35	0.432	0.567

* $p < 0.05$ vs. mild group, # $p < 0.05$ vs. control group.

Table 2. Levels of serological parameters and CPIS in recovery phase ($\bar{x} \pm s$).

Item	Severe group (n = 58)	Mild group (n = 50)	Control group (n = 40)	F	p
ESR (mm/h)	7.86 ± 2.21 *#	7.15 ± 2.14	5.41 ± 2.25 *	8.293	0.016
DD (mg/L)	0.92 ± 0.17 *#	0.74 ± 0.14	0.64 ± 0.06 *	4.791	0.024
LDH (IU/L)	332.52 ± 59.72 *#	306.12 ± 60.58	236.21 ± 87.46 *	47.231	0.047
IL-6 (pg/mL)	28.47 ± 8.63 *#	16.74 ± 5.62	5.66 ± 2.03 *	3.629	0.036
Gal-3 (μg/mL)	24.62 ± 10.11 *#	13.11 ± 5.02	10.06 ± 0.82 *	9.643	0.015
Hcy (μmol/L)	16.28 ± 4.25 *#	8.24 ± 3.05	5.69 ± 1.76 *	8.619	0.018
PCT (ng/L)	0.95 ± 0.13 *#	0.08 ± 0.01	0.05 ± 0.02 *	8.197	0.022
CPIS (point)	6.36 ± 1.49 *#	4.58 ± 0.27	3.02 ± 1.16 *	6.643	0.039

* $p < 0.05$ vs. mild group, # $p < 0.05$ vs. control group.

Table 3. Levels of serological parameters in MPP children with different prognoses ($\bar{x} \pm s$).

Item	Poor prognosis group (n = 28)	Good prognosis group (n = 80)	t	p
ESR (mm/h)	13.86 ± 4.21	7.15 ± 3.14	7.559	0.039
DD (mg/L)	1.65 ± 0.29	1.23 ± 0.33	5.049	0.021
LDH (IU/L)	367.46 ± 61.13	283.28 ± 54.69	4.916	0.048
IL-6 (pg/mL)	64.19 ± 7.36	20.16 ± 3.43	36.197	0.034
Gal-3 (μg/mL)	26.15 ± 9.16	12.82 ± 0.18	6.376	0.001
Hcy (μmol/L)	26.11 ± 4.97	9.46 ± 1.97	10.681	0.005
PCT (ng/mL)	0.85 ± 0.12	0.06 ± 0.02	7.466	0.028

Table 4. Predictive values of different serological parameters for poor prognosis.

Index	AUC	95% Confidence interval (CI)	Youden's index	Specificity (%)	Sensitivity (%)
ESR	0.845	0.695 - 0.857	0.679	81.9	86.0
DD	0.817	0.780 - 0.841	0.655	80.6	84.9
LDH	0.789	0.772 - 0.824	0.643	79.2	86.8
IL-6	0.839	0.742 - 0.906	0.661	80.4	85.7
Gal-3	0.764	0.718 - 0.863	0.651	82.5	83.7
Hcy	0.791	0.693 - 0.797	0.676	84.3	87.2
PCT	0.826	0.816 - 0.862	0.629	83.3	88.1
Combined indices	0.918	0.879 - 0.973	0.782	87.5	90.7

Combined indices include ESR + DD + LDH + IL-6 + Gal-3 + Hcy + PCT.

Table 5. Multivariate logistic regression analysis results of poor prognosis.

Variable	β	SE	Wald χ^2 value	OR value	95% CI	p
ESR	0.697	0.294	4.821	2.032	(1.193, 4.541)	0.012
DD	0.716	0.329	3.916	3.264	(1.016, 3.264)	0.001
LDH	0.813	0.294	4.168	2.591	(1.319, 3.968)	0.039
IL-6	0.849	0.364	5.166	2.351	(1.169, 4.553)	0.002
Gal-3	0.749	0.373	4.553	2.202	(1.187, 4.113)	0.005
Hcy	0.803	0.397	5.102	2.439	(1.262, 4.339)	0.024
PCT	0.821	0.287	4.624	2.406	(1.074, 6.459)	0.009

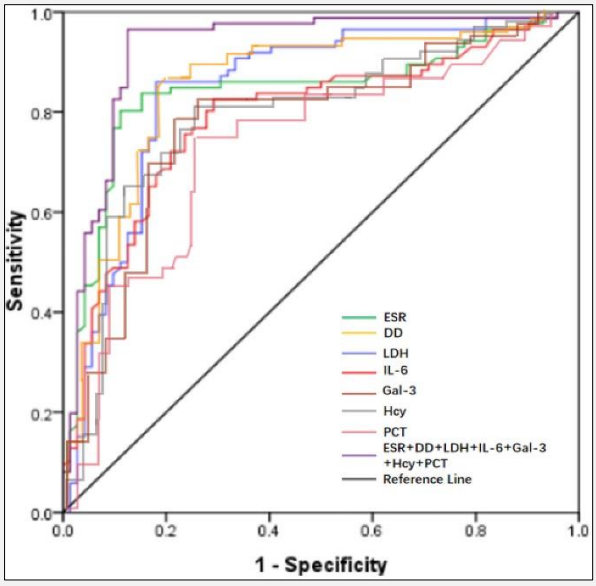

Figure 1. Predictive values of different serological parameters for poor prognosis.

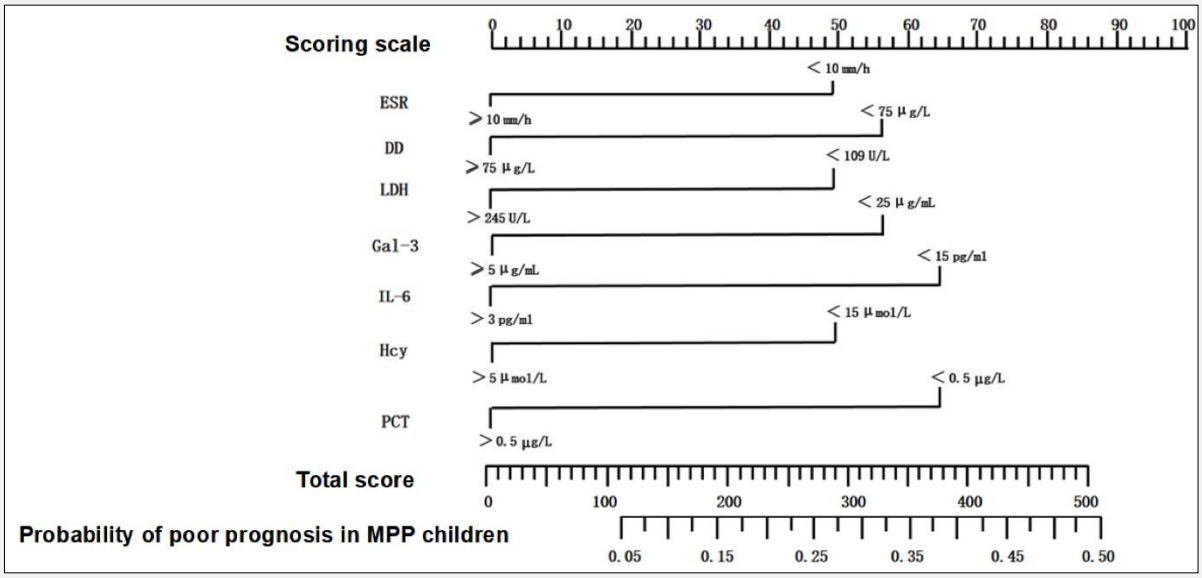

Figure 2. Nomogram model for predicting poor prognosis of MPP children.

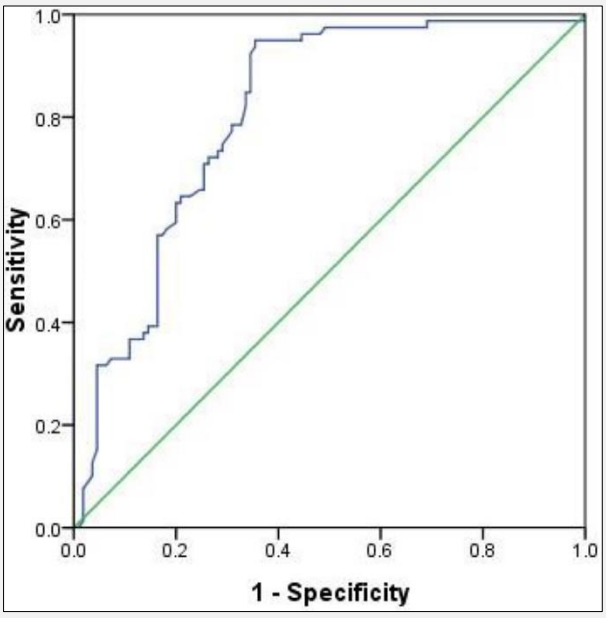

Figure 3. ROC curve of nomogram model.

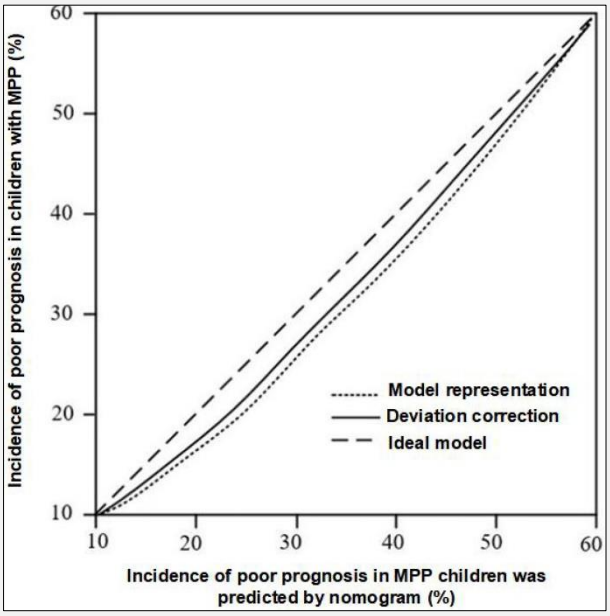

Figure 4. Calibration curve of nomogram model for predicting poor prognosis of MPP children.

consistent with the actual one. The mean error between predicted and actual risks was 0.012, and the accuracy was high. Taken together, the nomogram model has a preferable predictive value for poor prognosis (Figure 4).

DISCUSSION

Immune function plays a vital role in the onset and progression of MPP. In the complicated pathogenesis of MPP, considerable inflammatory mediators are produced after infection, thus causing immunologic dysfunction and accelerating disease progression [11]. The severity of MPP and extrapulmonary complications in children have special immunological manifestations and obvious associations with serum inflammatory factors [12]. Hence, seeking effective serological parameters for diagnosing MPP and evaluating the prognosis is of great significance to prevention and treatment.

When severe pneumonia occurs, the inflammatory mediators damage vascular endothelial cells and further stimulate the generation of various substances including plasma endothelin, often accompanied by coagulation abnormality [13]. ESR is a key marker capable of reflecting infection and disease activities, and its level was markedly higher in severe MPP children than that in non-severe children according to the research of Zheng et al. [14]. The increased expression of DD, a sensitive index of coagulation function, reflects hypercoagulable states and promotes thrombosis [15]. Ling et al. [16] found that DD was related to the severity of MPP, and its level was elevated in severe MPP children compared with that in mild MPP children. LDH is distributed in the cells of vital organs, which is released outside the cells in the case of cytolysis or cell membrane destruction, thereby prominently increasing serum LDH [17]. Izumikawa et al. [18] reported that LDH was a pivotal index for the early prediction of severe and refractory MPP. According to studies in recent years [19, 20], Gal-3 can facilitate the chemotaxis of monocytes, activate the function of macrophages, and participate in immune response. Likewise, Zhang et al. [21] found that the expression of serum Hcy was up-regulated in children with pneumonia. As a crucial inflammatory mediator synthesized in the acute phase of inflammation, IL-6 essentially participates in inflammatory response, anti-infection, and autoimmunity. Excessively strong inflammatory response can induce massive release of cytokines and immune dysfunction when MMP occurs, resulting in a notably higher serum IL-6 level in MPP children than that in normal children [22]. Serum PCT is secreted by thyroid C cells, and its level should be lower than 0.10 ng/mL under normal conditions. The production of PCT is enhanced if infection occurs. Lee et al. [23] first reported in 1993 that PCT was a new index of bacterial infection. In this study, the severe group had significantly higher levels of ESR, DD, LDH, IL-6,

Gal-3, Hcy, and PCT as well as CPIS than those of the mild group in both acute and recovery phases, and both severe and mild groups had significantly raised serological parameter levels and CPIS compared with those of the control group. Moreover, all the indices were significantly positively correlated with CPIS, suggesting that the detection of serum ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT not only provides references for MPP diagnosis, but also helps determine the progression of MPP. As a result, such indices can work as evaluation indices for the severity and overall situation of MMP in children. Ling et al. evaluated the predictive values of peripheral blood cell parameters [neutrophil, neutrophil/lymphocyte ratio (NLR), platelet count/lymphocyte ratio, mean platelet volume/lymphocyte ratio (MPVLR), C-reactive protein, LDH, and IL-6] for refractory *Mycoplasma pneumoniae* pneumonia in children over 6 years old. They finally found that NLR > 3.92 and MPVLR > 5.29 had high predictive values [24].

The multivariate logistic regression analysis results showed that ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT were independent influencing factors for the prognosis of MPP children. Besides, the levels of serum ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT were significantly elevated in the poor prognosis group compared with those in the good prognosis group, implying that these indices had high predictive values for prognosis. In addition, the ROC curve analysis revealed that all the serological parameters had certain predictive values for the prognosis of MPP children, and the prediction combining with these indices was more valuable for poor prognosis than that using single index. Based on the independent influencing factors for prognosis, the nomogram risk prediction model was established to rate ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT, and the total score was calculated. Finally, the discrimination and accuracy of the model were assessed by ROC curve, Harrell's C-index analysis, and calibration curve. The results showed that the C-index and AUC were 0.745 (95% CI: 0.684 - 0.830) and 0.726 (95% CI: 0.701 - 0.815), respectively, suggesting that the model had high predictive value and can accurately distinguish poor prognosis. The mean error of the calibration curve was 0.012, indicating high accuracy of the prediction model and certain predictive values of serum ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT levels for poor prognosis.

Nevertheless, this study still has limitations. For example, the dynamic changes in the levels of ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT were not monitored, the samples were regionally collected, and the study was conducted in a single center. Therefore, further multicenter studies with larger sample sizes are ongoing in our group to obtain more reliable clinical data.

CONCLUSION

In conclusion, the levels of serum ESR, DD, LDH, IL-6, Gal-3, Hcy, and PCT are closely correlated with the severity and prognosis of MPP children. The treatment regimens can be adjusted according to the changes of these levels, thereby improving the prognosis of MPP children.

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None.

Declaration of Interest:
The authors report no conflicts of interest.

References:

1. Medjo B, Atanaskovic-Markovic M, Radic S, Nikolic D, Lukac M, Djukic S. Mycoplasma pneumoniae as a causative agent of community-acquired pneumonia in children: clinical features and laboratory diagnosis. Ital J Pediatr 2014;40:104. (PMID: 25518734)

2. Lanks CW, Musani AI, Hsia DW. Community-acquired Pneumonia and Hospital-acquired Pneumonia. Med Clin North Am 2019; 103:487-501. (PMID: 30955516)

3. Rogozinski LE, Alverson BK, Biondi EA. Diagnosis and treatment of Mycoplasma pneumoniae in children. Minerva Pediatr 2017;69:156-60. (PMID: 28178776)

4. Lee KL, Lee CM, Yang TL, et al. Severe Mycoplasma pneumoniae pneumonia requiring intensive care in children, 2010-2019. J Formos Med Assoc 2021;120:281-91. (PMID: 32948415)

5. Varghese SM, Kerkar VV. Macrolide Resistant Mycoplasma pneumoniae in Community Acquired Pneumonia. Indian J Pediatr 2020;8:958. (PMID: 32333367)

6. Chen YC, Hsu WY, Chang TH. Macrolide-Resistant Mycoplasma pneumoniae Infections in Pediatric Community-Acquired Pneumonia. Emerg Infect Dis 2020;26:1382-91. (PMID: 32568052)

7. Chang AB, Bush A, Grimwood K. Bronchiectasis in children: diagnosis and treatment. Lancet 2018;392:866-79. (PMID: 30215382)

8. Cheng Q, Zhang H, Shang Y, et al. Clinical features and risk factors analysis of bronchitis obliterans due to refractory Mycoplasma pneumoniae pneumonia in children: a nomogram prediction model. BMC Infect Dis 2021;21:1085. (PMID: 34674642)

9. Xue M, Guo Z, Cai C, Sun B, Wang H. Evaluation of the Diagnostic Efficacies of Serological Markers KL-6, SP-A, SP-D, CCL2, and CXCL13 in Idiopathic Interstitial Pneumonia. Respiration 2019;98(6):534-45. (PMID: 31665737)

10. Søndergaard MJ, Friis MB, Hansen DS, Jørgensen IM. Clinical manifestations in infants and children with Mycoplasma pneumoniae infection. PLoS One 2018;13:e0195288. (PMID: 29698412)

11. Chkhaidze I, Kapanadze N. Cytokines as the predictors of severe mycoplasma pneumoniae pneumonia in children (review). Georgian Med News 2017;267:89-95. (PMID: 28726662)

12. Zhang C, Zhang Q, Du JL, et al. Correlation Between the Clinical Severity, Bacterial Load, and Inflammatory Reaction in Children with Mycoplasma Pneumoniae Pneumonia. Curr Med Sci 2020; 40:822-8. (PMID: 33123897)

13. Torres A, Chalmers JD, Dela Cruz CS, et al. Challenges in severe community-acquired pneumonia: a point-of-view review. Intensive Care Med 2019;45:159-71. (PMID: 30706119)

14. Zheng Y, Hua L, Zhao Q, et al. The Level of D-Dimer Is Positively Correlated With the Severity of Mycoplasma pneumoniae Pneumonia in Children. Front Cell Infect Microbiol 2021;11: 687391. (PMID: 34336714)

15. Huang X, Li D, Liu F, Zhao D, Zhu Y, Tang H. Clinical significance of D-dimer levels in refractory Mycoplasma pneumoniae pneumonia. BMC Infect Dis 2021;21:14. (PMID: 33407216)

16. Ling Y, Zhang T, Guo W, et al. Identify clinical factors related to Mycoplasma pneumoniae pneumonia with hypoxia in children. BMC Infect Dis 2020;20:534. (PMID: 32698769)

17. Zhang Y, Zhou Y, Li S, Yang D, Wu X, Chen Z. The Clinical Characteristics and Predictors of Refractory Mycoplasma pneumoniae Pneumonia in Children. PLoS One 2016;11:e0156465. (PMID: 27227519)

18. Izumikawa K. Clinical Features of Severe or Fatal Mycoplasma pneumoniae Pneumonia. Front Microbiol 2016;7:800. (PMID: 27313568)

19. Tian F, Chen LP, Yuan G, Zhang AM, Jiang Y, Li S. Differences of TNF-α, IL-6 and Gal-3 in lobar pneumonia and bronchial pneumonia caused by mycoplasma pneumoniae. Technol Health Care 2020;28(6):711-9. (PMID: 32200365)

20. Tian F, Han B, Duan M. [Serum tumor necrosis factor-α, interleukin -6 and galctin-3 concentrations in children with Mycoplasma pneumoniae pneumonia]. Zhongguo Dang Dai Er Ke Za Zhi 2014;16:1001-4. (PMID: 25344180)

21. Imamura K, Takeshima T, Nakaso K, Nakashima K. Homocysteine is toxic for dopaminergic neurons in primary mesencephalic culture. Neuroreport 2007;18:1319-22. (PMID: 17762705)

22. Yan Y, Wei Y, Jiang W, Hao C. The clinical characteristics of corticosteroid-resistant refractory Mycoplasma Pneumoniae pneumonia in children. Sci Rep 2016;6:39929. (PMID: 28008989)

23. Lee JY, Hwang SJ, Shim JW, et al. Clinical significance of serum procalcitonin in patients with community-acquired lobar pneumonia. Korean J Lab Me 2010;30:406-13. (PMID: 20805714)

24. Ling Y, Ning J, Xu Y. Explore the predictive value of peripheral blood cell parameters in refractory Mycoplasma pneumoniae pneumonia in children over 6 years old. Front Pediatr 2021;9: 659677. (PMID: 34869089)