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Significance of Lactate Dehydrogenase to Diagnosis and Treatment of Refractory *Mycoplasma Pneumoniae* Pneumonia

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ABSTRACT

Objective: To explore the significance of lactate dehydrogenase (LDH) to the diagnosis and treatment of refractory *Mycoplasma pneumoniae* pneumonia (RMPP).

Methods: A total of 70 children with RMPP (RMPP group) and another 70 children with non-refractory MPP (MPP group) who were treated in our hospital from January 2017 to January 2020 were enrolled using the propensity score matching method. According to the therapeutic effect of RMPP, the children in RMPP group were divided into effective group and ineffective group. The value of serum LDH level before treatment for diagnosing RMPP and predicting the therapeutic effect of RMPP was analyzed.

Results: The febrile course was longer, and the neutrophil ratio (N), white blood cell count (WBC), levels of C-reactive protein (CRP) and LDH and the proportions of cases of cough, gasping, double pneumonia, skin lesion and short breath were higher in RMPP group than those in MPP group (P<0.05). Upon admission, the course of disease and febrile course were longer, and the N, levels of CRP and LDH and the proportion of involvement of >2 lobes were higher in ineffective group than those in effective group (P<0.05). Multivariate logistic regression analysis revealed that LDH, febrile course and double pneumonia were related factors for the occurrence of RMPP (P<0.05). LDH and involvement of >2 lobes were the factors influencing the therapeutic effect of RMPP (P<0.05). ROC curve analysis showed that the area under the curve (AUC) of LDH in diagnosing RMPP was 0.81, and the specificity and sensitivity were 71.2% and 85.1%, respectively. AUC of LDH in predicting the therapeutic effect of RMPP was 0.75, and the specificity and sensitivity were 64.2% and 78.1%, respectively.

Conclusion: LDH is an independent factor affecting the occurrence and therapeutic effect of RMPP. The LDH level in peripheral blood has a certain value for diagnosing RMPP and predicting the prognosis of RMPP.

KEYWORDS: refractory *Mycoplasma pneumoniae* pneumonia; lactate dehydrogenase; diagnosis; treatment; biomarker

INTRODUCTION

Mycoplasma pneumoniae (MP) is one of the common pathogens of community-acquired pneumonia (CAP) in children [1]. MP accounts for about 40% of CAP cases, and 18% of children with MP need to be hospitalized [2]. Although MP pneumonia (MPP) is generally regarded as a self-limited disease, it may induce a variety of pulmonary and extrapulmonary complications, such as obliterative bronchiolitis, necrotic pneumonia, encephalitis, arthritis, pericarditis and hemolytic anemia, and develop into severe pneumonia [1]. For children, macrolides are the first choice of antibiotics for MP infection. However, in some cases, macrolides are ineffective, and the disease can progress to refractory MPP (RMPP) [3]. It is very important for clinicians to identify RMPP as early as possible and seize the appropriate treatment opportunities. Lactate dehydrogenase (LDH), a ubiquitous enzyme in human bodies, is able to catalyze the oxidative conversion of substrate pyruvate to lactate and has been taken as an inflammatory marker. As a non-specific biomarker, LDH level is elevated in many inflammatory processes [4]. According to a recent

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study, the serum total LDH level in patients with RMPP is elevated and may be a good predictor of steroid use [5]. Thus, it is necessary to further explore the clinical significance of LDH in RMPP. The present study aims to explore the significance of LDH in the diagnosis and treatment of RMPP, aiming to improve the basis for clinical diagnosis and treatment of RMPP.

MATERIALS AND METHODS

Baseline clinical data

A total of 70 children with RMPP who were admitted to our hospital from January 2017 to January 2020 were selected as subjects (RMPP group). According to the age, course of disease at admission, gender and body weight in RMPP group, another 70 children with non-refractory MPP (MPP group) were enrolled using the propensity score matching method. Diagnostic criteria for RMPP [6]: (1) Patients with MP-IgM positive or MP-DNA positive in peripheral blood (or bronchial lavage fluid). (2) The patients suffered from symptoms and signs of pneumonia, such as typical respiratory symptoms, hilar lymph node enlargement with pulmonary consolidation and pulmonary interstitial infiltration. (3) Refractoriness: After treatment with macrolide antibiotics such as azithromycin for 7 d, the clinical symptoms were not relieved or even aggravated, which was confirmed by imaging results. The diagnostic criteria for MPP were in accordance with (1) and (2). Inclusion criteria: (1) Children meeting the diagnostic criteria for RMPP and MPP, respectively, (2) those who received no other related treatment before enrollment, (3) those with complete data, and (4) those whose guardian signed the informed consent. Exclusion criteria: (1) Children complicated with other respiratory diseases, (2) those with refractory pneumonia caused by other causes, such as necrotic pneumonia, (3) those with a history of drug or food allergy, (4) those with heart disease, tumor or other major diseases, (5) those who took hormone drugs or immunosuppressants within 3 months before participating in the study, (6) those who had long-term drug use, (7) those with other acute or chronic infections, (8) those with hematological diseases, autoimmune deficiency, congenital lung diseases, connective tissue diseases or endocrine diseases (such as type 1 diabetes), (9) those with moderate or severe malnutrition, or (10) those with mixed infection by other pathogens.

Methods

RMPP treatment and grouping

The treatment of RMPP was strictly in accordance with the Expert consensus on diagnosis and treatment of Mycoplasma pneumoniae pneumonia in children [6]. After 2 weeks of treatment, the children in RMPP group were divided into effective group and ineffective group according to the treatment results. In effective group, the children had obvious improvement of clinical symptoms and signs, while in ineffective group, the patients exhibited no evident improvement of clinical symptoms and signs, or the disease aggravated after 2 weeks of treatment [6].

Data collection

The clinical data included age, course of disease at admission, gender, body weight, febrile course, pleural effusion, lesion site of pneumonia, and clinical manifestations (such as short breath, wheezing sound and skin lesion). The blood biochemical data included LDH and C-reactive protein (CRP) levels, neutrophil ratio (N), white blood cell count (WBC), erythrocyte sedimentation rate (ESR), etc., which were measured upon admission.

Statistical analysis

SPSS 20.0 was utilized for statistical analysis of research data. The quantitative data in accordance with normal distribution, such as LDH and CRP levels, were expressed as ($\bar{\chi} \pm s$), and compared with independent-samples t-test. The quantitative data that do not accord with normal distribution were expressed as median (inter-quartile range) and compared by Mann-Whitney U test. The qualitative data were compared using χ^2 test or Fisher exact probability method. ROC curve analysis was conducted to study the value of LDH for diagnosing RMPP and predicting the therapeutic effect of RMPP. Multivariate logistic analysis was performed to determine the related factors for RMPP and the risk factors for ineffective treatment of RMPP. $P<0.05$ suggested that the difference was statistically significant.

RESULTS

Clinical manifestations and biochemical data

The febrile course was longer, and the N, WBC, levels of CRP and LDH and the proportions of cases of cough, gasping, double pneumonia, skin lesion and short breath were higher in RMPP group than those in MPP group ($P<0.05$) (Table 1).

Table 1. **Clinical manifestations and biochemical data**

Clinical data	RMPP group (n=70)	MPP group (n=70)	χ^2/t	P
Gender (male, n)	38	37	0.029	0.865
Age (y)	6.7±2.0	6.6±2.1	0.288	0.773
Course of disease at admission (d)	5.1(3.1)	5.2(3.1)	0.059	0.854
Body weight (kg)	20.3±3.5	20.4±3.6	0.167	0.868
Febrile course (d)	7.8±2.0	4.9±2.1	8.367	0.000
Cough (%)	68	62	3.877	0.049
Gasping (%)	28	15	5.673	0.017
Pleural effusion (%)	10	7	0.603	0.438
Pneumonia location (%)			6.193	0.045
Left side	34	37		
Right side	24	30		
Both sides	12	3		
Skin lesion	20	8	6.429	0.011
Wheezing sound	14	11	0.438	0.508
Short breath	41	29	4.114	0.043
N (%)	78.5±5.6	62.4±5.2	17.626	0.000
ESR (mm/hr)	20.3±4.0	21.0±4.1	1.022	0.308
CRP (mg/L)	17.2±3.8	10.1±1.8	14.127	0.000
WBC ($\times 10^9$/L)	10.1±1.9	8.6±1.4	5.137	0.000
LDH (U/L)	516.8±97.1	315.5±84.8	13.064	0.000

Multivariate logistic regression analysis results for RMPP

The febrile course, N, hemoglobin (Hb), CRP, WBC, LDH, cough, gasping, pneumonia location, skin lesion and short breath were included in the multivariate logistic regression analysis. It was found that LDH, febrile course and double pneumonia were related factors for the occurrence of RMPP (P<0.05) (Table 2).

Table 2. **Multivariate analysis results for RMPP**

Factor	β	SE	Wald χ^2	OR	P	95% CI
LDH	1.588	0.477	7.514	2.154	0.011	1.125-11.235
Febrile course	2.102	0.421	10.234	3.254	0.002	1.355-14.254
Double pneumonia	1.325	0.578	6.321	1.521	0.031	1.066-8.214

Diagnostic value of LDH for RMPP

The results of ROC curve analysis demonstrated that AUC of LDH in diagnosing RMPP was 0.81 (P=0.001, 95% CI: 0.69-0.92), the specificity and sensitivity were 71.2% and 85.1%, respectively, and the cutoff value was 410 U/L (Figure 1).

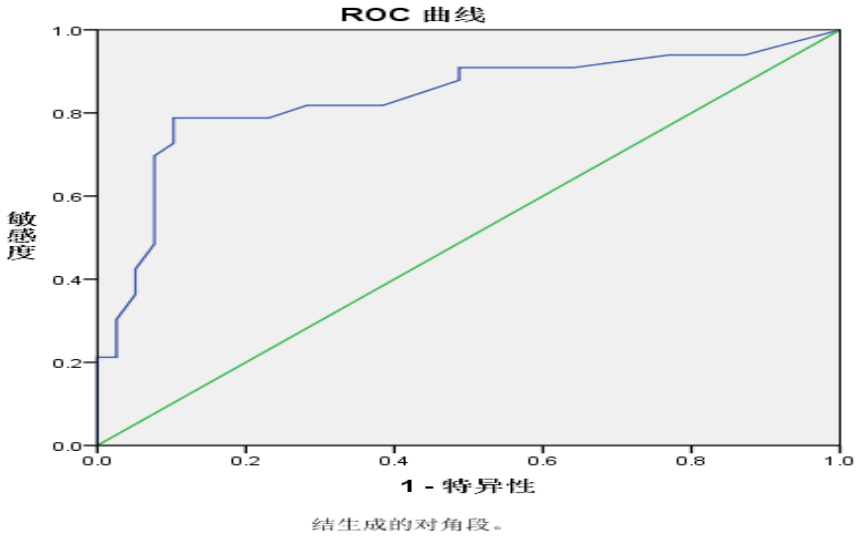

Figure 1. **ROC curve of LDH for diagnosing RMPP.**

Factors affecting therapeutic effect of RMPP

The therapy was effective in 60 children and ineffective in the other 10 after 2 weeks of treatment. The course of disease and febrile course were longer, and the N, levels of CRP and LDH and proportion of involvement of >2 lobes were higher in ineffective group than those in effective group (P<0.05) (Table 3). With statistically different indices as the independent variables and the therapeutic effect as the dependent variable, multivariate regression analysis was conducted. The results manifested that LDH level and involvement of >2 lobes were the factors influencing the therapeutic effect of RMPP (P<0.05) (Table 4).

Table 3. Baseline clinical data of ineffective and effective groups

Clinical data	Ineffective group (n=10)	Effective group (n=60)	χ^2/t	P
Gender (male)	6	32	0.154	0.695
Age (y)	6.6±1.5	6.8±2.3	0.265	0.792
Course of disease at admission (d)	7.2 (4.1)	5.5(3.0)	4.052	0.044
Febrile course (d)	8.9±2.1	6.4±2.0	3.635	0.001
Pleural effusion	3	7	2.353	0.125
Pneumonia location (%)			4.426	0.109
Left side	4	30		
Right side	2	22		
Both sides	4	8		
Skin lesion	5	15	2.625	0.105
Short breath	8	33	2.208	0.137
N (%)	78.5±5.6	62.4±5.2	8.970	0.000
Hb (g/L)	109.2 (108.6)	110.0 (109.7)	1.234	0.451
ESR (mm/hr)	19.3±5.0	21.3±5.2	1.132	0.262
CRP (mg/L)	26.2±4.8	17.1±3.8	6.750	0.000
WBC ($\times 10^9$/L)	10.1±1.8	9.9±1.9	0.130	0.757
LDH (U/L)	581.2 (562.8)	458.5 (439.8)	14.521	0.000
Hormone therapy	8	37	1.225	0.263
Gamma globulin therapy	4	20	0.169	0.681
Involvement of >2 lobes	8	20	7.778	0.005

Table 4. Factors affecting therapeutic effect of RMPP

Factors	β	SE	Wald χ^2	OR	P	95% CI
LDH	1.324	0.455	5.697	1.442	0.029	1.099-5.285
Involvement of >2 lobes	3.214	0.410	11.203	3.011	0.004	1.464-21.961

Predictive value of LDH for therapeutic effect

The results of ROC curve analysis suggested that AUC of LDH in predicting the therapeutic effect was 0.75 (P=0.009, 95% CI: 0.61-0.88), the specificity and sensitivity were 64.2% and 78.1%, respectively, and the cutoff value was 480 U/L (Figure 2).

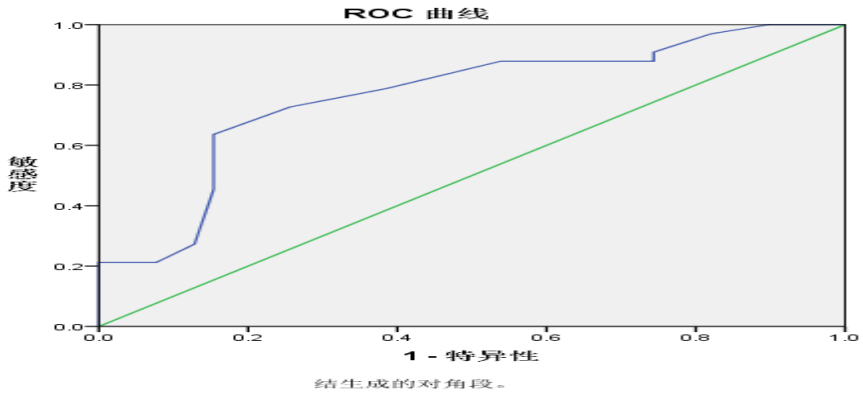

Figure 2. ROC curve of LDH for predicting therapeutic effect.

DISCUSSION

Recent studies have indicated that the prevalence rate and related mortality rate of children with RMPP are increasing gradually. Compared with MPP children, those with RMPP are characterized by serious disease status, complex treatment, multiple complications, poor prognosis, and a high mortality rate [3]. In this study, the febrile course was longer, and the N, WBC and levels of Hb, CRP and LDH and the incidence rate of cough, gasping, double pneumonia, skin lesion and short breath were markedly higher in RMPP group than those in MPP group. These suggest that in contrast with MPP, RMPP is featured by clinical manifestations of higher incidence rates of cough, gasping, skin lesion, short breath, a longer febrile course and a higher LDH level, which is consistent with the results of a previous study [7]. There are evident differences in the clinical manifestations and biochemical examination results between RMPP and MPP, so clinicians can differentiate RMPP from MPP by evaluating the clinical manifestations and biochemical examination results of the children. In this study, the blood biochemical data were obtained from admission examinations, implying that there were significant differences in the inflammatory response and LDH level between RMPP and MPP patients upon admission. However, most clinical manifestations such as gasping, skin lesion, short breath and long febrile course may occur during treatment, and their value of early differential diagnosis is lower than that of biochemical data.

LDH catalyzes the oxidative conversion of substrate pyruvate to lactate and has been taken as a marker of inflammation [4]. LDH can be found in all tissues, but only in the cytoplasm, not in secretions. Therefore, serum LDH level reflects the destruction of cell membrane. LDH is released from cells after cell damage and can be used to monitor cell and tissue injuries [8]. It has been confirmed in a study that the content of the isozymes of LDH3 and LDH4 in the lungs is higher than that in normal serum, and lung tissue injury is related to the increase of serum LDH level [9]. Another study has proven that the levels of LDH in serum and bronchoalveolar lavage fluid are increased in patients with lung diseases [10]. In patients with lung diseases, pulmonary parenchymal cells and/or local inflammatory cells, including pulmonary alveolar macrophages and polymorphonuclear neutrophils, may be the potential sources of elevated serum LDH level [10]. In contrast with children with MPP, the lung injury of those with RMPP is more serious, and there are more pulmonary parenchymal cells and local inflammatory cells that are damaged. The intracellular LDH is released into tissue fluid after cell damage, and then enters the blood. Therefore, the LDH level in peripheral blood of children with RMPP is markedly higher.

LDH exists extensively in human tissues and derives from a wide range of sources in the blood. Besides, damage to other cells and tissues can also lead to the elevation of LDH level. Therefore, in this study, patients with other acute diseases or complicated with other diseases that may lead to the elevation of LDH level were excluded, such as myocardial infarction, liver diseases (including acute hepatitis, chronic active hepatitis, liver cancer, liver cirrhosis, and obstructive jaundice), hematological diseases (leukemia, anemia, and malignant lymphoma), skeletal muscle injury, pulmonary infarction and increased LDH level in chest and ascites induced by malignant tumor metastasis. Moreover, due to the high content of LDH in erythrocytes, the activity of serum LDH increases prominently during hemolysis, which can be increased by 1,000 times. Therefore, the hemolytic samples should be removed, and for hemolytic samples, the peripheral venous blood needs to be re-drawn from subjects. Additionally, oxalate inhibits LDH, so the serum samples should be used. If the blood clot is not removed in the serum, the LDH activity will be remarkably increased. Thus, the detection was carried out after removal of blood clots. The above steps ensure that the research conclusions are more reliable.

It was verified in this study that LDH was a related factor for the occurrence of RMPP. RMPP in children with a higher LDH level is more likely to be aggravated, so the risk of RMPP is higher. A previous study has confirmed the value of LDH in the diagnosis of RMPP [11]. In this study, AUC of LDH in diagnosing RMPP was 0.81, and the specificity and sensitivity were 71.2% and 85.1%, respectively. The serum LDH level combined with clinical manifestations such as cough, gasping, skin lesion, short breath and febrile course can assist in the early clinical diagnosis of RMPP [12]. It has been evidenced that the elevation of total LDH level in the case of RMPP is related to host immune response or MP toxicity. Therefore, LDH level may be used to monitor treatment response [13]. Herein, LDH was a factor influencing the therapeutic effect of RMPP, and LDH had a certain value in predicting the therapeutic effect, suggesting that LDH can be

used to initially evaluate the outcome of children in clinic, which can help adjust the treatment plan in time. Currently, there is a lack of reliable indices for diagnosing RMPP and predicting the therapeutic effect. Therefore, predicting the therapeutic effect of RMPP before treatment is of great clinical significance for changing the treatment plan in time.

In clinical studies, immunosuppressive therapies (e.g. systemic steroids) have brought satisfactory results in treating RMPP [14]. According to the study of Lu et al. [15], the serum LDH level could be used to guide the clinical use of glucocorticoid therapy in treating RMPP, and the cutoff LDH level (412 IU/L) was the appropriate standard to start glucocorticoid therapy. Therefore, serum LDH level may be a useful marker for monitoring and evaluating the therapeutic effect of RMPP, which was confirmed in the present study. In this study, it was proved that the serum LDH level upon admission could be used to evaluate the efficacy of immunotherapy. Currently, there have been few reports on the predictive indices of the efficacy of immunotherapy. In this study, the predictive value of serum LDH level was promised, which provides some reference for exploring the indices for predicting the efficacy of immunotherapy. It was also confirmed that the therapeutic effect of children with involvement of >2 lobes was poor, and the treatment became more difficult with the increase of the number of involved pulmonary lobes. In children with involvement of >2 lobes, the larger the range of pulmonary lobe involvement was, the more severe the disease was, and the higher the inflammatory response level was, so the treatment was more difficult.

In summary, LDH is an independent factor affecting the occurrence and therapeutic effect of RMPP. The LDH level in peripheral blood has a certain value in diagnosing RMPP and predicting the prognosis of RMPP. Therefore, measurement of LDH can be used to assist in the clinical diagnosis and treatment of RMPP. However, there were some limitations in this study. The sample size was small, and some children who may be complicated with undetectable pathogens could not be excluded. For in-depth study, the sample size should be further expanded.

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