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Lactate Dehydrogenase as a Biomarker for Prediction of Refractory *Mycoplasma pneumoniae* Pneumonia in Children

Aizhen Lu MD PhD, Chuankai Wang, Xiaobo Zhang MD PhD, Libo Wang MD, and Liling Qian MD PhD

BACKGROUND: Corticosteroids have been used for refractory *Mycoplasma pneumoniae* pneumonia and have beneficial effects. The aim of this study was to identify the biomarkers for predicting refractory *M. pneumoniae* pneumonia in a timely fashion to initiate steroid therapy. METHODS: This was a prospective cohort study of children with *M. pneumoniae* pneumonia admitted to the Children's Hospital of Fudan University from September 2012 to August 2013. Lactate dehydrogenase (LDH) and other laboratory tests, including complete blood counts, C-reactive protein, erythrocyte sedimentation rate (ESR), alanine aminotransferase, aspartate aminotransferase, α-hydroxybutyrate dehydrogenase (HBDH), creatine kinase, and creatine kinase MB, were performed on admission. Based on the definition of refractory *M. pneumoniae* pneumonia, subjects were divided into 2 groups: refractory *M. pneumoniae* pneumonia and usual *M. pneumoniae* pneumonia. The diagnostic values of laboratory findings were analyzed. RESULTS: In total, 653 subjects were enrolled, including 300 in the refractory pneumonia group and 353 in the usual pneumonia group. There was no significant difference in sex distribution between the 2 groups. The average age in the refractory *M. pneumoniae* pneumonia group was greater than that in the usual *M. pneumoniae* pneumonia group. Compared with the usual pneumonia group, the refractory pneumonia group showed significantly higher levels of C-reactive protein, serum LDH, serum HBDH, serum alanine aminotransferase, serum aspartate aminotransferase, and neutrophils and higher ESRs. Logistic regression showed that age, LDH, and ESR were the significant factors in predicting refractory *M. pneumoniae* pneumonia. In addition, LDH and HBDH were strongly correlated, and receiver operating characteristic curve analysis showed that the area under the curve of LDH was 0.718 with a cutoff of 379 IU/L, that of ESR was 0.683 with a cutoff of 32.5 IU/L, and that of HBDH was 0.691 with a cutoff of 259.5 IU/L. CONCLUSIONS: Serum LDH can be used as a biomarker to predict refractory *M. pneumoniae* pneumonia at the early stage of hospitalization. *Key words: Refractory Mycoplasma pneumoniae pneumonia; lactate dehydrogenase; α-hydroxybutyrate dehydrogenase; erythrocyte sedimentation rate; receiver operating curve.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Mycoplasma pneumoniae is one of the major causative pathogens of community-acquired respiratory tract infections in children. *M. pneumoniae* infections occur both endemically and in cyclic epidemics every 3–7 y and account for 10–40% of community-acquired pneumonia cases in children.[1] Although pneumonia due to *M. pneumoniae* is usually a benign, self-limited disease, some cases become refractory or severe and life-threatening.[2-4] It can also cause a wide array of extrapulmonary manifestations[5-9] and even lead to sequelae and disability, such as bronchi-

The authors are affiliated with the Respiratory Department, Children's Hospital of Fudan University, Shanghai, China.

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Correspondence: Libo Wang MD and Liling Qian MD PhD, Children's Hospital of Fudan University, 399 Wan Yuan Road, Shanghai 201102, China. E-mail: wanglbc@163.com and llqian@126.com.

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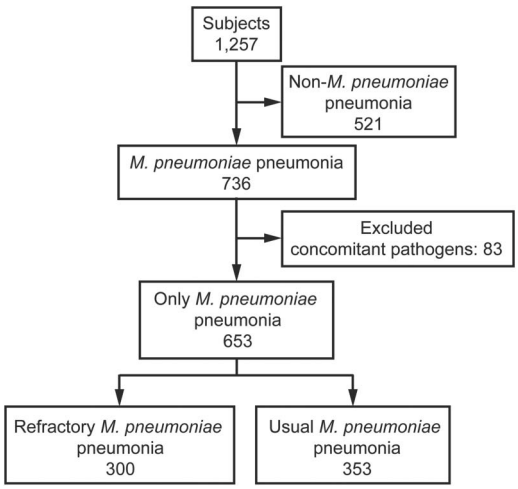

Fig. 1. Flow chart.

ectasis, bronchiolitis obliterans, interstitial pulmonary fibrosis, and paralysis.[10,11]

Clinically, corticosteroids have been used for refractory *M. pneumoniae* pneumonia and have a dramatic beneficial effect in both children and adults.[2,4,12] Clinicians must be cognizant of children with *M. pneumoniae* pneumonia at risk for developing refractory or serious illnesses and initiate steroid therapy in a timely fashion. Thus, it is desirable to predict refractory illness as soon as possible.

In a previous study,[4] we found that lactate dehydrogenase (LDH), C-reactive protein, and erythrocyte sedimentation rate (ESR) on admission were increased in subjects with refractory *M. pneumoniae* pneumonia. We hypothesized that they play important roles in this illness. Based on a review of the literature, there are a few reports on the role of LDH, C-reactive protein, and ESR in refractory *M. pneumoniae* pneumonia, but they are limited to case series.[4,13,14] In this study, we explored whether LDH, C-reactive protein, and ESR are potential laboratory markers that could be used to predict refractory *M. pneumoniae* pneumonia in a large sample.

QUICK LOOK

Current knowledge

M. pneumoniae is one of the major causative pathogens of community-acquired respiratory tract infections in children. Although pneumonia due to *M. pneumoniae* is usually benign, some cases develop into refractory, life-threatening disease. Corticosteroids are an effective treatment for severe disease. A biomarker or method to predict patients at risk for developing refractory disease could improve the timing of corticosteroid treatment and improve patient outcomes.

What this paper contributes to our knowledge

In a group of children admitted to the hospital for *M. pneumoniae* pneumonia, serum lactate dehydrogenase (LDH) predicted refractory disease at hospitalization. LDH may prove useful as a biomarker for predicting refractory disease and determining which candidates may benefit from early corticosteroid therapy.

Methods

Subjects and Groups

This was a planned secondary analysis of a prospective cohort study (Fig. 1). Children with *M. pneumoniae* pneumonia admitted to the Children's Hospital of Fudan University from September 2012 to September 2013 were enrolled. *M. pneumoniae* infection was confirmed by serologic testing to detect *M. pneumoniae* immunoglobulin M (IgM) by enzyme-linked immunosorbent assay and/or polymerase chain reaction testing for *M. pneumoniae* in nasopharyngeal secretions. Subjects with immune deficiencies, chronic diseases, or heart diseases or who were using immunosuppressive drugs were excluded. All enrolled subjects had negative tuberculosis IgM or purified protein derivative tests. In addition, their nasopharyngeal secretions were negative for respiratory syncytial viruses, influenza viruses, adenovirus, parainfluenza virus, and *Chlamydia trachomatis*. The subjects also had negative bacterial cultures of nasopharyngeal secretions and double-negative blood cultures. Consent for participation was obtained. The study was approved by the hospital's ethics committee.

Refractory *M. pneumoniae* pneumonia is defined as a case with prolonged fever accompanied by deterioration of radiological findings despite appropriate management with macrolide treatment for ≥ 7 d.[2,15,16] On the basis of this definition, we reviewed subjects' records and divided them into 2 groups: a refractory *M. pneumoniae* pneumonia group and a usual *M. pneumoniae* pneumonia group.

Study Variables and Data Collection

The main outcome measure of the study was serum LDH on admission. We also obtained complete blood counts, ESRs, and levels of C-reactive protein, alanine aminotransferase, aspartate aminotransferase, and other enzymes, including serum α-hydroxybutyrate dehydrogenase (HBDH), creatine kinase, and creatine kinase MB. Demographic characteristics were collected from the subjects' records.

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Table 1. Comparison of Laboratory Findings on Admission for the Refractory and Usual *M. pneumoniae* Pneumonia Groups

Laboratory Test	Refractory *M. pneumoniae* Pneumonia Group	Usual *M. pneumoniae* Pneumonia Group	*P*
Creatine kinase, IU/L	116 ± 1,266 (13–986, 74)	89 ± 70 (2–825, 72)	.85
Creatine kinase MB, IU/L	35.7 ± 35.7 (9–189, 24)	30.2 ± 21.0 (6–230, 25)	.40
LDH, IU/L	449 ± 258	304 ± 78.1	< .01
HBDH, IU/L	357 ± 233	249 ± 69.3	< .01
Alanine aminotransferase, IU/L	23.2 ± 42.8 (1–394, 11.5)	12.4 ± 18.2 (1–219, 8.5)	< .01
Aspartate aminotransferase, IU/L	30.1 ± 28.7 (1–242, 21)	21.9 ± 20.7 (2–249, 18)	< .01
White blood cells, $\times 10^9/\mu L$	8.62 ± 3.81 (2.1–28.9, 7.85)	8.23 ± 3.99 (1.8–43.9, 7.86)	< .01
Neutrophils, %	61.9 ± 15.0 (12.9–90.7, 63.7)	51.7 ± 17.1 (1.1–85.8, 54.0)	< .01
Lymphocytes, %	28.8 ± 13.5 (3.6–75.7, 27.0)	39.3 ± 16.3 (3.40–91.2, 35.6)	< .01
Platelets, $\times 10^9/\mu L$	315 ± 125 (88–936, 299)	320 ± 116 (24–710, 315)	.23
C-reactive protein, mg/L	31.4 ± 39.1 (7–161, 7)	15.5 ± 20.5 (7–161, 7)	< .01
ESR, mm/h	40.8 ± 23.4 (6–125, 36)	28.2 ± 20.0 (0–102, 21)	< .01

Values are presented as mean ± SD (range, median).
LDH = lactate dehydrogenase
HBDH = α-hydroxybutyrate dehydrogenase
ESR = erythrocyte sedimentation rate

Respiratory Pathogens

Nasopharyngeal aspirates were tested for respiratory pathogens using a real-time, multiplex polymerase chain reaction assay (Diagnostic Hybrids, Athens, Ohio) in our hospital's clinical virology laboratory. The specific pathogens identified included influenza A and B, respiratory syncytial viruses, adenovirus, parainfluenza virus, *C. trachomatis*, and *M. pneumoniae*. A positive polymerase chain reaction (Shanghai Shen Yousheng Biotech, Shanghai, China) result for *M. pneumoniae* was a copy number of >2,500/mL. Bacterial culture results based on nasopharyngeal aspirates and blood were obtained from the hospital's microbiology laboratory. *M. pneumoniae* IgM was detected using a commercial enzyme-linked immunosorbent assay kit (Beijing Rongzhi Haida Biotech, Beijing, China) according to the manufacturer's instructions, and the positive result was an *M. pneumoniae* IgM titer of > 1:320.

Statistical Analysis

Statistical analysis was performed with SPSS 16.0 (SPSS, Chicago, Illinois) and MedCalc (MedCalc Software, Mariakerke, Belgium), and $P < .05$ was considered statistically significant. Categorical variables were analyzed using the chi-square test. Normally distributed measurement data were analyzed with *t* tests, and non-normally distributed measurement data were analyzed with Mann-Whitney *U* tests. Multivariate analysis was performed using a stepwise logistic regression model. Receiver operating characteristic (ROC) curves were used to analyze the power of the laboratory markers for prediction of refractory *M. pneumoniae* pneumonia.

Results

Demographical Characteristics

We enrolled 653 subjects. There were 300 cases (171 boys and 129 girls) in the refractory *M. pneumoniae* pneumonia group, and 353 cases (221 boys and 132 girls) in the usual *M. pneumoniae* pneumonia group. There was no significant difference in sex distribution between the 2 groups ($P = .15$). The average age in the refractory *M. pneumoniae* pneumonia group was 66.8 ± 37.5 months (range of 3–184 months, median of 66 months) and 51.4 ± 34.4 months (range of 1–156 months, median of 46 months) in the usual *M. pneumoniae* pneumonia group. The average age in the refractory pneumonia group was greater than that in the usual pneumonia group ($P < .001$).

Laboratory Findings

The laboratory findings on admission are summarized in Table 1. Compared with the usual *M. pneumoniae* pneumonia group, the refractory *M. pneumoniae* pneumonia group showed significantly higher levels of C-reactive protein (31.4 ± 39.1 vs 15.5 ± 20.5 mg/L, $P < .01$), neutrophils (61.9 ± 15.0% vs 51.7 ± 17.1%, $P < .01$), serum LDH (449 ± 258 vs 304 ± 78.1 IU/L, $P < .01$), serum HBDH (357 ± 233 vs 249 ± 69.3 IU/L, $P < .001$), serum alanine aminotransferase (23.2 ± 42.8 vs 12.4 ± 18.2 IU/L, $P < .001$), and serum aspartate amino-

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Table 2. Logistic Regression Analysis of Associated Factors in Refractory *M. pneumoniae* Pneumonia

Relevant Factor	B	SE	Wald	*P*	Odds Ratio	95% CI for OR	
						Lower	Upper
Age	0.014	0.004	10.197	.001	1.01	1.00	1.02
LDH	0.009	0.001	33.821	< .001	1.01	1.00	1.01
ESR	0.020	0.007	8.081	.004	1.02	1.00	1.03

LDH = lactate dehydrogenase
ESR = erythrocyte sedimentation rate

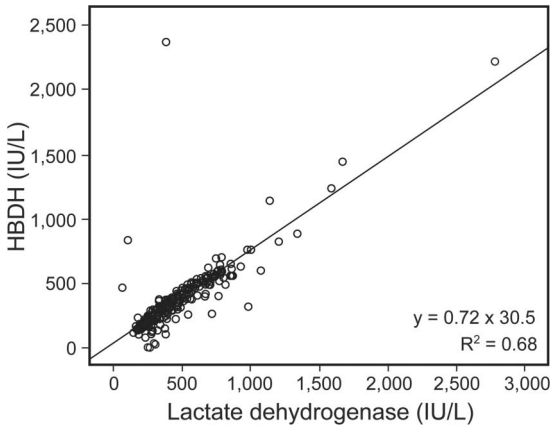

Fig. 2. Correlation between lactate dehydrogenase and α-hydroxybutyrate dehydrogenase (HBDH).

transferase (30.1 ± 28.7 vs 21.9 ± 20.7 IU/L, $P < .01$) and higher ESRs (40.8 ± 23.4 vs 28.2 ± 20.0 mm/h, $P < .01$). However, the percentage of lymphocytes in the refractory *M. pneumoniae* pneumonia group was lower than that in the usual *M. pneumoniae* pneumonia group (28.8 ± 13.5% vs 39.3 ± 16.3%, $P < .01$). The other laboratory findings were not significantly different between the 2 groups.

Logistic Regression

Age, LDH, HBDH, alanine aminotransferase, aspartate aminotransferase, neutrophils, lymphocytes, C-reactive protein, and ESR were analyzed in a stepwise logistic regression model. The results showed that serum LDH (odds ratio of 1.01, 95% CI 1.00–1.01, $P < .001$) and ESR (odds ratio of 1.02, 95% CI 1.00–1.03, $P < .001$) on admission were significant risk factors for refractory *M. pneumoniae* pneumonia (Table 2). In all covariates, we found that LDH and HBDH had a positive correlation, and the Pearson correlation was 0.822 ($P = .01$) (Fig. 2).

ROC Curve Analysis

The area under the curve for LDH was 0.718 (95% CI 0.678–0.758) as determined by ROC curve analysis (Fig. 3). The optimal cutoff of LDH for predicting refractory *M. pneumoniae* pneumonia was 379 IU/L, with a sensitivity of 48%, specificity of 85.8%, positive predictive value of 74.2%, and negative predictive value of 65.9% (Table 3). The area under the curve for ESR was 0.683 (95% CI 0.626–0.740), and that for HBDH was 0.691 (95% CI 0.650–0.733) (Fig. 3 and Table 3).

Discussion

The incidence of refractory *M. pneumoniae* pneumonia has recently increased,[4,16,17] and it is associated with macrolide-resistant strains.[18-21] Cell-mediated immunity of the host rather than direct microbial damage plays an important role in the progression of this illness.[22,23] Clinically and experimentally, steroids have a positive effect on refractory *M. pneumoniae* pneumonia.[2,4,16,24] However, steroids are usually initiated after the condition deteriorates. Thus, those with unrecoverable damage due to refractory *M. pneumoniae* pneumonia cannot rehabilitate completely.[25-28] Although there is no case-control study on the benefit of steroids in refractory *M. pneumoniae* pneumonia, it is believed that early steroid therapy might prevent disease progression and reduce disease morbidity without adverse reactions.[29,30] However, it is impossible to initiate steroids early for all *M. pneumoniae* infections because most of them are self-limited, and there is no evidence to support the use of systemic steroids in community-acquired pneumonia due to other pathogens.[31] In addition, an epidemiological investigation showed that there is no apparent risk factor for refractory *M. pneumoniae* pneumonia[32]; therefore, predicting this illness at an early stage may improve the prognosis of *M. pneumoniae* infection, as this might help identify subjects for trials of early steroid administration.

Logistic regression showed that serum LDH and ESR were the main risk factors for refractory *M. pneumoniae* pneumonia after age difference was adjusted. Studies showed that LDH was associated with many pulmonary diseases, such as obstructive diseases, microbial pulmonary diseases, and interstitial lung diseases.[33,34] Several studies[2,4,13] also found that serum LDH was elevated in refractory *M. pneumoniae* pneumonia; however, there was

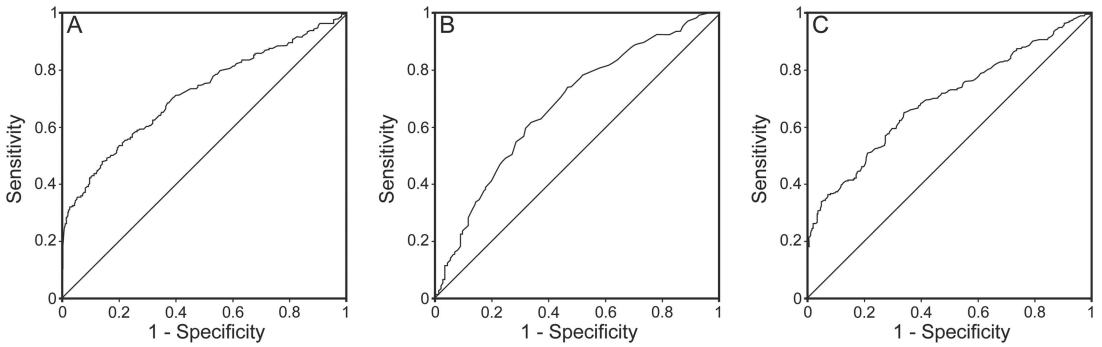

Fig. 3. Receiver operator characteristic curves for predicting refractory *M. pneumoniae* pneumonia. A: Lactate dehydrogenase. B: Erythrocyte sedimentation rate. C: α-Hydroxybutyrate dehydrogenase.

Table 3. Predictive Value of LDH, ESR, and HBDH

Parameter	Area Under the Curve	Cutoff (IU/L)	Sensitivity (%)	Specificity (%)	Positive LR (%)	Negative LR (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
LDH	0.718	379	48	85.8	3.37	0.61	74.2	65.9
ESR	0.683	32.5	62	66.4	1.84	0.57	61.2	67.1
HBDH	0.691	259.5	65	66.1	1.90	0.54	61.9	68.5

Receiver operating characteristic curve analysis was performed with suitable parameters to create cutoffs to determine the predictive value of each parameter with regard to refractory *M. pneumoniae* pneumonia.
LDH = lactate dehydrogenase
ESR = erythrocyte sedimentation rate
HBDH = α-hydroxybutyrate dehydrogenase
LR = likelihood ratio

no evidence showing that this elevation was associated with host immune response or virulence of *M. pneumoniae*. In this study, we found that the area under the curve for LDH was 0.718 in ROC curve analysis, indicating fair discriminative power for predicting refractory *M. pneumoniae* pneumonia. The optimal cutoff for LDH was 379 IU/L, with a sensitivity of 48% and specificity of 85.8%. This indicates its clinical utility in identifying patients at high risk for refractory *M. pneumoniae* pneumonia: namely, patients with usual *M. pneumoniae* pneumonia will not be misdiagnosed with refractory pneumonia and started on steroid therapy. Another study showed that children with *M. pneumoniae* infection who were possible candidates for steroid therapy usually had significantly elevated levels of LDH (> 480 IU/L).[35] Inamura et al[13] performed ROC curve analysis and showed that the cutoff of LDH for refractory *M. pneumoniae* pneumonia was 410 IU/L. The cutoffs were greater than in our study. The main reason may be that their results were obtained from a small case series, and they had more serious illnesses. In this study, at the cutoff point, the positive predictive value of LDH was 74.2%. As positive predictive value is also sensitive to disease prevalence, which may be different in different clinical settings, the LDH test may have a lower positive predictive value in populations with a lower prevalence of refractory *M. pneumoniae* pneumonia.

The serum HBDH test measures mainly the LDH-1 and LDH-2 isoforms, reflecting serum LDH activity.[36] Few reports are available on the serum activity of HBDH in pulmonary disease. In this study, we found that HBDH was associated with refractory *M. pneumoniae* pneumonia and could be used as a potential predictive marker for this illness. However, ROC curve analysis in this study showed that it was not an ideal biomarker for predicting refractory *M. pneumoniae* pneumonia. In addition, we found that HBDH was positively correlated with LDH in *M. pneumoniae* infections, which may be the reason why HBDH was not a risk factor in the logistic regression analysis. To our knowledge, this is the first report on the association between HBDH and refractory *M. pneumoniae* pneumonia.

There are limitations to our study. First, we divided our subjects into 2 groups based on the definition of refractory *M. pneumoniae* pneumonia,[2,16] and this definition was broad. Therefore, spectrum bias was introduced into our results. Moreover, this bias may be the main reason why the ROC curve analysis of LDH showed just a fair discriminative power for refractory *M. pneumoniae* pneumonia. However, the children in the refrac-

tory pneumonia group remained at the highest risk for severe or refractory illness. Thus, our findings could still be applied to a very common clinical scenario for screening those refractory cases.

Conclusions

In summary, serum LDH can be used as a biomarker for predicting refractory *M. pneumoniae* pneumonia and determining candidates who may benefit from corticosteroid therapy during the early stages of hospitalization. Furthermore, more research is needed to identify the potential utility of early steroid administration, which could be performed based on the use of LDH as a biomarker to initiate steroid treatment.

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