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Original Article

Clinical value of serum albumin and prealbumin levels in children with lobar pneumonia caused by *Mycoplasma pneumoniae*

Jiang-Jiang Xu[1], Hai-Qin Zhong[2], Lin-Hua Shu[2]

Departments of [1]Infection Control, [2]Respiratory Medicine, Shanghai Children's Hospital, Shanghai Jiaotong University, Shanghai, China

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Abstract: Once lung consolidation forms, children with Community-acquired pneumonia (CAP) are at high-risk of developing severe clinical illness and pulmonary injury. This study aimed to explore the pathogenesis of lobar consolidation in children with *M. pneumoniae* (*M. pneumoniae*) and sought to identify a sensitive outpatient diagnostic tool to rapidly recognize early lobar consolidation. The study was conducted in hospitalized children aged 5-14 years diagnosed with *M. pneumoniae* pneumonia. Children were divided into lobar and non-lobar pneumonia groups. Healthy children undergoing elective surgery were selected as healthy controls. Totally, 71 children with lobar pneumonia and 107 with non-lobar pneumonia were assessed. The healthy control group consisted of 425 children. Total protein (TP), Albumin (Alb) and Prealbumin (PA) levels in the lobar pneumonia group were significantly higher than those of the non-lobar group. Multivariable logistic regression analysis showed that serum Alb levels (OR = 0.867) and PA levels below 88 mg/L (OR = 2.282) were important risk factors for lobar pneumonia in children. Serum Alb values lower than 41 g/L could detect lobar pneumonia with a sensitivity of 71.70% and a specificity of 83.10%; serum PA values lower than 88 mg/L could detect lobar pneumonia with a sensitivity of 51.89% and a specificity of 76.06%. Alb and PA are causally associated with the development of lobar consolidation. Serum Alb and PA could be used as simple and fast outpatient diagnostic tools to recognize lobar pneumonia at an early stage in children with *M. pneumoniae* pneumonia.

Keywords: Community-acquired pneumonia, Mycoplasma pneumoniae, albumin, prealbumin, children

Introduction

More than half of the cases of Community-acquired pneumonia (CAP) are caused by *Mycoplasma pneumoniae (M. pneumoniae)* infection in Chinese children aged over 5 years [1-3]. *M. pneumoniae* is one of the most common pathogens in children with CAP, causing infection in the airways, stroma and alveolar space. Recent studies that reviewed pathological and radiological studies of *M. pneumoniae* pneumonia revealed a correlation between lung consolidation and ground-glass opacities for *M. pneumoniae* [4]. However, the frequency of consolidation in association with *M. pneumoniae* infection appears to vary greatly between studies [5].

Once lung consolidation has formed, children frequently develop severe clinical illness and pulmonary injury. In this scenario, exudation increases, lung consolidation range expands, ventilation/perfusion loses balance, and the effective gas exchange area in lung tissue is reduced. These changes lead to a shortness of breath and ultimate dyspnea. Due to lung cell damage and the necrosis of lung tissue (termed necrotizing pneumonia), lung abscesses form and pneumothorax can develop, which is life-threatening. Patients with *M. pneumoniae* pneumonia showing lobar consolidation are typically hospitalized for an extended time-period [5].

In China, the guide entitled "Administration Guide for Children with Community-Acquired Pneumonia" [6] does not provide clear recommendations on the optimal treatment course for lobar pneumonia. Currently, macrolides are used as the first-choice antibiotic for lobar pneumo-

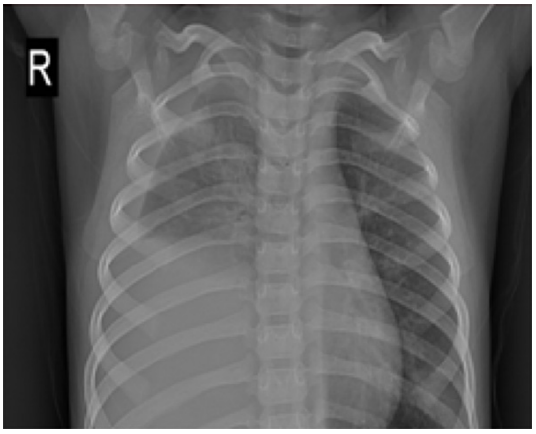

Figure 1. Lobe consolidation in the right lung (chest X-ray).

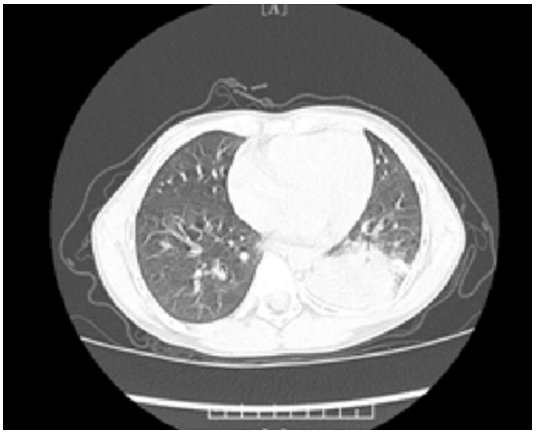

Figure 2. Lobe consolidation in the left lung (lung CT).

nia attributed to *M. pneumoniae*, until consolidation disappears. This inevitably leads to the use of off-label macrolide treatments [7]. However, studies suggest that the core treatment of *M. pneumoniae* lobar pneumonia is "lung consolidation", rather than "*M. pneumoniae".* Guo and colleagues [5], found that lobar involvement did not correlate with IgM titres in *M. pneumoniae* pneumonia patients. A systematic review evaluating the effects of treating children with *M. pneumoniae* pneumonia also demonstrated no significant clinical benefits of antimicrobial therapy [8]. In addition, Yoon and colleagues demonstrated that the fever duration in *M. pneumoniae* pneumonia was determined by homogeneous lobar consolidation and parapneumonic effusion, but is not influenced by macrolide resistance [9]. These results highlight the need to explore the pathogenesis of lung consolidation in children with *M. pneumoniae* pneumonia, for the development of more effective treatment regimens.

Although the clinical manifestations of fever and respiratory symptoms are recommended for the diagnosis of CAP, chest X-ray remains the primary diagnostic tool for severity assessment [10]. This is problematic as its use for the routine examination of CAP is not advised in children [11] due to its known potential to evoke genetic changes, increasing the risk of childhood leukemia [12]. It is therefore necessary to identify serum biomarkers as an alternative to chest X-ray to determine lung consolidation, and to screen for lobar pneumonia from *M. pneumoniae* pneumonia at an early stage. This will allow the correct treatment regimen to be initiated in a timely manner, including the use of antibiotics, glucocorticoids and fiberoptic bronchoscopy to improve disease prognosis.

The aim of this study was to explore the pathogenesis of consolidation in children with *M. pneumoniae* pneumonia and to identify a highly sensitive and specific outpatient diagnostic tool that can be used to screen for lobar consolidation at an early stage.

Materials and methods

Study population

From May 1, 2014, to May 30, 2015, hospitalized children aged 5-14 years with a diagnosis of pneumonia were recruited into the study at the Shanghai Children's Hospital of Shanghai Jiao Tong University in Shanghai, China. Pneumonia was diagnosed on the basis of the clinical presentation of fever, respiratory symptoms, and chest X-ray and/or lung CT showing alveolar infiltration consistent with pneumonia. Children with viruses, bacteria and other pathogenic infections, pulmonary malformations, cystic fibrosis, heart disease with hemodynamic repercussions, neurological disorders and/or genetic disease were excluded from the study. We also excluded children lacking chest imaging- or clinical-data. In total, 178 children were included for analysis. According to the results of chest X-ray and/or lung CT examinations, children were divided into the lobar pneumonia group (disease group) or the non-lobar pneumonia group (disease control group). Healthy children admitted during the study period

Table 1. Demographic, clinical characteristics, and laboratory findings

Characteristics	Disease Group (N = 107)	Disease Control Group (N = 71)	Healthy Controls (N = 425)
Gender			
Boy [n (%)]	58 (54.2)	36 (50.7)	244 (57.4)
Girl [n (%)]	49 (45.8)	35 (49.3)	181 (42.6)
Age (y, mean ± SD)	7.61 ± 1.97	7.53 ± 2.13	7.87 ± 2.84
Length of Hospital Stay (day, mean ± SD)	8.90 ± 3.40##	6.32 ± 2.98	N/A
Infection Indicators			
WBC (*10^9/L, mean ± SD)	7.23 ± 3.07	8.40 ± 4.74	7.47 ± 1.73
Ne (%, mean ± SD)	61.88 ± 12.91**	60.81 ± 15.72**	48.32 ± 9.40
Lc (%, mean ± SD)	30.09 ± 11.87**	32.84 ± 14.21**	42.27 ± 9.07
CRP [mg/L, median (IQR)]	14.00 (7.75, 26.25)**	13.50 (7.00, 26.25)**	3.0 (0, 4.00)
PCT [ng/mL, median (IQR)]	0.16 (0, 0.32)	0.13 (0, 0.22)	N/A
Biochemical Indicators			
ALT (U/L, mean ± SD)	18.49 ± 16.85**	16.95 ± 15.46*	13.02 ± 5.35
AST (U/L, mean ± SD)	34.81 ± 22.37**	32.42 ± 11.71**	27.40 ± 5.48
TP (g/L, mean ± SD)	66.10 ± 5.61**,#	67.99 ± 4.55**	69.88 ± 4.68
Alb (g/L, mean ± SD)	38.99 ± 3.56**,##	41.10 ± 2.99**	44.33 ± 2.40
PA (mg/L, mean ± SD)	101.85 ± 40.76**,#	116.98 ± 43.22**	177.09 ± 34.21

Abbreviations: SD, standard deviation; WBC, White blood cell counts; Ne, Neutrophil; Lc, Lymphocytes; CRP, C-reactive protein; IQR, interquartile range; PCT, Procalcitonin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TP, Total protein; Alb, Albumin; PA, Prealbumin; N/A: not applicable. Note: *$P < 0.05$, **$P < 0.01$, compared with "healthy control group"; #$P < 0.05$, ##$P < 0.01$, differences between the disease group and the disease control group.

who were undergoing elective surgery were selected as healthy controls, matching in age and gender. The exclusion criteria of the healthy population were the same as for children with pneumonia. Healthy controls were also excluded if they had displayed fever or respiratory symptoms within 14 days before or after enrollment. A total of 425 eligible control subjects were selected.

The study was approved by the Research Ethics Committee of Shanghai Children's Hospital of Shanghai Jiao Tong University (Approval No: 2016R004-F01) and the participants consented to attend the study.

Radiographic confirmation

Chest radiographs were interpreted by two radiologists who were supervised by a senior pediatrician. Radiographic evidence of lobar pneumonia was defined as: chest X-ray and/or lung CT showing at least one lobe and/or multiple segmental consolidation; lung CT showing a consolidation area larger than one third of the total area of the ipsilateral lung, without any consolidation on the other side (**Figures 1** and **2**).

Specimen and data collection

Trained staff obtained blood samples from the enrolled children for laboratory testing. Venous blood was drawn on admission. Blood samples were immediately placed into sterile EDTA test tubes at 4°C and immediately sent for laboratory analysis. Children's demographic (including gender and age), radiological (except for healthy controls) and clinical data (including infection and biochemical parameters) were also collected systematically.

Laboratory testing

White blood cell (WBC) counts and classifications were determined by flow cytometry using a Sysmex XS 800i blood analyzer. C-reactive protein (CRP) measurements were performed using immunoturbidimetric assays on the Hitachi 911 automated clinical chemistry analyzer. Procalcitonin (PCT) concentrations were analyzed using a sandwich immunoassay on an automated analyzer (mini VIDAS, Biomerieux, France). Blood Chemistry for renal and liver function was performed using a Beckman Coulter Biochemical Analysis System (AU5800, Beck-

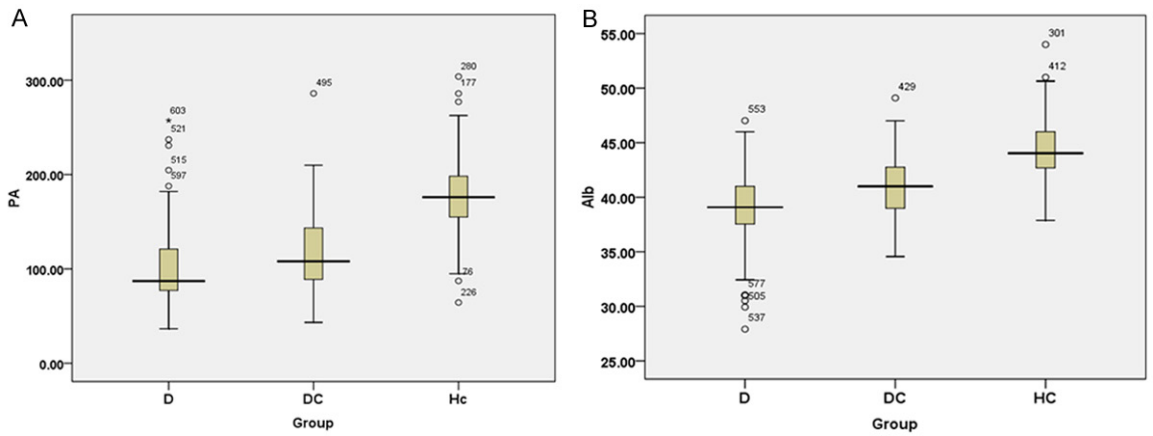

Figure 3. Alb (A) and PA (B) concentrations in the serum of children with lobar pneumonia, non-lobar pneumonia and healthy controls. Note: D, disease group; DC, disease control group; HC, healthy controls.

man Coulter, Inc. America). Alanine aminotransferase (ALT) levels were determined using the Lactate dehydrogenase method. Aspartate aminotransferase (AST) levels were determined using an MDH method. Total protein (TP) was determined via the Biuret method. Albumin (Alb) was assessed using molecular absorption spectrometry utilizing bromocresol green. Prealbumin (PA) was determined by immunonephelometry. *M. pneumoniae* was detected in the blood by means of indirect Immunofluorescence Assays (Vircell, Spain) or Particle Agglutination Tests (Serodia-Myco II Fujirebio Inc., Japan). *M. pneumoniae* was determined to be present if: (1) Immunoglobulin M was positive; or (2) An agent-specific antibody titer increased by a factor of 4 or more at the acute-phase in the serum specimen.

Statistical analysis

Statistical analysis was performed using the SPSS 16.0 statistical package (SPSS Inc., Chicago, IL, USA). The categorical variables were presented as counts and percentages, and continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range) as appropriate. Statistical significance for the differences between groups was assessed using a chi-square test for categorical variables, and a t-test, Mann-Whitney U test, or one-way analysis of variance (ANOVA) test for continuous variables. Multivariate analyses were performed to determine the associated risk factors of MP-lobar pneumonia, adjusted by confounding variables according to the results of the univariate analysis. Cutoff values of Alb and PA levels that optimally predicted lobar pneumonia were established by drawing Receiver operating characteristic (ROC) curves, combined with clinical significance. The statistical level of significance for all tests was $P < 0.05$.

Results

Demographic data, clinical characteristics, and laboratory findings are shown in **Table 1**. During the study period, 178 children with *M. pneumoniae* pneumonia, including 71 children in the lobar pneumonia group and 107 children in non-lobar pneumonia group, were finally included in the analysis. Additionally, 425 healthy children were eligible as healthy controls. There were 58 boys and 49 girls in the lobar pneumonia group with a mean (± SD) age of 7.61 (± 1.97) years, 36 boys and 35 girls in non-lobar pneumonia group with a mean (± SD) age of 7.53 (± 2.13) years and 244 boys and 181 girls in the healthy control group with a mean (± SD) age of 7.87 (± 2.84) years. The distribution in age and sex across the three groups did not statistically differ (all $P > 0.05$). The average length of hospital stay in the lobar pneumonia group was significantly longer than the non-lobar pneumonia group (8.90 days and 6.32 days respectively, $P < 0.05$) (**Table 1**). The percentage of Neutrophils [Ne (%)], Lymphocytes [Lc (%)] and serum CRP values were significantly higher in both pneumonia groups than healthy controls, while the differences in these indicators between the lobar and non-lobar pneumonia groups were not significant, in addition to WBC and serum PCT values (**Table 1**). Serum ALT, AST, TP, Alb and PA levels were significantly higher in both the lobar

Table 2. Multivariate logistic regression model

Parameters	Reference	Comparison	B	OR	95% CI	*P*-value
TP (g/L)	Continuous variables		0.042	1.042	0.961-1.131	0.315
Alb (g/L)	Continuous variables		-0.143	0.867	0.755-0.995	0.042
PA (mg/L)	≥ 88	< 88	0.825	2.282	1.072-4.859	0.032
Length of Hospital Stay (day)	Continuous variables		0.244	1.276	1.122-1.452	< 0.001

Abbreviations: TP, Total protein; Alb, Albumin; PA, Prealbumin; OR, odds ratio; CI, confidence interval.

Table 3. Diagnostic accuracy of screening tests and biomarkers using pre-determined cutoff values

Parameters	Alb	PA
AUC	0.664 (0.583-0.745)	0.628 (0.543-0.713)
Cutoff Value	41 g/L	88 mg/L
Sensitivity	71.70%	51.89%
Specificity	83.10%	76.06%
+LR	4.24	2.17
-LR	0.34	0.63
PPV	70.37%	74.32%
NPV	56.52%	51.43%

Abbreviations: AUC, area under curve; +LR, positive likelihood ratio; -LR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

and non-lobar pneumonia groups (all P < 0.05). Furthermore, in the lobar pneumonia group, TP, Alb and PA levels were significantly lower than those of the non-lobar pneumonia group (**Table 1**; **Figure 3**). Serum ALT and AST levels did not differ significantly between the two pneumonia groups (**Table 1**).

For TP, Alb and PA, a level of < 60 g/L, < 38 g/L and < 150 mg/L indicates children with parameters below normal, respectively. Only 11.2% and 2.8% of the children in the lobar and non-lobar groups displayed below-normal levels of serum TP (χ^2 = 4.154, P = 0.042); and 28.3% and 12.7% had serum Alb levels that were below normal (χ^2 = 6.041, P = 0.014), respectively. The proportion of children in the lobar and non-lobar pneumonia groups displaying decreased serum PA levels was up to 88.7% and 78.9% respectively, but these differences were not significant (χ^2 = 3.163, P = 0.075).

Upon building a multivariable logistic regression model, the addition of TP, Alb and PA together as continuous variables, showed that Alb was an associated risk factor for lobar pneumonia (OR = 0.837, 95% CI: 0.726-0.964, P = 0.014), while TP and PA were not significantly associated with lobar pneumonia in children (both P > 0.05). However, when the PA levels were divided into two groups (≥ 88 mg/L and < 88 mg/L group) and added to the logistic regression model together with TP and Alb, the results identified PA levels below 88 mg/L as an important risk factor for lobar pneumonia in children (OR = 2.282, 95% CI: 1.072-4.859). This analysis was adjusted for the effects of the length of hospital stay (**Table 2**).

The diagnostic accuracy of the screening tests and biomarkers at their pre-determined cutoff values are demonstrated in **Table 3**. In our study population, the ROC of Alb and PA had an AUC (area under curve) of 0.664 (95% CI: 0.583-0.745) and 0.628 (95% CI: 0.543-0.713), respectively. Serum Alb values lower than 41 g/L on admission could detect lobar pneumonia with a sensitivity of 71.70%, specificity of 83.10%, a positive likelihood ratio (+LR) of 4.24, and a negative likelihood ratio (-LR) of 0.34; serum PA values lower than 88mg/L on admission could detect lobar pneumonia with a sensitivity of 51.89%, a specificity of 76.06%, a +LR of 2.17, and a -LR of 0.63 (**Table 3**; **Figure 4**).

Discussion

The results of this study show that the serum Alb and PA concentrations decreased in both pneumonia groups, and that the levels of Alb and PA in the lobar pneumonia group were significantly lower than those of the non-lobar pneumonia group. Low levels of protein are a known consequence of diminished synthesis, increased catabolism, or a combination of both factors. In this study, although no significant differences in ALT and AST levels were observed between the two pneumonia groups, the levels of both indicators were significantly higher than healthy controls. These data suggest that pneumonia caused by *M. pneumoniae* infection causes liver function damage in children. The liver is the site of Alb and PA synthesis, the produc-

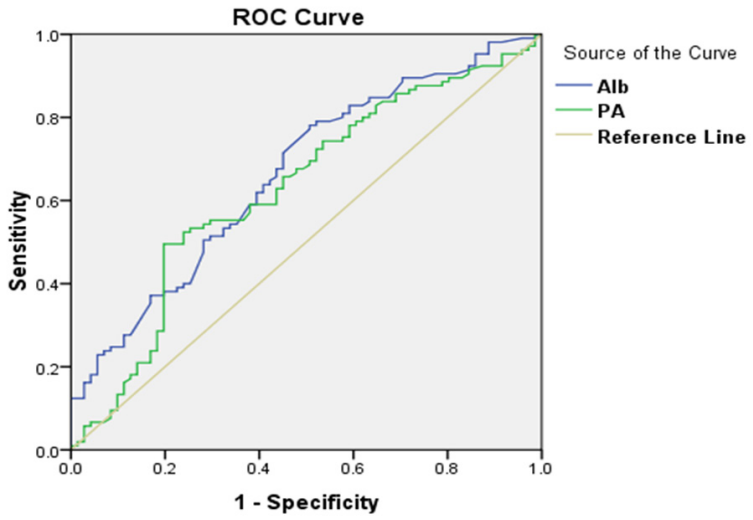

Figure 4. Receiver-operating-characteristic (ROC) curves for Alb and PA levels.

tion of which is reduced following liver injury. This may be one-direct cause of decreased serum Alb and PA levels observed in this study. In addition, children with pneumonia displayed enhanced permeability of the alveolocapillary membrane and the degree of protein exudation (mainly Alb and PA) was more pronounced [13]. This would play an important contributory role to the loss of serum Alb and PA concentrations observed.

As a carrier of numerous endogenous and exogenous substances, serum Alb is one of the basic indicators of nutritional status and disease severity. The major physiological role of Alb is to maintain the stability of plasma colloid osmotic pressure. Recent studies indicate that high CRP levels correlate with low Alb levels [14]. Alb may also indirectly reflect the severity of pulmonary infection. As an exemplar, a recent case report described a healthy child with severe acute pneumonia whose serum Alb concentrations decreased dramatically during their hospital stay. No conclusive evidence was provided to explain this clinical manifestation [15]. In other Japanese studies, hypoalbuminemia was found to be common in adult patients with CAP [16]. Serum PA is a small molecule that can penetrate the interstitial space through the capillaries in situations of increased permeability. As an acute phase protein, the half-life of PA is approximately 1.9 days, which is shorter than that of Alb (approximately 20-26 days), meaning PA serum levels will much more rapidly decline. PA was also shown to be a sensitive marker for nutritional status, and an equally effective marker for the determination of the severity of infection, treatment efficacy and the duration of hospital stay [17]. Studies have also shown that hypoalbuminemia is related to the onset of postoperative infections [18, 19]. Furthermore, the levels of PA play an important contributing role to the prediction of pneumonia severity. Li and colleagues revealed a negative linear correlation between serum PA and infection severity in elderly pneumonia patients [20]; Zhang and coworkers also found that the levels of PA in refractory childhood *M. pneumoniae* pneumonia were lower than those of general *M. pneumoniae* pneumonia groups [21].

According to the results of our study, serum Alb and PA values lower than 41 g/L and 88 mg/L on admission can detect lobar pneumonia with a sensitivity of 71.70% and 83.10%, and a specificity of 51.89% and 76.06%, respectively. This demonstrates that serum Alb and PA have high diagnostic value for predicting lung consolidation in children with *M. pneumoniae* pneumonia. Furthermore, we found that differences in the proportion of children with serum PA levels below normal, did not significantly differ between the two pneumonia groups. When a multivariate logistic regression model was constructed combining TP, Alb and PA as continuous variables for analysis, our results showed that only Alb was an independent risk factor for lobar pneumonia in children. However, when the PA levels were divided into two groups (≥ 88 mg/L and < 88 mg/L) and added to the logistic regression model together with TP and Alb, our results revealed serum PA levels below 88 mg/L as an important risk factor for lobar pneumonia. PA levels thus cannot indicate lobar pneumonia until they decline below 88 mg/L, equivalent to 50% of the levels of healthy children.

Respiratory sound is known to weaken or even disappear following the formation of pulmonary consolidation. It is therefore difficult for pediatricians to recognize lobar pneumonia according to changes in lung auscultation. Our study show-

ed that the levels of specific peripheral blood infection indicators, including Ne (%) and PCT, were significantly higher in the two pneumonia groups compared to healthy controls, whilst no significant differences in any of the other infection indicators between the lobar and non-lobar pneumonia groups were observed. This suggested that lobar pneumonia cannot be recognized using common infection indicators. We therefore propose serum Alb and PA as more accurate biomarkers of lung consolidation in children with *M. pneumoniae* pneumonia.

From our data, we hypothesis the following model for the pathogenesis of lobar consolidation in children with *M. pneumoniae* pneumonia. Once infected, a large amount of PA is exuded through the alveolocapillary membrane due to its high permeability. Within a short timeframe, this accumulates in the alveolar cavity and PA distribution becomes abnormal during infection. During the early stages of disease progression, the levels of PA exuded from the capillaries is small, as are the amounts accumulating in the alveolar space, which cannot be observed via chest radiograph for the visible diagnosis of lung consolidation. Upon aggravation by infection and a prolonged course of disease, the number of alveolar and capillaries involved in this process increases, leading to higher levels of PA accumulating over-time. If the PA is not absorbed in a timely manner, the permeability of the alveolar cavity increases, which is further exasperated by the presence of necrotic cells, sputum and other substances. This further increases the release of PA and other small molecules from the capillaries into the alveolar space. These small molecules rapidly spread to the adjacent alveolar space from infected alveoli cavities through the alveolar holes, and then to affected lung segments and lobes. Thus lobar consolidation is formed. We therefore propose that the levels and rates of PA exudation from the capillaries are causally associated with the development of lobar pneumonia. This hypothesis is confirmed by our finding that Alb and PA are higher in the bronchoalveolar lavage fluid in children with *M. pneumoniae* lobar pneumonia.

Conclusion

Our study reveals that Alb and PA are causally associated with the development of lobar consolidation, which cannot be recognized using commonly used indicators of infection. Serum Alb and PA are therefore applicable diagnostic tools that can rapidly identify early lobar pneumonia in children with *M. pneumoniae* pneumonia.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Lin-Hua Shu, Department of Respiratory Medicine, Shanghai Children's Hospital, Shanghai Jiaotong University, Shanghai, China. Tel: 86-021-52976251; Fax: 86-021-52976251; E-mail: shulinhua@126.com

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