Clinical features of severe *Mycoplasma pneumoniae* pneumonia with pulmonary complications in childhood: A retrospective study

Xue qin Luo MM | Jian Luo MM | Chong jie Wang MM | Zheng xiu Luo MD | Dai yin Tian PhD | Xiao hong Xie PhD

Division of Respiratory Medicine, Ministry of Education Key Laboratory of Child Development and Disorders, National Clinical Research Center for Child Health and Disorders (Chongqing), China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Chongqing Key Laboratory of Pediatrics, Chongqing, China

Correspondence
Xiao hong Xie, PhD, Division of Respiratory Medicine, Children’s Hospital of Chongqing Medical University, No. 136, Zhongshan 2nd Rd, Yuzhong District, Chongqing 400014, China.
Email: 400830@cqmu.edu.cn

Funding information
Chongqing Science and Technology Committee, Grant/Award Number: cstc2017shmsA130036; Program for Youth Innovation in Future Medicine, Chongqing Medical University, Grant/Award Number: W0063

Abstract
Introduction: Incidence of severe *M. pneumoniae* pneumonia (SMPP) reported in China has been increasing over the last decade. We aimed to evaluate the clinical features of pediatric SMPP with pulmonary complications, according to laboratory tests and chest radiographic resolution patterns.

Material and Methods: We retrospectively reviewed 93 SMPP patients between January 2016 and February 2019, and grouped them by pneumonia pattern: pulmonary complications (63 patients) and extensive lung lesions without pulmonary complications (30 patients).

Results: SMPP patients with pleural effusion (medium or large) and necrotizing pneumonia showed longer duration of fever, high serum value of lactate dehydrogenase (LDH), D-dimer, and LDH to albumin ratio (LAR). LAR and D-dimer were associated with moderate or massive pleural effusion, and D-dimer was associated with lung necrosis. The average time of radiographic resolution in the pulmonary complication group was 12 weeks, while those with elevated D-dimer were significantly more likely to have longer time for radiographic clearance.

Conclusion: We conclude that *M. pneumoniae* pneumonia in patients with pleural effusion (medium or large) or lung necrosis was more severe than those without pulmonary complications. LAR and D-dimer might be used as parameters to identify children susceptible to pleural effusion (medium or large) or lung necrosis, and longer time for radiographic clearance among pediatric patients of SMPP.

Keywords
children, *Mycoplasma pneumoniae* pneumonia, pulmonary complications

Abbreviations: BALF, bronchoalveolar lavage fluid; BS, bronchoscopic scoring; CAP, community acquired pneumonia; CRP, C-reactive protein; LAR, lactate dehydrogenase to albumin ratio; LDH, lactate dehydrogenase; MP, Mycoplasma pneumonia; MPP, Mycoplasma pneumoniae pneumonia; NPA, nasopharyngeal aspiration; PCT, procalcitonin; RMPP, refractory *Mycoplasma pneumoniae* pneumonia; SMPP, severe *Mycoplasma pneumoniae* pneumonia.
1 | INTRODUCTION

Mycoplasma pneumoniae (MP) is a common respiratory pathogen of community-acquired pneumonia (CAP) in childhood. Epidemiological studies of Mycoplasma pneumoniae pneumonia (MPP) showed that 37.5% children with CAP were infected with MP. MP infection was traditionally thought to be self-limited with a good outcome, but the incidence of severe Mycoplasma pneumoniae pneumonia (SMPP) cases has gradually increased in recent years, rising from 0.7% in 2006 to 35% in 2016. Children with SMPP have a long hospitalization record, high medical expense and may have long-term complications such as bronchiectasis, bronchitis obliterans and bronchiolitis obliterans. There are no well-defined and unified diagnostic criteria for pediatric SMPP, and MPP patients either with extensive lung lesions spreading over more than two thirds of the chest area in radiographic image or developing intra-and extrapulmonary complications could be all considered as SMPP. Clearly, SMPP has been recognized to present diverse clinical phenotypes, including pulmonary complication subtype and nonpulmonary complication subtype, which might be associated with the occurrence of airway sequelae.

There are very few articles describing the relationship between pulmonary complications and prognosis in SMPP patients. Moynihan et al. identified 30 confirmed M. pneumoniae infection cases in 11,526 pediatric intensive care unit (PICU) admissions, which included 22 pneumonia cases receiving invasive or noninvasive respiratory support with a median length of 2.0 days in PICU, but no further information of intra-pulmonary complications was reported in these SMPP patients. In Taiwan, Lee et al. found 34 pediatric patients of SMPP, hospitalized in PICU between 2010 and 2019, and 22 of them presented with pleural effusion. The case of one SMPP patient with pleural effusion, showing rapid progression to acute respiratory distress syndrome and evolving into necrotizing pneumonia later, provided limited evidence of pulmonary complications as poor prognostic factor in SMPP. Other clinical studies found that MP genotypes might be useful to predict the progress of SMPP, or atopic individuals are more likely to suffer from SMPP for being more susceptible to extra-pulmonary complications. However, SMPP patients with or without pulmonary complications were not distinguished in these studies.

In the present study, we used serum biochemical indicators and airway secretion conditions obtained by bronchoscopy to describe the clinical features and prognosis in SMPP children with pulmonary complications, compared with nonpulmonary ones.

2 | MATERIALS AND METHODS

2.1 | Subjects and data collection

There were 892 patients with CAP, hospitalized between January 2016 and February 2019 in the Division of Respiratory Medicine at Children’s Hospital of Chongqing Medical University, who were diagnosed with MPP. The MPP diagnosis in our study is as follows: acute respiratory infection symptoms (fever, cough, or wheezing), physical examination and chest imaging with infiltrates, and laboratory tests in nasopharyngeal aspiration (NPA) or bronchoalveolar lavage fluid (BALF) samples to confirm MP infection. MPP patients that satisfied the criteria of severe CAP according to the “Guidelines for management of community-acquired pneumonia in children” published by the Society of Pediatrics, Chinese Medical Association were included. The following four characteristics were estimated as criteria of SMPP: (1) tachycardia (judgment criteria: <1 year old, respiratory rate >50 times/min; 1–5 years old, respiratory rate >40 times/min; >5 years old, respiratory rate >30 times/min), accompanied with three concave signs and cyanosis, (2) hypoxemia (pulse oxygen saturation is less than 0.92 in condition of air inhalation) (3) lung lesions over more than 2/3 area in chest radiographic image, (4) pulmonary complications such as atelectasis, pleural effusion or necrosis (also called as necrotizing pneumonia). The following patients were excluded from the study: (1) those with conditions of bronchopulmonary dysplasia, congenital heart disease, asthma, and malnutrition (17 patients); and (2) those with other pathogens detected in NPA or BALF (379 patients). In the end, 496 MPP patients were the only MP detected in respiratory samples without any other pathogens. Ninety-three patients (18.7%, 93/496) were diagnosed as SMPP and were enrolled in this study. All observations followed the relevant guidelines and regulations of the Children’s Hospital of Chongqing Medical University. The study was approved by the Institutional Review Board, Children’s Hospital of Chongqing Medical University. Medical records of all subjects were retrospectively reviewed. Collected data included clinical presentations, NAP and BALF detection of MP load by polymerase chain reaction (PCR), serum biochemical examination of all indicators, bronchoscopy record, and chest radiographic/computed tomography (CT) features. The degree of secretion in the tracheobronchial tree was determined by using a standardized bronchoscopy scoring system according to the research of Chang et al. This visual grading score graded the secretions in a scale from 1 to 6, based on distribution and amount of mucus in the airways. Trachea and lobar bronchi, including right main stem, right upper lobe, right bronchus intermedius, right middle lobe, right lower lobe, left main stem, left upper lobe, and left lower lobe, were scored. Subjects with grades 1 and 2 were considered to have no secretion, those with grade 3 had minimal secretion, and those with grades 4–6 had mild, moderate, and large secretion, respectively.

2.2 | Definition

Pulmonary complications were defined as the occurrence of lobar atelectasis, medium or large pleural effusion, and necrotizing pneumonia. Lobar atelectasis was referred to collapse or incomplete expansion of one or more lobes of lung observed by chest CT. Pleural effusion was confirmed by ultrasonographs; medium pleural effusion was defined as 300–500 mL fluid drained by thoracocentesis; and
large pleura effusion, as ≥500 mL fluid drained by thoracocentesis. Necrotizing pneumonia referred to MPP patients whose lung showed low attenuation area, with or without cavitation on postcontrast enhanced CT scan. Patients with high load of MP were referred to those whose sample exhibited MP DNA loads ≥10⁶ copies/mL. Patients with near-complete resolution of chest x-ray or CT referred to those whose chest radiographic or CT image showed the absence of any abnormal findings as infiltrates, alectasis, or pleural fluid, with only minimal residual changes left. Fever was defined as a temperature of 37.5°C or higher. The total duration of fever was calculated from the date of first symptom onset to the date of defervescence (defined as temperature <37.5°C for at least 24 h) during the hospital admission. Serum level of C-reactive protein (CRP) >8 mg/L, procalcitonin (PCT) >0.05 ng/ml, D-dimer >0.86 mg/L, lactate dehydrogenase (LDH) >330 IU/L, and albumin <38 g/L were considered abnormal.

2.3 | M. pneumoniae PCR assay

Extraction of DNA from NPA samples and detection of M. pneumoniae DNA by real-time fluorescence PCR assay (ABI 7500 Real-Time PCR System) in these samples were performed with one-step kit (Sansure Biotech Mycoplasma Pneumoniae DNA Fluorescence Diagnostic Kit). Primers were designed to amplify the nucleotides of MP P1 gene (forward primer: 5′-CCCACTCGCTGAACGTAGAT-3′ and reverse primer: 5′-GGGTAAACAACGGTGGTAAT-3′). The probe was FAM-CTGACACCTGGTTCCACAAGCGTGAA-BHQ1 for real-time PCR. The PCR reaction condition was: 45 amplification cycles of denaturation for 15 s at 94°C, annealing, elongation, and collection of fluorescence data for 30 s at 57°C. The minimum detection limit for MP was 400 copies/mL.

2.4 | Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 22.0). For continuous variables, comparison of means was conducted using t test or Bonferroni test for post hoc analysis in ANOVA. For non-normal data, Mann–Whitney test was used. For categorical variables, the chi-square test, Fisher’s exact test, or multiple chi-square test was used. Multiple regression analysis was performed to select the variables associated with intrapulmonary complication and radiographic resolution or complete absorption in chest CT scan. Probabilities of .05 or less were considered significant.

3 | RESULTS

3.1 | Clinical and laboratory examination characteristics in 93 severe MPP patients

A total of 93 patients (45 males and 48 females) fulfilled the severe MPP diagnostic criteria between January 2016 and February 2019.

| Variables | n (%) |
|-----------|-------|
| Age in years, mean ± SD | 6.16 ± 2.54 |
| Cases with pulmonary complication | 63 (67.7) |
| Cases with single pulmonary complication | 53 (56.9) |
| Cases with medium or large pleural effusion | 36 (38.7) |
| Cases with lobar atelectasis | 25 (26.8) |
| Cases with necrotizing pneumonia | 12 (12.9) |
| Case of MP load ≥10⁶ copies/mL in NPA | 73 (78.4) |
| Case underwent bronchoscopy | 86 (92.3) |
| Case of MP load ≥10⁶ copies/mL in BALF | 58/86 (67.4) |
| Use of corticosteroid therapy | 9 (9.7) |
| Case of complete/near complete radiographic resolution | 37/63 (58.7) |

Abbreviations: BALF, bronchoalveolar lavage fluid; MP, Mycoplasma pneumoniae; NPA, nasopharyngeal aspiration.

The descriptive statistics of the study population are shown in Table 1. The mean age was 6.16 ± 2.54 years, and 63 (67.7%) patients had pulmonary complications, including lobar atelectasis, medium or large pleura effusion, and necrotizing pneumonia. Single pulmonary complication was observed in 53 (56.9%) patients; and high load of MP in NPA was found in 73 (78.4%) patients. Flexible bronchoscopy was performed in 86 (92.3%) patients. Large secretion (grade 6) was found in 27 (31.3%) patients, moderate secretion (grade 5) in 41 (47.7%) patients, mild secretion (grade 4) in 10 (11.6%) patients, and minimal secretion (grade 3) was found in 8 (9.4%) patients. In terms of therapy, nine (9.7%) patients received low-dose corticosteroids.

We compared age, total fever duration, and laboratory examination characteristics in SMPP patients with and without pulmonary complications, and the data are shown in Table 2. SMPP patients with pulmonary complications were associated with older age, longer fever days, higher levels of CRP, PCT, D-dimer, LDH, and LDH to albumin ratio (LAR), but lower levels of albumin in serum, when compared to those with no pulmonary complications. Other variables (MP load in NPA, airway secretion conditions, and white blood cell count) showed no difference. One noticeable trend was that the number of patients on corticosteroid therapy was higher in the pulmonary complication group (9/63 vs. 0/30, p = .0537).

3.2 | Laboratory examination characteristics and risk indicators of SMPP with different pulmonary complications

Cases of single pulmonary complication were selected, and the data were analyzed and presented in Table 3. There were significant differences in the total duration of fever and levels of CRP, D-dimer,
### TABLE 2  Laboratory findings in SMPP patients with and without pulmonary complication.

| Variables                              | Pulmonary complication (n = 63) | No pulmonary complication (n = 30) | p     |
|----------------------------------------|---------------------------------|-----------------------------------|-------|
| Age in years                           | 6.88 ± 2.39                     | 5.07 ± 2.44                       | .0011 |
| Total fever duration in days           | 11.46 ± 0.61                    | 6.50 ± 0.82                       | <0.0001|
| CRP, mg/L                              | 51.70 ± 5.27                    | 22.53 ± 4.14                      | <0.0001|
| PCT, ng/L                              | 1.84 ± 0.59                     | 0.62 ± 0.24                       | 0.0043 |
| d-dimer, mg/L                          | 7.06 ± 0.84                     | 2.01 ± 0.50                       | <0.0001|
| LDH, IU/L                              | 617.2 ± 37.14                   | 411.0 ± 30.90                     | <0.0001|
| Albumin, g/L                           | 32.81 ± 0.8728                  | 38.83 ± 0.7643                    | <0.0001|
| LDH to albumin ratio, IU/g             | 20.89 ± 1.75                    | 10.98 ± 1.06                      | <0.0001|
| Case of MP load ≥10⁶ copies/mL in BALF, n (%) | 47/63 (74.6)                   | 11/23 (47.8)                      | 0.037  |

Abbreviations: BALF, bronchoalveolar lavage fluid; CRP, C-reactive protein; LDH, lactate dehydrogenase; MP, *Mycoplasma pneumoniae*; PCT, procalcitonin.

### TABLE 3  Laboratory findings in SMPP patients with different pulmonary complications.

| Variables                              | Lobar atelectasis (n = 19) | Medium or large pleural effusion (n = 26) | Necrotizing pneumonia (n = 8) | p          |
|----------------------------------------|-----------------------------|-------------------------------------------|------------------------------|------------|
| Total fever duration in days           | 7.78 ± 0.65                 | 13.81 ± 0.85                              | 12.50 ± 2.55                | a < 0.001  |
|                                        |                             |                                           |                              | b = 0.013  |
|                                        |                             |                                           |                              | c = 1.000  |
| CRP, mg/L                              | 30.05 ± 5.38                | 61.58 ± 8.36                              | 55.25 ± 12.92               | a = 0.006  |
|                                        |                             |                                           |                              | b = 0.207  |
|                                        |                             |                                           |                              | c = 1.000  |
| d-dimer, mg/L                          | 2.03 ± 0.40                 | 8.28 ± 1.09                               | 8.56 ± 1.64                 | a < 0.001  |
|                                        |                             |                                           |                              | b = 0.002  |
|                                        |                             |                                           |                              | c = 1.000  |
| LDH, IU/L                              | 435.40 ± 42.01              | 725.70 ± 62.04                            | 602.8 ± 122.0               | a = 0.001  |
|                                        |                             |                                           |                              | b = 0.381  |
|                                        |                             |                                           |                              | c = 0.827  |
| Albumin, g/L                           | 39.63 ± 1.25                | 29.50 ± 1.02                              | 30.88 ± 1.74                | a < 0.001  |
|                                        |                             |                                           |                              | b < 0.001  |
|                                        |                             |                                           |                              | c = 1.000  |
| LDH to albumin ratio, IU/g             | 11.40 ± 1.25                | 26.20 ± 2.97                              | 21.54 ± 6.13                | a < 0.001  |
|                                        |                             |                                           |                              | b = 0.155  |
|                                        |                             |                                           |                              | c = 1.000  |
| Case of MP load ≥10⁶ copies/mL in BALF, n (%) | 9/19 (47.3)                 | 21/26 (80.7)                              | 6/8 (75.0)                  | NS         |

Note: a: cases of lobar atelectasis versus cases of pleural effusion; b: cases of lobar atelectasis versus cases of necrotizing pneumonia; c: cases of pleural effusion versus cases of necrotizing pneumonia.

Abbreviations: BALF, bronchoalveolar lavage fluid; CRP, C-reactive protein; LDH, lactate dehydrogenase; MP, *Mycoplasma pneumoniae*; PCT, procalcitonin; SMPP, severe *Mycoplasma pneumoniae* pneumonia.
LDH, albumin as well as LAR among the lobar atelectasis, pleural effusion (medium or large), and necrotizing pneumonia groups. The percentage of large and moderate airway secretion cases in atelectasis, pleural effusion (medium or large), and necrotizing pneumonia groups were 68.2% (13/19), 84.6% (22/26), and 87.5% (7/8), respectively. Compared with the lobar atelectasis group, longer total fever duration, and higher levels of CRP, d-dimer, LDH, and LAR were found in the medium or large pleural effusion group with significant differences. These variants in the lobar atelectasis group showed no differences from those of the no-pulmonary complication group, except in age (6.89 ± 2.25, n = 19 vs. 5.07 ± 2.44, n = 30, p = .0129).

To find potential indicators for predicting the risk of pleural effusion and necrotizing pneumonia in SMPP patients, we compared the difference of various laboratory indicators between each complication group and the no-pulmonary complication group. Both d-dimer (odds ratio [OR] = 1.314, 95% confidence interval [CI] = 1.042–1.658, p = .021) and LAR (OR = 1.215, 95% CI = 1.054–1.401, p = .007) were significant indicators in the multivariable logistic regression model for predicting medium or large pleural effusion in SMPP patients, and only d-dimer (OR = 1.468, 95% CI = 1.139–1.892, p = .003) was the significant indicator for predicting necrotizing pneumonia.

### 3.3 | Time and indicators of chest radiography resolution in SMPP patients

At least one chest x-ray or chest CT was performed on 63 (67.7%) patients who returned for their follow-up examinations, and complete or near-complete resolution was reported in 37 (58.7%) patients, including 22 patients with pulmonary complication. Table 4 presents the time of complete and near-complete chest radiography resolution in SMPP patients. Radiographic clearance in 4 weeks was observed in 86.6% (13/15) patients without pulmonary complications, whereas 72.7% (16/22) patients with pulmonary complications had radiographic clearance in 12 weeks. The resolution time of pulmonary complication group was significantly longer than the no-pulmonary complication group (1.16 ± 0.15 months, n = 15 vs. 2.43 ± 0.44 months, n = 22, p = .0276), but there was no difference in the atelectasis group (2.46 ± 0.49 months, n = 15), the medium or large pleural effusion group (2.38 ± 0.73 months, n = 9), and the necrotizing pneumonia group (3.66 ± 2.1 months, n = 3) as well as in the single complication group, when compared with the multiple complications group (2.25 ± 0.42 months, n = 18 vs. 3.25 ± 1.60 months, n = 4, p = .3943).

We further analyzed the laboratory data in no-complication patients without radiographic resolution in 4 weeks. Statistical analysis revealed that d-dimer (5.21 ± 2.49, n = 4 vs. 1.11 ± 0.26, n = 13, t = 4, p = .0149), LDH (553.80 ± 37.91, n = 4 vs. 347.10 ± 25.45, n = 13, p = .001) and LAR (15.62 ± 1.98, n = 4 vs. 8.91 ± 0.74, n = 13, p = .0013) were significantly higher in the no-complication patients without radiographic resolution in 4 weeks, compared with those who had radiographic resolution ≤ 4 weeks. The percentage of large and moderate airway secretion patients by first-time FB test was not different between these two groups (4/4 vs. 11/13, p = 1). As shown, LDH (OR = 1.024, 95% CI = 0.999–1.051, p = .059) appears to be a predictor in the multivariable logistic regression for long-time resolution in the no-complication group. We also found that 27.2% (6/22) of pulmonary complication patients exhibited radiographic resolution in >12 weeks, including 1 lobar atelectasis patient, 4 pleural effusion patients, and 1 patient with pleural effusion combined with necrotizing pneumonia. Duration of fever (12.00 ± 0.89 days, n = 6 vs. 8.44 ± 0.57 days, n = 16, p = .0044), d-dimer (9.92 ± 2.90, n = 6 vs. 3.96 ± 0.91, n = 16, p = .0155) and LDH (748.70 ± 178.60, n = 6 vs. 484.50 ± 45.81, n = 16, p = .0496) were significantly different between complication groups with radiographic resolution >12 weeks or ≤12 weeks. The percentage of large and moderate airway secretion patients by first-time FB test was higher in complication patients with ≤12 weeks radiographic resolution (3/6 vs. 16/16, p = .013) compared with those of >12 weeks radiographic clearance. d-dimer (OR = 1.241, 95% CI = 1.009–1.527, p = .041) was a predictor in the multivariable logistic regression model for >12 weeks resolution in the complication group.

On the other hand, 26 SMPP patients failed to return who still had abnormal chest images (segmental consolidation, segmental atelectasis, bronchiectasis, and mosaic attenuation) in the last known follow-up, including 23 patients with pulmonary complication (Table 5).

### Table 4 | Radiographic resolution time of SMPP patients with pulmonary complication.

| Period (weeks) | SMPP patients | SMPP patients with pulmonary complications, n (%) |
|---------------|---------------|-----------------------------------------------|
| 4             | 21            | 8 (38.1)                                      |
| 8             | 9             | 7 (77.7)                                      |
| ≥12           | 7             | 7 (100.0)                                     |

**Table 5** | Abnormality in the last known chest image examination of SMPP patients failed to follow up.

| Period (weeks) | Pulmonary complications, n (%) | No pulmonary complications, n (%) |
|---------------|-------------------------------|----------------------------------|
|               | Segmental consolidation | Segmental atelectasis | Bronchiectasis | Segmental consolidation | Segmental atelectasis | Mosaic attenuation |
| 4             | 10 (43.5%)                  | 0                      | 0             | 2 (66.7%)                | 0                      | 0                  |
| 8             | 0                           | 4 (17.4%)               | 2 (8.7%)      | 0                        | 0                      | 0                  |
| ≥12           | 0                           | 6 (26.1%)               | 1 (4.3%)      | 0                        | 0                      | 1 (33.3%)           |

Abbreviation: SMPP, severe Mycoplasma pneumoniae pneumonia.
The incidence of SMPP in our study during the year from 2016 to early 2019 was 18.7%. In apparent contrast, Gao et al. reported that the percentage of SMPP between 2015 and 2016 in North China was 35%, which was higher than ours. However, a state-wide multicenter retrospective study in Australia reported that the incidence of SMPP was only 0.3% in PICU admission in Queensland from 2008 to 2013. Approximately 5% of SMPP hospitalized children required ICU admission in a children's hospital in Taipei from 2010 to 2019. It is quite possible that the observed differences are due to geographical and climatic factors as well as the requirement of respiratory support.

We retrospectively analyzed the characteristics of 93 SMPP patients, including 30 patients with extensive pulmonary lesions and 63 patients with intrapulmonary complications, and no case of MP-associated myocarditis or encephalitis was found. Among the patients with pulmonary complications, 84.1% patients had single complication, and 49.1% of them presented pleural effusion. Similar to our results, 64.7% (22/34) of SMPP patients requiring PICU admission presented with pleura effusion in the Taipei study, indicating a high occurrence of pleural effusion as pulmonary complication in SMPP.

Differences were found in clinical indicators between SMPP patients with and without pulmonary complications. Those with no intrapulmonary complications were mostly preschool children, while the ages of the intrapulmonary complications group were mostly over 6 years. SMPP patients with atelectasis tend to be school-age children, which was a major difference from those with extensive lung lesions. Unlike the atelectasis group, in pleura effusion and necrotizing pneumonia group, fever time was significantly prolonged, and levels of CRP, d-dimer, and LDH, as well as MP load in BALF, were significantly higher than those without complications. Similarly, SMPP patients with pleural effusion in PICU were associated with higher CRP levels and longer fever duration. Differences in these parameters were seen in SMPP patients with pleura effusion or necrotizing pneumonia, but not in the atelectasis patients. The current evidence indicates that any inflammation resulting in atelectasis might be relatively mild in comparison to that causing pleural effusion and lung necrosis.

LDH is widely distributed in various tissues of the body, including the lung tissue, and serum LDH levels have long been used for the diagnosis and management of pulmonary infectious diseases as well as for outcome prediction. A previous study that quantified LDH, combined with ferritin, documented their roles as useful indicators for evaluating MPP conditions, while the severity of MPP in this study was defined as hypoxia, dyspnea, extent of pleural effusion, and lung lesion in chest radiographic images; as mentioned earlier, patients with intrapulmonary complications were not included. Our study found that high LDH and low albumin levels were observed in SMPP patients with intrapulmonary complications, and both indicators were easy to obtain quickly. LAR was elevated in the pleural effusion or lung necrosis group and was in fact found to be one of the independent risk factors for moderate to large pleural effusion occurrence. Of note, LAR represents tissue damage, nutritional status, and systemic inflammatory response, and thus, could help the clinicians to fully assess the progression of severe MP infection. Coagulation abnormalities were common and persistent in CAP patients, especially related to d-dimer levels that were significantly increased in the pleural effusion or lung necrosis group and were also an independent risk factor for pleural effusion and lung necrosis. These results indicate that a hypercoagulable state existed in these patients, which might not only contribute to microthrombus in pulmonary circulation, involved in pathogenesis of these two complications, but also alert us to the possibility of pulmonary thrombosis and lower venous thrombosis. Through retrieval of literature between 2009 and 2015, we located reports of three children of MPP with pulmonary embolism or lower extremity venous thrombosis, and two patients with moderate pleural effusion, whereby the d-dimer levels fluctuated between 6.8 and 55.8 mg/L. Furthermore, asthmatic patients might have a different response after MP infection, as the IL-18 response was found to be significantly decreased in the asthmatic SMPP group compared to the non-severe group. Yet another study showed that asthma patients were prone to be suffering from refractory Mycoplasma pneumoniae pneumonia (RMPP) indicating that the immune status of asthma patients may have a different pattern in the course of MPP. Since our study excluded asthma patients, further research will be needed to explore the indicators of SMPP with pulmonary complications in asthmatic children.

Previous studies reported that the chest radiographic resolution of 90.3% of RMPP patients occurred in 12 weeks. Our study showed that 86.6% of patients without intrapulmonary complications had imaging resolution at 4 weeks, and 72.7% of patients with resolution at 12 weeks. Our results also suggest that the high-level LDH in patients without complication may indicate delayed resolution, which is consistent with the study by Huang et al. d-dimer is also involved in the severity and prognosis of CAP, and likewise, we found high levels of d-dimer to be an independent risk factor for delayed resolution in patients with intrapulmonary complications, which suggests that the benefits of early use of anticoagulant therapy need to be evaluated. The bronchoscopic secretion (BS) scoring system was first used to quantify the extent of airway secretions to identify wet coughs. Moderate to high airway secretion, as evaluated by this system, was found in over 70% of patients, suggesting that the invasion pathway of MP in our SMPP patients was likely through the respiratory tract and not via the bloodstream. There was no significant correlation between BS grade and the presence of intrapulmonary complications, but patients with complications and lower BS grade showed a tendency of delayed resolution. We speculate that mycoplasma causes damage from distal parenchyma to proximal airways as the invasion progresses. One pleural effusion patient presented minimal airway secretion in the course of 2 weeks, and found mucus plug in the course of 6 weeks, followed by bronchi obliterations in lobe bronchus in the 8th week, suggesting that the local inflammatory injury gradually progressed from the distal alveolar to the large proximal airway and that the recovery was slow and delayed. Intervention of bronchoscopy, therefore, may be beneficial for discharged patients with delayed resolution, especially those with pulmonary complications in the acute phase of MPP.

The advantage of this study is that all three markers studied, namely LDH, d-dimer, and LAR, can be easily detected, quantified,
and calculated for a quick evaluation of disease severity and prognosis, combined with clinical manifestations. Nevertheless, some limitations of this study can be noted. First, it is a retrospective study, and we had relatively low amounts of follow-up data after patient discharge. Overall, 32.3% of subjects did not come back for follow-up once after discharge. Second, macrolide-resistant MP was not detected, and hence was not studied. There were four patients with delayed clearance of chest image and they presented moderate mucus in the lumen of affected segment bronchus by follow-up bronchoscopy test. In such cases, macrolide-resistant MP might be associated with the delayed chest image clearance.

5 | CONCLUSIONS

The clinical features of SMPP were different between the pulmonary complication subtype and the non-complication subtype. Older age, longer duration of fever, higher levels of CRP, LDH, D-dimer, and LAR, and longer time of radiographic resolution were observed in patients with pulmonary complication. LAR and D-dimer might serve as useful predictors of medium or large pleural effusion in SMPP patients; D-dimer might also be an indicator of lung necrosis and delayed radiographic resolution in SMPP patients with intrapulmonary complications. Further studies should shed light on the distribution of macrolide-resistant MP in pulmonary complications and its influence on the chest radiographic resolution.

AUTHOR CONTRIBUTIONS
Xue qin Luo: Data curation; writing—original draft; investigation; formal analysis; writing—review and editing. Jian Luo: Conceptualization; methodology; project administration; writing—review and editing. Chong je Wang: Investigation; formal analysis; writing—review and editing. Zheng xiu Luo: Investigation; supervision; writing—review and editing. Hai yin Tian: Formal analysis; funding acquisition. Xiao hong Xie: Conceptualization; funding acquisition; methodology; project administration; supervision; writing—original draft; writing—review and editing.

ACKNOWLEDGMENTS
The study was supported by the people livelihood project of Chongqing Science and Technology Committee (cstc2017shmsA130036) and the Program for Youth Innovation in Future Medicine, Chongqing Medical University (W0063).

CONFLICT OF INTEREST STATEMENT
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT
The Ethics Committee consists of the Institutional Review Board, Children’s Hospital of Chongqing Medical University. The reference number of approval ethics is 2019-181. This is a retrospective study, and as such, all the data used here were obtained from existing medical records; thus, there was no process of study participant recruitment, which is declared in the documents of ethics approval.

ORCID
Xiao hong Xie http://orcid.org/0000-0002-5297-9578

REFERENCES
1. Gao LW, Yin J, Hu Y, et al. The epidemiology of paediatric Mycoplasma pneumoniae pneumonia in North China: 2006 to 2016. Epidemiol Infect. 2019;147:e192.
2. Han Q, Shi Y, Li HX, Tang WW, Liu HX, Zhao DY. [Bronchitis obliterans associated with bronchiolitis obliterans with organizing pneumonia in a child and literature review]. Zhonghua Er Ke Za Zhi. 2016;54:523-526. Chinese.
3. Zhao C, Liu J, Yang H, Xiang L, Zhao S. Mycoplasma pneumoniae–associated bronchiolitis obliterans following acute bronchiolitis. Sci Rep. 2017;7:8478.
4. Moynihan KM, Barlow A, Nourse C, Heney C, Schlesbusch S, Schlapbach LJ. Severe Mycoplasma pneumoniae infection in children admitted to pediatric intensive care. Pediatr Infect Dis J. 2018;37: e336-e338.
5. Lee KL, Lee CM, Yang TL, et al. Severe Mycoplasma pneumoniae pneumonia requiring intensive care in children, 2010-2019. J Formos Med Assoc. 2021;120:281-291.
6. Yan C, Xue G, Zhao H, et al. Molecular and clinical characteristics of severe Mycoplasma pneumoniae pneumonia in children. Pediatr Pulmonol. 2019;54:1012-1021.
7. Wang Z, Sun J, Liu Y, Wang Y. Impact of atopy on the severity and extrapulmonary manifestations of childhood Mycoplasma pneumoniae pneumonia. J Clin Lab Anal. 2019;33(5):e22887.
8. The Subspecialty Group of Respiratory Disease, The Society of Pediatrics, Chinese Medical Association, The Editorial Board, Chinese Journal of Pediatrics. Guidelines for management of community acquired pneumonia in children (the revised edition of 2013) (I). Chin J Pediatr. 2013:51:745-799. Chinese.
9. Chang AB, Faoagali J, Cox NC, et al. A bronchoscopic scoring system for airway secretions—airway cellularity and microbiological validation. Pediatr Pulmonol. 2006;41:887-892.
10. Esteves F, Lee CH, de Sousa B, et al. (1-3)-beta-D-glucan in association with lactate dehydrogenase as biomarkers of Pneumocystis pneumonia (PCP) in HIV-infected patients. Eur J Clin Microbiol Infect Dis. 2014;33:1173-1180.
11. Vogel M, Weissgerber P, Goeppert B, et al. Accuracy of serum LDH elevation for the diagnosis of Pneumocystis jiroveci pneumonia. Swiss Med Wkly. 2011;141:w13184.
12. Kawamata R, Yokoyama K, Sato M, et al. Utility of serum ferritin and lactate dehydrogenase as surrogate markers for steroid therapy for Mycoplasma pneumoniae pneumonia. J Infect Chemother. 2015;21:783-789.
13. Milbrandt EB, Reade MC, Lee M, et al. Prevalence and significance of coagulation abnormalities in community-acquired pneumonia. Mol Med. 2009;15(11-12):438-445.
14. Graw-Panzer KD, Verma S, Rao S, Miller ST, Lee H. Venous thrombosis and pulmonary embolism in a child with pneumonia due to Mycoplasma pneumoniae. J Natl Med Assoc. 2009;101:956-958.
15. Su HY, Jin WJ, Zhang HL, Li CC. [Clinical analysis of pulmonary embolism in a child with Mycoplasma pneumoniae pneumonia]. Zhonghua er ke za zhi. 2012;50:151-154. Chinese.
16. Zhuo Z, Li F, Chen X, Jin P, Guo Q, Wang H. Mycoplasma pneumonia combined with pulmonary infarction in a child. *Int J Clin Exp Med*. 2015;8:1482-1486.

17. Chung HL, Shin JY, Ju M, Kim WT, Kim SG. Decreased interleukin-18 response in asthmatic children with severe *Mycoplasma pneumoniae* pneumonia. *Cytokine*. 2011;54:218-221.

18. Shin JE, Cheon BR, Shim JW, et al. Increased risk of refractory *Mycoplasma pneumoniae* pneumonia in children with atopic sensitization and asthma. *Korean J Pediatr*. 2014;57:271-277.

19. Huang L, Huang X, Jiang W, Zhang R, Yan Y, Huang L. Independent predictors for longer radiographic resolution in patients with refractory *Mycoplasma pneumoniae* pneumonia: a prospective cohort study. *BMJ Open*. 2018;8:e023719.

20. Snijders D, Schoorl M, Schoorl M, Bartels PC, van der Werf TS, Boersma WG. D-dimer levels in assessing severity and clinical outcome in patients with community-acquired pneumonia. A secondary analysis of a randomised clinical trial. *Eur J Intern Med*. 2012;23:436-441.

21. Querol-Ribelles JM, Tenias JM, Grau E, et al. Plasma d-dimer levels correlate with outcomes in patients with community-acquired pneumonia. *Chest*. 2004;126:1087-1092.

22. Chang BA, Gaffney JT, Eastburn MM, Faoagali J, Cox NC, Masters IB. Cough quality in children: a comparison of subjective vs. bronchoscopic findings. *Respir Res*. 2005;6:3.