Clinical features of severe mycoplasma pneumoniae pneumonia with pulmonary complications in childhood: a retrospective study.

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Abstract

Background Incidence of severe M. pneumoniae pneumonia (SMPP) reported in China was increasing in the last decade. We aimed to evaluate clinical features in pediatric SMPP with pulmonary complications according to laboratory test and chest radiographic resolution patterns.

Methods We retrospectively reviewed 93 SMPP patients between January 2016 and December 2018, and they were grouped by pneumonia pattern: pulmonary complication group (63 patients) and extensive lung lesion without pulmonary complication group (30 patients).

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

Conclusions M. pneumoniae pneumonia patients with pleural effusion or lung necrosis were more severe than those without pulmonary complication, LAR and D-dimer might be used as parameters to identify susceptible children of pleural effusion or lung necrosis and longer time to radiographic clearance among patients with SMPP.

Background

Mycoplasma pneumoniae (MP) is a common respiratory pathogen of community acquired pneumonia (CAP) in childhood. *Mycoplasma pneumoniae* pneumonia (MPP) epidemics have occurred every 2–3 years from 2006 to 2016 in North China[1], and incidence rate of popular years usually increases several times compared with those of non-popular years. The epidemiology study of MPP showed that 37.5% children with CAP are infected with MP[[1]. A tendency of younger peak age in MPP patients was observed in Korean children[2], but peak age of MPP in North China was between 6 and 10 years, indicating that school-age children and adolescents are major population prone to MPP in this area. Although MP infection was traditionally thought to be self limited with a good outcome, the incidence of severe *mycoplasma pneumoniae* pneumonia (SMPP) case has gradually increased in recent years,and the change was from 0.7% in 2006 to 35% in 2016[1]. Children with SMPP have long hospitalization, high medical expenses and may have long-term complications such as atelectasis, bronchiectasis, bronchitis obliterans and bronchiolitis obliterans [3–5]. There are no well-defined and unified diagnostic criteria for pediatric SMPP, and patients who were definitely diagnosed as MPP satisfied the criteria of severe CAP according to “Guidelines for management of community-acquired pneumonia in children”[6] could be confirmed as SMPP. Other patients whose lung lesions were more than 2/3 areas in the chest radiographic image, who developed intra-and extra-pulmonary complications, and who were defined as refractory *mycoplasma pneumoniae* (RMPP) by presence of persistent fever, clinical features as well as

radiological deterioration after azithromycin treatment for 7 days or longer, were also treated as SMPP, suggesting different clinical phenotype existed in disease of SMPP. In the past 10 years, a large number of studies have focused on RMPP including pathogenesis due to host and pathogenic variation, biological indicators for prediction and prognosis, airway damage and management by bronchoscopy as well as evaluation of steroid therapy[7–12]. Only a few number of case report described the diagnosis and treatment of pediatric SMPP with massive pleural effusion[13]. Recent clinical study about SMPP found that different MP genotype might be useful to predict progress of SMPP[14] and another study pointed out that atopy individuals are more likely to suffer from SMPP because patients with serum low IL–17 and elevated total IgE were more susceptible to extrapulmonary complications[15]. However, clinical phenotypes of SMPP were not distinguished in these studies.

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

Methods

Subjects

There were 892 patients with community acquired pneumonia hospitalized in the Division of Respiratory Medicine in Children's Hospital of Chongqing Medical University who were diagnosed as MPP by MP DNA positive detected in nasopharyngeal aspiration (NPA) between January 2016 and February 2019. Diagnostic criteria of SMPP are as follows: (1) tachycardia (judgment criteria: <l years old, respiratory rate > 50 times /min, 1 to 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 more than 2 / 3 area in chest radiographic image, (4) pulmonary complications such as atelectasis diagnosed by chest CT, pleural effusion with performance of pleural puncture and necrosis diagnosed by enhanced chest CT. The following patients were excluded from the study: (1) There were 17 patients with conditions of bronchopulmonary dysplasia, congenital heart disease, asthma and malnutrition; and (2) There were 379 patients who had other pathogens detected in NPA or bronchoalveolar lavage fluid (BALF). 93 patients (18.7%, 93/496) diagnosed as SMPP were enrolled in this study. All observations were following the relevant guidelines and regulations of Children's Hospital of Chongqing Medical University. The study was approved by Institutional Review Board, Children's Hospital of Chongqing Medical University.

Method

This was an descriptive study and the medical records of all subjects were retrospectively reviewed. Collected data were including clinical presentations, NAP and BALF detection of common respiratory virus (respiratory syncytial virus, adenovirus, influenza viru A and B, parainfluenza virus type 1,2 and 3) by direct fluorescence assay, MP load by polymerase chain reaction, bacterium culture in both NPA and BALF, serum biochemical examination of all indicators, bronchoscopy record and radiographic features.

Grade of airway secretion was qualified by bronchoscopy secretion scoring system described by Chang AB.et al [16].

Statistic 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 and one-way analysis of variation. For informetic data, Mann-Whitney test was used. For categorical variables, χ^2 or Fisher's exact test was used. Multiple regression analysis was performed to select the variables associated with intrapulmonary complication and radiographic resolution. Probabilities of 0.05 or less were considered significant.

Results

Clinical and laboratory examination characteristics in 93 severe MPP patients

A total of 93 patients (45 males, 48 females) fulfilled the severe MPP diagnostic criteria from January 2016 to December 2018. Descriptive statistics of study population are shown in table 1.The mean age was 6.16 ± 0.33 years, and 63 (67.7%) patients had pulmonary complication, including lobe atelectasis, medium or large pleura effusion and necrotizing pneumonia. 53(56.9%) patients had single pulmonary complication. High loading 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) was found in 41 (47.7%)patients, mild secretion (grade 4) was found in 10 (11.6%) patients and minimal secretion was found in 8 (9.4%) patients. 9 (9.7%) patients received low-dose corticosteroid therapy. 63 (67.7%) patients returned for their follow-up chest radiography at least once, and complete or near complete resolution was reported in 37 (58.7%) patients.

We compared age, total fever duration and laboratory examinations in SMPP patients with and without pulmonary complications and the data are shown in table 2.SMPP patients with pulmonary complication were associated with age, total fever days, % Neutrophils in blood sample, C-reactive protein (CRP), procalcitonin(PCT),D-dimer, lactic dehydrogenase (LDH),albumin,LDH to albumin ratio (LAR) and high load of MP in BALF when compared with those of no pulmonary complications. Other variables (MP loading in NPA, airway secretion condition and White blood cell count) showed no difference. There was a tendency that patients of corticosteroid therapy were higher in pulmonary complication group (9/63 vs 0/30,P = 0.0537)

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

Cases of single pulmonary complication were selected, data were analyzed and presented in table 3. There were significant differences in total fever duration, CRP, D-dimer,LDH,albumin and LAR among lobe atelectasis, pleural effusion and necrotizing pneumonia group. Percentage of large and moderate airway

section cases in atelectasis, pleural effusion and necrotizing pneumonia group was 68.2%(13/19), 84.6% (22/26) and87.5% (7/8) respectively. Compared with lobe atelectasis group, higher level of total fever duration, CRP, D-dimer,LDH and LAR were found in pleural effusion group with significant differences as well as those of necrotizing pneumonia group except LDH. These variants in lobe atelectasis group showed no difference with those of no pulmonary complication group except age (6.89 ± 0.51 n = 19 vs 5.07 ± 0.45 n = 30, P = 0.0129).To find some indicators to predict the risk of pleural effusion and necrotizing pneumonia in severe MPP patients, we compared the difference of various laboratory indicators between each group and no pulmonary complication group.Both D-dimer (OR = 1.314,95%CI = 1.042 to 1.658,P = 0.021) and LAR(OR:1.215,95%CI 1.054 to 1.401, P = 0.007)was significant indicator 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 to 1.892, P = 0.003) was significant indicator for predicting necrotizing pneumonia.

Time and indicators of chest radiography resolution in SMPP patients

Table 4 presents the time of complete and near complete chest radiography resolution in severe MPP patients. Radiographic clearance in 4 weeks was shown in 86.6% (13/15) patients without pulmonary complication patients. 72.7% (16/22) patients with pulmonary complication had radiographic clearance in 12 weeks. The resolution time of pulmonary complication group was significant longer than no pulmonary complication group (1.16 ± 0.15 n = 15 vs 2.43 ± 0.44 n = 22, P = 0.0276), but there was no difference among atelectasis group (2.46 ± 0.49 months n = 15), pleural effusion group (2.38 ± 0.73 months n = 9) and necrotizing pneumonia group (3.66 ± 2.1 months n = 3) as well as single complication group compared with multiple complications group(2.25 ± 0.42 n = 18 vs 3.25 ± 1.60 n = 4, P = 0.3943).

We further analyzed the laboratory data in no complication patients without radiograhic resolution in 4 weeks. Statistic analysis showed that D-dimer (5.21 ± 2.49 n = 4 vs 1.11 ± 0.26 n = 13 t = 4,p = 0.0149), LDH (553.80 ± 37.91 n = 4 vs 347.10 ± 25.45 n = 13,P = 0.001) and LAR (15.62 ± 1.98 n = 4 vs 8.91 ± 0.74 n = 13,P = 0.0013) were significant higher in no complication patients with radiograhic resolution > 4 weeks compared with those who had radiograhic resolution ≤ 4 weeks. 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). LDH(OR = 1.024,95%CI = 0.999 to 1.051, P = 0.059) might be an predictor in the multivariable logistic regression for long time resolution in no complication group. We also found that there were 27.2% (6/22) pulmonary complication patients with radiographic resolution > 12 weeks, including one lobe atelectasis patient, four pleural effusion patient and one patient of pleural effusion combined with necrotizing. Fever duration (12.00 ± 0.894 n = 6 vs 8.44 ± 0.57 n = 16,P = 0.0044), D-dimer (9.92 ± 2.90 n = 6 vs 3.96 ± 0.91 n = 16,P = 0.0155) and LDH (748.70 ± 178.60 n = 6 vs 484.50 ± 45.81 n = 16,P = 0.0496) were significant different between complication groups with radiographic resolution > 12 weeks or ≤ 12 weeks. Percentage of large and moderate airway secretion by first-time FB test was higher in complication patients with ≤ 12 weeks radiographic resolution (3/6 vs 16/16, P = 0.013) compared with those of > 12 weeks radiographic clearance.D-dimer (OR = 1.241,95%CI = 1.009 to 1.527, P = 0.041)

was an predictor in the multivariable logistic regression model for > 12 weeks resolution in complication group.

Discussion

The incidence of SMPP in our study during the year of 2016–2018 was 18.7%, and Gao LW et al [1]reported that the percentage of SMPP between 2015 to 2016 in North China was 35%, which was higher than ours, and it might be explained by different geographical and climatic factors. We retrospectively analyzed 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. 84.1% of patients were single complications, and 49.1% of patients were single pleural effusion, indicating a high occurrence of pleural effusion as pulmonary complication in SMPP. Differences were found in clinical indicators between SMPP patients with or without pulmonary complications.No intrapulmonary complications patients were mostly preschool children, while and the age of intrapulmonary complications group are mostly over 6 years old. In the pulmonary complication group, fever time was significantly prolonged and CRP, D-dimer, LDH levels as well as MP load in BALF were significantly higher than those without complications. Differences of these were derived from pleura effusion and necrotizing pneumonia patients,but not atelectasis patients. The clinical severity of MPP is positively correlated with MP load in respiratory tract[17]. High-load MP could cause overwhelming immune response by direct and indirect damage to the host, causing the release of various enzymes, complements and biologically active substances to increase pleural capillary permeability resulting in formation of pleural effusion. In vitro and in vivo studies [18,19]have found that MP could causes extensive damage to airway and alveolar epithelial cells by pathogenic factor MPN 372, and MPN372 was capable of stimulating tumor necrosis factor-alpha production by macrophages[20], which might be involved in lung parenchymal necrosis. The formation of atelectasis is courses of lung collapse caused by airway obstruction,and MPP-associated atelectasis was resulted from mucus plug formation in local airway[5], indicating the inflammation of forming mucus plug might be mild compared with that contributing pleural effusion and lung necrosis. SMPP patients with atelectasis tend to be school-age children which was the only difference with those of extensive lung lesion. Therefore awareness should be improved in SMPP patients of this age to develop atelectasis by mucus plug formation.

LDH is widely distributed in various tissues of the body, including lung tissue, and serum LDH levels have long been used for diagnosis and management of pulmonary infectious diseases as well as outcome prediction[21,22]. Researches of LDH application had demonstrated its role in RMPP. For example, Lu A et al [8]reported that LDH could be used as a biomarker to predict RMPP at the early stage of hospitalization with a cut-off value of 379 IU/L, and Inamura N et al[12]. reported that the LDH level which was more than 410 IU/L seemed to be an appropriate criterion for the initiation of steroid therapy and to be a useful marker for the evaluation of therapeutic efficacy in RMPP. Although Tomohiro Oishi et al [23]found that LDH could be used as an indirect indicator for evaluating MPP conditions because of its positive correlation with IL−18 level, the degree of correlation between IL−18 and LDH was not very strong,

suggesting an limited indicating value of single LDH. Serum LDH combined with ferritin might be useful as indicators for the severity of pediatric MPP by both positive correlations between the levels of serum IL–18 [24]. Severity of MPP in the study was defined as hypoxia, dyspnea, extent of pleural effusion and lung lesion in chest radiographic image, and patients with intrapulmonary complications of atelectasis or pulmonary necrosis were excluded. Our study found that patients SMPP patients had an average fever time of ten days and two weeks were observed in patients with pleural effusion and lung necrosis. State of high-stress consumption accompanied by less food intake and poor appetite during the course contributed to negative nitrogen balance and proteinemia. In addition to reflecting nutrition of the patient, serum albumin levels also reflect systemic inflammatory response[25,26]. High LDH level and low albumin level was observed in SMPP patients with intrapulmonary complications. LAR was increased in pleural effusion and lung necrosis group and found to be one of the independent risk factors for moderate-large pleural effusion occurrence, and LAR represents tissue damage, nutritional status and systemic inflammatory response, which will help clinicians to fully assess development of complication in SMPP. Coagulation abnormalities were common and persistent in CAP patients, especially D-dimer[27], D-dimer was significantly increased in the pleural effusion and lung necrosis group and was an independent risk factor for pleural effusion and lung necrosis, indicating that the 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 the possibility of pulmonary thrombosis and lower venous thrombosis.Through literature retrieval between 2009 and 2015, three children of MPP were reported with pulmonary embolism or lower extremity venous thrombosis, and two patients had moderate pleural effusion and D-dimer levels fluctuated between 6.8–55.8mg /L[28–30]. Asthmatic patients might have a different response after MP infection supported by studies [31] that IL–18 response was significantly decreased in the asthmatic SMPP group compared to the non-severe group. Another study [32] showed that asthma patients were prone to suffering RMPP, indicating the immune status of asthma patients might have different pattern in course of MPP. Since our study excludes asthma patients, further studies will be needed to explore the indicators of SMPP with pulmonary complications in asthmatic children.

The study found that chest radiographic resolution of 90.3% RMPP patients occurred in 12 weeks[11]. Our study showed that 86.6% of patients without intrapulmonary complications had imaging resolution at 4 weeks, and 72.7% of patients with intrapulmonary complications had radiographic resolution imaging at 12 weeks, and high level LDH in patients without complication might indicate delayed resolution, consist with the study by Huang L et al[11]. D-dimer also involved in the severity and prognosis of CAP[33,34], we found that high level of D-dimer was an independent risk factor for delayed resolution in patients with intrapulmonary complications, and the benefits of early use of anticoagulant therapy need to be evaluated. The bronchoscopic secretion scoring system was first used to quantify the extent of airway secretions to identify wet cough[35]. Moderate to large airway secretion evaluated by this system was found in 73.1% patients, suggesting invading pathway of MP infection in our SMPP patients was through respirator tract not blood stream pathogen. No significant correlation between BSS and presence of intrapulmonary complications, but patients of complications and lower BS grade had a

tendency of delayed resolution. We speculated that mycoplasma might make damage from distal alveolar cell to proximal airways. One pleural effusion patient was observed to have minimal airway secretion in course of 2 weeks,and mucus plug in course of 6 weeks and found bronchi obliterans in lobe bronchus in the 8th week, suggesting the local inflammatory response may be gradually progressed from alveolar to conducting airway. Intervention of bronchoscopy might be beneficial for discharged patients with delayed resolution, especially with pulmonary complication in acute phase of MPP.

The advantage of this study is that LDH,D-dimer level and LAR can be easily detected and calculated for quick evaluation of disease severity and prognosis combined with clinical manifestations. There are some limitations in this study. First, it is a retrospective study, and we have a relative high loss of follow-up data after patients discharge. 32.3% subjects didn't come to us for follow-up chest radiographic examination or bronchoscopy once and 22.2% complication subjects whose chest radiographic image was not resolved less than 12 weeks didn't come for follow-up chest radiographic examination after that time. Second, macrolide-resistant MP was not detected. Mucus blocking more than 1/3 area of the lumen was found in affected segment bronchus by follow-up bronchoscopy test in 4/10 patients with delayed clearance of chest radiographic image, and in this case, macrolide-resistant MP besides secondary bacterial infection should be considered to contribute to mucus hypersecretion.

Conclusions

The clinical phenotype of SMPP differs with age, longer fever duration, higher CRP, LDH, D-dimer LAR, and longer time of radiographic resolution observed in pulmonary complication patients. LAR and D-dimer might be useful to predict pleural effusion in SMPP patients, D-dimer also might be an indicator for lung necrosis and delayed radiographic resolution in SMPP patients with intrapulmonary complications. Further studies are required into distribution of macrolide-resistant MP in pulmonary complications and influence to the chest radiographic resolution.

Declarations

*Ethics approval and consent to participate

- Full name of the ethics committee (and the institute to which it belongs to):

Institutional Review Board, Children's Hospital of Chongqing Medical University. The reference number of approval ethics will be informed by the committee in late September or early October 2019.

- Ethics approval and consent for participate statement

This is a retrospective study, all the data used are from medical records, and there is no process of study participant recruitment which is declared in document of ethics approval.

*Consent for publication

Not Applicable

*Availability of data and material

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

*Competing interests

All the authors of this paper declare that they have no competing financial or non-financial interests.

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*Authors' contributions

All authors read and approved the final manuscript. XHX had primary responsibility for the study concept, data analysis and writing the manuscript. XQL participated in preliminary data collection, data analysis, and writing the manuscript. CJW contributed to data collection and data analysis. LZ participated in data collection. JL, ZXL and EML contributed to interpretation of the data.

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Not Applicable

References

1. Gao LW, Yin J, Hu YH, Liu XY, Feng XL, He JX, Liu J, Guo Y, Xu BP, Shen KL.**The epidemiology of paediatric Mycoplasma pneumoniae pneumonia in North China: 2006 to 2016**. *Epidemiol Infect.* 2019,147:e192.
2. Kim JW, Seo HK, Yoo EG, Park SJ, Yoon SH, Jung HY. **Mycoplasa pneumoniae pneumonia in Korean children, from 1979 to 2006: a meta analysis.** *Korean J Pediatr* 2009, 52:315-323.
3. 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.
4. Chengsong Zhao, Jinrong Liu, Haiming Yang, Li Xiang, Shunying Zhao. **Mycoplasma pneumoniae–Associated Bronchiolitis Obliterans Following Acute Bronchiolitis.** *Sci Rep* 2017, 7: 8478.
5. Panigada S, Ullmann N, Gardella C, Ferrari C, Sacco O, Rossi GA. **Bilobar atelectasis as clinical presentation of Mycoplasma pneumoniae infection**.*Pediatr Int* 2011, 53:1100-1101.
6. 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.

7. Wang M, Wang Y, Yan Y, Zhu C, Huang L, Shao X, Xu J, Zhu H, Sun X, Ji W, Chen Z.**Clinical and laboratory profiles of refractory Mycoplasma pneumoniae pneumonia in children.***Int J Infect Dis* 2014,29:18-23.
8. Lu A, Wang C, Zhang X, Wang L, Qian L. **Lactate Dehydrogenase as a Biomarker for Prediction of Refractory Mycoplasma pneumoniae Pneumonia in Children.** Respir Care 2015, 60:1469-1475.
9. Guo H, He Z, Li M, Wang T, Zhang L.**Imbalance of peripheral blood Th17 and Treg responses in children with refractory Mycoplasma pneumoniae pneumonia.**J Infect Chemother 2016,22:162-166.
10. Zhang Y, Chen Y, Chen Z, Zhou Y, Sheng Y, Xu D, Wang Y. **Effects of bronchoalveolar lavage on refractory Mycoplasma pneumoniae pneumonia.***Respir Care* 2014, 59:1433-1439.
11. 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.
12. Inamura N, Miyashita N, Hasegawa S, Kato A, Fukuda Y, Saitoh A, Kondo E, Teranishi H, Wakabayashi T, Akaike H, Tanaka T, Ogita S, Nakano T, Terada K, Ouchi K.**Management of refractory Mycoplasma pneumoniae pneumonia: utility of measuring serum lactate dehydrogenase level.** *J Infect Chemother* 2014, 20:270-273.
13. Al Yazidi LS, Hameed H, Kesson A, Herath A, Pandit C, Britton P. **A 6-year-old girl with severe, focal Mycoplasma pneumoniae pneumonia.***J Paediatr Child Health* 2019, 55:107-109.
14. Yan C, Xue G, Zhao H, Feng Y, Li S, Cui J, Ni S, Sun H. **Molecular and clinical characteristics of severe Mycoplasma pneumoniae pneumonia in children.** Pediatr Pulmonol 2019,54:1012-1021.
15. 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.
16. Chang AB, Faoagali J, Cox NC, Marchant JM, Dean B, Petsky HL, Masters IB.**A bronchoscopic scoring system for airway secretions–airway cellularity and microbiological validation.** *Pediatr Pulmonol* 2006, 41:887-892.
17. Nilsson AC, Björkman P, Welinder-Olsson C, Widell A, Persson K.**Clinical severity of Mycoplasma pneumoniae (MP) infection is associated with bacterial load in oropharyngeal secretions but not with MP genotype.***BMC Infect Dis*, 2010, 10:39.
18. Kannan TR, Baseman JB.**ADP-ribosylating and vacuolating cytotoxin of Mycoplasma pneumoniae represents unique virulence determinant among bacterial pathogens.***Proc Natl Acad Sci U S A* 2006,103:6724-6729.
19. Kannan TR, Coalson JJ, Cagle M, Musatovova O, Hardy RD, Baseman JB. **Synthesis and distribution of CARDS toxin during Mycoplasma pneumoniae infection in a murine model.***J Infect Dis* 2011, 204:1596-1604.
20. Li G, Fan L, Wang Y, Huang L, Wang M, Zhu C, Hao C, Ji W, Liang H, Yan Y, Chen Z.**High co-expression of TNF-α and CARDS toxin is a good predictor for refractory Mycoplasma pneumoniae pneumonia.**

Mol Med 2019,25:38.

21. Esteves F, Lee CH, de Sousa B, Badura R, Seringa M, Fernandes C, Gaspar JF, Antunes F, Matos O.**(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.
22. Vogel M, Weissgerber P, Goeppert B, Hetzel J, Vatlach M, Claussen C, Horger M.**Accuracy of serum LDH elevation for the diagnosis of Pneumocystis jiroveci pneumonia.***Swiss Med Wkly* 2011,141:w13184.
23. Oishi T, Narita M, Matsui K, Shirai T, Matsuo M, Negishi J, Kaneko T, Tsukano S, Taguchi T, Uchiyama M. **Clinical implications of interleukin-18 levels in pediatric patients with Mycoplasma pneumoniae pneumonia.** *J Infect Chemother* 2011,17:803-806.
24. Kawamata R, Yokoyama K, Sato M, Goto M, Nozaki Y, Takagi T, Kumagai H, Yamagata T.**Utility of serum ferritin and lactate dehydrogenase as surrogate markers for steroid therapy for Mycoplasma pneumoniae pneumonia.***J Infect Chemother* 2015, 21:783-789.
25. Kinoshita A, Onoda H, Imai N, Iwaku A, Oishi M, Tanaka K, Fushiya N, Koike K, Nishino H, Matsushima M.**The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score, predicts outcomes in patients with hepatocellular carcinoma.** *Ann Surg Oncol* 2015,22:803-810.
26. Kuo HC, Liang CD, Wang CL, Yu HR, Hwang KP, Yang KD.**Serum albumin level predicts initial intravenous immunoglobulin treatment failure in Kawasaki disease.** *Acta Paediatr* 2010,99:1578-1583.
27. Milbrandt EB, Reade MC, Lee M, Shook SL, Angus DC, Kong L, Carter M, Yealy DM, Kellum JA; GenIMS Investigators. **Prevalence and significance of coagulation abnormalities in community-acquired pneumonia.***Mol Med* 2009,15(11-12):438-445.
28. Graw-Panzer KD, Verma S, Rao S, Miller ST, Lee H J. **Venous thrombosis and pulmonary embolism in a child with pneumonia due to Mycoplasma pneumoniae.** *Natl Med Assoc.* 2009,101:956-958.
29. 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.
30. 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.
31. 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(2):218-221.
32. Shin JE, Cheon BR, Shim JW, Kim DS, Jung HL, Park MS, Shim JY. **Increased risk of refractory Mycoplasma pneumoniae pneumonia in children with atopic sensitization and asthma.***Korean J Pediatr* 2014,57:271-277.
33. 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.
34. Querol-Ribelles JM, Tenias JM, Grau E, Querol-Borras JM, Climent JL, Gomez E, Martinez I.**Plasma d-dimer levels correlate with outcomes in patients with community-acquired pneumonia.***Chest*

2004,126:1087-1092.

35. Chang AB, 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.

Tables

Table 1.Descriptive analysis of demographic, laboratory and radiographic findings of subjects.

Variables	
Age in years, mean±SEM	6.16 ± 0.33
Cases with pulmonary complication, n(%)	63 (67.7)
Cases with single pulmonary complication, n(%)	53 (56.9)
Cases with pleural effusion, n (%)	36 (38.7)
Cases with lobe atelectasis, n (%)	25 (26.8)
Cases with necrotizing pneumonia, n (%)	12 (12.9)
Case of MP load $\geq 10^6$ copies/ml in NPA, n(%)	73 (78.4)
Case underwent bronchoscopy	86 (92.3)
Case of MP load $\geq 10^6$ copies/ml in BALF, n(%)	58/86 (67.4)
Use of corticosteroid therapy, n(%)	9 (9.7)
Case of complete/near complete radiographic resolution, n(%)	37/63 (58.7)

Table2. 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 ± 0.30	5.07 ± 0.44	0.0011
Total fever duration in days	11.46 ± 0.61	6.50 ± 0.82	<0.0001
% Neutrophils in blood	76.69 ± 1.66	63.73 ± 3.01	<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 $\geq 10^6$ copies/ml in BALF, n(%)	47/63 (74.6)	11/23 (47.8)	0.037

Table3. Laboratory findings in SMPP patients with different pulmonary complication.

Variables	Lobe atelectasis (n=19)	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	*<.0001 **0.204
CRP,mg/L	30.05 ± 5.38	61.58 ± 8.36	55.25 ± 12.92	*0.0057 **0.041
D-dimer, mg/L	2.034 ± 0.40	8.286 ± 1.09	8.569 ± 1.64	*<0.001 **<0.0001
LDH IU/L	435.4 ± 42.01	725.70 ± 62.04	602.8 ± 122.0	*=0.0002 **=0.1933
Albumin g/L	39.63 ± 1.257	29.50 ± 1.026	30.88 ± 1.747	*<0.0001 **=0.0006
LDH to albumin ratio, IU/g	11.40 ± 1.25	26.20 ± 2.97	21.54 ± 6.13	*<0.001 **<0.0001
Case of MP load ≥10^6 copies/ml in BALF, n(%)	9/19 (47.3)	21/26 (80.7)	6/8(75.0)	*=0.0426 **=0.2357

*：cases of lobe atelectasis vs cases of pleural effusion

**: cases of lobe atelectasis vs cases of necrotizing pneumonia

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

Period (Weeks)	Severe MPP Patients	Patients with pulmonary complication n(%)
4	21	8 (38.1)
8	9	7 (77.7)
≥12	7	7 (100.0)

Abbreviations

BALF:bronchoalveolar lavage fluid;CAP:community acquired pneumonia;CRP: C-reactive protein;

LDH:lactic dehydrogenase ; LAR:lactic dehydrogenase to albumin ratio; MP: *mycoplasma pneumoniae*; MPP: *mycoplasma pneumoniae* pneumonia; NPA:nasopharyngeal aspiration; PCT:procalcitonin; RMPP:refractory *mycoplasma pneumoniae* pneumonia; SMPP: severe *mycoplasma pneumoniae* pneumonia.