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CLINICAL RESEARCH ARTICLE

The role of flexible bronchoscopy in children with *Mycoplasma pneumoniae* pneumonia

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PURPOSE: To explore the effectiveness of flexible bronchoscopy in pediatric *Mycoplasma pneumoniae* pneumonia (MPP).
METHODS: This retrospective cohort study included children with MPP admitted between 2016 and 2019 in Shanghai. Tracheobronchial manifestations, etiologic findings, therapeutic effect, and health-economic indicators were assessed in bronchoscopy (plus bronchoalveolar lavage (BAL)) and non-bronchoscopy group. We used propensity-score matching and multivariable logistic regression to investigate the effect of bronchoscopy and BAL on disease recovery.
RESULTS: In 900 children with MPP, 24/278 (8.6%) of those who underwent bronchoscopy had sputum plugs. Coinfection rate was four-fold enhanced by BAL (19.6% vs. 4.5%, $p < 0.01$) in patients with severe MPP (SMPP) and nearly doubled (10.8% vs. 5.9%, $p = 0.03$) in those without SMPP, compared with no BAL. Total of 224 (24.9%) patients had multilobar consolidation; after BAL, a significantly shorter lesion-resolution duration was observed on imaging (OR: 0.2, 95% CI: 0.0−0.7). However, longer fever duration (OR: 2.8, 95% CI: 1.7−4.8), hospital stay (OR: 3.1, 95% CI: 1.9−5.1), and higher costs were found in the bronchoscopy group than in the non-bronchoscopy group.
CONCLUSIONS: Through BAL, coinfection may explain one-fifth of causes for SMPP. Bronchoscopy with BAL may increase the detection rate of pathogen and resolve pulmonary lesions in patients with multilobar consolidation.

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IMPACT:

- Flexible bronchoscopy with bronchoalveolar lavage is of great assistance in the timely detection of coinfection, sputum plug and inflammatory polyps in children with *Mycoplasma pneumoniae* pneumonia (MPP), and improves the recovery of lung damage in MPP patients with multilobar consolidation.
- This study provides new insights into the indications of flexible bronchoscopy for the diagnosis and treatment of pediatric patients with MPP.

INTRODUCTION

Mycoplasma pneumoniae is the leading cause of community-acquired pneumonia (CAP) in school-aged children and young adults.[1,2] Approximately a quarter of patients with *M. pneumoniae* pneumonia (MPP) experience prolonged fever, worsening of clinical symptoms, and deteriorating radiological findings, despite appropriate macrolide therapy for 7 days or longer.[3,4] Some even develop severe CAP or extrapulmonary manifestations, including pleural effusion, multilobar infiltrates, hypoxia,[5] hemolysis, mucocutaneous disease, and central nervous system manifestations.[6,7] Pathological studies focusing on severe *M. pneumoniae* pneumonia (SMPP) have been quite limited due to the rarely obtained specimens; subsequently, speculations continue on why a case of pneumonia progress to severe or critical stage. The presence of a resistant *M. pneumoniae* strain has been suggested as an important factor[8]; however, recent research has revealed that macrolide-resistant *M. pneumoniae* is not associated with the infection's clinical severity, including radiographic findings, hospitalization rates, viral coinfections, mean duration for antimicrobial treatment, and clinical outcomes.[9] Moreover, the proportion of MPP hospitalization requiring intensive care has no corresponding increase as macrolide resistance increases.[10]

Coinfections may also account for certain clinical manifestations attributed to SMPP; the emerging revolutionary technology is being intensively applied to pathogen identification. In young children with *M. pneumoniae* infections, the codetection rate of viruses by reverse transcription-polymerase chain reaction in the nasopharyngeal aspirate is as high as 30%.[11] Due to the small

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fraction of high-quality sputum samples obtained from infected children, the coinfection rate of other bacteria with *M. pneumoniae* in lower respiratory tract remains under-investigated. Recent evidence supports the feasibility and safety of performing diagnostic flexible bronchoscopy (bronchoscopy) when it is difficult to collect sputum.[12] Performing bronchoscopy would increase the sensitivity of bacterial detection in patients with SMPP through examination of bronchoalveolar lavage fluid (BALF), over that of blood and sputum, and also more clearly reveal pathological damage. In children with MPP, mucus accumulation in the airways and bronchial cast formation have been frequently observed[13]; however, studies specifically addressing these issues are lacking. In this study, we examined the effect of bronchoscopy on 900 hospitalized patients with MPP over a period of 3 years.

MATERIALS AND METHODS

Patients and study design

This was a cohort study of patients with MPP admitted to Xinhua Hospital, affiliated to Shanghai Jiao Tong University School of Medicine between February 2016 and July 2019. MPP was diagnosed based on the following conditions: (i) fever, cough, or auscultatory findings and a pulmonary infiltrate visible on chest imaging; and (ii) *M. pneumoniae* DNA detected in nasopharyngeal secretions by polymerase chain reaction (PCR), or ≥4-fold changes in *M. pneumoniae* IgM and IgG antibody titer between paired acute and convalescent sera, according to the Infectious Diseases Society of America guidelines of 2018.[14,15] Patients with congenital heart diseases, motor developmental delay, and immunodeficiency were excluded. Informed consent was waived as the data were analyzed anonymously.

For every patient, blood samples were obtained for bacterial culture; respiratory syncytial virus, influenza A and B viruses, parainfluenza viruses, adenoviruses, *Legionella pneumophila*, *Coxiella burnetii*, *Chlamydia pneumoniae*, and *M. pneumoniae* serology for IgG and IgM antibodies was measured. Nasopharyngeal secretion samples were obtained for the detection of *C. pneumoniae and M. pneumoniae* using PCR. Conventional procedures for BALF microbiologic testing were performed in patients who underwent bronchoscopy, including cultures for bacteria, mycobacteria, and fungi.[16] During this time, additional samples were sent to Huada Laboratories (Shenzhen, China) for next-generation sequencing (NGS), including sample processing and DNA extraction, construction of DNA libraries and sequencing, and bioinformatic analysis.[17] Additional data are given in supplement material.

Bronchoalveolar lavage under bronchoscopy

After fasting for >6 h, patients were sedated with intravenous midazolam (0.1–0.2 mg/kg), and topical anesthesia with 1% lidocaine was applied to the nose, vocal cords, and trachea. Three types of flexible bronchoscopes were used; Olympus BFXP40, BF-3C30, and BF-P40 (Olympus Optical, Tokyo, Japan), depending on the patient's age and body weight. The bronchoscope was wedged in the subsegmental bronchus of the most affected lobe seen on the chest radiograph. BAL with normal saline (weight < 20 kg: 1 mL/kg/time, 3 times; weight >20 kg: 20 mL/time, 3 times) was performed with −25 to −100 mmHg (1 mmHg = 0.133 kPa) suction, as per the Official American Thoracic Society Technical Standards.[18] We also collected BALF samples for microbiological determinations. All manipulations were performed under sterile conditions. During the procedure, heart rate, respiratory rate, and saturation of pulse oxygen (SpO_2) were monitored continuously. In case of occurrence of hypoxia, oxygen of appropriate concentration was administered immediately, and the procedure was stopped when necessary. The indications for bronchoscopy in our hospital included patients with recurrent/persistent atelectasis, recurrent pneumonia, poor response to standard anti-MP therapy treatment, suspected coinfection and severe conditions such as consolidation that requires rinsing and draining of infection.[3,18–22]

Data collection

We collected patient demographics (age, sex, weight, and parents' income), clinical data (fever duration before admission, hypoxemia, neurological symptoms and signs (convulsion, seizures, lethargy, and abnormal reflex), and encephalitis), imaging features (atelectasis, pleural effusion, and lobar consolidation based on chest radiographs or low-dose computed tomography (CT) scans), and laboratory test results (interleukin (IL)-1, IL-2 receptor (IL-2R), IL-6, IL-8, IL-10, lactate dehydrogenase (LDH), C-reactive protein (CRP), partial pressure of CO_2, white blood cell count, platelet count, total bilirubin, and creatinine) from medical histories. Low-dose CT was performed on a 64-detector row CT (Brilliance iCT, Philips) with 80–100 kV and 20–50 mA. The data were missing for IL ($n = 253$) and LDH ($n = 125$). Hypoxemia was defined as any recorded oxygen saturation <92% based on room-air pulse oximetry.[23] The body temperature was monitored every day, and fever was defined as a body temperature exceeding 37.5 °C (99.5 °F). Routine blood and CRP examination were examined at admission and followed-up every 2−3 days until discharge. The data from the chest radiographs and CT scans during hospitalization were retrospectively collected.

After discharge, the patients were followed-up at 2 weeks, 1 month, and 3 months until a physician from the Infectious Diseases or Respiratory Department confirmed the resolution of pulmonary lesions on imaging. A re-examination of low-dose CT scan was considered in patients with pulmonary consolidation, atelectasis, pleural effusion and multiple lobes infiltration.

Each patient's medical history was re-evaluated by a group of pediatricians, radiologists, and infection specialists. Severe pneumonia was assessed according to the guidelines by the Paediatric Infectious Diseases Society and Infectious Diseases Society of America on the management of CAP in infants and children older than 3 months.[24] Refractory pneumonia was defined as prolonged fever, worsening of clinical symptoms, emergence of extrapulmonary complications, and deteriorating radiological findings, despite administration of appropriate macrolide therapy ≥7 days.[3]

Statistical analysis

All patients were classified into either the SMPP or the non-SMPP group, according to disease severity. Data are expressed as the median (25th −75th percentiles) and number (percentage) as appropriate. We used parametric (two-tailed *t* test) and nonparametric (Mann−Whitney *U* test) analyses for continuous data, as appropriate, and chi-squared (χ^2) tests for categorical data to compare the two groups. First, patient characteristics between both groups were compared using descriptive statistics. Next, we summarized the bronchoscopic findings in the patients with and without SMPP. We subsequently analyzed the pathogen distribution in all patients. Finally, we assessed the effectiveness and cost of bronchoscopy in the patients with MPP using logistic regression analyses. Odds ratios (OR) were calculated for fever duration after admission, length of hospital stay, time to recovery of CRP, and resolution of pulmonary lesions on imaging, which represent the process of clinical improvement. The 75th-percentile value was used as the cut-off to calculate each OR.

To address indication bias, we applied 1:1 propensity-score matching according to age, income, fever duration before admission, duration of azithromycin therapy before admission, severe pneumonia, white blood cell count, and LDH, as these variables showed statistically significant differences between the bronchoscopy and non-bronchoscopy groups (excluding income, white blood cell count, LDH, and fever duration before admission). We also stratified the data by SMPP, lobar consolidation, and atelectasis to evaluate whether the effect was modified with the severity. Regarding confounding, we examined the collinearity of the variables in the model and discovered a strong collinearity between the following pairs of variables: IL-6 and IL-8, LDH and IL-2R, and LDH and IL-10. Finally, we adjusted the model for age, income, white blood count, LDH, fever duration before admission, and duration of azithromycin therapy before admission.

Statistical analyses were conducted using R (https://www.R-project.org, R foundation for Statistical Computing, Vienna, Austria). A two-tailed *p* value ≤0.05 was considered statistically significant.

RESULTS

Among the 5112 children hospitalized due to CAP in our institution, 917 were diagnosed with MPP. Finally, the data of 900 patients with MPP were included for the analysis (Fig. 1). Most patients were pre-school and school-aged children (Table 1). A total of 224 (24.9%) patients had multilobar consolidation and 85 (9.4%) had atelectasis. The patients with SMPP were older, and with a higher rate of hypoxemia, neurological symptoms and signs, encephalitis, refractory pneumonia, atelectasis, pleural effusion and multilobar consolidation. Inflammation biomarkers

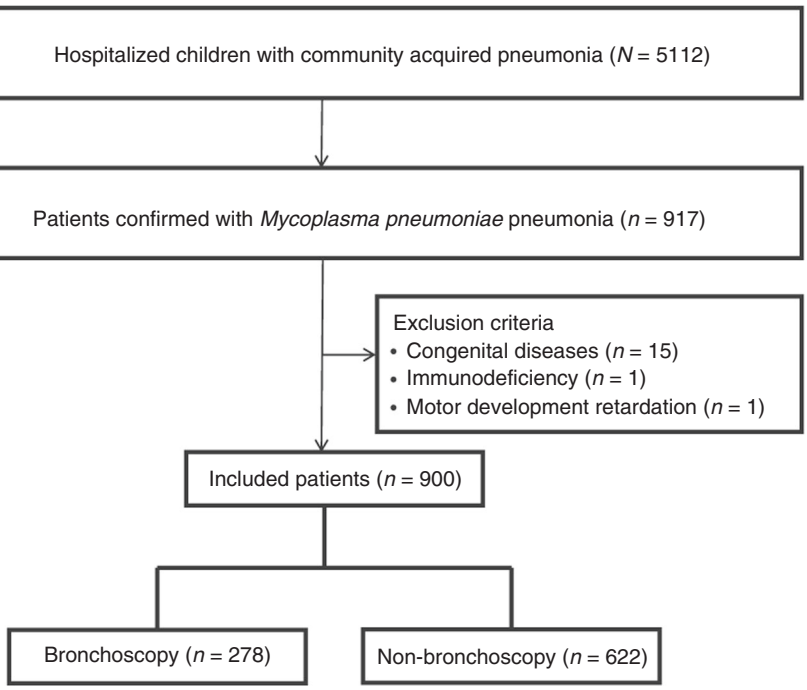

Fig. 1 Flowchart of study participants.

such as IL-2 R, LDH, and CRP were significantly higher in patients with SMPP than those without SMPP. There were only seven intensive care unit admissions and no deaths.

There were 278 (30.9%) underwent bronchoscopy. Complications were quite mild, only one patient experienced decreased oxygen saturation ($SpO_2 < 85\%$), which resolved quickly upon ventilation with a bag-valve mask. No one had severe complications, such as pneumothorax, pulmonary hemorrhaging, or respiratory failure occurred during the procedure. A total of four (1.4%) patients had polyps and 24 (8.6%) had sputum plugs (Fig. 2). Notably, the proportion of patients with sputum plug was higher in the SMPP group than in the non-SMPP group (10.9% vs. 7.5%) although without significance.

Besides mycoplasma, other pathogens were detected in 74 (8.2%) of 900 patients. Viruses were the most frequent etiology (7.1%, 64/900), followed by bacteria (1.1%, 10/900) and fungi (0.1%, 1/900) (Table 2). Two viral coinfections in addition to *M. pneumoniae* were identified in three cases; one patient had fungi and virus coinfection. The overall rate of coinfection in the SMPP group (13.3%) was higher than that in the non-SMPP group (7.1%). Viruses and bacteria were more prevalent in the patients with SMPP; in particular, the detection rate of bacteria in the SMPP group was three times higher than that in the non-SMPP group (2.5% vs. 0.8%, $p = 0.06$). More coinfections were observed in the bronchoscopy group than in the non-bronchoscopy group, among the patients with SMPP (19.6% vs. 4.5%; $p < 0.01$) and without SMPP (10.8% vs. 5.9%; $p = 0.03$). In patients with SMPP, bacterial coinfection was only detected in those who underwent bronchoscopy. The rate of viral codetection in the SMPP bronchoscopy group was almost four times higher than that in the SMPP non-bronchoscopy group (15.2% vs. 4.5%, $p = 0.03$). Compared with patients without coinfections, those with coinfections were more likely to experience severe clinical symptoms (hypoxemia, 1.6% vs. 5.4%; severe pneumonia, 16.6% vs. 28.4%; refractory pneumonia, 28.1% vs. 52.7%, and multilobar consolidation, 23.6% vs. 39.2%) (Appendix Table 1). Patients with coinfections had a longer total fever duration and length of hospital stay than those without coinfections (median total fever duration: 9.5 [6.0−14.0] vs. 8.0 [6.0−10.0] days, $p < 0.01$; mean length of hospital stay: 9.3 ± 7.5 vs. 7.2 ± 3.6 days, $p < 0.01$).

Before propensity-score matching, there were differences between bronchoscopy and non-bronchoscopy group in the several of baseline variables. Patients who underwent bronchoscopy were older, heavier, and often severer with a higher rate of atelectasis and multilobar consolidation. The inflammation biomarkers such as IL-1 and IL-8 are slighter higher in the patients who did not undergo bronchoscopy, compared with those who did. After attempting to control for confounding factors especially illness severity using propensity-score matching, 474 (52.7%) patients remained for the final analysis, with appropriately balanced baseline characteristics (Appendix Table 2). The mean fever duration after admission (2.5 days vs. 1.7 days), hospital stay (9.0 days vs. 6.9 days) and the time to recovery of CRP (5.3 days vs. 4.7 days) were longer in the patients who underwent bronchoscopy than in those who did not; however, the time to resolution of pulmonary lesions on imaging was shorter in the bronchoscopy group (14.0 days) than in the non-bronchoscopy group (15.8 days). Further, undergoing bronchoscopy was associated with increased odds of experiencing fever for >3 days after admission (OR: 2.8, 95% confidence interval [CI]: 1.7−4.8), and a hospital stay >9 days (OR: 3.1, 95% CI: 1.9−5.1) (Table 3). Those who underwent bronchoscopy had an earlier resolution of pulmonary lesions on imaging, although the difference was not statistically significant. Bronchoscopy was not significantly associated with the recovery of CRP (OR: 1.5, 95% CI: 0.8−2.8).

In the matched cohort, 59/108 patients with SMPP underwent bronchoscopy. Undergoing bronchoscopy was associated with increased odds of staying in hospital for >13 days among the patients with SMPP, compared with that of patients with SMPP who did not undergo bronchoscopy (OR: 2.4, 95% CI: 1.1−5.1). Similarly, among the 118 patients with multilobar consolidation in the matched cohort, undergoing bronchoscopy increased the odds of a hospital stay for >9 days (OR: 3.3, 95% CI 1.3−8.5). No statistically significant ORs were observed among the 56 patients with atelectasis in the matched cohort. Undergoing bronchoscopy did not have a significant effect on the recovery of CRP in any

Table 1. Characteristics of patients with *Mycoplasma pneumoniae* pneumonia stratified by severe *Mycoplasma pneumoniae* pneumonia (SMPP) ($n = 900$).

Variables	Total $N = 900$	Non-SMPP $N = 742$	SMPP $N = 158$	*p* value
General information				
Age, years	5.0 (3.0−7.0)	5.0 (3.0−7.0)	6.0 (4.0−7.0)	0.01
Sex, male	418 (46.4)	348 (46.9)	70 (44.3)	0.55
Weight, kg	19.4 (15.0−25.0)	19.0 (15.0−25.0)	20.5 (16.9−25.9)	0.21
Income, $, per year				0.07
≤15,000	180 (20.0)	140 (18.9)	40 (25.3)	
>15,000	720 (80.0)	602 (81.1)	118 (74.7)	
Clinical signs				
Fever duration before admission, days	6.0 (5.0−8.0)	6.0 (5.0−8.0)	7.0 (5.0−9.0)	0.05
Total fever duration, days	8.0 (6.0−10.0)	8.0 (6.0−10.0)	10.0 (7.0−13.0)	<0.01
Hypoxemia	17 (1.9)	0 (0.0)	17 (10.8)	<0.01
Neurological symptoms and signs	12 (1.3)	0 (0.0)	12 (7.6)	<0.01
Encephalitis	2 (0.2)	0 (0.0)	2 (1.3)	<0.01
Refractory pneumonia	271 (30.1)	189 (25.5)	82 (51.9)	<0.01
Atelectasis	85 (9.4)	48 (6.5)	37 (23.4)	<0.01
Pleural effusion	150 (16.7)	17 (2.3)	133 (84.2)	<0.01
Multilobar consolidation[a]	224 (24.9)	154 (20.8)	70 (44.3)	<0.01
Interleukin 1, pg/mL	2.5 (2.5–8.8)	2.5 (2.5–10.7)	2.5 (2.5–2.5)	0.03
Interleukin 2 receptor, U/mL	1009.0 (743.0–1418.0)	973.0 (725.0–1336.0)	1349.0 (932.5–1973.8)	<0.01
Interleukin 6, pg/mL	13.9 (6.1–72.1)	13.1 (5.7–94.7)	19.5 (8.3–52.8)	0.07
Interleukin 8, pg/mL	24.0 (10.3–191.0)	22.7 (10.0–246.0)	28.4 (12.5–77.8)	0.18
Interleukin 10, pg/mL	2.5 (2.5–9.6)	2.5 (2.5–8.3)	8.1 (2.5–20.7)	<0.01
Lactic dehydrogenase, U/L	343.0 (288.0–409.0)	331.0 (284.0–391.0)	421.0 (331.2–588.8)	<0.01
C-reactive protein, mg/L	11.0 (4.0−26.0)	10.0 (4.0–22.0)	17.5 (8.0–40.8)	<0.01
Partial pressure of CO_2, kpa	4.9 (4.4−5.5)	5.0 (4.5−5.5)	4.6 (4.3−5.3)	0.22
White blood cell count, 10^9/L	6.9 (5.3−9.1)	6.9 (5.4–9.1)	6.6 (4.8–9.6)	0.40
Platelet count, 10^9/L	287.0 (224.0−363.0)	290.0 (226.0−367.2)	264.5 (207.2–344.2)	0.13
Total bilirubin, μmol/L	4.9 (3.7−6.4)	4.8 (3.7–6.2)	5.3 (4.0–7.2)	<0.01
Creatinine, μmol/L	30.5 (26.0−36.0)	30.7 (26.0–36.0)	30.0 (26.0–35.0)	0.47
Duration of azithromycin therapy before admission, days	2.0 (1.0−4.0)	2.0 (1.0−4.0)	3.0 (1.0−4.0)	0.04

Sex, income, hypoxemia, neurological symptoms and signs, encephalitis, refractory pneumonia, atelectasis, pleural effusion, and multilobar consolidation are presented as *n* (%); the rest of the variables are indicated as median (25th−75th percentiles).
[a]Defined as consolidation of two or more lobes.

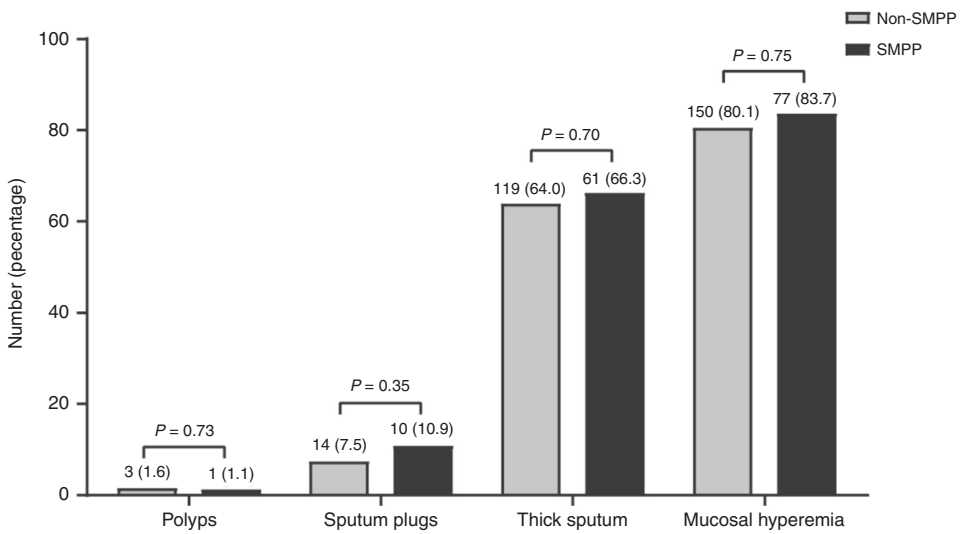

Fig. 2 The observed morphology during flexible bronchoscopy of patients with severe *Mycoplasma pneumoniae* pneumonia (SMPP) and without SMPP. *P* represents difference in rate of polyps, sputum plugs, thick sputum and mucosal hyperemia under flexible bronchoscopy between non-SMPP and SMPP patients.

Table 2. Distribution of pathogens detected in the non-bronchoscopy and bronchoscopy groups of patients with *Mycoplasma pneumoniae* pneumonia stratified by severity.

Pathogen detected, *n* (%)	SMPP				Non-SMPP				
	Total *N* = 158	Non-bronchoscopy *N* = 66	Bronchoscopy *N* = 92	p^a value	Total *N* = 742	Non-bronchoscopy *N* = 556	Bronchoscopy *N* = 186	p^b value	p^c value
Total	21 (13.3)	3 (4.5)	18 (19.6)	< 0.01	53 (7.1)	33 (5.9)	20 (10.8)	0.03	0.04
Bacterial	4 (2.5)	0 (0.0)	4 (4.3)	0.09	6 (0.8)	2 (0.4)	4 (2.2)	0.02	0.30
Streptococcus pneumoniae	1 (0.6)	0 (0.0)	1 (1.1)		2 (0.3)	0 (0.0)	2 (1.1)		
Klebsiella pneumoniae	1 (0.6)	0 (0.0)	1 (1.1)		0 (0.0)	0 (0.0)	0 (0.0)		
Haemophilus influenzae	1 (0.6)	0 (0.0)	1 (1.1)		0 (0.0)	0 (0.0)	0 (0.0)		
Legionella pneumophila	1 (0.6)	0 (0.0)	1 (1.1)		1 (0.1)	1 (0.2)	0 (0.0)		
Chlamydia pneumoniae	0 (0.0)	0 (0.0)	0 (0.0)		3 (0.4)	1 (0.2)	2 (1.1)		
Viral	17 (10.8)	3 (4.5)	14 (15.2)	0.03	47 (6.3)	31 (5.6)	16 (8.6)	0.14	0.09
Adenovirus	5 (3.2)	0 (1.7)	5 (5.4)		14 (1.9)	9 (1.6)	5 (2.7)		
Respiratory syncytial virus	2 (1.3)	0 (0.0)	2 (2.2)		1 (0.1)	1 (0.2)	0 (0)		
Parainfluenza virus	6 (3.8)	2 (3.0)	4 (4.3)		8 (1.1)	4 (0.7)	4 (2.2)		
Influenzavirus A	0 (0.0)	0 (0.0)	0 (0.0)		1 (0.1)	1 (0.2)	0 (0.0)		
Influenzavirus B	6 (3.8)	2 (3.0)	4 (4.3)		23 (3.1)	16 (2.9)	7 (3.8)		
Coxsackievirus A16	0 (0.0)	0 (0.0)	0 (0.0)		1 (0.1)	1 (0.2)	0 (0.0)		
Fungal	0 (0.0)	0 (0.0)	0 (0.0)	-	1 (0.1)	0 (0.0)	1 (0.5)	0.08	0.48
Candida albicans	0 (0.0)	0 (0.0)	0 (0.0)		1 (0.1)	0 (0.0)	1 (0.5)		

Data are presented as No. (%).
SMPP severe *Mycoplasma pneumoniae* pneumonia.
P^a represents the difference in pathogens between patients who underwent bronchoscopy and who not underwent bronchoscopy in the SMPP group.
P^b represents the difference in pathogens between patients who underwent bronchoscopy and who not underwent bronchoscopy in the non-SMPP group.
P^c represents the difference in pathogens between the SMPP and non-SMPP groups who underwent bronchoscopy.

Table 3. Efficiency of bronchoscopy in total patients with *Mycoplasma pneumoniae* pneumonia and clinical complications after propensity-score matching.

Variables	Total $N = 474$	Non-bronchoscopy $N = 237$	Bronchoscopy $N = 237$	OR[a] (95% CI)
Fever duration > 75th (3 days)	98 (28.5)	29 (17.7)	69 (38.3)	2.8 (1.7−4.8)
Length of stay > 75th (9 days)	104 (21.9)	30 (12.7)	74 (31.2)	3.1 (1.9−5.1)
Time to the resolution of pulmonary lesions on imaging > 75th (19 days)	70 (24.0)	34 (26.6)	36 (22.0)	0.7 (0.4−1.3)
Time to the recovery of CRP > 75th (6 days)	67 (27.3)	25 (23.6)	42 (30.2)	1.5 (0.8−2.8)
Patients with severe *Mycoplasma pneumoniae* pneumonia	$N = 108$	$N = 49$	$N = 59$	
Fever duration > 75th (4 days)	24 (26.7)	8 (21.1)	16 (30.8)	1.5 (0.5−4.3)
Length of stay > 75th (13 days)	23 (21.3)	8 (16.3)	15 (25.4)	2.4 (1.1−5.1)
Time to the resolution of pulmonary lesions on imaging > 75th (18 days)	17 (27.0)	9 (25.7)	8 (19.0)	0.7 (0.4−1.1)
Time to the recovery of CRP > 75th (7 days)	17 (27.0)	6 (24.0)	11 (28.9)	1.8 (0.9−3.6)
Patients with multilobar consolidation	$N = 118$	$N = 50$	$N = 68$	
Fever duration > 75th (4 days)	37 (38.9)	9 (23.1)	28 (50.0)	1.7 (0.5−5.7)
Length of stay > 75th (9 days)	33 (28.0)	8 (16.0)	25 (36.8)	3.3 (1.3−8.5)
Time to the resolution of pulmonary lesions on imaging > 75th (19 days)	19 (25.7)	10 (41.7)	9 (18.0)	0.2 (0.0−0.7)
Time to the recovery of CRP > 75th (6 days)	23 (31.1)	9 (32.1)	14 (30.4)	1.0 (0.3−3.3)
Patients with atelectasis	$N = 56$	$N = 15$	$N = 41$	
Fever duration > 75th (4 days)	12 (26.7)	2 (20.0)	10 (28.6)	4.6 (0.2−90.1)
Length of stay > 75th (11 days)	15 (26.8)	3 (20.0)	12 (29.3)	1.4 (0.2−9.1)
Time to the resolution of pulmonary lesions on imaging > 75th (20 days)	12 (28.6)	4 (40.0)	8 (25.0)	0.5 (0.1−3.2)
Time to the recovery of CRP > 75th (8 days)	8 (26.7)	2 (28.6)	6 (26.1)	0.6 (0.0−8.6)

Data are presented as No. (%). All OR calculations were made using ≤75th-percentile value data as a reference.
OR odds ratio, *CI* confidence interval, *CRP* C-reactive protein.
[a]Adjusted for age, parents' income, white blood count, lactic dehydrogenase, fever duration before admission, and duration of azithromycin therapy before admission.

subgroup. Notably, the time to resolution of pulmonary lesions on imaging was shorter in the bronchoscopy group than in the non-bronchoscopy group, in both the total matched cohort and in each of the three subgroups; although this difference was only statistically significant in patients with multilobar consolidation (OR for >19 days recovery time: 0.2, 95% CI: 0.0−0.7, $p < 0.05$). However, all patients eventually had complete resolution of pulmonary lesions, including patients in whom polyps were observed during bronchoscopy.

Table 4 summarizes the per capita medical costs of the bronchoscopy and non-bronchoscopy groups before and after propensity-score matching. The overall cost of healthcare per patient with MPP was $1335.1; the median cost of hospital charges for patients who underwent bronchoscopy was 66% higher than that for patients who did not undergo bronchoscopy ($1850.3 vs. $1114.1; $p < 0.01$). The direct operating costs increased by $137.3 due to the bronchoscopy procedure in the matched cohort. The patients who underwent bronchoscopy also incurred higher costs related to laboratory tests, imaging, and medication due to preoperative preparation, anesthesia, and post-surgical recovery (all $p < 0.01$ after propensity-score matching).

DISCUSSION

In this large-scale clinical study of MPP in China, bronchoscopy was observed to be of great assistance in the timely detection of inflammatory polyps and coinfection. Bronchoscopy was capable of improving the detection rate of coinfection greatly, especially in the patients with SMPP, which contributed significantly to the definitive diagnosis and the cause of intractable condition. Regardless of whether the MPP is severe or not, BAL may improve the recovery from inflammatory multilobar consolidation; however, it does not help decrease the overall inflammatory reaction, and may even prolong fever duration and hospital stay. As such, bronchoscopy may not be suitable for therapeutic application in patients with MPP, unless it is suspected that SMPP requires further diagnosis. This study also provides evidence for the indication of bronchoscopy in CAP.

The role of obstructing lesion such as mucus plug in SMPP remains unclear. Mucus plug formation was commonly discovered under bronchoscopy in children with MPP[13,25,26]; however, few studies have emphasized its significance for the disease. A previous study found that mucus plug was significantly more commonly seen in the patients with refractory MPP than those with general MPP, and it combined with clinical features and laboratory data could improve the early identification of refractory pneumonia.[27] In our study, the prevalence of sputum plugs in patients with SMPP was higher than in patients without SMPP, suggesting that sputum plugs may be associated with severe pneumonia. Severe bronchial inflammation and cilia abnormalities could make the airways produce extra mucus and decrease mucus clearance,[28] leading to the formation of sputum plug. What's more, we observed four cases of bronchial polyps under bronchoscopy, which are poorly recognized lesions in children with pneumonia.[29,30]

The etiologic diagnosis of CAP is known to be challenging in clinical practice. In several cases, the diagnosis is "non-resolving pneumonia", which includes cases of presumed pneumonia that progress, resolve slowly, or fail to completely resolve despite the application of what is considered appropriate therapy. In a national survey, it has been found 27.7% of American patients with MPP had one or more concurrent viral infections[9]; however, this study does not link coinfection with clinical progress. In our study, upon BALF analysis, coinfection was observed in nearly one fifth of children with SMPP, especially bacterial infection. The detection rate of mucus plug and pathogen in the bronchoscopy

Table 4. Cost comparison in individuals stratified by bronchoscopy before and after propensity-score matching.

	Before matching				After matching			
Variables	**Non-bronchoscopy $N = 622$**	**Bronchoscopy $N = 278$**	**Difference**	***p* value**	**Non-bronchoscopy $N = 237$**	**Bronchoscopy $N = 237$**	**Difference**	***p* value**
Laboratory tests, $	444.6 (320.3−689.1)	553.9 (287.9−643.6)	−109.3	0.05	487.3 (318.1−727.7)	683.9 (453.9−784.3)	−196.6	<0.01
NGS costs, $	0 (0−0)	500.0 (500.0−500.0)	−500	<0.01	0 (0−0)	500.0 (500.0−500.0)	−500	<0.01
Imaging costs, $	75.7 (44.3−109.1)	109.1 (71.4−127.8)	−33.4	<0.01	89.3 (55.7−110.1)	109.1 (65.7−122.9)	−19.8	<0.01
Medication, $	253.7 (189.8−377.8)	417.0 (312.0−568.8)	−163.3	<0.01	272.4 (214.5−409.7)	391.6 (304.3−552.1)	−119.2	<0.01
Direct operating costs, $	5.7 (4.3−20.6)	290.9 (276.0−328.8)	−285.2	<0.01	8.6 (0.0−35.0)	145.9 (132.7−175.0)	−137.3	<0.01
Hospital charges, $	1114.1 (854.3−1523.3)	1850.3 (1526.8−2222.7)	−736.2	<0.01	1393.7 (945.1−1594.4)	1826.3 (1476.5−2143.9)	432.6	<0.01

Data are presented as median (25th−75th percentile).
NGS next-generation sequencing.

and non-bronchoscopy groups may be associated with sampling, and it was not necessarily representative of the pathogens per se. However, in patients with the same severity, such as SMPP, we found that bronchoscopy significantly improved the detection rate of pathogens, with significant differences, which could address the clinical question. Thus, we inferred that coinfection may be a possible cause for SMPP, which may be overlooked as the sputum sample from the upper respiratory tract may be easily contaminated, and blood cultures/serological tests are of low specificity and sensitivity. BALF collected by bronchoscopy may be quite a suitable option for patients with pneumonia who do not respond to antibiotic treatment. Moreover, a major proportion of patients underwent bronchoscopy within 5 days of hospitalization. Thus, it is important to distinguish between initial coinfection and in-hospital infection after severe pneumonia. Furthermore, approximately 20% of presumed nonresponding CAP cases are due to non-infectious causes;[31] to the best of our knowledge, the existence of non-infectious etiologies of pulmonary infiltrates in SMPP has not been studied. Atelectasis and pleural effusion are common abnormalities in children with MPP, at rates of 29% and 16%−26%, respectively.[5,10,32] Since non-resolving pneumonia often develops as a result of poor cough or mucus plugging in the lower lobes, it may be warranted in patients with persistent atelectasis due to an unknown cause or suspected airway obstruction. Bronchoscopy is especially indicated for unresolving pneumonia complicated with atelectasis and a large area of consolidation,[18,20] as it allows direct observation of the airways and acquiring samples directly from the infected lobe.

Bronchoscopy for therapeutic purpose remains controversial in children with CAP. Although it is of some benefits, bronchoscopy poses the risk of additional trauma to the airway and other complications. There are no absolute contraindications to performing BAL in patients with CAP and this may lead to overtreatment. In some places it is recommended in the guideline of refractory pneumonia.[22] Bronchoscopy and BAL enable removal of mucous plugs or foreign bodies and may help relieve the immunological reaction by washing with warm saline.[33] In a small-sample study ($n = 46$), BAL was substantially more effective than non-BAL in improving clinical symptoms and resolution of pulmonary lesions on radiography in children with SMPP.[34] Bronchoscopy was also associated with shorter fever duration and improvement of pulmonary lesions in several studies.[34,35] However, in these studies, the sample size is often limited with insufficient statistical power, and the definition of clinical prognosis were not defined standardly. In this study, we used the bronchoscopy to exclude malignant endobronchial obstruction in patents with MPP, remove any obstructing lesion especially mucus plug and the time of resolution of pulmonary lesions shortened after BAL, however, the fever time and length of hospital stay are extended. A possible explanation for this might be that flexible bronchoscope may spread the organisms form the localized lesion to normal areas of bystander lung by BAL, which leads to new infiltration or exacerbation.[36] The longer recovery time may also be related to the mechanical damage, like alveolar flooding after BAL, postobstructive atelectasis from mucosal swelling, blood clots, or impaired mucociliary clearance caused by BAL. Furthermore, in our follow-up, the atelectasis resolved spontaneously under routine treatment without bronchoscopy, the same as those with polyps. More studies are needed in the therapeutical effect of BAL in patients with MPP.

There are several limitations to our study. First, as a retrospective single-centered study, selection bias may have been a possibility. To reduce confounding, we conducted propensity-score matching, after which the results coincided with those for the whole population. Second, the amount of BALF retrieved, the sampling conditions, and the time of transportation to the laboratory might have interfered with the positive culture rate of the samples. Thus, we strived to standardize every step of the

procedure. Third, the NGS testing in our study was supported by our research funding, which will be a concern in clinical practice for most patients. In our study, all the BALF samples were transferred to a centralized laboratory for NGS testing, which could increase transportation costs and the turnaround time. For further studies, we are committed to exploring ways to reduce costs, including steaming workflow, automating library preparation, and localization of the sequencing platform.

CONCLUSIONS

Coinfection may be an important factor for SMPP, and may explain one fifth of the cause. Bronchoscopy is a good choice to confirm the diagnosis. Randomized clinical trials are warranted to evaluate the therapeutic application in patients with SMPP.

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AUTHOR CONTRIBUTIONS

L.W. and Q.X. conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. S.X., H.L., L.Z. and J.A. collected data, carried out the initial analyses, and reviewed and revised the manuscript. Q.L., C.C., and X.Z. coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. L.H. and W.Z. designed the study and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for the content of the work.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

This study was approved by the Ethics Committee of Xinhua Hospital (XHEC-C-2018-107). This study was conducted in accordance with the Declaration of Helsinki.

ADDITIONAL INFORMATION

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