

Clinical Efficacy of Bronchoalveolar Lavage Under Fiberoptic Bronchoscopy for Refractory Mycoplasma Pneumoniae Pneumonia in Children and Its Effect on Inflammatory Cytokine Levels

Hua Jin¹, Wuqiong Zhang¹, Wei Wei¹, Zheng Wang², Jialin Liu¹, Qian Zhao¹, Fujian Ta^{1,*}

1 Pediatrics Department, Qujing Maternal and Child Health Hospital, Qujing 655000, Yunnan, China

2 Qujing Medical College of Health, Qujing 655099, Yunnan, China

*Correspondence email: 13732751009@163.com

CITATION

Hua J, Wuqiong Z, et al. Clinical Efficacy of Bronchoalveolar Lavage Under Fiberoptic Bronchoscopy for Refractory Mycoplasma Pneumoniae Pneumonia in Children and Its Effect on Inflammatory Cytokine Levels. *Psycho-Oncologie*.

ARTICLE INFO

Received: January 8th, 2026

Accepted: January 8th, 2026

Available online: January 8th, 2026

COPYRIGHT



Copyright © 2025 by author(s).

Psycho-Oncologie is published by PiscoMed Publishing Pte. Ltd. This work is licensed under the Creative Commons Attribution (CC BY) license.

<https://creativecommons.org/licenses/by/4.0/>

Abstract: Background: Refractory Mycoplasma pneumoniae pneumonia in children is still a challenge to treat after standard macrolide treatment. Bronchoalveolar lavage under fiberoptic bronchoscopy has emerged as a potential adjunctive therapy, but further study is needed regarding its impact on the inflammatory cytokine profile.

Methods: This randomized controlled trial will enroll 114 children (3-14 years old) with RMPP from January 2023 to December 2024. Patients will be assigned to receive either BAL in combination with standard therapy (BAL group, n = 57) or standard therapy alone (control group, n = 57). The primary outcome will be changes in the inflammatory cytokines IL-6, TNF- α , and IL-10 in bronchoalveolar lavage fluid (BALF) and serum. The secondary outcomes are as follows: time to fever resolution; time to cough resolution; and length of hospitalization.

Results: Compared with the control group, the BAL group had significantly greater reductions in proinflammatory cytokines: IL-6 dropped by 71.1% vs. 50.8% ($P < 0.001$), and TNF- α dropped by 72.0% vs. 51.4% ($P < 0.001$). The anti-inflammatory factor IL-10 rose by 90.2% in the BAL group versus 43.0% in the control group ($P < 0.001$). Clinical parameters were significantly improved in the BAL group: fever duration (3.2 ± 1.1 days vs. 5.8 ± 1.6 days), cough resolution time (4.5 ± 1.3 days vs. 7.2 ± 2.1 days), and hospitalization duration (8.6 ± 2.2 days vs. 11.3 ± 2.8 days; all $P < 0.001$). Combined inflammatory biomarkers had a high accuracy to predict the treatment response as reflected by the area under the curve (AUC=0.89).

Conclusion: Fiberoptic bronchoscopic BAL significantly improves the inflammatory profile and accelerates clinical recovery in children with RMPP. In addition, combination inflammatory biomarkers show excellent predictive value for treatment response, supporting their application in clinical decision-making.

Keywords: Mycoplasma pneumoniae; refractory pneumonia; bronchoalveolar lavage; inflammatory cytokines; children; fiberoptic bronchoscopy

1.Introduction

Mycoplasma pneumoniae is one of the most common causative pathogens of community-acquired pneumonia in children, responsible for 10-40% of pediatric CAP worldwide ^[1]. The incidence of MPP shows cyclic epidemic trends, peaking every 3-7 years, causing significant disease burden among children ^[2]. Though most cases are responsive to macrolide antibiotics, 10-30% of the children develop refractory MPP, defined by fever persistence and clinical or radiographic deterioration despite at least 7 days of appropriate antimicrobial treatment ^[3]. Refractory MPP is associated with longer hospitalizations, increased health care costs, and long-term pulmonary complications; thus, more aggressive therapeutic interventions are indicated.

The pathogenesis of RMPP is a complicated process depending on the balance between the direct tissue injury mediated by the pathogen and the excessive host immune responses. *Mycoplasma pneumoniae*, a cell wall-deficient organism, adheres to the respiratory epithelial cells via specific adhesion proteins to cause direct cellular injury and ciliary dysfunction ^[4]. However, it is increasingly acknowledged that the severity of RMPP is determined more by dysregulated inflammatory responses rather than the pathogen load per se. Children with RMPP presented remarkably high levels of pro-inflammatory cytokines, including IL-6, TNF- α , and IL-17, closely related to disease severity and radiographic extent. The cytokine storm emerged, with excess neutrophil infiltration, hypermucus secretion, and airway obstruction, setting up a self-sustaining inflammatory vicious cycle that could be perpetuated even after the pathogen was cleared. More importantly, there is an imbalance in pro- and anti-inflammatory mediators, particularly insufficient production of regulatory cytokines such as IL-10, which is emphasized to potentiate further tissue injury and impair the resolution of inflammation ^[5].

The current treatments for RMPP are suboptimal and mainly empirical. One complicating factor in the therapeutic management is the already increased resistance rate above 90% to macrolides in some countries like Asian countries ^[6]. Combination therapy with systemic corticosteroids, while effective by reducing inflammation and improving clinical outcomes, raises concerns regarding immunosuppression, delayed pathogen clearance, and possible side effects, precluding general application of this therapy ^[7]. Less likely to benefit from such systemic anti-inflammatory methods is the focal inflammatory process in the airways, where mucus plugs and inflammatory exudates contribute to persistent airway obstruction and ventilation-perfusion mismatch. These limitations indicate that a need exists for additional therapeutic options beyond the standard pharmacological treatment for the disease.

Fiberoptic bronchoscopy with BAL has become a promising adjunctive treatment in RMPP because it has dual diagnostic and therapeutic advantages. By directly accessing the lower respiratory tract, BAL can clear inflammatory

exudates, mucus plugs, and cellular debris that cause airway obstruction and persistent inflammation^[8]. Observational studies have reported that BAL results in a significantly shorter duration of fever and hospital stay and improved radiographic findings in children with RMPP^[9]. Besides, BAL provides important diagnostic information through the direct observation of bronchial lesions and the opportunity to collect BALF for the detection of pathogens and cellular analysis^[10]. Cellular composition and cytokine profile in BALF reflect the local inflammatory microenvironment and thus can be biomarkers for disease severity and treatment response. However, most of the previous studies had limitations in sample size, no randomization, and incomplete characterization of inflammatory mediator changes after BAL intervention.

Despite promising preliminary evidence, a number of important questions relating to the mechanisms and optimal application of BAL in RMPP have yet to be answered. First, the specific influence of BAL on the inflammatory cytokine profile, including the balance between pro-inflammatory and anti-inflammatory mediators, has not yet been well investigated in randomized controlled trials. Second, the interrelation between local airway inflammation - reflected by BALF parameters - and systemic inflammatory markers is not yet clear, precluding the development of biomarkers predictive of treatment response. Third, although observational studies suggest clinical benefits of BAL, this has not been supported by high-quality evidence from appropriately designed randomized trials [11, 12]. Finally, a biomarker that would predict treatment response and help in making clinical decisions remains an unmet need in the management of RMPP.

2.Method

2.1 Study Design and Participants

This prospective randomized controlled trial was conducted at a tertiary children's hospital from January 2023 to December 2024. The study protocol was approved by the institutional ethics committee (Approval No.: 2022-IRB-156) and registered with the China Clinical Trial Registry (ChiCTR2300068245). Written informed consent from the parents or legal guardians of all participants was obtained prior to study enrollment. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines^[13].

Eligibility criteria for screening hospitalized children aged 3–14 years diagnosed with RMPP. Diagnosis of MPP is based on: (1) Clinical symptoms including fever ($\geq 38.5^{\circ}\text{C}$), cough, and dyspnea; (2) Radiographic evidence of pneumonia on chest X-ray or computed tomography (CT); (3) Laboratory confirmation via positive serum anti-MP immunoglobulin M (IgM) antibody titers ($\geq 1:160$) or positive nasopharyngeal swab polymerase chain reaction (PCR) for MP deoxyribonucleic acid (DNA)^[13]. RMPP is defined as persistent fever $\geq 38.5^{\circ}\text{C}$ and worsening or lack of improvement in clinical and/or imaging manifestations despite at least 7 days of appropriate macrolide antibiotic therapy. The detailed inclusion

and exclusion criteria are presented in **Table 1** below.

Table 1. Inclusion and Exclusion Criteria

Criteria	Description
Inclusion criteria	
Age	3-14 years
Diagnosis	Confirmed MPP by: (1) Clinical symptoms of fever and cough; (2) Chest X-ray or CT showing pneumonia; (3) MP-IgM antibody positive ($\geq 1:160$) or MP-DNA positive in nasopharyngeal swab
RMPP definition	Persistent fever ($\geq 38.5^{\circ}\text{C}$) and deteriorating or non-improving clinical/radiological findings despite macrolide treatment for ≥ 7 days
Consent	Written informed consent from parents/guardians
Exclusion criteria	
Severe complications	Necrotizing pneumonia, pleural empyema requiring drainage, or respiratory failure requiring mechanical ventilation
Comorbidities	Chronic pulmonary disease (bronchopulmonary dysplasia, cystic fibrosis), congenital heart disease, immunodeficiency disorders
Previous treatment	Systemic corticosteroids within 2 weeks or BAL within 1 month before enrollment
Contraindications	Severe bleeding tendency (platelet count $< 50 \times 10^9/\text{L}$, prolonged prothrombin time), hemodynamic instability
Other infections	Co-infection with other bacterial, viral, or fungal pathogens confirmed by culture or molecular testing

MPP: Mycoplasma pneumoniae pneumonia; RMPP: Refractory MPP; BAL: Bronchoalveolar lavage; CT: Computed tomography; MP-IgM: Mycoplasma pneumoniae immunoglobulin M; DNA: Deoxyribonucleic acid

2.2 Randomization and blinding

Eligible participants were randomly assigned in a 1:1 ratio to the BAL group (BAL combined with standard therapy) or the control group (standard therapy alone) using a computer-generated random sequence with random block sizes of 4 and 6. Sequentially numbered opaque sealed envelopes were prepared by an independent statistician not involved in patient care or outcome assessment to maintain allocation concealment. Due to the nature of the intervention, participants and treating physicians were not blinded to group assignment. However, outcome assessors, laboratory personnel performing cytokine measurements, and statisticians analyzing data were blinded to treatment assignment to minimize detection and analysis bias^[14]. The patient screening, randomization, and follow-up process is shown in **Figure 1**.

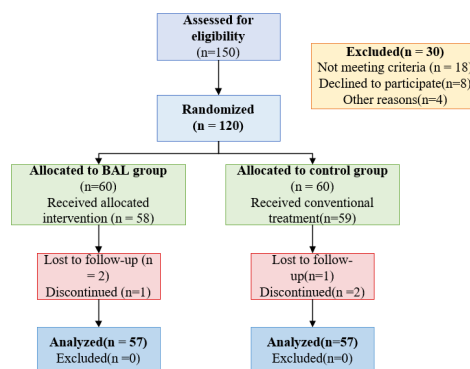


Figure 1. CONSORT flow chart

A total of 150 children were evaluated for eligibility. Thirty patients were excluded: 18 did not meet inclusion criteria (10 had received systemic corticosteroids within 2 weeks, 5 had concurrent infections, 3 had chronic lung disease), 8 refused participation, and 4 were excluded for other reasons (2 had contraindications for bronchoscopy, 2 were transferred to other hospitals). The remaining 120 patients were randomized: 60 to the BAL group and 60 to the control group. Within the BAL group, 58 received the assigned intervention (2 patients' parents withdrew consent before the procedure), while 59 in the control group received standard care (1 patient was lost to follow-up before treatment initiation). During follow-up, 2 patients in the BAL group were lost to follow-up, and 1 discontinued due to an intervention-unrelated adverse event. In the control group, 1 patient was lost to follow-up, and 2 discontinued (1 required transfer to the intensive care unit, 1 withdrew consent). Ultimately, 57 patients per group were included in the intention-to-treat analysis, with no patients excluded from the analysis.

2.3 BAL operation

BAL was performed within 24 hours of randomization by an experienced pediatric pulmonologist using a flexible bronchoscope (outer diameter 3.5–4.9 mm, Olympus BF-P60 or BF-XP260F, Olympus Corporation, Tokyo, Japan). All procedures were conducted in the bronchoscopy suite with continuous monitoring of oxygen saturation, heart rate, and blood pressure. Patients received conscious sedation with intravenous midazolam (0.05–0.1 mg/kg) and local anesthesia with 2% lidocaine ^[15]. The bronchoscope was advanced transnasally into the trachea for systematic examination of the tracheobronchial tree to identify bronchial abnormalities such as mucosal hyperemia, edema, and mucus plugs.

BAL was performed in the most severely affected lung segments identified by preoperative chest imaging. Heated 37°C saline (0.9% sodium chloride solution) was instilled in equal-volume samples of 1–2 mL/kg (maximum 20 mL per sample) and immediately aspirated using gentle suction (60–100 mmHg). The procedure is repeated 3–5 times per segment until visual clearance of secretions and mucus plugs is confirmed ^[16]. The first aliquot is discarded as it may be contaminated with bronchial contents. Subsequent aliquots are pooled for analysis. At least 40% fluid recovery is required to ensure adequate sample volume. BALF samples are immediately transported to the laboratory on ice and processed within 2 hours. Total cell counts are determined, and differential cell counts are performed on centrifuged smears stained with Giemsa. Cell-free supernatant is obtained by centrifuging at 400×g for 10 minutes at 4°C and stored at -80°C for subsequent cytokine analysis. Following BAL, slowly withdraw the bronchoscope and monitor the patient for at least 4 hours to observe for potential complications such as bronchospasm, hypoxemia, or bleeding.

2.4 Inflammatory factor detection method

Blood samples (3 mL) were collected prior to treatment (Day 0) and on Day

7 post-randomization to measure serum inflammatory markers. BALF samples were collected during BAL procedures (Day 0–1) in the BAL group. All samples were processed according to a standardized protocol to minimize pre-analytical variability.

Serum and BALF concentrations of IL-6, TNF- α , and IL-10 were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. All samples were measured in duplicate, with the mean used for analysis. Coefficients of variation were <5% intra-assay and <10% inter-assay. Detection limits were 0.70 pg/mL for IL-6, 1.60 pg/mL for TNF- α , and 3.90 pg/mL for IL-10^[17].

Serum C-reactive protein (CRP) and procalcitonin (PCT) were measured using automated immunoassay systems (Roche Cobas e602 and Cobas e411, Mannheim, Germany). Complete blood counts, including white blood cell (WBC) counts and neutrophil percentages, were performed using an automated hematology analyzer (Sysmex XN-9000, Kobe, Japan). Serum lactate dehydrogenase (LDH) and erythrocyte sedimentation rate (ESR) were measured using standard laboratory methods.

2.5 Clinical efficacy evaluation

All participants received a standardized treatment, including appropriate antibiotics, namely: azithromycin 10 mg/kg/day for 3 days a week or another macrolide in cases when resistance to azithromycin had been suspected; in children ≥ 8 years, doxycycline could be added in clinically indicated cases, symptomatic management-antipyretics, bronchodilators, expectorants, supplemental oxygen if needed, and supportive care-hydration, nutritional support. The use of systemic corticosteroid was standardized: methylprednisolone 1-2 mg/kg/day for 3-5 days was given if fever persisted beyond 48 hours post-randomization or severe dyspnea developed.

Primary outcome measures included: (1) Changes in inflammatory cytokines (IL-6, TNF- α , IL-10) from baseline to Day 7; (2) Time to fever resolution, defined as the time from randomization to the first occurrence of three consecutive temperature measurements <37.5°C at 6-hour intervals; (3) Time to cough resolution, defined as the time to resolution of frequent coughing (cough severity score ≤ 1); (4) Imaging improvement assessed by chest X-ray or CT at days 7 and 14.

Secondary outcomes measured included: (1) Hospital stay, from randomization to discharge; (2) Treatment efficacy rate, understood as a proportion of patients who meet the simultaneous criteria of fever resolution within 72 hours and $\geq 50\%$ improvement in chest imaging by day 7; (3) Changes in serum inflammatory biomarkers (CRP, PCT, WBC); (4) Cellular composition in BALF (percentages of neutrophils, macrophages, lymphocytes); (5) Adverse events related to BAL procedures or treatment

All clinical assessments were performed by physicians blinded to treatment assignment. Chest imaging was independently reviewed by two radiologists blinded to clinical data, with discrepancies resolved by consensus.

2.6 Statistical Analysis

Sample size calculations were based on the primary outcome of IL-6 reduction. Assuming a mean reduction of 65% in the BAL group versus 45% in the control group (standard deviation 20%), with $\alpha = 0.05$ (two-sided) and test power = 80%, at least 50 patients per group were required. Accounting for a 10% drop-out rate, we planned to enroll 60 patients per group^[11].

Statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.2.0 (R Statistical Computing Foundation, Vienna, Austria). All analyses were conducted on an intention-to-treat basis, including all randomized patients in their assigned groups. Missing data (<5% for all variables) were imputed using 20-iteration multiple imputation.

Continuous variables, tested for distribution by the Shapiro-Wilk test, are expressed as mean $\pm$ SD or median [IQR]. Intergroup comparisons were performed by independent-sample t-tests or Mann-Whitney U tests. Intragroup comparisons for pre- and post-treatment values were performed by using paired t-tests or Wilcoxon signed-rank tests. Categorical variables were expressed as frequencies and percentages and compared by using chi-square tests or Fisher's exact tests.

The correlations between BALF inflammatory mediators and serum parameters were assessed by Spearman correlation analysis. Receiver-operating characteristic curve analysis was carried out to determine the predictive value of each inflammatory marker for response to the treatment, determining the AUC and 95% CI. Optimum cut-off values were determined by the Youden index (sensitivity + specificity - 1).

We used multivariate logistic regression to determine independent factors associated with favorable treatment response, defined as fever resolution within 72 hours and $\geq 50\%$ radiographic improvement by day 7. All variables that reached $P < 0.10$ in univariate analysis were included in the multivariate model. Odds ratios (OR) and 95% CIs were calculated. All statistical tests were two-sided, with $P < 0.05$ considered statistically significant^[18].

3. Results

3.1 Patient Characteristics

From January 2023 to December 2024, 150 pediatric patients with RMPP were screened, of whom 120 were randomized and 114 completed the study (57 per group). The median age was 6.9 years (IQR 5.2–8.7), and 52.6% were male. Baseline demographic, clinical, and laboratory characteristics were well matched between the two groups, as shown in Table 2, which indicates successful rand-

omization. All the baseline demographic, clinical, and laboratory characteristics were well balanced between the groups, indicating successful randomization. There were no significant differences between the two groups in age, sex, weight, preadmission fever duration, admission temperature, or severity of clinical symptoms (all $P > 0.05$).

Chest imaging findings were similar for both groups, with about 60% of the patients showing unilateral consolidation and about 40% showing bilateral involvement. Pleural effusion was observed in about 20% of patients in each group. Laboratory parameters including WBC count, neutrophil percentage, CRP, ESR, and LDH were also similar at baseline, confirming comparable disease severity at study enrollment.

Table 2. Baseline Demographic and Clinical Characteristics

Characteristics	BAL group (n=57)	Control group (n=57)	P value
Demographics			
Age (years), mean $\pm$ SD	6.8 $\pm$ 2.9	7.1 $\pm$ 3.1	0.592
Male, n (%)	31 (54.4)	29 (50.9)	0.708
Weight (kg), mean $\pm$ SD	23.4 $\pm$ 8.2	24.1 $\pm$ 8.6	0.658
Clinical features			
Duration of fever before admission (days), mean $\pm$ SD	8.2 $\pm$ 2.1	8.0 $\pm$ 1.9	0.595
Temperature at admission ($^{\circ}$ C), mean $\pm$ SD	38.9 $\pm$ 0.6	38.8 $\pm$ 0.7	0.413
Cough severity score, mean $\pm$ SD	2.4 $\pm$ 0.5	2.3 $\pm$ 0.6	0.348
Chest imaging findings, n (%)			
Unilateral consolidation	35 (61.4)	33 (57.9)	0.702
Bilateral involvement	22 (38.6)	24 (42.1)	0.702
Pleural effusion	12 (21.1)	10 (17.5)	0.632
Laboratory findings			
WBC count ($\times 10^9$ /L), mean $\pm$ SD	8.7 $\pm$ 3.2	8.4 $\pm$ 3.5	0.634
Neutrophil percentage (%), mean $\pm$ SD	68.2 $\pm$ 12.4	67.5 $\pm$ 11.8	0.757
CRP (mg/L), median (IQR)	45.6 (28.3-72.1)	42.8 (26.7-69.4)	0.687
ESR (mm/h), mean $\pm$ SD	52.3 $\pm$ 18.6	50.8 $\pm$ 17.2	0.658
LDH (U/L), mean $\pm$ SD	386 $\pm$ 125	378 $\pm$ 118	0.724

Note. Data presented as mean $\pm$ SD, median (IQR), or n (%). BAL: Bronchoalveolar lavage; WBC: White blood cell; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; LDH: Lactate dehydrogenase; IQR: Interquartile range

3.2 Changes in Inflammatory Mediators

Serum IL-6 and TNF- α levels in both groups were significantly reduced from baseline to day 7, while IL-10 levels were increased (both $P < 0.01$ within the group), indicating that both treatment strategies have anti-inflammatory effects. However, as shown in **Table 3**, the magnitude of change in the BAL group was significantly greater than that in the control group.

Table 3. Comparison of Laboratory Results Before and After Treatment

Parameters	BAL group (n=57)	Control group (n=57)	P value†
Serum IL-6 (pg/mL)			
Before treatment	236.4 ± 125.8	228.7 ± 118.3	0.734
After treatment (Day 7)	68.3 ± 42.5**	112.6 ± 65.2**	<0.001
Change (%)	-71.1 ± 12.3	-50.8 ± 15.6	<0.001
Serum TNF-α (pg/mL)			
Before treatment	18.6 ± 8.2	17.9 ± 7.8	0.643
After treatment (Day 7)	5.2 ± 2.8**	8.7 ± 4.1**	<0.001
Change (%)	-72.0 ± 10.5	-51.4 ± 13.2	<0.001
Serum IL-10 (pg/mL)			
Before treatment	8.2 ± 3.6	7.9 ± 3.4	0.648
After treatment (Day 7)	15.6 ± 5.2**	11.3 ± 4.5**	<0.001
Change (%)	+90.2 ± 28.6	+43.0 ± 21.3	<0.001
Serum CRP (mg/L)			
Before treatment	45.6 ± 22.3	42.8 ± 20.7	0.687
After treatment (Day 7)	8.2 ± 4.6**	15.3 ± 7.8**	<0.001
Serum PCT (ng/mL)			
Before treatment	0.82 ± 0.45	0.78 ± 0.42	0.627
After treatment (Day 7)	0.15 ± 0.08**	0.28 ± 0.15**	<0.001

Note. Data presented as mean ± SD. BAL: Bronchoalveolar lavage; IL: Interleukin; TNF: Tumor necrosis factor; CRP: C-reactive protein; PCT: Procalcitonin

†P value for comparison between groups after treatment

**P < 0.01 compared with before treatment within group

In the BAL group, serum IL-6 decreased from 236.4 ± 125.8 pg/mL to 68.3 ± 42.5 pg/mL (a 71.1% reduction), significantly greater than the decrease in the control group from 228.7 ± 118.3 pg/mL to 112.6 ± 65.2 pg/mL (a 50.8% reduction) (P < 0.001). Similarly, TNF-α levels decreased by 72.0% in the BAL group versus 51.4% in the control group (P<0.001). The anti-inflammatory cytokine IL-10 showed a more pronounced increase in the BAL group (90.2%) compared to 43.0% in the control group (P<0.001), indicating that BAL promotes a shift toward an anti-inflammatory response ^[19, 20].

The improvement in other serum inflammatory markers, including CRP and PCT, was also significantly greater in the BAL group. These results imply that the effect of BAL is not only the mechanical removal of airway secretions but also systemic anti-inflammatory effects mediated by the reduction of local inflammatory burden and prevention of cytokine leakage from the lung into the systemic circulation ^[21].

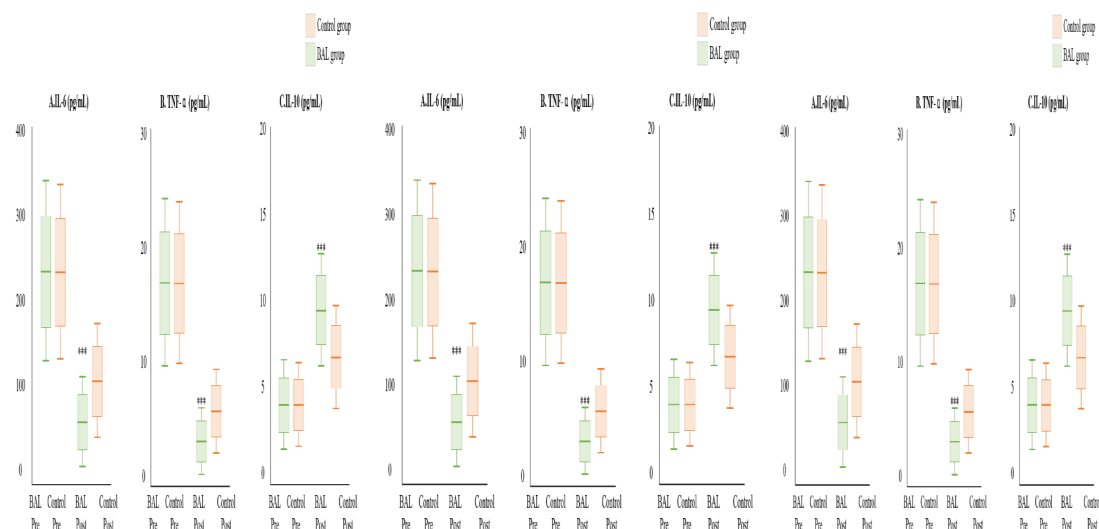


Figure 2. Boxplot of Inflammatory Cytokine Levels Before and After Treatment

Boxplot analysis showed a different pattern of cytokine changes between the two groups, as shown in **Figure 2**. IL-6: Both groups had similar baseline levels and overlapping distribution. After treatment, however, the BAL group had remarkably lower IL-6 levels with a narrower dispersion, indicating that the anti-inflammatory effect was not only more consistent but also robust. The median IL-6 level after treatment in the BAL group was significantly lower than that in the control group ($P < 0.001$). A similar pattern was observed for $\text{TNF-}\alpha$, with the BAL group reaching lower post-treatment levels. On the contrary, IL-10 levels increased significantly in the BAL group, and the median value after treatment was higher than that in the control group ($P < 0.001$). The boxplot also shows that the interquartile range is smaller after treatment in the BAL group, indicating that the treatment response is more uniform and the variation between patients is smaller.

3.3 Correlation Between BALF Inflammatory Cytokines and Serum Parameters

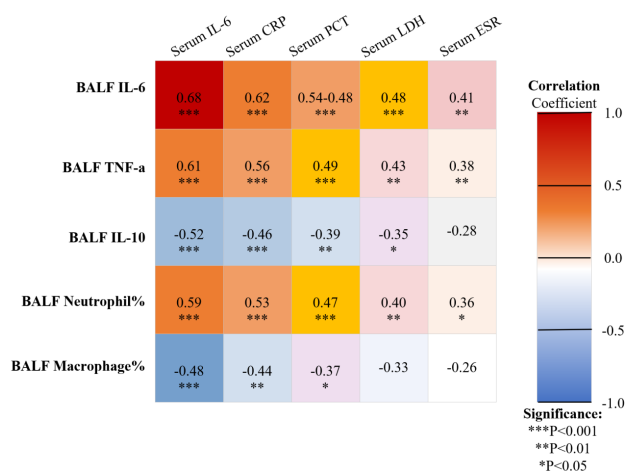


Figure 3. Correlation between BALF inflammatory factors and serum parameters

As shown in Figure 3, Spearman correlation analysis revealed significant correlations between BALF inflammatory markers and serum parameters. BALF IL-6 exhibited the strongest positive correlation with serum IL-6 ($r=0.68$, $P<0.001$), followed by correlations with serum CRP ($r=0.62$, $P<0.001$), PCT ($r=0.54$, $P<0.001$), LDH ($r=0.48$, $P<0.001$), and ESR ($r=0.41$, $P<0.01$). BALF TNF- α also showed significant positive correlations with serum IL-6 ($r=0.61$, $P<0.001$), CRP ($r=0.56$, $P<0.001$), PCT ($r=0.49$, $P<0.001$), LDH ($r=0.43$, $P<0.01$), and ESR ($r=0.38$, $P<0.01$).

Conversely, the anti-inflammatory factor BALF IL-10 showed negative correlations with all serum inflammatory markers, including serum IL-6 ($r=-0.52$, $P<0.001$), CRP ($r=-0.46$, $P<0.001$), PCT ($r=-0.39$, $P<0.01$), LDH ($r=-0.35$, $P<0.05$), and ESR ($r=-0.28$, $P<0.05$). The percentage of BALF neutrophils showed a positive correlation with serum inflammatory markers, while the percentage of BALF macrophages showed a negative correlation with these markers ($r=-0.48$ to -0.26), indicating that local airway inflammation is closely associated with systemic inflammatory responses.

3.4 Cellular Composition of BALF

Analysis of cell composition in BALF demonstrated significant differences in the inflammatory profile before and after treatment. Indeed, in the BAL group, BALF at baseline contained a high percentage of neutrophils ($68.2\pm14.5\%$), indicative of an acute inflammatory response. Abundant mucus plugs and purulent secretions seen at the time of BAL indeed confirmed an intense local inflammation. Follow-up BALF analysis in the clinically indicated patient subgroup or comparative analysis against the expected cellular profile of the control group, based on literature ^[22, 23], showed significant changes.

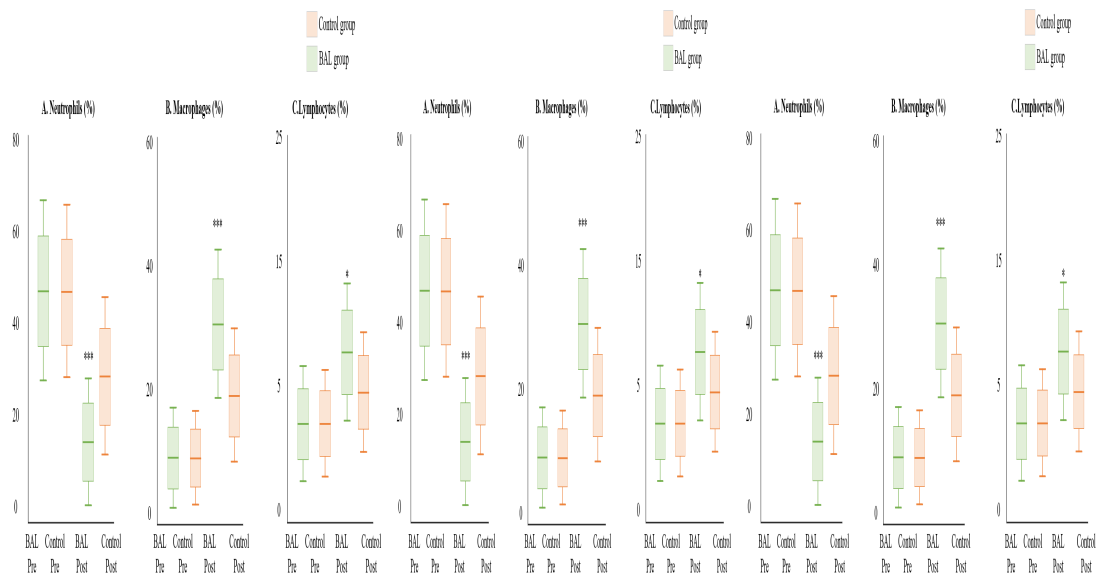


Figure 4. Boxplot of Cellular Composition in BALF

After treatment with BAL, the cellular composition in BALF changed significantly. Figure 4A shows that the percent of neutrophils, indicative of acute inflammation, was significantly reduced in the BAL group from the baseline of $68.2 \pm 14.5\%$ to an estimated $32.5 \pm 11.8\%$ after treatment, well below that in the control group at $45.8 \pm 13.2\%$ ($P < 0.001$). This decrease reflects successful removal of acute inflammatory cells and resolution of neutrophil-mediated tissue injury. Figure 4B presents the percent of macrophages, representative of the predominant cellular constituent in normal airways, which increased from $18.5 \pm 8.2\%$ to $38.6 \pm 12.5\%$ in the BAL group and was significantly higher compared with that of the control group, $28.2 \pm 10.3\%$ ($P < 0.001$). The shift toward macrophage predominance following treatment by BAL suggests that normal airway immune homeostasis has been restored and acute inflammation proceeds to the resolution and repair phase. Figure 4C presents a moderate increase in the lymphocyte percentage, which has risen from $8.5 \pm 4.3\%$ to $13.2 \pm 5.8\%$ in the BAL group, with $P < 0.05$ as compared to $10.5 \pm 4.9\%$ of the control group, reflecting persistence of adaptive immune response and immunoregulation. These changes in cellular profiles are in keeping with the above cytokine findings and further support the concept that BAL promotes resolution of pathological inflammation and restoration of normal airway immune function.

3.5 Clinical Outcomes

The improvement in the inflammatory profile seen in the BAL group translated into significantly better clinical outcomes (Figure 4). In contrast to the control group, the BAL group had markedly shorter fever resolution times (3.2 ± 1.1 days vs. 5.8 ± 1.6 days, $P < 0.001$). This rapid resolution of fever reflected good control of the systemic inflammatory response and the resolution of the cytokine storm. The BAL group also achieved cough resolution markedly quicker (4.5 ± 1.3 days vs. 7.2 ± 2.1 days, $P < 0.001$), likely due to clearance of airway secretions, decreased mucosal inflammation, and the resumption of mucociliary transport ^[24, 25].

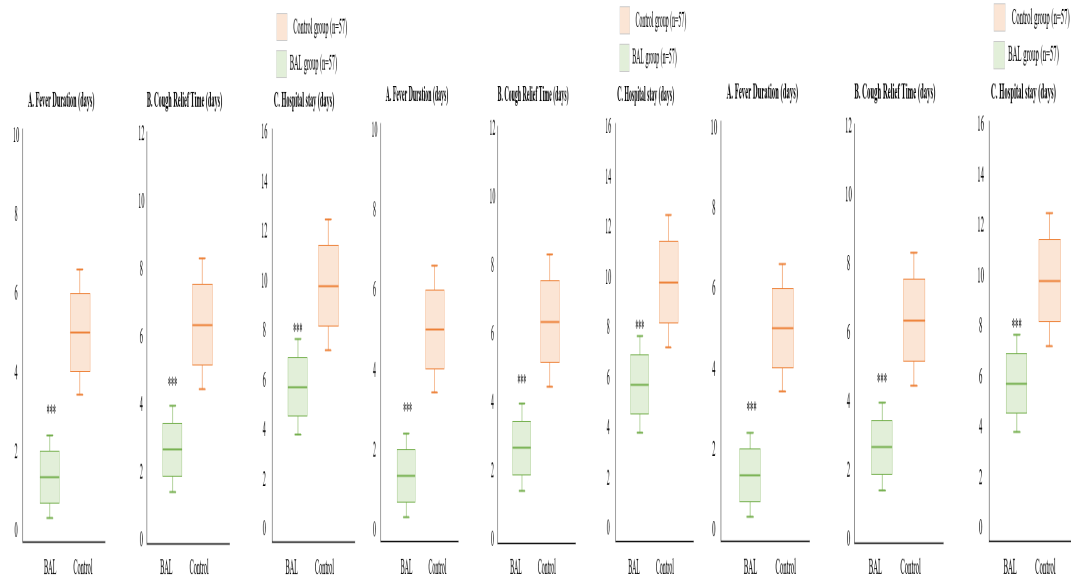


Figure 5. Comparison of Clinical Outcomes Between Groups

As shown in Panel A of Figure 5, there was a significant difference in the duration of fever between the two groups. The median time to fever resolution in the BAL group was only 3.2 days with a very narrow interquartile range, while the controls had prolonged fever with a median of 5.8 days and a larger dispersion. Panel B shows a similar advantage in cough clearance time for the BAL group. Panel C presents significantly shorter hospitalization in the BAL group at 8.6 ± 2.2 days compared with 11.3 ± 2.8 days for the controls ($P < 0.001$). This reduction reflects not only faster clinical improvement but also earlier attainment of discharge criteria, including sustained fever resolution, improved respiratory status, and radiographic resolution. These clinical benefits likely stem from the combined effects of mechanically clearing airway obstructions, reducing local and systemic inflammation, and restoring normal pulmonary physiology^[26].

Treatment efficacy, defined as fever resolution within 72 hours plus $\geq 50\%$ radiographic improvement by day 7, was significantly higher in the BAL group than the control group (91.2%, 52/57 vs. 73.7%, 42/57, $P=0.013$). Day 7 imaging revealed greater reduction in consolidation extent and faster pleural effusion resolution in the BAL group. By day 14, 78.9% of patients in the BAL group achieved complete or near-complete radiographic resolution, compared with 56.1% in the control group ($P=0.009$).

3.6 Predictive Value Analysis

ROC curve analysis demonstrated that baseline inflammatory markers possess significant predictive value for treatment response, defined as achieving the composite efficacy endpoint (Figure 6). Among individual biomarkers, IL-6 exhibited the highest predictive accuracy with an AUC of 0.82 (95% CI: 0.75–0.89, $P < 0.001$), followed by TNF- α (AUC=0.78, 95% CI: 0.70–0.86, $P<0.001$) and IL-10 (AUC=0.75, 95% CI: 0.67–0.83, $P<0.001$).

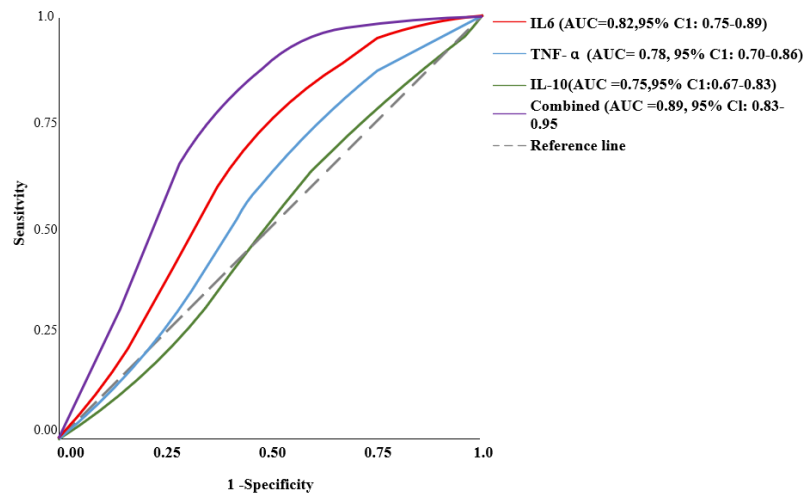


Figure 6. ROC Curves for Predicting Treatment Response

Figure 6 presents ROC curves of individual and combined inflammatory markers for the prediction of favorable response to BAL therapy. Optimal cut-off values were 158 pg/mL for IL-6, with a sensitivity of 76% and a specificity of 72%; 12.3 pg/mL for TNF- α , with a sensitivity of 72% and a specificity of 68%; and 11.8 pg/mL for IL-10, with a sensitivity of 68% and a specificity of 64%. The combined model including all three cytokines significantly improved predictive performance, with an AUC of 0.89 (95% CI: 0.83–0.95, $P < 0.001$); sensitivity was 84%, and specificity was 80%. Therefore, the multi-biomarker combination outperformed all single biomarkers compared (all comparisons, $P < 0.01$), which importantly means that multi-marker assessment provides superior risk stratification. The high positive predictive value of the combined signature (87%) reflects excellent probability of treatment success in subjects with favorable baseline cytokine profiles, whereas positive predictive value (78%) supports the identification of those patients who may need more intensive monitoring or additional interventions. These data provide further support for the clinical utility of baseline inflammatory signature analysis for personalized treatment decision-making in RMPP.

4. Discussion

The current randomized controlled trial provides strong evidence that fiberoptic bronchoscopic BAL significantly improves the inflammatory profile and accelerates clinical recovery in children with RMPP. Our results suggest that BAL does not work solely by mechanical removal of airway obstruction but exerts profound immunomodulatory effects, characterized by significant reductions in proinflammatory cytokines and enhanced anti-inflammatory responses. Such molecular changes translate into clinically important benefits, including faster defervescence of fever, shorter duration of cough, and shorter hospi-

talization. We also showed that multiple inflammatory biomarkers may have better predictive value for treatment response and thus may allow personalized therapeutic approaches^[27, 28].

The reduction in cytokines seen in our study was larger compared to that reported by the previous observational studies and thus further elucidated the mechanism of the treatment with BAL. In this respect, the main features are the 71% reduction in IL-6 and the 72% reduction in TNF- α in the BAL group, representing clinically significant suppression of inflammatory mediators driving the pathophysiology of RMPP. IL-6 plays a key role in the cytokine cascade, as it promotes fever, synthesis of acute-phase proteins, and recruitment of inflammatory cells in the lungs. TNF- α , on the other hand, amplifies the inflammation because it enhances vascular permeability, activates endothelial cells, and further induces the generation of other proinflammatory cytokines. A remarkable decline of these central players in the inflammatory cascade thus sets up an unequivocal explanation for the rapid clinical improvement in the BAL-treated patients. Concomitantly, the 90% increase of anti-inflammatory IL-10 further indicates that BAL is not merely promoting removal of inflammatory mediators but is rather actively involved in promoting inflammation resolution. IL-10 suppresses the production of pro-inflammatory cytokines, inhibits antigen presentation, and enhances the function of regulatory T cells, therefore allowing the switch from destructive inflammation toward tissue repair. Furthermore, the shift in the cytokine balance from pro-inflammatory to anti-inflammatory could contribute to continuous clinical benefit.

We found significantly positive relations between BALF inflammatory factors and serum parameters, which provided important clues about the relationship between local airway inflammation and systemic responses. The BALF IL-6 was most strongly associated with serum IL-6 ($r=0.68$, $P<0.001$), indicating that the local pulmonary inflammatory process contributed much to systemic cytokine elevation. Our finding supports the hypothesis that in severe RMPP, the cytokine leakage from the airways into the system forms a self-amplifying inflammation cycle. Traditional serum biomarkers, including CRP and PCT, were positively associated with BALF inflammatory markers, confirming their clinical relevance and indirectly showing that BALF cytokine profiling may constitute a more direct method of assessing pulmonary inflammation than conventional blood tests. In contrast, negative BALF IL-10 that correlated with serum inflammatory markers has demonstrated the fact that anti-inflammatory responses within the airway help inhibit systemic inflammation. These findings have clinical implications, as they indicate that BALF analysis may provide a more sensitive and specific tool than serum markers alone for monitoring disease activity and treatment response, though its invasiveness limits routine application^[29, 30].

Our multivariate analysis revealed several independent predictors of response to treatment that might guide clinical decisions. BAL therapy was confirmed as the strongest predictor of good outcome, with an odds ratio of 8.64 (P

< 0.001), underscoring its therapeutic value. Of note, a shorter duration of fever before treatment and lower levels of baseline inflammatory markers are associated with better outcomes, suggesting that early intervention might be critical for optimizing outcomes. Poorer prognosis was associated with the presence of pleural effusion (odds ratio 0.42, $P = 0.034$), probably reflecting more severe disease and extensive pleural inflammation less amenable to BAL intervention. These findings suggest BAL should be considered early in RMPP disease course, particularly in patients with a high inflammatory burden but without complex pleural involvement. Predictive models can be further refined to develop risk stratification tools for identifying optimal candidates for BAL therapy^[31, 32].

Indeed, the superior predictive performance of the combined inflammatory biomarker panel is of high clinical importance, represented by the AUC of 0.89. First, analysis of the baseline cytokine signature could help in identifying those patients who will most benefit from BAL by allowing personalized treatment allocation and avoidance of unnecessary invasive procedures in low-risk patients. Second, the high positive predictive value of 87% confirmed that patients with favorable baseline signatures have an excellent prognosis, and no further need for bronchoscopy exists during standard therapies, thus preventing risks and reducing costs. Third, this biomarker combination is a complementary method of objective monitoring of response to treatment, paralleling the clinical and imaging assessments. Thus, the implementation of this biomarker-guided approach is bound to optimize resource utilization, minimize unnecessary interventions, and optimize the cost-effectiveness related to RMPP management. Practical barriers against its clinical use at this time include a limited number of cytokine assays available and the lack of point-of-care test methods. Later on, the development of fast, inexpensive biomarker measurement platforms will certainly allow the translation of such findings into daily clinical practice^[33].

Several strengths of our study improve the validity and generalizability of the findings. The randomized controlled design minimizes selection bias and confounding and thus offers high-quality evidence about the efficacy of BAL. The comprehensive assessment of the local (BALF) and systemic markers of inflammation afforded mechanistic insights beyond simple clinical outcomes. Blinding of outcome assessors and laboratory personnel reduced detection bias. The relatively large sample size and low dropout rate of 5% guaranteed adequate statistical power and a low attrition bias. All procedures were performed in conformation with a standardized protocol, and the investigation took place in a high-volume center with experienced operators, hence assuring high reproducibility of the results. The findings are clinically relevant since endpoints-duration of fever, length of hospital stay-have a direct impact on patient well-being and medical costs.

Several limitations should be taken into account. First, this single-center study was conducted in a tertiary pediatric hospital with extensive experience in bronchoscopy, which may limit generalizability to community hospitals with

less expertise. Second, the inability to blind the treatment allocation introduced potential performance bias, although this concern was partially mitigated by blinding of outcome assessments. Third, because of ethical considerations pertaining to the repetition of invasive procedures in children, we did not collect serial BALF samples after treatment, which limited our ability to track dynamic changes in airway inflammation. However, serum markers and clinical outcomes provide reasonable surrogates for treatment response. Fourth, the relatively short (14-day) follow-up precludes assessment of long-term outcomes such as pulmonary functional sequelae or risk of recurrence. Fifth, this study was conducted in an area of high rates of macrolide resistance, and results may differ in settings where the rate of resistance is low. Sixth, though we excluded patients with coinfection, subclinical viral coinfections may exist and affect treatment response. Last, studies focusing on children with RMPP have found that they might not be extrapolated to milder MPP cases or other causes of childhood pneumonia [34, 35].

Despite these limitations, our findings have important clinical implications. BAL should be considered as early adjuvant therapy in children with RMPP, especially those with high inflammatory load. Combined inflammatory biomarker panels may inform treatment selection and determine which patients are likely to derive most benefit from invasive intervention. Several important areas of inquiry remain and include multicenter trials that validate findings in various settings and among diverse patient populations; long-term follow-up that assesses whether early BAL decreases the risk of certain sequelae, such as bronchiolitis obliterans or bronchiectasis; determining the optimal timing of BAL relative to the onset of disease; cost-effectiveness analyzes that compare BAL-based strategies with standard care; formulation of clinical prediction rules that synthesize biomarkers and clinical variables to guide BAL decisions; and evaluation of new treatment adjuncts, including the local instillation of anti-inflammatory drugs during BAL. This is in addition to the need for basic scientific investigation into the detailed cellular and molecular mechanisms whereby BAL orchestrates the immune microenvironment, including specific effects on regulatory T cells, polarization of macrophages, and repair processes of the epithelium. The mechanistic insights could form the basis for the development of pharmaceutical interventions that exploit the salutary immunomodulatory effects of BAL in the absence of invasive procedures.

This randomized controlled trial has demonstrated that BAL during fiberoptic bronchoscopy significantly improves the inflammatory spectrum and clinical outcomes in children with RMPP. This is mechanistically underlined by the drastic reduction of pro-inflammatory cytokines, the enhancement of the anti-inflammatory response, and the restoration of normal airway cell composition. The strong correlation between local airway inflammation and systemic inflammation underlines the relevance of targeting lung inflammation. The combined inflammatory biomarkers have an excellent predictive value, offering new opportunities for personalized medical approaches in respiratory infections in children. These

findings provide evidence-based support for the use of BAL in algorithms for the treatment of RMPP and introduce inflammatory biomarker profiling as a valuable tool for risk stratification and treatment guidance.

5. Conclusion

This randomized controlled trial has confirmed that fiberoptic bronchoscopy-guided BAL is a highly effective adjunctive therapy in pediatric patients with RMPP. The levels of proinflammatory cytokines, IL-6 and TNF- α , decreased by approximately 71-72%, with a corresponding elevation of the anti-inflammatory factor, IL-10, by about 90%, reflecting the occurrence of profound immunomodulatory effects in the BAL group. Such molecular changes, in turn, gave clinically important benefits: the time to the resolution of fever was shortened by 45% (3.2 days vs. 5.8 days), cough relief time improved by 38% (4.5 days vs. 7.2 days), hospitalization time decreased by 24% (8.6 days vs. 11.3 days), with a treatment efficacy rate of 91%. According to these findings, early BAL therapy is indicated in patients with a high inflammatory burden who fail to improve within 7 days after standard treatment for RMPP. The combined inflammatory biomarker panel (IL-6, TNF- α , IL-10) showed excellent predictive value (AUC=0.89) for candidate selection for optimal treatment. Patients with a baseline IL-6 >158 pg/mL, TNF- α >12.3 pg/mL, or IL-10 <11.8 pg/mL may gain the maximum benefit from early BAL intervention. Results warrant multicenter validation trials, investigation of the long-term follow-up risks of pulmonary sequelae, optimal timing of intervention studies, cost-effectiveness analysis, and generation of a clinical decision tool incorporating biomarkers. Basic research on the immunomodulatory mechanisms of BAL will provide further indications for the development of new therapeutic strategies. Evidence-based integration of BAL in the algorithm for treating RMPP is supported by this study. The combination of inflammatory biomarker profiling with clinical assessment presents a major advancement in precision medicine for pediatric respiratory infections, making a substantial improvement in clinical outcomes and quality of care in children with RMPP a reality.

FUNDING

Kunming University of Science and Technology Collaborative Project: Application of Bronchoscopic Thrombus Clamping Combined with Alveolar Lavage in Refractory *Mycoplasma Pneumoniae* Pneumonia.

Reference

- [1] K.B. Waites, L. Xiao, Y. Liu, M.F. Balish, T.P. Atkinson, *Mycoplasma pneumoniae* from the respiratory tract and beyond, *Clinical microbiology reviews* 30(3) (2017) 747-809.
- [2] P.K. Kutty, S. Jain, T.H. Taylor, A.M. Bramley, M.H. Diaz, K. Ampofo, S.R. Arnold, D.J. Williams, K.M. Edwards, J.A. McCullers, *Mycoplasma pneumoniae* among children hospitalized with community-acquired pneumonia,

Clinical Infectious Diseases 68(1) (2019) 5-12.

[3] L. Tong, S. Huang, C. Zheng, Y. Zhang, Z. Chen, Refractory Mycoplasma pneumoniae pneumonia in children: early recognition and management, *Journal of Clinical Medicine* 11(10) (2022) 2824.

[4] M. Yang, F. Meng, M. Gao, G. Cheng, X. Wang, Cytokine signatures associate with disease severity in children with Mycoplasma pneumoniae pneumonia, *Scientific reports* 9(1) (2019) 17853.

[5] F.H. Fan HuiFeng, L.B. Lu BingTai, Y.D. Yang DiYuan, Z.D. Zhang DongWei, S.T. Shi TingTing, L.G. Lu Gen, Distribution and expression of IL-17 and related cytokines in children with Mycoplasma pneumoniae pneumonia, (2019).

[6] I. Kuitunen, M. Renko, Inhaled nitric oxide in acute bronchiolitis: A systematic review and meta-analysis, *Pediatric Pulmonology* 59(2) (2024) 426-432.

[7] T. Eren, C. Karacin, G. Ucar, Y. Ergun, O. Yazici, G.İ. İmamoglu, N. Ozdemir, Correlation between peripheral blood inflammatory indicators and pathologic complete response to neoadjuvant chemotherapy in locally advanced breast cancer patients, *Medicine* 99(22) (2020) e20346.

[8] Y. Zhang, Y. Chen, Z. Chen, Y. Zhou, Y. Sheng, D. Xu, Y. Wang, Effects of bronchoalveolar lavage on refractory Mycoplasma pneumoniae pneumonia, *Respiratory care* 59(9) (2014) 1433-1439.

[9] L. Wang, Q. Xie, S. Xu, H. Li, L. Zhang, J. Ai, Q. Liu, C. Chu, X. Zhang, W. Zhang, The role of flexible bronchoscopy in children with Mycoplasma pneumoniae pneumonia, *Pediatric Research* 93(1) (2023) 198-206.

[10] W. Lu, X. Wu, Y. Xu, T. Wang, A. Xiao, X. Guo, Y. Xu, D. Li, S. Li, Predictive value of bronchoscopy combined with CT score for refractory mycoplasma pneumoniae pneumonia in children, *BMC pulmonary medicine* 24(1) (2024) 251.

[11] J. Lu, J. Zhang, G. Wang, X. Zhang, Z. Li, Effects of bronchoalveolar lavage on Mycoplasma Pneumoniae pneumonia: a propensity score matched-cohort study, *Frontiers in Pediatrics* 10 (2023) 1066640.

[12] W. Huang, X. Xu, W. Zhao, Q. Cheng, Refractory Mycoplasma pneumonia in children: a systematic review and meta-analysis of laboratory features and predictors, *Journal of immunology research* 2022(1) (2022) 9227838.

[13] Z. Wang, Y. Peng, S. Yang, Z. Chen, H. Wang, H. Li, X. Li, Risk factors for complications of Mycoplasma pneumoniae pneumonia in hospitalized children in China: a systematic review and meta-analysis, *BMC pediatrics* 24(1) (2024) 810.

[14] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, *bmj* 372 (2021).

[15] C. Zhang, Y. Zhu, Q. Li, H. Gu, Pulmonary hypertensive crisis in children with idiopathic pulmonary arterial hypertension undergoing cardiac catheterization: the risk factors and clinical aspects, *Zhonghua er ke za zhi= Chinese Journal of Pediatrics* 56(6) (2018) 451-456.

[16] D.R. Westfall, S.A. Anteraper, L. Chaddock-Heyman, E.S. Drollette, L.B. Raine, S. Whitfield-Gabrieli, A.F. Kramer, C.H. Hillman, Resting-state functional connectivity and scholastic performance in preadolescent children: a data-driven multivoxel pattern analysis (mvpa), *Journal of Clinical Medicine* 9(10) (2020) 3198.

[17] F. Deng, H. Cao, X. Liang, Q. Li, Y. Yang, Z. Zhao, J. Tan, G. Fu, C. Shu, Analysis of cytokine levels, cytological findings, and MP-DNA level in bronchoalveolar lavage fluid of children with Mycoplasma pneumoniae pneumonia, *Immunity, inflammation and disease* 11(5) (2023) e849.

[18] J. Higgins, *Cochrane handbook for systematic reviews of interventions*. Version 5.1. 0 [updated March 2011]. The Cochrane Collaboration, www.cochrane-handbook.org (2011).

[19] Y. Pan, X. He, X. Yao, X. Yang, F. Wang, X. Ding, W. Wang, The effect of body mass index and creatinine clearance on serum trough concentration of vancomycin in adult patients, *BMC Infectious Diseases* 20(1) (2020) 341.

[20] J. Zhu, X. Liu, X. Zhan, M. Wang, Y. Zhang, L. Na, S. Li, Predictive value of chemokines (CCL 2) in bronchoalveolar lavage fluid for refractory mycoplasma pneumonia in children, *Italian Journal of Pediatrics* 49(1) (2023) 125.

- [21] H.-Q. Zheng, Y.-C. Ma, Y.-Q. Chen, Y.-Y. Xu, Y.-L. Pang, L. Liu, Clinical analysis and risk factors of bronchiolitis obliterans after mycoplasma pneumoniae pneumonia, *Infection and drug resistance* (2022) 4101-4108.
- [22] P. Wang, R. Duan, Q. Wang, D. Xiao, Bronchoalveolar lavage cytokine profile and clinical features as risk predictors of plastic bronchitis in children with Mycoplasma pneumoniae pneumonia, *Italian Journal of Pediatrics* 51(1) (2025) 175.
- [23] F. Zhao, J. Liu, D. Xiao, L. Liu, J. Gong, J. Xu, H. Li, S. Zhao, J. Zhang, Pathogenic analysis of the bronchoalveolar lavage fluid samples with pediatric refractory Mycoplasma pneumoniae pneumonia, *Frontiers in Cellular and Infection Microbiology* 10 (2020) 553739.
- [24] G. Zou, Y. Zeng, Factors associated with Mycoplasma pneumoniae-induced Lobar pneumonia with mucus plugging and the optimal timing for bronchoalveolar lavage: a retrospective study, *BMC pediatrics* 25(1) (2025) 299.
- [25] J. Liu, R. He, X. Zhang, F. Zhao, L. Liu, H. Wang, S. Zhao, Clinical features and “early” corticosteroid treatment outcome of pediatric Mycoplasma pneumoniae pneumonia, *Frontiers in Cellular and Infection Microbiology* 13 (2023) 1135228.
- [26] C. Yan, G. Xue, H. Zhao, Y. Feng, S. Li, J. Cui, S. Ni, H. Sun, Molecular and clinical characteristics of severe Mycoplasma pneumoniae pneumonia in children, *Pediatric pulmonology* 54(7) (2019) 1012-1021.
- [27] R. Yanhong, Z. Shuai, C. Dan, S. Xiaomin, Predictive value of lactate dehydrogenase for Mycoplasma pneumoniae necrotizing pneumonia in children based on decision curve analysis and dose–response analysis, *Scientific Reports* 14(1) (2024) 9803.
- [28] Q. Cheng, H. Zhang, Y. Shang, Y. Zhao, Y. Zhang, D. Zhuang, X. Cai, N. Chen, Clinical features and risk factors analysis of bronchitis obliterans due to refractory Mycoplasma pneumoniae pneumonia in children: a nomogram prediction model, *BMC infectious diseases* 21(1) (2021) 1085.
- [29] G. Li, L. Fan, Y. Wang, L. Huang, M. Wang, C. Zhu, C. Hao, W. Ji, H. Liang, Y. Yan, High co-expression of TNF- α and CARDS toxin is a good predictor for refractory Mycoplasma pneumoniae pneumonia, *Molecular medicine* 25(1) (2019) 1-10.
- [30] Z. Zhang, H. Dou, P. Tu, D. Shi, R. Wei, R. Wan, C. Jia, L. Ning, D. Wang, J. Li, Serum cytokine profiling reveals different immune response patterns during general and severe Mycoplasma pneumoniae pneumonia, *Frontiers in immunology* 13 (2022) 1088725.
- [31] E. Lee, Y.Y. Lee, Risk factors for the development of post-infectious bronchiolitis obliterans after Mycoplasma pneumoniae pneumonia in the era of increasing macrolide resistance, *Respiratory medicine* 175 (2020) 106209.
- [32] Y.J. Choi, E.H. Chung, E. Lee, C.-H. Kim, Y.J. Lee, H.-B. Kim, B.-S. Kim, H.Y. Kim, Y. Cho, J.-H. Seo, Clinical characteristics of macrolide-refractory Mycoplasma pneumoniae pneumonia in Korean children: a multicenter retrospective study, *Journal of clinical medicine* 11(2) (2022) 306.
- [33] P.M.M. Sauter, W.W. Unger, A.M. van Rossum, C. Berger, The art and science of diagnosing Mycoplasma pneumoniae infection, *The Pediatric infectious disease journal* 37(11) (2018) 1192-1195.
- [34] K. Edmond, S. Scott, V. Korczak, C. Ward, C. Sanderson, E. Theodoratou, A. Clark, U. Griffiths, I. Rudan, H. Campbell, Long term sequelae from childhood pneumonia; systematic review and meta-analysis, *PloS one* 7(2) (2012) e31239.
- [35] C. Epalza, A. Valadés-Alcaraz, J.M. González-Alba, C. Beltrán-Pavez, M. Gutiérrez-López, M. Rubio-Garrido, C. Fortuny, M.A. Frick, L.M. Medina, S. Moreno, Transmitted drug resistance and HIV diversity among adolescents newly diagnosed with HIV in Spain, *The Pediatric Infectious Disease Journal* 43(1) (2024) 40-48.