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*Original Article*

# Therapeutic outcomes and inflammatory modulation of inhaled N-acetylcysteine bronchoalveolar lavage in severe pneumonia

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**Abstract:** Objective: To evaluate the therapeutic efficacy of inhaled N-acetylcysteine (NAC) bronchoalveolar lavage (iNAC-BAL) in severe pneumonia (SP) and explore its effects on inflammatory cytokines modulation. Methods: A total of 146 SP cases were assigned to two groups: the control group received bronchoalveolar lavage with isotonic saline (0.9% NaCl) alone, while the observation group received additional NAC aerosol inhalation. Clinical efficacy, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, intensive care unit (ICU) stay, duration of ventilator dependence, adverse reactions, symptom resolution times, respiratory mechanics, pulmonary function, inflammatory cytokines, and humoral immunity were assessed and compared between the two groups. Results: The observation group achieved better therapeutic effects ($P=0.007$), with significantly lower APACHE II scores, shorter ICU stays, reduced ventilator dependence, faster symptom resolution, and fewer adverse events (all $P<0.05$). Additionally, respiratory dynamics, lung function, inflammatory cytokines, and humoral immunity improved markedly in the observation group compared with the control group (all $P<0.05$). Conclusion: iNAC-BAL demonstrates significant clinical efficacy and potent anti-inflammatory effects in the management of SP.

**Keywords:** Inhaled N-acetylcysteine, bronchoalveolar lavage, severe pneumonia, effectiveness, inflammatory cytokines

## Introduction

Lower respiratory tract infections accounted for 2.5 million deaths in 2019 globally [1], ranking the fourth leading cause of mortality worldwide. Severe pneumonia (SP), a particularly lethal form of these infections, carries a 20-50% death risk and often leads to life-threatening sequelae such as respiratory failure and neurological complications, posing a substantial economic burden on both families and society [2, 3]. SP typically presents with fever, cough, tachypnea, and discomfort, among other symptoms, compromising patient health to varying extents [4]. It is primarily caused by bacterial, viral, or fungal infections that induce pulmonary inflammation, with additional risk factors including pre-existing comorbidities, immunosuppression, and environmental exposures [5, 6]. Standard treatment relies on pathogen-specific antibiotics; however, this approach contributes to the growing problem of antimicrobial resistance, thereby diminishing treatment effectiveness [7]. This situation underscores the need for more effective interventions.

Bronchoalveolar lavage (BAL) is a therapeutic procedure performed via a bronchoscopy, in which saline is instilled into the bronchial and alveolar spaces, and then aspirated to remove pathological secretions [8]. In pediatric patients with treatment-resistant pneumonia, BAL effectively reduces inflammation while improving both immune defenses and pulmonary ventilation [9]. As a mucolytic drug, N-acetylcysteine (NAC) effectively decreases sputum viscosity and elasticity while exerting anti-inflammatory and antioxidant benefits, with a favorable safety profile and minimal systemic side effects

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[10, 11]. Although animal studies have demonstrated its efficacy in acute lung injury, results from human trials have been heterogeneous [12].

To address this knowledge gap, we compared inhaled NAC (iNAC) BAL (iNAC-BAL) with 0.9% saline BAL in SP treatment. This study introduces a novel BAL protocol utilizing aerosolized acetylcysteine, demonstrating potential advantages over conventional saline lavage in improving clinical outcomes. Second, by employing a comprehensive evaluation framework encompassing therapeutic efficacy, adverse events, symptom resolution time, respiratory mechanics, pulmonary function, inflammatory cytokines, and humoral immunity, our findings provide robust evidence supporting the clinical adoption of iNAC-BAL in SP treatment.

## Information and methodology

### *Patient data*

This retrospective study included 146 cases of SP treated at the First Affiliated Hospital of Guangxi Medical University between February 2022 and February 2025. Among them, 70 cases were assigned to the control group (0.9% saline BAL) and 76 to the observation group (iNAC-BAL). The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University. Based on standard statistical power analysis for two-group proportion comparisons ($\alpha=0.05$, power =80%), the minimum required sample size was calculated as 63 cases per group. The final enrollment met this requirement.

### *Inclusion and exclusion criteria*

Inclusion criteria: Clinically diagnosed SP [13]; Eligibility for BAL therapy without contraindications; Inadequate response to standard antibiotic treatment; Good treatment compliance; Complete clinical documentation.

Exclusion criteria: Allergy to study drugs; Severe hepatic, renal, or other organ disorders; Concurrent malignancy; Major respiratory disorders (e.g., asthma, airway obstructions, or structural malformations).

### *Treatment methods*

In the control group, therapeutic BAL was performed using 0.9% saline solution (Shanghai QiMing Biotechnology Co., Ltd., QMPB0351). Under anesthesia, a catheter was inserted transnasally or transorally into the bronchial airways. Fiberoptic bronchoscopy was utilized to continuously monitor insertion depth and final catheter placement, ensuring accurate positioning. Subsequently, 0.9% sodium chloride solution (500-1,000 mL per lavage cycle) was instilled, allowed to remain in contact with the airways for several minutes, and then aspirated along with pathological secretions using a suction device.

In the observation group, BAL was conducted using iNAC. Depending on patient condition, local or general anesthesia was applied, supplemented with sedatives as needed to maintain procedural tolerance. A ventilator was then connected via tracheal intubation to provide mechanical ventilation. Subsequently, NAC (Zhajiang Apeloa Pharmaceutical Co., Ltd., H20223651) was delivered to patients through nebulization to reduce sputum viscosity. This was followed by a saline-based lavage in which sterile saline was instilled into the lungs and then aspirated under negative pressure together with dissolved secretions. Post-lavage, NAC and saline administration were gradually withdrawn, and tracheal extubation was performed once the patient's condition stabilized.

### *Detection indicators*

(1) Efficacy [14]. Treatment response was radiologically assessed by comparing pre-treatment and day 4 post-treatment CT scans. Marked effectiveness: >50% lesion absorption; Effectiveness: <50% absorption; Ineffectiveness: No significant changes. Overall effectiveness (%) = (Marked effectiveness + Effectiveness cases)/ Total cases × 100%.

(2) Clinical outcomes [15]. Clinical status was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring, intensive care unit (ICU) stay, and duration of ventilator dependence. The APACHE-II system (total score 0-71) integrates physiological, chronic health, age, and coma indices, with higher scores indicating worse clinical status.

(3) Adverse events [16]. Treatment-related adverse events (e.g., nausea, vomiting, rashes, and leukopenia) were recorded, and incidence rates were calculated.

**Table 1.** Comparison of baseline characteristics between the two groups

| Data | Control group (n=70) | Observation group (n=76) | $\chi^2$/t | P |
|---|---|---|---|---|
| Male | 42 (60.00) | 44 (57.89) | 0.067 | 0.796 |
| Age (years) | 56.56±6.60 | 57.79±7.30 | 1.065 | 0.289 |
| Disease duration (d) | 4.90±1.95 | 5.64±2.54 | 1.962 | 0.052 |
| Affected site | | | 0.759 | 0.859 |
| Right upper lobe | 21 (30.00) | 24 (31.58) | | |
| Right middle lobe | 19 (27.14) | 16 (21.05) | | |
| Right lower lobe | 14 (20.00) | 17 (22.37) | | |
| Left upper lobe | 16 (22.86) | 19 (25.00) | | |
| Cerebrovascular disease | 21 (30.00) | 24 (31.58) | 0.043 | 0.837 |
| Coronary heart disease | 7 (10.00) | 10 (13.16) | 0.353 | 0.552 |
| Diabetes | 13 (18.57) | 12 (15.79) | 0.199 | 0.656 |
| Hypertension | 20 (28.57) | 16 (21.05) | 1.109 | 0.292 |

(4) Symptomatic recovery time [17]. Time to clinical improvement for dyspnea, fever, chest distress, and cough were compared between groups.

(5) Respiratory mechanics [18]. Pulmonary mechanics, including airway resistance (Raw), work of breathing (WOB), dynamic compliance (Cdyn) were measured using an electronic spirometer (Shanghai Huanyi Medical Devices Co., Ltd., SF-1) at baseline and after 7 days of treatment.

(6) Lung function [19]. Peak expiratory flow (PEF), maximum voluntary ventilation (MMV), and forced expiratory volume in 1 second (FEV1) were measured using a digital spirometer (Shanghai Zhiheng Medical Devices Co., Ltd., HI-205) before treatment initiation and after 7 days of therapy.

(7) Inflammatory cytokines [20]. Enzyme-linked immunosorbent assay (ELISA) was employed to measure circulating inflammatory mediators (interleukin [IL]-6, IL-8, tumor necrosis factor (TNF)-α) in serum samples of fasting venous blood (5 mL) at treatment initiation and day 7. All procedures followed the manufacturers' instructions (YOBIBIO (Shanghai) Biotechnology Co., Ltd.; U96-1510E, U96-1513E, U96-3716E).

(8) Humoral immunity [21]. Immunonephelometric assays were conducted to quantify serum immunoglobulin (Ig)G, IgA, and IgM levels. The experimental operations were conducted with strict adherence to the specifications of the corresponding measurement kits (Shanghai Yuduo Biotechnology Co., Ltd.; YDLC-5784, YDLC-2705, YDLC-5777).

*Statistical methods*

All statistical analyses were performed using SPSS 21.0 (IBM). Categorical variables were expressed as counts and percentages (n/%) and compared using Pearson's chi-square test. Continuous variables were expressed as mean ± standard error of the mean (SEM) and analyzed using independent-samples t-tests for between-group comparisons and paired t-tests for within-group (pre- vs. post-treatment) comparisons. All tests were two-tailed, and a *P* value <0.05 was considered statistically significant.

## Results

*Comparison of baseline characteristics between the two groups*

As shown in **Table 1**, there were no significant differences between groups in sex distribution, disease course, affected site, or comorbidities (cerebrovascular disease, coronary artery disease, diabetes, and hypertension) (P>0.05), indicating good baseline comparability.

*Comparison of treatment efficacy between the two groups*

As presented in **Table 2**, the observation group demonstrated significantly higher clinical effectiveness compared to the control group (P<0.01).

*Comparison of clinical outcomes between the two groups*

Post-treatment APACHE II scores, length of ICU stay, and duration of ventilator dependence were all significantly lower in the observation group compared to the controls (P<0.001; **Table 3**).

**Table 2.** Comparison of treatment efficacy between the two groups

| Therapeutic effectiveness | Control group (n=70) | Observation group (n=76) | $\chi^2$ | P |
|---|---|---|---|---|
| Marked effectiveness | 28 (40.00) | 38 (50.00) | | |
| Effectiveness | 25 (35.71) | 32 (42.11) | | |
| Ineffectiveness | 17 (24.29) | 6 (7.89) | | |
| Overall effectiveness | 53 (75.71) | 70 (92.11) | 7.376 | 0.007 |

**Table 3.** Comparison of clinical outcomes between the two groups

| Parameters | Control group (n=70) | Observation group (n=76) | t | P |
|---|---|---|---|---|
| APACHE II | | | | |
| Before | 22.60±4.15 | 21.53±4.91 | 1.416 | 0.159 |
| After | 18.11±5.06 | 12.80±4.70 | 6.574 | <0.001 |
| Length of ICU stay (d) | 16.96±5.36 | 12.92±4.61 | 4.894 | <0.001 |
| Ventilator dependence duration (d) | 27.64±8.30 | 19.11±7.44 | 6.548 | <0.001 |

Note: APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit.

**Table 4.** Comparison of incidence of adverse events between the two groups

| Categories | Control group (n=70) | Observation group (n=76) | $\chi^2$ | P |
|---|---|---|---|---|
| Nausea/vomiting | 3 (4.29) | 0 (0.00) | | |
| Rash | 4 (5.71) | 1 (1.32) | | |
| Leukopenia | 4 (5.71) | 2 (2.63) | | |
| Total | 11 (15.71) | 3 (3.95) | 5.820 | 0.016 |

**Table 5.** Comparison of symptom resolution time between the two groups

| Categories | Control group (n=70) | Observation group (n=76) | t | P |
|---|---|---|---|---|
| Dyspnea (d) | 2.29±0.87 | 1.51±0.60 | 6.348 | <0.001 |
| Fever (d) | 3.09±1.10 | 1.71±0.67 | 9.235 | <0.001 |
| Chest distress (d) | 3.60±1.50 | 1.58±0.59 | 10.865 | <0.001 |
| Cough (d) | 3.69±1.81 | 2.68±1.16 | 4.046 | <0.001 |

*Comparison of incidence of adverse events between the two groups*

The safety profiles of both groups were assessed by documenting the occurrence of nausea/vomiting, rashes, and leukopenia. The overall incidence of adverse events was significantly lower in the observation group (3.95%) compared to the control group (15.71%) (P<0.05; **Table 4**).

*Comparison of time to symptom improvement between the two groups*

As shown in **Table 5**, the observation group experienced significantly shorter times to improvement in dyspnea, fever, chest distress, and cough compared with the control group (P<0.001).

*Comparison of respiratory mechanics between the two groups*

As shown in **Figure 1**, baseline Raw, WOB, and Cdyn values were comparable between groups (P>0.05). After treatment, both groups showed significant improvements, with declined Raw and WOB and increased Cdyn (P<0.05). The observation group outperformed controls, with notably lower Raw and WOB values and higher Cdyn levels (P<0.05).

*Comparison of pulmonary function between the two groups*

As illustrated in **Figure 2**, baseline PEF, MMV, and FEV1 were similar between groups (P>0.05). After treatment, all these metrics improved significantly, with the observation group achieving significantly higher PEF, MMV, and FEV1 values than the control group (P<0.05).

*Comparison of inflammatory cytokine levels between the two groups*

**Figure 3** presents changes in IL-6, IL-8, and TNF-α levels. Baseline values were comparable between groups (P>0.05). After treatment,

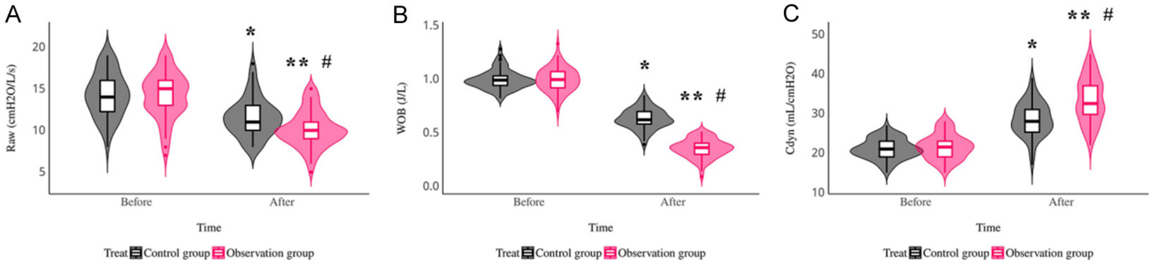


**Figure 1.** Comparison of respiratory mechanics between the two groups before and after treatment. A. Airway resistance (Raw); B. Work of breathing (WOB); C. Dynamic compliance (Cdyn). *P<0.05, **P<0.01, compared with baseline value; #P<0.05, compared with control group at the same time.

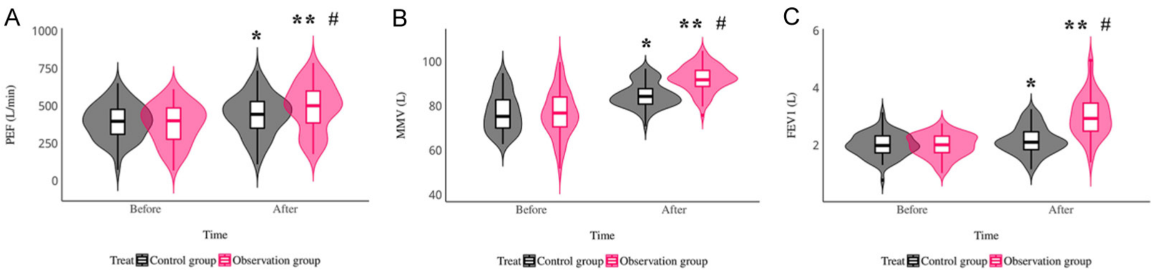


**Figure 2.** Comparison of pulmonary function between the two groups before and after treatment. A. Peak expiratory flow (PEF); B. Maximum voluntary ventilation (MMV); C. Forced expiratory volume in 1 second (FEV1). Note: *P<0.05, **P<0.01, compared with baseline value; #P<0.05, compared with control group at the same time.

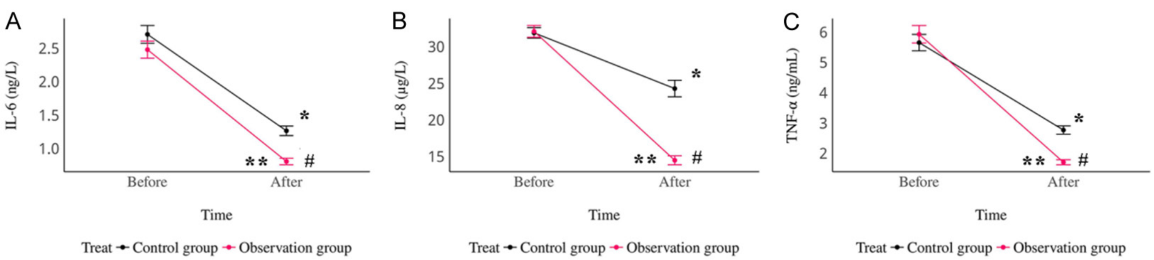


**Figure 3.** Comparison of inflammatory cytokine levels between the two groups before and after treatment. A. IL-6; B. IL-8; C. TNF-α. Note: IL, interleukin; TNF, tumor necrosis factor; *P<0.05, **P<0.01, compared with baseline value; #P<0.05, compared with control group at the same time.

all three cytokines decreased significantly in both groups, with significantly greater reductions observed in the observation cohort (P<0.05).

*Comparison of humoral immunity between the two groups*

As presented in **Figure 4**, baseline serum IgA, IgM, and IgG levels were similar between groups (P>0.05). Following therapy, all immunoglobulin levels increased significantly in both groups (P<0.05), with the observation group showing significantly greater increases for all isotypes compared with the control group (P<0.05).

## Discussion

Our research revealed that iNAC-BAL provides superior therapeutic efficacy over saline lavage in the treatment of SP. This aligns with the results of Li et al. [11], who reported similar benefits in pediatric children with refractory *Mycoplasma pneumoniae* pneumonia. In our study, iNAC-BAL was associated with greater reductions in APACHE II scores, shorter ICU stays, and reduced mechanical ventilation

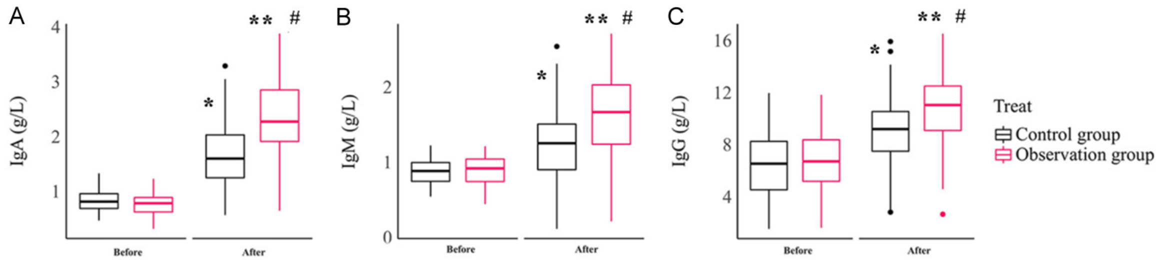


**Figure 4.** Comparison of humoral immune parameters between the two groups before and after treatment. A. IgA; B. IgM; C. IgG. Note: Ig, immunoglobulin; *P<0.05, **P<0.01, compared with baseline value; #P<0.05, compared with control group at the same time.

duration, demonstrating improved disease control and overall treatment effectiveness. Tomioka et al. [22] reported in their study that iNAC delays the progression of idiopathic pulmonary fibrosis, which was associated with the alleviation of alveolar injury, inhibition of active lesions on CT imaging, and reduced serum Krebs Von den Lungen-6 (KL-6) levels. Such mechanisms may partly underlie the therapeutic benefits of iNAC in SP. Furthermore, Sharafkhah M et al. [23], demonstrated that nasogastric administration of NAC in patients with ventilator-associated pneumonia significantly reduced both ICU and total hospital stay lengths, supporting our current observations. In murine lung injury models, NAC administration effectively mitigated lipopolysaccharide-induced inflammation and pulmonary tissue damage. This therapeutic effect is potentially mediated through upregulation of antioxidant gene expression at the mRNA level, which provides a plausible mechanistic basis for the observed clinical benefits of iNAC-BAL in SP management and its disease-modifying effects [24].

For SP cases, iNAC-BAL enhanced patient safety and accelerated recovery. It minimized the incidence of complications such as nausea/vomiting, rash, and leukopenia, while shortening the resolution time for symptoms including dyspnea, fever, chest distress, and persistent cough. The likely explanation is that iNAC delivers targeted treatment to the airways, enabling rapid local action at lower doses and thereby promoting faster symptom resolution [25]. Calverley et al. [26] reported that NAC exhibits a favorable safety and tolerability profile across multiple respiratory diseases, including chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, bronchiectasis, chronic bronchitis, and cystic fibrosis, with no significant safety differences between high and standard doses. Similarly, Xue et al. [27] showed in a cohort of 98 pediatric pneumonia patients that NAC plus ambroxol hydrochloride effectively shortened fever duration, relieved cough, and resolved pulmonary rales. Furthermore, improvements in lung function and immune response were observed, with elevated levels of FVC, FEV1, IgA, IgG, and IgM, corroborating our findings.

SP is clinically recognized to impair pulmonary oxygenation efficiency, leading to adverse changes in respiratory mechanics and lung function. These impairments are reflected by elevated Raw and WOB values, accompanied by reduced Cdyn value [28, 29]. Moreover, lesioned tissues induce excessive inflammatory cytokine production, which not only exacerbate airway injury but also increase lung infection risks, further compromising patients' pulmonary function [30]. In our study, iNAC-BAL significantly improved respiratory mechanics and lung function in SP cases compared with saline lavage. Similar findings were reported by Wu L et al. [31], who reported that this intervention enhanced respiratory mechanics and blood gas parameters in elderly patients with severe ventilator-associated pneumonia, while also shortening the duration of mechanical ventilation and antibiotic therapy. Li et al. [32], further demonstrated, in a prospective randomized controlled trial, that NAC not only enhanced respiratory function but also effectively decreased TNF-α and IL-8 levels in exhaled breath condensate of surgical patients, results that are consistent with and complementary to our findings. Moreover, therapeutic bronchoscopy with iNAC was shown to be clinically effective in managing SP by suppressing systemic inflammation and enhancing humoral immunity. Controlling the cytokine storm to prevent inflammatory lung injury has been emphasized as a vital therapeutic strategy for critically ill patients [33]. In individuals with impaired immune defenses, immune dysregulation often manifest as persistent fever and dyspnea; In severe infections, this dysregulation may escalate into a cytokine storm characterized by excessive secretion of IL-6 and TNF-α, further aggravating the condition [34]. Research has demonstrated that iNAC administered via BAL can effectively regulate cytokine and growth factor profiles in animal models of allergic asthma, although with potential drawbacks such as reduced respiratory protective mechanisms [35]. The anti-inflammatory effects of iNAC may be mediated by reductions in lactoferrin, antichymotrypsin, and eosinophil cationic protein (ECP) levels, as well as by attenuation of neutrophil chemotaxis and partial suppression of the NF-κB axis, contributing to multi-targeted airway inflammation relief [36].

This study has several limitations that warrant consideration. First, the absence of 3-5 year follow-up data precludes a comprehensive evaluation of the long-term benefits of iNAC-BAL. Second, potential predictors of treatment response and long-term prognosis in SP remain unidentified; incorporating such assessments may facilitate risk-stratified management. Third, no fundamental experiments were conducted to decipher the biological mechanisms underlying iNAC-BAL's effects. Future mechanistic studies are therefore essential for a more comprehensive understanding.

## Conclusion

iNAC-BAL is an effective treatment for SP, capable of improving therapeutic outcomes, accelerating disease control, and reducing ICU stays and ventilation dependence duration. In addition to its favorable safety profile, it promotes symptom resolution, enhances respiratory mechanics and lung function, strengthens humoral immunity, and suppresses inflammation.

## Disclosure of conflict of interest

None.

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