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Ipratropium bromide nebulization plus SOM: Protective effects in severe pneumonia with respiratory failure

Xiao Fang#, Fangfang Zhang# and Tingting Wu*

Department of Emergency Intensive Care Unit, Nanjing First Hospital, Nanjing Medical University;Nanjing First Hospital, China Pharmaceutical University, Nanjing First Hospital, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, 210000, China.

Abstract: **Background**: The additional pharmacological effects of ipratropium bromide, a short-acting anticholinergic agent, remain controversial within the context of standardized stress-oriented management (SOM). **Objectives**: To evaluate the effects of SOM combined with ipratropium bromide nebulization therapy on oxygenation status, respiratory mechanics, inflammatory stress responses and clinical outcomes in patients with severe pneumonia (SP) complicated with respiratory failure (RF) (SP+RF). **Methods**: This study retrospectively analyzed 168 patients with SP and RF admitted between March 2024 and August 2025 were enrolled and divided into an observation group (n = 81) and a control group (n = 87) based on whether they received ipratropium bromide nebulization therapy. Primary outcome measures included: oxygenation status, respiratory mechanics parameters, incidence of multiple organ dysfunction syndrome (MODS) and organ function indicators, inflammatory and stress markers, and clinical outcomes. **Results**: Regarding oxygenation status, the observation group demonstrated superior PaO_2/FiO_2, SpO_2 and blood lactate results compared to the control group at 24 hours post-treatment (T1) and 48 hours post-treatment (T2) ($p<0.05$). Respiratory mechanics parameters showed that airway resistance (Raw), peak airway pressure (Ppeak) and plateau pressure (Pplat) were lower in the observation group than in the control group at T1 ($p<0.05$); static lung compliance (Cst) showed more pronounced improvement at T2. Additionally, the incidence of MODS was lower in the observation group ($p<0.05$). Regarding inflammatory markers, the observation group exhibited lower levels of CRP and cortisol ($p<0.05$). Clinical outcomes demonstrated shorter DMV and length of hospital stay in the observation group ($p<0.05$), but no statistically significant difference was observed between the two groups in 28d-M ($p>0.05$). **Conclusion**: In patients with SP+RF, SOM plus ipratropium bromide nebulization significantly improves oxygenation status, respiratory mechanics, and inflammatory stress responses, shortens the duration of mechanical ventilation and the length of hospital stay, and reduces the risk of MODS.

Keywords: Ipratropium bromide; Inflammatory response; MODS; RF; Stress-oriented management

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INTRODUCTION

Severe pneumonia (SP) complicated with respiratory failure (RF) (SP+RF) is a common critical condition in respiratory medicine (Jackson, 2023). Research indicates that approximately 40% to 60% of patients with SP progress to RF and persistent oxygenation impairment may activate systemic inflammatory responses, triggering multiple organ dysfunction syndrome (MODS) and further exacerbating disease progression (G. Liu *et al.*, 2023; Wilcox & Condella, 2021). Therefore, in addition to anti-infection treatment, improving oxygenation status and blocking inflammatory cascades to reduce the risk of MODS are critical therapeutic components (Anai *et al.*, 2021). Current clinical management strategies for such patients primarily include mechanical ventilation support, anti-inflammatory therapy and complication prevention (Ling *et al.*, 2024). Among them, stress-oriented management (SOM), which reduces the release of stress hormones by precisely regulating the depth of sedation and maintaining hemodynamic stability, has been proven to mitigate systemic inflammatory responses (Tu *et al.*, 2025; Koehler *et al.*, 2021). It has now become the mainstream management strategy for these patients (Liu B *et al*., 2023; Tu X *et al*., 2025), supported by clinical evidence on stress regulation in critical respiratory illness. For this study, the term pharmacological protective effects is defined as the organ-protective and clinically beneficial effects of a drug exerted through its specific pharmacological actions, including improving oxygenation status and respiratory mechanics, inhibiting inflammatory and stress responses, reducing the incidence of multiple organ dysfunction syndrome (MODS) and shortening the duration of mechanical ventilation and hospital stay in patients with SP+RF. However, controversy persists regarding the specific medications used.

Ipratropium bromide, a short-acting anticholinergic agent, dilates bronchi and reduces airway secretions by selectively antagonizing M receptors when administered via nebulization (Gong *et al.*, 2025). Theoretically, it can improve the ventilation-perfusion ratio, but its actual efficacy under a standardized SOM background remains controversial. Existing studies predominantly focus on the independent effects of single drugs or SOM (Llor *et al.*,

**Corresponding author:* e-mail: 13851521623@163.com
#These authors contributed equally and are the co-first authors.

2023), lacking comparative analyses centered on ipratropium bromide as the core variable within the "standardized SOM + adjunctive drug" model. Evidence remains insufficient, particularly regarding its clinical pharmacologic effects in dynamically improving oxygenation, suppressing inflammatory stress and reducing MODS risk.

Therefore, this retrospective cohort study was conducted to investigate the clinical pharmacologic effects of SOM combined with ipratropium bromide nebulization in patients with SP+RF. By minimizing confounding factors associated with variations in SOM implementation, this study aimed to primarily evaluate its additive pharmacological effects, thereby overcoming the limitations of multiple-factor confounding in traditional "comprehensive management" studies and providing direct evidence for precise medication. This study thus addresses a critical research gap: the paucity of clinical evidence regarding the efficacy of ipratropium bromide when administered within a standardized SOM framework for patients with SP+RF. The findings were to clarify the pharmacologic and protective effects of ipratropium bromide in patients with SP+RF and to provide evidence-based support for optimizing the selection of respiratory support drugs and reducing the risk of MODS in clinical practice, demonstrating significant practical importance.

MATERIALS AND METHODS

Study design

A retrospective cohort analysis was conducted based on the medical records of patients with SP+RF admitted to our hospital between March 2024 and August 2025. The primary endpoint was 28-day mortality (28d-M). Based on prior studies (Antonakos *et al.,* 2025), it was hypothesized that SOM plus ipratropium bromide would reduce mortality from 40% to 25%. The significance level was set at $\alpha = 0.05$ (two-sided), with a power of $1- \beta = 0.8$. Additionally, a 10% dropout rate was taken into account. Using PASS software for calculations, each group shall include at least 76 participants. To minimize and overcome potential confounding factors in this retrospective cohort study, multiple methodological strategies were adopted: Strict standardization of stress-oriented management (SOM) for all enrolled patients, including unified sedation/analgesia targets, hemodynamic maintenance criteria and metabolic regulation protocols, to eliminate variations in basic management; (2) Rigorous inclusion and exclusion criteria to exclude patients with comorbidities that may interfere with the study outcomes (e.g., severe heart failure, immunosuppression, COPD/asthma); (3) Baseline data balance verification (Table 1), confirming no statistically significant differences in age, gender, Acute Physiology and Chronic Health Evaluation II (APACHE II) (Lanspa *et al.*, 2021), Sequential Organ Failure Assessment (SOFA) (Moreno *et al.*, 2023) and other clinical characteristics between the two groups, which reduced the impact of baseline heterogeneity; (4) Group assignment based on real-world clinical treatment preference with consistent clinical practice protocols, to avoid artificial confounding in intervention allocation.

Study participants

Inclusion criteria: (1) Meeting the diagnosis criteria for SP (Su & He, 2025); (2) Confirmed RF ($PaO_2/FiO_2 \leq 300$ mmHg, or requiring invasive/non-invasive mechanical ventilation) (Chen & Rackley, 2024); (3) Aged 18–70 years; (4) Complete medical records (including baseline indicators, treatment records and follow-up data); (5) Having received standardized SOM after admission *Exclusion criteria*: (1) Complicated with acute exacerbation of COPD or status asthmaticus; (2) Serious heart failure (LVEF < 35%) or acute myocardial infarction; (3) Immunosuppressed state (e.g., chemotherapy for malignancy, long-term glucocorticoid use > 10 mg/day prednisone equivalent); (4) Death or transfer to another hospital within 48 hours of admission; (5) Pregnant or lactating women; (6) History of ipratropium bromide allergy. After screening, 168 participants were enrolled: 81 in the observation group and 87 in the control group. The Ethics committee of our hospital approved this study and all subjects signed an informed consent form. Group assignment was based on clinical physician treatment preference in real-world practice.

Grouping and intervention

All patients received SOM upon admission. For sedation and analgesia, the target Richmond Agitation-Sedation Scale (RASS) score was -2 to 0 (Medlej, 2021). Sedation was achieved using propofol or dexmedetomidine, with fentanyl administered when necessary. For hemodynamics, the mean arterial pressure (MAP) was maintained at ≥65 mmHg, avoiding blood pressure fluctuations (<20%), with norepinephrine administered as needed (De Backer *et al*., 2024). For metabolic regulation: Blood glucose was maintained between 7.8–10 mmol/L (via continuous insulin pump infusion), with early enteral nutrition provided within 24–48 hours of ICU admission. In the control group, Salbutamol nebulizer solution (2.5 mg/dose, diluted with 3 mL of normal saline) was administered via oxygen-driven nebulization (flow rate: 6–8 L/min) for a single inhalation. If ineffective after 15–20 minutes, the dose could be re-administered once, with a maximum dose of ≤10 mg (i.e., 4 doses) within 24 hours. Salbutamol was selected for the control group because it is the first-line, short-acting bronchodilator in clinical practice for patients with SP+RF at our institution, consistent with routine clinical therapeutic strategies for respiratory failure associated with airway obstruction. In the observation group, ipratropium bromide (0.5 mg/dose, diluted with 3 mL of normal saline) was administered via oxygen-driven nebulization (flow rate: 6–8 L/min) for a single inhalation,

once every 6–8 hours. Drug administration in both groups continued until correction of RF (PaO_2/FiO_2 > 300 mmHg and weaning from mechanical ventilation), with a maximum duration of 14 days.

Outcome measures

Baseline data (age, gender, APACHE II score, SOFA score, and Smoking Status) for patients were collected. (2) PaO_2/FiO_2, SpO_2, blood lactate, airway resistance (Raw), static lung compliance (Cst), peak airway pressure (Ppeak) and plateau pressure (Pplat) were monitored before treatment (T0), at 24 hours after treatment (T1) and at 48 hours after treatment (T2). (3) The incidence of MODS was calculated and the Marshall score (six organ systems: respiratory, cardiovascular, renal, hepatic, coagulation and neurological) was used as a reference (Ware *et al.*, 2024). MODS was defined as any organ with a score ≥2 and a cumulative involvement of ≥2 organs (Tang *et al.*, 2024). Organ function was assessed by monitoring the following indicators: respiratory system ($PaCO_2$), renal function (serum creatinine, urine output), hepatic function (ALT) and coagulation function (PLT). (4) ELISA for measuring IL-6, TNF-α, CRP and Cor levels [before (T0) and after treatment (T2)]. (5) The 28d-M, duration of mechanical ventilation (DMV), length of ICU stay and total length of hospital stay.

Statistical analysis

SPSS 26.0 software was adopted. Measurement data were expressed as ($\bar{\chi}\pm s$), with intergroup comparisons conducted using the independent-samples t-test. Repeated-measures data were analyzed using a repeated-measures analysis of variance (ANOVA). Enumeration data were presented as frequencies (%), with intergroup comparisons performed using the χ^2 test or Fisher's exact test. $p<0.05$ was considered statistically significant.

RESULTS

Clinical baseline data

There was no difference in the age, gender, APACHE II, SOFA and Smoking between the two groups of patients ($p>0.05$) (Table 1).

Oxygenation status

Dynamic monitoring of oxygenation status during patient treatment revealed no differences between groups in PaO_2/FiO_2, SpO_2, or blood lactate levels at T0 ($p>0.05$). From T1 to T2, PaO_2/FiO_2 and SpO_2 continued to increase in both groups and were higher in the observation group ($p<0.05$); while blood lactate levels showed a decreasing trend and were lower in the observation group ($p<0.05$) (Fig. 1).

Respiratory mechanics

Regarding respiratory mechanics, no differences were observed in Raw, Cst, Ppeak and Pplat at T0 between the two groups ($p>0.05$). At T1, Raw, Ppeak and Pplat began to decrease in both groups, while Cst increased ($p<0.05$). At T1, there was no difference in Cst ($p>0.05$), but the Raw, Ppeak and Pplat in the observation group were lower ($p<0.05$). At T2, the Cst in the observation group was also higher than that in the control group ($p<0.05$) (Fig. 2).

Safety parameters

Baseline Marshall scores for organ function prior to treatment and the temporal progression of MODS in both groups were not collected and analyzed in this study due to retrospective data limitations. Regarding safety, the incidence of MODS was lower in the observation group relative to the control group ($p<0.05$). Specifically, no differences were observed between the two groups in ALT and PLT levels ($p>0.05$). However, compared to the control group, the observation group demonstrated lower $PaCO_2$ and serum creatinine levels and higher 24-hour urine output ($p<0.05$) (Table 2).

Inflammatory and stress reactions

Inflammatory and stress factors were measured in both groups, with no differences in pre-treatment data between groups ($p>0.05$). After treatment, IL-6, TNF-α, CRP and Cor levels decreased in both groups ($p<0.05$). Specifically, there were no differences in IL-6 and TNF-α between the two groups ($p>0.05$), but CRP and Cor were significantly lower in the observation group compared to the control group ($p<0.05$) (Fig. 3).

Clinical outcomes

There was no difference in 28d-M between the two groups ($p>0.05$). However, shorter DMV, length of ICU stays and total length of hospital stay were observed in the observation group ($p<0.05$) (Table 3).

DISCUSSION

This retrospective cohort analysis revealed that, in patients with SP+RF, SOM combined with nebulized ipratropium bromide therapy improved oxygenation status, respiratory mechanics, and inflammatory stress responses, and shortened the DMV and length of hospital stay. However, it had no significant impact on 28d-M. These findings suggest the potential value of ipratropium bromide in optimizing short-term efficacy and organ protection. Specifically, the combination of ipratropium bromide and SOM rapidly improves the oxygenation index (PaO_2/FiO_2) and respiratory mechanics parameters (Raw, Ppeak, Pplat). It is worth noting that the Cst of the observation group was higher at T2, suggesting that ipratropium bromide may improve alveolar elasticity by alleviating pulmonary parenchymal inflammation and edema—a mechanistic hypothesis supported by prior studies but not directly verified by the data of this study.

Table 1: Baseline data of the study subjects

Groups	Age	Gender		APACHE II	SOFA	Smoking	
		male	female	score	score	yes	no
Control (n=76)	54.12±11.35	42 (55.3)	34 (44.7)	19.96±3.97	8.74±1.74	34 (44.7)	42 (55.3)
Observation (n=76)	52.75±13.52	46 (60.5)	30 (39.5)	19.59±4.16	8.91±2.07	38 (50.00)	38 (50.00)
t or χ2	0.676	0.432		0.558	0.552	0.422	
p	0.500	0.511		0.577	0.582	0.516	

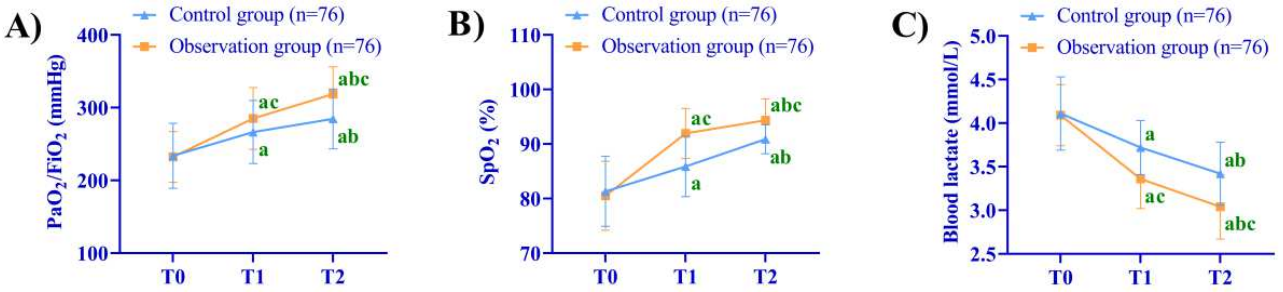

Fig. 1: Changes in oxygenation status during treatment. A) Changes and comparisons of SpO2. B) Changes and comparisons of PaO2/FiO2. C) Changes and comparisons of blood lactate. Note: vs. T0, ap<0.05, vs. T1 bp<0.05, vs. control group, cp<0.05.

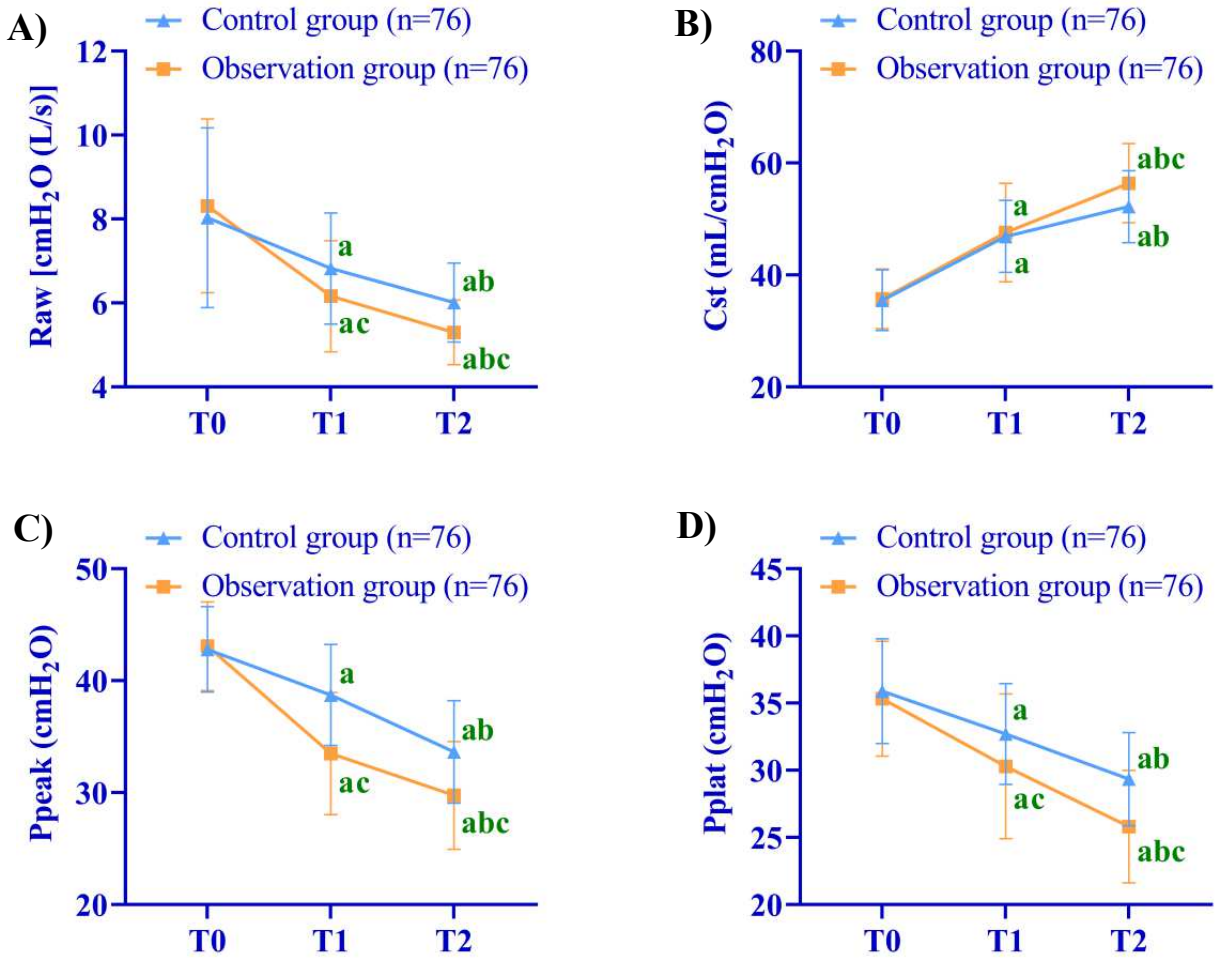

Fig 2: Changes in respiratory mechanics during treatment. A) Changes and comparisons of Raw. B) Changes and comparisons of Cst. C) Changes and comparisons of Ppeak. D) Changes and comparisons of Pplat. Note: vs. T0, ap<0.05, vs. T1 bp<0.05, vs. control group, cp<0.05.

Table 2: Safety parameters of the study subjects

Groups	MODS	ALT (U/L)	PLT (×109/L)	PaCO2 (mmHg)	Serum creatinine (μmol/L)	24h urine output (mL/kg/h)
Control (n=76)	17 (22.4)	34.29±4.72	92.15±11.78	45.00±4.31	76.42±11.95	0.42±0.08
Observation (n=76)	8 (10.5)	34.21±4.51	94.82±15.64	42.57±3.25	71.52±10.83	0.47±0.14
t or χ2	3.878	0.098	1.186	3.933	2.645	2.839
p	0.049	0.922	0.238	<0.001	0.009	0.005

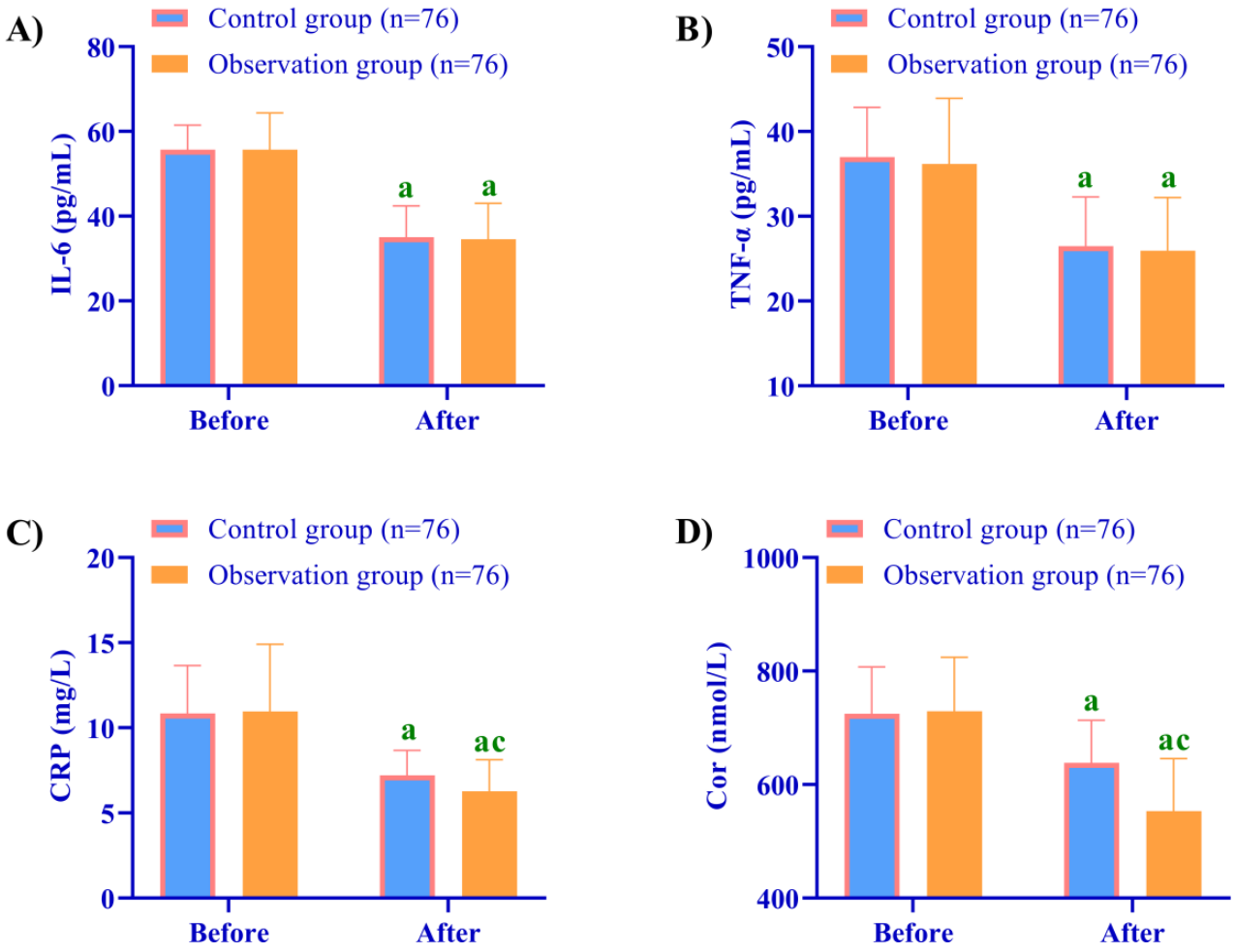

Fig. 3: Changes in inflammatory and stress reactions during treatment. A) Changes and comparisons of IL-6. B) Changes and comparisons of TNF-α. C) Changes and comparisons of CRP. D) Changes and comparisons of Cor. Note: vs. T0, ap<0.05, vs. control group, cp<0.05.

Table 3: Clinical outcomes of the study subjects

Group	28d-M	DMV (d)	Length of ICU stay (d)	Length of stay (d)
Control (n=76)	20 (26.3)	10.51±2.36	14.32±2.56	25.32±3.26
Observation (n=76)	15 (19.7)	9.49±2.14	12.54±2.04	22.82±2.92
t or χ2	0.928	2.811	4.732	4.974
p	0.335	0.006	<0.001	<0.001

Similarly, the assertions that ipratropium bromide protects alveolar epithelial integrity and inhibits vagal nerve-mediated pro-inflammatory signal transduction are based on existing mechanistic research in the field, rather than direct experimental or clinical data collected in the present study (El Khoury *et al.*, 2023). Concurrently, SOM indirectly improves pulmonary perfusion and promotes alveolar recruitment by stabilizing hemodynamics and reducing stress hormone release (e.g., cortisol) (B. Liu *et al.*, 2023). The combination may enhance oxygenation efficiency through a dual mechanism of "airway dilation + optimized oxygen delivery." It is worth noting that the Cst of the observation group was lower at T2, suggesting that ipratropium bromide may improve alveolar elasticity by alleviating pulmonary parenchymal inflammation and edema. This aligns with previous studies indicating that ipratropium bromide mitigates alveolar epithelial injury by inhibiting the release of cholinergic neurogenic inflammatory mediators such as IL-8 and TNF-α (Lin *et al.*, 2022). However, unlike previous studies, no intergroup differences in IL-6 or TNF-α were observed in this study, which may be related to sample size or timing of determination (e.g., the inflammatory peak occurring at an earlier stage); it is also plausible that ipratropium bromide has no true modulatory effect on these specific inflammatory markers. As an acute-phase protein, CRP levels correlate positively with the severity of inflammation (Xie *et al.*, 2024). Elevated Cor reflects the body's stress state, and long-term hypercortisolemia is closely associated with immunosuppression and organ failure (Wu *et al.*, 2023). The decrease in CRP and Cor in the observation group suggests that ipratropium bromide may exert organ-protective effects by inhibiting inflammatory cascades and stress responses. Therefore, we hypothesize that ipratropium bromide may regulate inflammation through the following pathways: 1. inhibiting vagal nerve-mediated pro-inflammatory signal transduction (Arslan *et al.*, 2023); 2. improving alveolar ventilation and reducing hypoxia-induced inflammatory factor release (Duan *et al.*, 2021). Additionally, SOM further synergistically suppresses systemic inflammatory responses by maintaining hemodynamic stability and glucose regulation (Al-Rouq *et al.*, 2022).

A key mismatch in this study is the lack of a statistically significant difference in the primary endpoint (28-day mortality), despite the a priori hypothesis that ipratropium bromide would reduce mortality, while most positive findings are limited to secondary endpoints (e.g., oxygenation, respiratory mechanics, DMV, hospital stay). This mismatch raises concerns about the potential inflation of Type I error, which may be attributed to multiple factors: the small sample size leading to insufficient statistical power for the primary endpoint, the pharmacological confounding of salbutamol in the control group and the high heterogeneity of mortality-related factors (e.g., comorbidities, pathogen virulence) in critically ill patients. Therefore, the positive findings of the secondary endpoints should be interpreted with caution and their clinical significance should be combined with real-world clinical practice rather than overinterpretation.

All mechanistic claims regarding the pharmacological actions of ipratropium bromide in this study, including improvements in alveolar elasticity, epithelial protection and inhibition of vagal-mediated inflammatory signaling, are labeled as hypotheses derived from clinical indicator changes and existing literature evidence, rather than definitive conclusions inferred directly from the study's own data. Although no significant difference in 28d-M was observed between the two groups, the DMV and the length of ICU stay were shorter in the observation group. Factors potentially contributing to the failure to achieve the expected difference in mortality include: 1. sample size limitations (although calculated via PASS, the actual MODS incidence was lower than the preset threshold); 2. the use of salbutamol in the control group may have partially offset the therapeutic difference of ipratropium bromide. It is important to acknowledge that this study does not compare ipratropium bromide with a placebo or no bronchodilator therapy, but rather compares an anticholinergic bronchodilator strategy with a β_2-adrenergic agonist strategy. The use of salbutamol introduces a pharmacological confounder and thus the observed therapeutic differences cannot be solely attributed to ipratropium bromide monotherapy effects; 3. mortality risk is significantly influenced by underlying conditions (e.g., comorbidities, pathogen virulence), necessitating further expanded stratified analysis. 4. use of salbutamol in the control group, which may have attenuated the observed between-group differences in therapeutic efficacy. As a short-acting β2 agonist, salbutamol exerts bronchodilatory effects that partially overlap with the pharmacological actions of ipratropium bromide, potentially masking the full additive benefits of ipratropium bromide combined with SOM. Furthermore, the retrospective cohort design inherently limits causal inference, as treatment allocation was not randomized despite standardized SOM implementation, leaving potential room for selection bias in group assignment. Notably, this study did not perform propensity score matching or multivariable regression analysis to further adjust for potential confounding variables, which could have strengthened the statistical confidence in the observed associations between the intervention and clinical outcomes. Future studies are recommended to adopt these statistical methods to validate the findings. Additionally, this study did not assess specific biomarkers of alveolar epithelial injury (e.g., surfactant protein-D [SP-D], receptor for advanced glycation end products [RAGE]), nor did it measure indicators related to airway mucus secretion and vascular permeability, which limits the ability to verify the hypothesized epithelial protective effects of ipratropium bromide directly. The lack of

baseline Marshall score data and dynamic analysis of MODS progression also weakens the persuasiveness of the conclusion that ipratropium bromide reduces MODS risk, as it is impossible to determine the intervention's effect on the temporal changes of organ dysfunction.

We propose that nebulized ipratropium bromide may be considered a potential adjunctive therapy to standard SOM therapy in the management of SP with RF. However, given the inherent biases of retrospective designs, prospective RCT are needed for future validation. Furthermore, as mentioned above, although the sample size was calculated using the PASS, only 168 cases were actually included, and the use of salbutamol in the control group may have diluted the treatment effect. Moreover, the lack of stratification based on pneumonia severity or pathogen type may limit the generalizability of the findings. Finally, although certain inflammatory markers were assessed, direct pathological alterations such as increased airway mucus secretion and alveolar epithelial permeability were not analyzed. Further validation using biomarkers or radiomics is warranted.

CONCLUSION

In patients with SP+RF, the addition of ipratropium bromide nebulization, based on the standardized SOM, improves oxygenation status, respiratory mechanics, and inflammatory stress responses, and shortens the DMV and length of hospital stay. Although the reduction in 28d-M was not observed, the short-term efficacy and organ-protective effects of such a combination provide new evidence for optimizing respiratory support strategies.

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Authors' contributions
TT.W. conceived and designed the study,X.F. and FF.Z. wrote and revised the manuscript, X.F. collected and analyzed data, FF.Z. Supervised the study; X.F. and FF.Z. made equal contributions to this work as co-first authors.All authors read and approved the final submitted manuscript.

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Data availability statement
The data used to support the findings of this study are available from the corresponding author upon request.

Ethical approval
The study involving human subjects complied with the Declaration of Helsinki and was approved by the ethical committee of Nanjing First Hospital (No. KY20230829-03), and all participants provided written informed consent. This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Conflicts of interest
The authors report no conflict of interest.

Supplementary data
https://www.pjps.pk/uploads/2026/05/SUP1778246619.pdf

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