Uncorrected Proof

Jundishapur J Chronic Dis Care. 2026 October; 15(4): e167401 https://doi.org/10.5812/jjcdc-167401

Published Online: 2026 October 31 **Research Article**

Effectiveness of Nebulized Furosemide in Clinical and Pulmonary Function Improvement Among Hospitalized Patients with Chronic Obstructive Pulmonary Disease Exacerbation: A Randomized Controlled Trial

Zohreh Kahramfar [1], Ebrahim Nadi [1], Shakiba Yousefi [1], Hanieh Jormand [2, *], Erfan Ayubi [3]

[1] Department of Internal Medicine, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran
[2] Urology and Nephrology Research Center, Hamadan University of Medical Sciences, Hamadan, Iran
[3] Cancer Research Center, Institute of Cancer, Hamadan University of Medical Sciences, Hamadan, Iran

[*] ***Corresponding Author:*** Urology and Nephrology Research Center, Hamadan University of Medical Sciences, Hamadan, Iran. Email: jormand69h@gmail.com

Received: 20 September, 2025; **Revised:** 7 October, 2026; **Accepted:** 20 October, 2026

Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) causes recurrent hospital admissions and high mortality. Nebulized furosemide has been proposed as an adjunct to standard therapy, but evidence in hospitalized patients with an acute exacerbation is limited.

Methods: This open-label randomized controlled trial enrolled 86 adults admitted to Shahid Beheshti Hospital, Hamadan, Iran, with an exacerbation of COPD between June and July 2025. Patients were randomly allocated to receive nebulized furosemide 20 mg every 6 hours plus standard treatment (n = 43) or standard treatment alone (n = 43). The primary outcome was respiratory rate at 48 hours, analyzed using analysis of covariance adjusted for the baseline value. Secondary outcomes were other vital signs, peripheral oxygen saturation (SpO_2), peak expiratory flow rate (PEFR), blood gases, and the Borg dyspnea score. The Holm adjustment was applied across 13 outcomes, and a two-sided $P < 0.05$ was considered statistically significant.

Results: The groups were comparable except for baseline respiratory rate and PEFR, for which adjustments were made. All 86 randomized patients completed the 48-hour assessment. Respiratory rate at 48 hours was lower in the intervention group (adjusted mean difference −1.53 breaths/min, 95% CI −2.40 to −0.65; $P < 0.001$). In a post hoc, exploratory responder analysis, a reduction of at least 2 breaths/min occurred in 44.2% vs 18.6% of patients. There were no significant between-group differences in SpO_2, PEFR, Borg score, or blood gases, and no significant adverse effects were reported.

Conclusions: In this open-label trial, nebulized furosemide added to standard treatment was associated with a small reduction in respiratory rate at 48 hours, of uncertain clinical significance, without improvement in oxygen saturation, peak expiratory flow, blood gases, or dyspnea. These findings do not support its routine use in hospitalized patients with COPD exacerbations; blinded, placebo-controlled trials with longer follow-up are needed.

Keywords: Pulmonary Disease, Chronic Obstructive, Furosemide, Respiratory Function Tests

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive and largely irreversible respiratory illness and the third leading cause of death worldwide (1). It affects more than 400 million people, and the number of cases is projected to reach approximately 592 million by 2050 owing to population aging and persistent exposure to tobacco smoke, air pollution, and occupational hazards (1, 2). In addition, COPD imposes substantial direct and indirect economic costs (3).

Copyright © 2026, Kahramfar et al. This open-access article is available under the Creative Commons Attribution 4.0 (CC BY 4.0) International License (https://creativecommons.org/licenses/by/4.0/), which allows for unrestricted use, distribution, and reproduction in any medium, provided that the original work is properly cited.

How to Cite: Kahramfar Z, Nadi E, Yousefi S, Jormand H, Ayubi E. Effectiveness of Nebulized Furosemide in Clinical and Pulmonary Function Improvement Among Hospitalized Patients with Chronic Obstructive Pulmonary Disease Exacerbation: A Randomized Controlled Trial. Jundishapur J Chronic Dis Care. 2026;15(4):e167401. doi: https://doi.org/10.5812/jjcdc-167401

Standard management focuses on relieving symptoms, improving quality of life, preventing exacerbations, and slowing disease progression through the use of bronchodilators, corticosteroids, and pulmonary rehabilitation (4-9). Nevertheless, many patients continue to experience dyspnea, frequent exacerbations, and reduced quality of life, and many of those hospitalized with acute exacerbation show limited improvement in objective respiratory indices (4, 10).

Nebulized furosemide, a loop diuretic traditionally used for its renal effects, may reduce dyspnea through actions on airway sensory nerves and bronchial smooth muscle, independently of diuresis (10). However, reported findings are mixed, and evidence in patients hospitalized with acute exacerbation, particularly regarding vital signs, pulmonary function, and blood gases, remains limited (11-13).

2. Objectives

We therefore tested the hypothesis that adding nebulized furosemide to standard therapy in patients hospitalized with acute COPD exacerbation would produce greater short-term improvement in respiratory rate, SpO_2, and peak expiratory flow rate (PEFR) within 48 hours and would favorably affect blood gases and dyspnea without significant adverse effects (14).

3. Methods

This parallel-group randomized controlled trial was conducted at Shahid Beheshti Hospital, Hamadan, Iran. Recruitment took place from 8 June to 8 July 2025, and the last participant completed the 48-hour follow-up on 10 July 2025. Hospitalized adults with an exacerbation of COPD, diagnosed by a pulmonologist on the basis of clinical, paraclinical, and laboratory criteria, were eligible. The trial followed the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement (15). It was registered in the Iranian Registry of Clinical Trials on 1 July 2025 (1404/04/10), after recruitment had begun; therefore, registration was not prospective.

3.1. Interventions and Eligibility Criteria

Patients were randomly allocated using block randomization to either the intervention group, which received standard COPD therapy plus nebulized furosemide 20 mg every 6 hours (13, 14), or the control group, which received standard COPD therapy alone. Inclusion criteria were a history of COPD; a diagnosis of COPD exacerbation by a pulmonologist based on clinical, paraclinical, and laboratory criteria; age of at least 18 years; and voluntary informed consent. Exclusion criteria were other chronic respiratory diseases (eg, asthma or lung cancer).

Sample size: An effect size of 0.80 was taken from the study by Sheikh Motahar Vahedi et al. (14). Assuming 90% power and a one-sided significance level of 0.01, G*Power estimated a minimum of 43 patients per group for the primary outcome (respiratory rate at 48 hours).

Randomization method: Block randomization with blocks of four was used. Two sheets marked I (intervention) and two marked C (control) were shuffled and placed in a drawer. For each eligible patient, one sheet was drawn at random, and the patient was allocated accordingly. Drawn sheets were not returned until all four had been used; all four were then returned for the next block.

3.2. Blinding

This was an open-label trial without a placebo, because the taste and throat sensation of nebulized furosemide are difficult to replicate (16). Participants, treating clinicians, and outcome assessors were aware of group allocation, and outcome assessors were not blinded. Performance and detection bias are therefore possible, particularly for the patient-reported Borg score and the manually counted respiratory rate.

3.3. Data Collection

All outcomes were measured at baseline and at 48 hours. The primary outcome was respiratory rate at 48 hours. Secondary outcomes were heart rate, systolic and diastolic blood pressure, SpO_2, peak expiratory flow rate (PEFR; measured with a Besmed peak flow meter), arterial/venous blood gases (pH, PCO_2, PO_2, TCO_2, HCO_3, and SO_2), and dyspnea severity (Borg scale).

3.4. Statistical Analysis

Analyses were performed using SPSS v26 and Python (SciPy/NumPy). Baseline characteristics were compared using independent-samples t tests and the chi-squared test. The primary analysis for each outcome was an analysis of covariance (ANCOVA) with the 48-hour value as the dependent variable, group as a fixed factor, and the baseline value as a covariate; results are reported as adjusted mean differences (intervention minus control) with 95% CIs and Cohen's d. Robustness was checked using rank-based ANCOVA, bootstrap CIs (5,000 resamples), and exclusion of extreme values; where the group-by-baseline interaction was significant (PCO_2, PO_2, and SO_2; $P \leq 0.002$), average adjusted differences are interpreted with caution. Within-group changes were assessed with paired t tests for descriptive purposes only. Analyses followed the intention-

to-treat principle; the few missing or implausible laboratory values (one each for baseline TCO_2, baseline HCO_3, 48-hour PCO_2, and 48-hour TCO_2, and one pH of 5.80) were not imputed, so those analyses are complete-case (n = 85). Holm-adjusted P values account for the 13 outcomes, with respiratory rate as the sole primary outcome and a two-sided P < 0.05 as the significance threshold. The post hoc responder analysis (Fisher's exact test; Newcombe hybrid-score CI) was not prespecified and is exploratory.

4. Results

Of 95 patients assessed for eligibility, 9 were excluded (4 did not meet the inclusion criteria and 5 were excluded for other reasons; none declined), and 86 were randomized: 43 to the intervention group and 43 to the control group (Figure 1). All patients received their allocated treatment and completed the 48-hour assessment; none was lost to follow-up. The mean age was 68.9 ± 8.2 years in the intervention group and 71.9 ± 10.4 years in the control group (P = 0.141), with 38 (88.4%) and 35 (81.4%) men, respectively (P = 0.366). Baseline respiratory rate (17.93 ± 1.84 vs 18.86 ± 2.28 breaths/min, P = 0.041) and PEFR (139.5 ± 72.3 vs 109.1 ± 64.0 L/min, P = 0.042) differed between groups; therefore, all between-group comparisons were adjusted for baseline values (Table 1).

Primary outcome. After baseline adjustment, the respiratory rate at 48 hours was 1.53 breaths/min lower in the intervention group (adjusted mean difference −1.53, 95% CI −2.40 to −0.65; Cohen's d = −0.69; P < 0.001; Holm-adjusted P = 0.011) (Table 2). Descriptively, the respiratory rate fell from 17.93 to 16.95 breaths/min in the intervention group and was unchanged in the control group (18.86 to 18.93) (Table 3). Sensitivity analyses yielded consistent results (bootstrap 95% CI −2.42 to −0.71; rank-based ANCOVA P < 0.001); excluding one patient with an extreme 48-hour value of 7 breaths/min gave −1.25 (95% CI −1.96 to −0.53), which should be regarded as a sensitivity estimate only. In a post hoc responder analysis, a reduction of at least 2 breaths/min occurred in 19 of 43 (44.2%) intervention patients and 8 of 43 (18.6%) controls (risk difference 25.6 percentage points, 95% CI 5.9 to 42.8; Fisher's exact test P = 0.019) (Table 4). The 2-breath threshold was chosen pragmatically and is not a validated threshold; therefore, this analysis is exploratory.

Secondary outcomes. SpO_2, PEFR, and the Borg score improved to a similar extent within both groups (Table 3), which does not indicate a treatment effect. After baseline adjustment, there were no significant between-group differences in SpO_2 (−0.3%, 95% CI −1.6 to 1.0; P = 0.674), PEFR (−10.2 L/min, 95% CI −23.4 to 2.9; P = 0.126), Borg score (0.15, 95% CI −0.11 to 0.41; P = 0.245), heart rate, diastolic blood pressure, or any blood gas parameter (all P > 0.05; Table 2). Systolic blood pressure was nominally lower in the intervention group (−4.1 mmHg, 95% CI −7.8 to −0.4; P = 0.031); however, this difference did not survive multiplicity adjustment (Holm-adjusted P = 0.373) or sensitivity analyses and is considered a chance finding. PCO_2 was numerically higher in the intervention group (adjusted difference 2.8 mmHg, 95% CI −0.2 to 5.8; P = 0.066). No significant adverse effects were reported.

5. Discussion

This randomized trial found that adding nebulized furosemide to standard therapy was associated with a modest reduction in respiratory rate at 48 hours but with no improvement in SpO_2, PEFR, blood gases, or dyspnea. The change in respiratory rate was small, was measured only at 48 hours, and may partly reflect measurement variability and the open-label design. It should not be interpreted as evidence of symptomatic relief or sustained benefit.

These findings partly agree with earlier studies suggesting that inhaled furosemide may improve exertional dyspnea and endurance in COPD via airway sensory nerves, independently of diuresis (17, 18). Consistent with this mechanism, the reduction in respiratory rate may reflect a change in central perception rather than improved lung function, although measurement bias is an alternative explanation.

The wider evidence is mixed. A meta-analysis of COPD trials reported improved vital signs, with severe heterogeneity (I^2 = 72.2%) (9). A conference-abstract meta-analysis of five trials in acute exacerbation reported a moderate pooled improvement in dyspnea (standardized mean difference −0.67, 95% CI −0.87 to −0.46) (8). A recent trial in 92 hospitalized patients reported improved dyspnea, lung function, and blood gases when nebulized furosemide 20 mg was added to salbutamol–ipratropium (17). We found no difference in Borg score, which may reflect the open-label design, the 48-hour window, the single dosing regimen, or a true absence of effect. The unchanged SpO_2, PEFR, and blood gases suggest that any benefit is unlikely to be mediated by improved gas exchange or airflow. The systematic review by Veldhoen and Muscedere has so far been published only as a protocol (10); therefore, it cannot yet support pooled conclusions.

5.1. Physiological Implications and Potential Mechanisms

Respiratory rate during acute exacerbation depends on airway inflammation, hyperinflation, ventilation–perfusion mismatch, and chemoreceptor sensitivity. Nebulized furosemide is thought to blunt dyspnea by activating pulmonary rapidly adapting receptors and

Table 1. Baseline Characteristics of the Participants [a]

Characteristic	Group		P-Value
	Intervention (n = 43)	Control (n = 43)	
Age, y	68.9 ± 8.2	71.9 ± 10.4	0.141
Male sex, No. (%)	38 (88.4)	35 (81.4)	0.366
Systolic BP, mmHg	117.9 ± 12.0	112.9 ± 20.3	0.168
Diastolic BP, mmHg	74.7 ± 7.0	74.3 ± 10.6	0.858
Respiratory rate, breaths/min	17.93 ± 1.84	18.86 ± 2.28	0.041 [b]
Heart rate, beats/min	79.1 ± 6.9	81.5 ± 8.8	0.158
SpO_2, %	78.5 ± 7.6	77.4 ± 9.1	0.547
PEFR, L/min	139.5 ± 72.3	109.1 ± 64.0	0.042 [b]
Dyspnea score (Borg)	6.67 ± 1.44	6.74 ± 0.88	0.787
pH	7.398 ± 0.046	7.380 ± 0.063	0.135
PCO_2, mmHg	46.0 ± 10.3	48.9 ± 9.7	0.179
PO_2, mmHg	39.7 ± 19.1	34.0 ± 11.6	0.095
TCO_2, mmol/L	30.0 ± 4.7	30.3 ± 4.8	0.800
HCO_3, mmol/L	28.2 ± 4.8	28.0 ± 4.3	0.869
SO_2, %	68.3 ± 15.3	65.6 ± 15.4	0.415

[a] Values are mean ± SD unless otherwise stated. Baseline values refer to measurements before the intervention. P values are from independent-samples t tests (continuous variables) or the chi-squared test (sex). Abbreviations: BP, blood pressure; PEFR, peak expiratory flow rate; TCO_2, total CO_2; SO_2, oxygen saturation from blood gas analysis. No between-group inferences about treatment effects are drawn from this table. Baseline TCO_2 (one control patient) and HCO_3 (one intervention patient) values were missing.

[b] Statistically significant.

modulating C-fiber firing (17). Whether the lower respiratory rate reflects reduced air hunger cannot be determined from these data, because dyspnea scores did not differ. Without corresponding improvements in oxygenation or PEFR, any symptomatic effect may not translate into better functional outcomes or shorter hospitalization.

The difference in systolic blood pressure (−4.1 mmHg; P = 0.031) was not robust: it did not persist after adjustment for multiplicity or in the rank-based, bootstrap, and outlier-excluded analyses. In addition, baseline systolic pressure was higher in the intervention group (117.9 vs 112.9 mmHg), so regression to the mean may have contributed to this difference. We therefore do not regard it as a treatment effect, although a small systemic effect cannot be excluded.

In the intervention group, PCO_2 was numerically higher (adjusted difference, 2.8 mmHg; P = 0.066). Although this difference was not significant after adjustment for multiplicity, CO_2 retention is clinically important in exacerbations of COPD; therefore, PCO_2 should be monitored as a safety outcome in future trials.

5.2. Clinical Significance of Findings

The reduction in respiratory rate was statistically significant, but its clinical importance is uncertain. The adjusted difference of 1.53 breaths/min is approximately 8% of the mean baseline value (18.4 breaths/min), and no minimal clinically important difference has been established for respiratory rate in COPD exacerbation. Only 8 of 86 patients had a baseline rate above 20 breaths/min, which limited the scope for improvement. The difference also lies within the measurement variability of manually counted respiratory rate: when healthcare professionals measured against a known reference, only 78.2% of measurements were within 4 breaths/min, and interobserver agreement was moderate (intraclass correlation coefficient 0.64) (19). Because the staff performing the measurements were unblinded, small systematic counting differences could explain the result. For the Borg scale, the 95% CI (−0.11 to 0.41) excludes an improvement of the approximately 1-unit minimal clinically important difference proposed in COPD (20); thus, a clinically important effect on dyspnea is unlikely. The responder analysis is hypothesis-generating only. Because outcomes were measured only at 48 hours, no conclusion can be drawn regarding sustained benefit, length of stay, or other patient-important outcomes.

Our results do not justify the routine use of nebulized furosemide in COPD exacerbation. Whether selected subgroups, such as patients with pulmonary congestion or severe dyspnea not relieved by standard bronchodilators

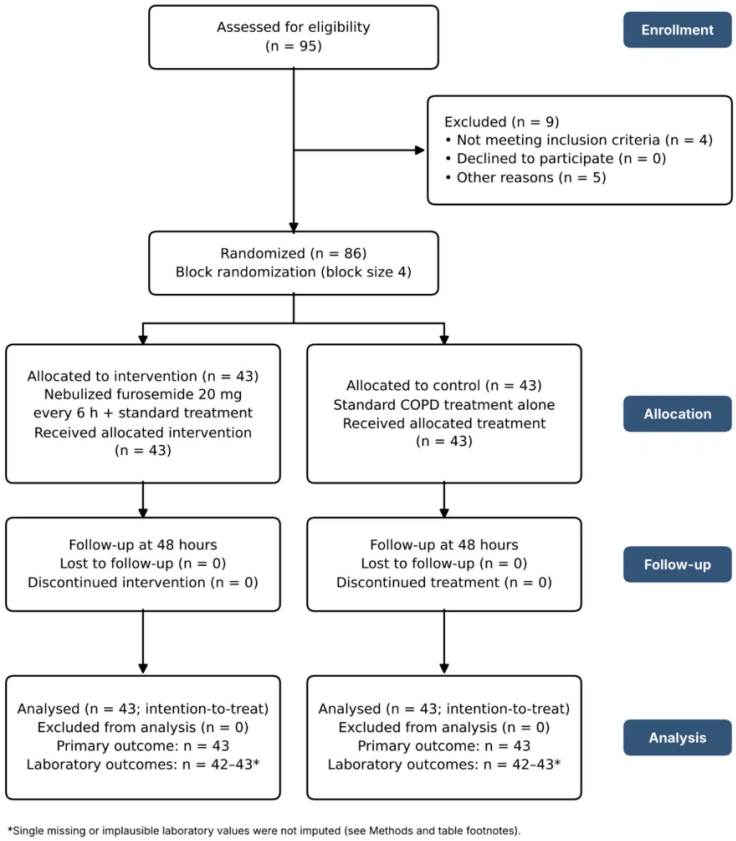

Figure 1. CONSORT flow diagram of participant enrollment, allocation, follow-up and analysis.

and corticosteroids, benefit remains to be tested prospectively (10).

Different dosing, longer treatment, or earlier intervention during exacerbation might produce larger effects, given that both our regimen (20 mg every 6 hours) and the follow-up period were short. These variables warrant systematic investigation.

5.3. Strengths and Limitations

A key strength of this study is its randomized design, which allowed direct comparison between groups, as well as its assessment of multiple objective and subjective outcomes.

The main limitation is the open-label design: participants, clinicians, and outcome assessors were aware of allocation, and no placebo was used. This introduces performance and detection bias, and nonblinded assessment of subjective or observer-dependent outcomes tends to exaggerate treatment effects (21, 22). The absence of a difference in Borg scores argues against a large expectation effect, but the difference in respiratory rate could be partly or wholly explained by detection bias. Allocation by drawing paper sheets also offered limited concealment: because sheets were not replaced within a block, the final allocation in each block could be predicted by anyone aware of the preceding allocations. Second, follow-up was limited to 48 hours; therefore, length of stay, treatment failure, need for ventilatory support, readmission, and mortality were not assessed. Third, because the sample size was based on a large effect ($d = 0.80$), 43 patients per group provided 80% power (two-sided $\alpha = 0.05$) only for a standardized difference of approximately 0.6 or larger; thus, smaller but clinically relevant differences may have been missed. Conversely, because 13 outcomes were examined, isolated significant findings may be due to chance, which is why only respiratory rate was designated as the primary outcome.

Fourth, baseline respiratory rate and PEFR differed between groups despite randomization; baseline-adjusted analyses were used, but residual confounding cannot be excluded. Fifth, we did not stratify by COPD severity, cor pulmonale, or baseline dyspnea, all of which could influence responsiveness to inhaled furosemide.

Respiratory rate is usually counted manually, SpO_2 and PEFR depend on technique and patient effort, and the Borg score is self-reported; thus, none of these outcomes is immune to observer expectation. Future research should prioritize placebo-controlled, double-blind designs where feasible.

External validity is also limited by the single-center design, specific inclusion criteria, and short follow-up. Participants were predominantly male (73 of 86, 84.9%), with a mean age of 70.4 years; therefore, the findings may not apply to women, younger patients, or other care settings. Larger multicenter trials with diverse populations and longer follow-up are warranted.

5.4. Future Research Directions

Targeted trials are needed to identify the patients most likely to benefit from nebulized furosemide, such as:

Patients with acute exacerbation of COPD complicated by pulmonary edema/congestion (13).

Patients with high Borg dyspnea scores at rest despite maximal inhaled therapy (10).

Subgroups stratified by severity of hypercapnia or hypoxemia (10).

Future studies should also examine mechanistic endpoints, such as respiratory muscle electromyography, inspiratory capacity, and neural respiratory drive (17, 18), as well as combinations with other adjunctive agents.

5.5. Conclusions

In this open-label trial, nebulized furosemide added to standard therapy was associated with a modest reduction in respiratory rate at 48 hours, of uncertain clinical significance, but did not improve oxygen saturation, peak expiratory flow, blood gases, or dyspnea. Whether it has a role in selected patients remains to be established by blinded, placebo-controlled trials with longer follow-up and patient-centered outcomes, including trials in subgroups with pulmonary congestion (10, 13).

Table 2. Between-Group Differences at 48 Hours Adjusted for Baseline Values (ANCOVA) [a]

Variables	Adjusted Mean Difference (95% CI)	Cohen's *d*	P-Value (ANCOVA)	Holm-Adjusted P-Value
Systolic BP, mmHg	−4.1 (−7.8 to −0.4)	−0.29	0.031	0.373
Diastolic BP, mmHg	−1.3 (−4.3 to 1.6)	−0.17	0.375	1.000
Respiratory rate, breaths/min †	−1.53 (−2.40 to −0.65)	−0.69	< 0.001	0.011
Heart rate, beats/min	−0.4 (−2.6 to 1.8)	−0.05	0.730	1.000
SpO_2, %	−0.3 (−1.6 to 1.0)	−0.03	0.674	1.000
PEFR, L/min	−10.2 (−23.4 to 2.9)	−0.14	0.126	1.000
Dyspnea score (Borg)	0.15 (−0.11 to 0.41)	0.13	0.245	1.000
pH	−0.015 (−0.036 to 0.007)	−0.25	0.174	1.000
PCO_2, mmHg	2.8 (−0.2 to 5.8)	0.31	0.066	0.729
PO_2, mmHg	0.5 (−4.5 to 5.4)	0.04	0.845	1.000
TCO_2, mmol/L	0.7 (−0.8 to 2.2)	0.16	0.334	1.000
HCO_3, mmol/L	0.9 (−0.6 to 2.4)	0.22	0.247	1.000
SO_2, %	2.5 (−2.7 to 7.7)	0.17	0.346	1.000

[a] Adjusted mean difference = intervention minus control, estimated by ANCOVA with the 48-hour value as the outcome and the baseline value of the same variable and treatment group as covariates (negative values indicate lower values in the intervention group). P values are from the t-test of the treatment-group coefficient in the ANCOVA model; no within-group test is used for inference. Cohen's d = adjusted mean difference divided by the pooled SD of the 48-hour values. Holm-adjusted P values account for the 13 outcomes examined. Analyses include 86 patients, except for pH, PCO_2, TCO_2, and HCO_3 (n = 85 each). For PCO_2, PO_2, and SO_2, the group × baseline interaction was significant ($P \leq 0.002$); the estimates shown are average adjusted differences from the main-effects model. Sensitivity estimates for the primary outcome were as follows: bootstrap 95% CI −2.42 to −0.71; after excluding one extreme value, −1.25 (95% CI −1.96 to −0.53). Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval.

† Primary outcome.

Table 3. Values at Baseline and 48 Hours and Within-Group Change in Each Group [a]

Variables	Baseline	48 h	Mean Change (95% CI)	P-Value [b]
Systolic BP, mmHg				
Intervention	117.9 ± 12.0	112.8 ± 10.1	−5.1 (−8.0 to −2.3)	< 0.001
Control	112.9 ± 20.3	113.5 ± 17.3	0.6 (−2.7 to 3.9)	0.725
Diastolic BP, mmHg				
Intervention	74.7 ± 7.0	75.5 ± 8.1	0.8 (−1.6 to 3.2)	0.501
Control	74.3 ± 10.6	76.6 ± 7.9	2.3 (−0.4 to 5.1)	0.094
Respiratory rate, breaths/min				
Intervention	17.93 ± 1.84	16.95 ± 2.38	−0.98 (−1.76 to −0.19)	0.016
Control	18.86 ± 2.28	18.93 ± 2.04	0.07 (−0.51 to 0.65)	0.810
Heart rate, beats/min				
Intervention	79.1 ± 6.9	79.4 ± 4.9	0.3 (−1.3 to 2.0)	0.695
Control	81.5 ± 8.8	81.3 ± 8.7	−0.2 (−2.1 to 1.8)	0.847
SpO_2, %				
Intervention	78.5 ± 7.6	81.0 ± 8.2	2.5 (1.4 to 3.6)	< 0.001
Control	77.4 ± 9.1	80.3 ± 7.9	2.9 (2.1 to 3.7)	< 0.001
PEFR, L/min				
Intervention	139.5 ± 72.3	157.9 ± 72.7	18.4 (10.7 to 26.1)	< 0.001
Control	109.1 ± 64.0	138.1 ± 74.3	29.1 (18.6 to 39.5)	< 0.001
Dyspnea score (Borg)				
Intervention	6.67 ± 1.44	7.21 ± 1.44	0.53 (0.32 to 0.75)	< 0.001
Control	6.74 ± 0.88	7.12 ± 0.88	0.37 (0.21 to 0.54)	< 0.001
pH				
Intervention	7.398 ± 0.046	7.378 ± 0.058	−0.020 (−0.040 to −0.001)	0.043
Control	7.380 ± 0.063	7.381 ± 0.062	0.001 (−0.011 to 0.014)	0.823
PCO_2, mmHg				
Intervention	45.6 ± 10.2	48.8 ± 9.4	3.1 (−0.2 to 6.4)	0.064
Control	48.9 ± 9.7	48.0 ± 8.9	−1.0 (−2.0 to 0.1)	0.068
PO_2, mmHg				
Intervention	39.7 ± 19.1	36.5 ± 12.6	−3.2 (−9.5 to 3.1)	0.314
Control	34.0 ± 11.6	34.3 ± 11.8	0.3 (−2.3 to 3.0)	0.805
TCO_2, mmol/L				
Intervention	30.0 ± 4.7	30.3 ± 4.3	0.3 (−1.0 to 1.7)	0.603
Control	30.3 ± 4.8	29.8 ± 4.6	−0.5 (−1.5 to 0.6)	0.356
HCO_3, mmol/L				
Intervention	28.2 ± 4.8	28.9 ± 4.2	0.7 (−0.9 to 2.3)	0.382
Control	28.0 ± 4.3	27.9 ± 4.0	−0.1 (−1.2 to 1.0)	0.835
SO_2, %				
Intervention	68.3 ± 15.3	70.3 ± 13.5	2.0 (−3.3 to 7.3)	0.455
Control	65.6 ± 15.4	66.3 ± 15.6	0.8 (−2.4 to 3.9)	0.623

[a] Values are mean ± SD. Change = 48-hour value minus baseline; P values are from paired-samples t tests and describe within-group change only; they do not test the treatment effect, which is assessed by the between-group ANCOVA in Table 2. Analyses include patients with both measurements (n = 43 per group, except pH, PCO_2, and HCO_3 in the intervention group, n = 42, and TCO_2 in the control group, n = 42). Baseline means may differ slightly from Table 1 because only patients with both measurements are included. One implausible 48-hour pH value (5.80) was treated as missing.

[b] Paired-Samples *t* test.

Table 4. Post Hoc Responder Analysis: Reduction in Respiratory Rate of at Least 2 breaths/min from Baseline to 48 Hours [a]

Outcome	Group		Estimate (95% CI)
	Intervention (n = 43)	Control (n = 43)	
Responders, No. (%)	19 (44.2)	8 (18.6)	P = 0.019 [b]
Risk difference, percentage points			25.6 (5.9 to 42.8)
Risk ratio			2.38 (1.17 to 4.83)

[a] Responder = reduction in respiratory rate of at least 2 breaths/min from baseline to 48 hours; all 86 randomized patients were included. This analysis was defined after the primary analysis (post hoc) and is exploratory; the threshold is not a validated minimal clinically important difference. Risk difference = intervention minus control, with Newcombe hybrid-score 95% CI; risk ratio with log-based 95% CI. Abbreviations: CI, confidence interval.

[b] Fisher's exact test.

Acknowledgements

The authors thank the Vice-Chancellor for Research and Technology of Hamadan University of Medical Sciences and the Clinical Research Development Unit of Shahid Beheshti Hospital for their approval, support, and cooperation.

Footnotes

AI Use Disclosure: The authors declare that no generative AI tools were used in the creation of this article.

Authors' Contribution: Conceptualization: Zohre Kahramfar, Ebrahim Nadi, Shakiba Yousefi, and Hanieh Jormand; Data curation: Shakiba Yousefi; Formal analysis: Hanieh Jormand and Erfan Ayubi; Funding acquisition: Zohre Kahramfar; Investigation: Ebrahim Nadi and Hanieh Jormand; Methodology: Zohre Kahramfar, Hanieh Jormand, and Erfan Ayubi; Project administration: Zohre Kahramfar; Software: Hanieh Jormand and Erfan Ayubi; Supervision: Zohre Kahramfar; Validation: Hanieh Jormand and Erfan Ayubi; Visualization: Hanieh Jormand; Writing—original draft: Zohre Kahramfar, Ebrahim Nadi, Shakiba Yousefi, Hanieh Jormand, and Erfan Ayubi; Writing—review and editing: Zohre Kahramfar, Ebrahim Nadi, Shakiba Yousefi, Hanieh Jormand, and Erfan Ayubi. All authors read and approved the final manuscript.

Clinical Trial Registration Code: IRCT20210730052016N1.

Conflict of Interests Statement: The authors declare no conflict of interests.

Data Availability: The data generated or analyzed during this study are not publicly available in order to protect the privacy of the participants. The dataset supporting the conclusions is available from the corresponding author upon reasonable request.

Ethical Approval: This study, including all consent procedures, was approved by the Ethics Committee of Hamadan University of Medical Sciences (No: IR.UMSHA.REC.1404.122). All methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all participants, who were informed of the confidentiality of their information and the purpose of the project. Participants were enrolled in the study only if they wished to participate.

Funding/Support: This study was funded by the Vice-Chancellor for Research and Technology, Hamadan University of Medical Sciences (No: 140402231517).

Informed Consent: Written informed consent was obtained from all participants. All participants were informed of the purpose of the project and the confidentiality of their information, and they were enrolled in the study only if they wished to participate.

References

1. de Oca MM, Perez-Padilla R, Celli B, Aaron SD, Wehrmeister FC, Amaral AFS, et al. The global burden of COPD: Epidemiology and effect of prevention strategies. *Lancet Respir Med*. 2025;**13**(8):709-724. [PubMed ID: 40684784]. https://doi.org/10.1016/S2213-2600(24)00339-4.
2. Boers E, Barrett M, Su JG, Benjafield AV, Sinha S, Kaye L, et al. Global burden of chronic obstructive pulmonary disease through 2050. *JAMA Netw Open*. 2023;**6**(12):e2346598. [PubMed ID: 38060225]. [PubMed Central ID: PMC10704283]. https://doi.org/10.1001/jamanetworkopen.2023.46598.
3. Lisspers K, Larsson K, Johansson G, Janson C, Costa-Scharplatz M, Gruenberger JB, et al. Economic burden of COPD in a Swedish cohort: The ARCTIC study. *Int J Chron Obstruct Pulmon Dis*. 2018;**13**:275-285. [PubMed ID: 29391785]. [PubMed Central ID: PMC5769573]. https://doi.org/10.2147/COPD.S149633.

4. Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2026 report [Internet]*. 2026. Available from: https://goldcopd.org/2026-gold-report-and-pocket-guide/.
5. Candrawati S, Pristika A, Rahmawati I. Slow Deep Breathing Exercise Improves Pulmonary Function in Hypertensive Patients. *Asian J Sports Med*. 2025;**16**(1):e158088. https://doi.org/10.5812/asjsm-158088.
6. Chen M, Wang H, Zhang W. Effect of High-frequency Oscillatory Ventilation-Assisted Pulmonary Surfactant Intervention on Children with Neonatal Respiratory Distress Syndrome. *Iran J Pediatr*. 2026;**36**(3):e160903. https://doi.org/10.5812/ijpediatr-160903.
7. Ramezani F, Arsalani N, Farahani MJH, Vahedi M. The Effect of a Nurse-Led Hybrid Pulmonary Rehabilitation Program on Sleep Quality in Patients with Chronic Obstructive Pulmonary Disease: A Randomized Controlled Trial. *J Nurs Midwifery Sci*. 2026;**13**(3):e169262. https://doi.org/10.5812/jnms-169262.
8. Taheritafti R, Hadizadeh A, Taslimi Taleghani N, Khoshnoud Shariati M. Nasal Continuous Positive Airway Pressure Versus Heated Humidified High-Flow Nasal Cannula for Post-Extubation Management in Preterm Neonates with Respiratory Distress Syndrome: A Pilot Randomized Controlled Trial. *J Compr Ped*. 2026;**17**(3):e174099. https://doi.org/10.5812/jcp-174099.
9. Akbari-Jokar Z, Hassanzad M, Ghaffaripour HA, Sadati E, Mirzendehdel M, Mohammadpour-Belvirdy L, et al. Pulmonary Outcomes of Fluticasone/Salmeterol via Dry Powder vs Metered-Dose Inhalers in Children with Moderate Asthma: A Randomized Crossover Trial. *J Compr Ped*. 2026;**17**(2):e172684. https://doi.org/10.5812/jcp-172684.
10. Veldhoen R, Muscedere J. Nebulised furosemide for the treatment of patients with obstructive lung disease: A systematic review protocol. *BMJ Open*. 2023;**13**(11):e070155. [PubMed ID: 37996224]. [PubMed Central ID: PMC10668269]. https://doi.org/10.1136/bmjopen-2022-070155.
11. Atwi Z. Effects of inhaled furosemide on dyspnea and pulmonary function in people with COPD: A literature review. *Can J Respir Ther*. 2022;**58**:170-174. [PubMed ID: 36320682]. [PubMed Central ID: PMC9586464]. https://doi.org/10.29390/cjrt-2022-007.
12. Behi M, Gholamine B, Darbandi MA, Masjedi MR, Eslaminejad A, Idani E, et al. Systematic review of nebulized furosemide for the management of dyspnea: Efficacy and safety in clinical practice. *J Adv Med Med Res*. 2025;**37**(7):251-262. https://doi.org/10.9734/jammr/2025/v37i75899.
13. Ghaysouri A, Basati G, Shams M, Tavan H. Efficiency of nebulizing furosemide in the treatment of chronic pulmonary obstructive disease: A systematic review and meta-analysis of clinical trials. *Tanaffos*. 2020;**19**(4):340-349. [PubMed ID: 33959171]. [PubMed Central ID: PMC8088148].
14. Sheikh Motahar Vahedi H, Mahshidfar B, Rabiee H, Saadat S, Shokoohi H, Chardoli M, et al. The adjunctive effect of nebulized furosemide in COPD exacerbation: A randomized controlled clinical trial. *Respir Care*. 2013;**58**(11):1873-1877. [PubMed ID: 23650431]. https://doi.org/10.4187/respcare.02160.
15. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *BMC Med*. 2010;**8**(1):18. [PubMed ID: 20334633]. [PubMed Central ID: PMC2860339]. https://doi.org/10.1186/1741-7015-8-18.
16. Beeh KM, Beier J, Donohue JF. Clinical trial design in chronic obstructive pulmonary disease: Current perspectives and considerations with regard to blinding of tiotropium. *Respir Res*. 2012;**13**(1):52. [PubMed ID: 22726538]. [PubMed Central ID: PMC3462669]. https://doi.org/10.1186/1465-9921-13-52.
17. Jensen D, Amjadi K, Harris-McAllister V, Webb KA, O'Donnell DE. Mechanisms of dyspnoea relief and improved exercise endurance after furosemide inhalation in COPD. *Thorax*. 2008;**63**(7):606-613. [PubMed ID: 18250181]. https://doi.org/10.1136/thx.2007.085993.
18. Ong KC, Kor AC, Chong WF, Earnest A, Wang YT. Effects of inhaled furosemide on exertional dyspnea in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2004;**169**(9):1028-1033. [PubMed ID: 14977622]. https://doi.org/10.1164/rccm.200308-1171OC.
19. Latten GHP, Spek M, Muris JWM, Cals JWL, Stassen PM. Accuracy and interobserver-agreement of respiratory rate measurements by healthcare professionals, and its effect on the outcomes of clinical prediction/diagnostic rules. *PLoS One*. 2019;**14**(10):e0223155. [PubMed ID: 31581207]. [PubMed Central ID: PMC6776326]. https://doi.org/10.1371/journal.pone.0223155.
20. Ries AL. Minimally clinically important difference for the UCSD shortness of breath questionnaire, Borg scale, and visual analog scale. *COPD*. 2005;**2**(1):105-110. [PubMed ID: 17136970]. https://doi.org/10.1081/copd-200050655.
21. Hróbjartsson A, Thomsen AS, Emanuelsson F, Tendal B, Hilden J, Boutron I, et al. Observer bias in randomized clinical trials with measurement scale outcomes: A systematic review of trials with both blinded and nonblinded assessors. *CMAJ*. 2013;**185**(4):E201-E211. [PubMed ID: 23359047]. [PubMed Central ID: PMC3589328]. https://doi.org/10.1503/cmaj.120744.
22. Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: Meta-epidemiological study. *BMJ*. 2008;**336**(7644):601-605. [PubMed ID: 18316340]. [PubMed Central ID: PMC2267990]. https://doi.org/10.1136/bmj.39465.451748.AD.