ORIGINAL ARTICLE

# Effectiveness of Dual Versus Triple Inhaled Therapy in Chronic Obstructive Pulmonary Disease Patients: Results from a Quasi-Experimental Study, Multan

Sidra Batool[1*], Javed Ahmed Khan[1], Faryal Asmat[2], Hamna Wajid[1], Zoha Hashmi[1]

**ABSTRACT**

**Objective:** To compare the efficacy of dual inhaled therapy and triple inhaled therapy in chronic obstructive pulmonary disease patients.

**Study Design:** Quasi-experimental study.

**Place and Duration of Study:** This study was conducted at the Department of Medicine, Combined Military Hospital (CMH), Multan, Pakistan from 1st January 2023 to 31st December 2023.

**Methods:** A total of 60 patients with chronic obstructive pulmonary disease were included in this study and allocated to 2 equal groups based on clinical criteria. In Group-D, patients were given dual inhaled inhaler therapy (Corticosteroid+ Long acting β-2 agonists) while patients in Group-T were given triple inhaled inhaler therapy (Corticosteroid+ Long acting β-2 agonists+ long-acting muscarinic antagonist) twice daily. The primary outcome was set as the percentage of patients achieving a reduced number of moderate-severe exacerbations, while the secondary outcomes included improved post-dose forced expiratory volume, number of patients achieving improved chronic obstructive pulmonary disease assessment test score, and baseline dyspnea index focal score after 6 months of treatment.

**Results:** The results of primary outcomes showed significantly better efficacy in Group-T compared to Group-D, as a considerably higher number of patients had reduced frequency of moderate-severe chronic obstructive pulmonary disease exacerbations after 6 months (86.66% vs 53.33%, *P*=0.035).

There was also significant improvement in secondary outcomes, including post-dose forced expiratory volume in 1 second, patients who had improved assessment test scores, as well as baseline dyspnea index focal score in Group-T compared to Group-D.

**Conclusion:** Triple inhaled therapy is more effective than dual inhaled therapy for reducing moderate-to-severe chronic obstructive pulmonary disease exacerbations.

**Keywords:** *Beta-2 Agonists, Chronic Obstructive Pulmonary Disease, Corticosteroid, Muscarinic Antagonist.*

***How to cite this:*** *Batool S, Khan JA, Asmat F, Wajid H, Hashmi Z. Effectiveness of Dual Versus Triple Inhaled Therapy in Chronic Obstructive Pulmonary Disease Patients: Results from a Quasi-Experimental Study, Multan. Life and Science. 2025; 6(4): 430-436. doi: http://doi.org/10.37185/LnS.1.1.763*



## Introduction

Chronic obstructive pulmonary disease (COPD) is identified by persistent airway restriction, chronic inflammations and aggravation of pulmonary symptoms. There is chronic obstructive bronchitis along with the shortness of breath (emphysema). A patient suffers occasional acute exacerbations of respiratory symptoms that become more severe on a typical day.[1,2] World Health Organization (WHO) has mentioned COPD among the major causes of global mortality as the reported incidence in 2019 was 3.23 Million. This marks the importance of managing COPD to improve quality of life and to reduce the burden of COPD on health care system.[3]

The diagnostic tests used for COPD is pulmonary

[1]*Department of Medicine*
*Combined Military Hospital (CMH), Multan, Pakistan*
[2]*Department of Radiology*
*Foundation University, Islamabad, Pakistan*

*Correspondence:*
*Dr. Sidra Batool*
*Department of Medicine*
*Combined Military Hospital (CMH), Multan, Pakistan*
*E-mail: shahidali299emebn@gmail.com*

*Received: July 16, 2024; 1st Revision Received: Mar 21, 2025*
*2nd Revision Received: Jun 13, 2025; Accepted: Jun 19, 2025*

function tests (PFTs) which gives a reliable assessment of declining lung function. These include "decreased forced expiratory volume in one second" (FEV1) and "forced vital capacity" (FVC).[4] The GOLD report suggests diagnosis of COPD with the use of spirometer to find non-fully reversible airflow limitation. History and physical examination are also important besides the PFTs and imaging techniques for a complete diagnosis.[5,6]

There is a long discussion and recommendations regarding management of COPD exacerbations; however, optimal treatment strategies remain a topic of dialogue. The goal of treatment is to reduce the stress of symptoms and decrease the intensity and frequency of exacerbations, which leads to improved exercise tolerance, raising the overall health status of these patients. The treatment recommended in acute exacerbation comprises systemic corticosteroids (CS), bronchodilators, and an antibiotic.[7]

The bronchodilators are the primary treatment strategy for these patients and include 2 types of drug classes, β-2 agonists and anti-muscarinic drugs. The types of β-2 agonists include the short-acting β-2 agonists (SABAs) and long-acting β-2 agonists (LABAs).[8] The long-acting muscarinic antagonist (LAMA) drugs prolong the bronchodilatory actions and have fewer side effects compared to β-2 agonists.[9] The commonly used first-choice drugs in inhalers for COPD are a combination of a corticosteroid and a LABA or a LAMA. Patients have proven to respond to these treatments in the form of reduced symptoms and exacerbations. A lot of patients, however, still have exacerbations despite these treatment options, and clinicians step up to a triple therapy inhaler regimen where patients take one inhaler comprising of corticosteroid+LABA and the other inhaler containing a LAMA.[10] Studies have reported that triple inhaled therapy offers greater benefits than dual therapy in symptomatic COPD patients with the risk of exacerbations. Janson C et al. reported that adding ICS to LABA or LABA/LAMA resulted in a significant reduction in exacerbations, particularly among patients with elevated blood eosinophil counts, highlighting the added advantage of triple therapy. Studies assessing COPD patients have mentioned that triple therapy provides benefits in symptomatic patients with a low risk of exacerbations compared to dual inhaled therapy.[7,11] In an overview by Rhee CK and co-workers, addition of a LAMA to a β-2 agonist provided significant improvement not only in lung function but also in overall health status and the need for rescue medicine, compared to a β-2 agonist treatment.[12]

During the past few years, new formulations have been introduced consisting of corticosteroid, LABA, and LAMA, which have improved the compliance of patients in using triple inhaled inhalers. This study was therefore designed to evaluate the efficacy of dual inhaled inhaler therapy versus triple inhaled inhaler therapy in our local COPD patients. These results will help our clinicians to opt for evidence-based strategies for their patients suffering from COPD.

## Methods

The study was conducted at the Department of Medicine, Combined Military Hospital (CMH), Multan, Pakistan from 1st January 2023 to 31st December 2023 after taking approval from the Ethical Review Committee of the hospital vide letter no: ERC-130/2023, dated 10th January 2023. Sample size was estimated with the following assumptions:

Alpha = 5% (two-sided), Power 80%.

p1 (Decrease in COPD exacerbation with dual combination) = 7%.

p2 (Decrease in COPD exacerbation with triple combination) = 68%.[13]

Estimated sample size:

N1= 7, N2= 7, estimated sample size was 14; however, we included 60 patients in the trial.

A total of 60 patients aged≥ 40 years reported with COPD having FEV1 < 50%, moderate-to-severe COPD exacerbation during the last 1 year ≥1, COPD Assessment Test (CAT) score ≥10 (0-40), and a Baseline Dyspnea Index (BDI) focal score of ≤10 was added in the study.[5,6] The exclusion criteria were set as the patients diagnosed with asthma, previous record of allergic rhinitis, exacerbation of COPD during the last 1 month before randomization, or any significant cardiovascular disease. Patients already taking a triple combination for COPD were also excluded.

All the patients were given a CS (beclomethasone dipropionate (BDP) in a dosage of 100 μg) and a LABA

(formoterol fumarate (FF) in a dosage of 6 µg) twice daily in a run-in period of two weeks. Patients were allocated into two groups of 30 each based on clinical presentation and physician assessment. Patients in Group-D were given dual inhaled inhaler therapy of CS (BDP 100 µg) and LABA (FF in a dosage of 6 µg). In contrast, the patients in Group-T were given triple inhaled inhaler therapy with a combination of CS (BDP 100 µg), LABA (FF in a dosage of 6 µg), and a LAMA (glycopyrronium bromide (GB) in a dosage of 12.5 µg twice daily.

All the demographic details, medical history, and clinical findings (like history of diagnosis of COPD, record of 1 year COPD exacerbations, results of spirometry, CAT score, and BDI focal score) were noted and recorded at the time of randomization. Salbutamol in a dosage of 100 µg was allowed as the rescue medication, but not within 6 hours of the Spirometry test.

Prior approval was received from the institutional ethical approval committee before start of study.

Eligible patients were informed and added in the study after taking written consent.

Both pre-dose and post-dose (2 hours) spirometry were conducted at each follow-up visit. Patients were asked to keep a daily record of exacerbations of COPD, rescue medications, and compliance with the treatment regimen in a diary provided to them, and it was reviewed at each follow-up visit by the study investigator.

The primary outcome was set as % percentage of patients achieving a reduced number of moderate-severe COPD exacerbations after 6 months.

The secondary outcomes included changes in post-dose (2 hours) FEV1, change in CAT score, and BDI focal score from the baseline to 6 months of treatment.

Mild exacerbation was declared when the worsened symptoms were treated using an increased salbutamol dose, moderate exacerbation was declared when it had to be treated with CS and an antibiotic, while severe exacerbation was declared when hospitalization was needed or the incidence of mortality.[14]

For the CAT score, a minimum difference of 2 units was considered clinically important.[15]

For BDI a minimum 1unit difference was taken as clinically important.[16]

Patients were advised to attend follow-up visits at weeks 4, 12, and 26 (final Visit).

The statistical analysis was conducted using SPSS 25. For quantitative data, the mean ± SD was computed, whereas frequencies and percentages were used to express qualitative variables. The chi-square test and independent t-test were used to compare outcomes, with $P < 0.05$ considered statistically significant.

## Results

The Mean±SD of age in this study was 56.71±6.85 years, with an age range of 44-71 years. The male gender was 66.66% of the total population, while females were 33.33%. The demographic details are given in Table 1.

**Table 1: Demographics (N=60)**

| Demographics and clinical assessments | | Group-D (N=30) | Group-T (N=30) |
|---|---|---|---|
| Age (Mean±SD) years | | 56.33±6.46 | 57.06±7.32 |
| Gender | Male N (%) | 19 (63.33) | 21 (70) |
| | Female N (%) | 11 (36.66) | 9 (30) |
| Smoking status | Smokers N (%) | 12 (40 ) | 13 (43.33) |
| | Ex-smokers N (%) | 14 (46.66) | 12 (40) |
| | No smoking N (%) | 4 ( 13.33) | 5 ( 16.66) |

The details of the clinical history of the patients show no statistically significant difference between the two groups regarding the important clinical parameters related to COPD, as shown in Table 2.

The primary outcomes showed significantly better efficacy with the triple inhaled inhaler compared to the dual inhaled inhaler with a reduced number of moderate to severe exacerbations, as shown in Table 3.

The results of secondary outcomes also show a significantly improved Post-dose FEV1 %, with a significantly higher number of patients achieving

**Table 2: Clinical History related to COPD (N=60)**

| Clinical History | | Group-A (N=30) | Group-B (N=30) | $\chi^2$ value | *P*-value |
|---|---|---|---|---|---|
| History of COPD (Mean±SD) years | | 6.3±1.26 | 6.66±1.12 | 1.169 | 0.246* |
| Eosinophil Counts (Mean±SD) cells/µL) | | 207.16±15.62 | 204.66±16.91 | 0.595 | 0.554* |
| Medium-Severe Exacerbations during the last 1 year | | 2.06±0.98 | 2.3±0.95 | 0.963 | 0.340* |
| Post-dose FEV1 (% ) | | 39.03±8.77 | 37.86±8.68 | 0.519 | 0.606* |
| Post-dose FEV1 status | 30% to <50% n (%) | 21 (70) | 20 (66.66) | 0.077 | 0.781** |
| | FEV1<30% n (%) | 9 ( 30) | 10 (33.33) | | |
| CAT score (Mean±SD) | | 7.37±1.39 | 7.03±1.32 | 0.972 | 0.335* |
| BDI Focal score (Mean±SD) | | 4.8±1.09 | 5.26±1.04 | 1.672 | 0.100* |

**Independent t-test, **Chi-square test*

**Table 3: Primary outcomes of the study (N=60)**

| Primary outcomes | Group-D (N=30) | Group-T (N=30) | $\chi^2$ value | *P*-value |
|---|---|---|---|---|
| Number of Med-Severe Exacerbations. for 6 months (Mean±SD) | 1.53±0.81 | 1.13±0.62 | 2.148 | 0.036* |
| Patients with reduced Med-Severe exacerbation events n (%) | 16 (53.33) | 26 (86.66) | 7.937 | 0.005** |

**Independent t-test, **Chi-square test*

**Table 4: Secondary outcomes of the study (N=60)**

| Secondary outcomes | Group-D (N=30) | Group-T (N=30) | $\chi^2$ value | *P*-value |
|---|---|---|---|---|
| Post-dose FEV1 % at 6 months (Mean±SD) | 48.6±10.90 | 54.5±9.32 | 2.253 | 0.028* |
| CAT score at 6 months (Mean±SD) | 9.76±1.54 | 10.93±1.25 | 3.231 | 0.002* |
| Number of patients with improved CAT score n (%) | 22 (73.33) | 29 (96.66) | 6.405 | 0.011** |
| BDI focal score (Mean±SD) | 5.23±1.22 | 6.3±1.17 | 3.467 | 0.001* |
| Number of patients with improved BDI focal score n (%) | 15 (50) | 24 (80) | 5.934 | 0.015** |

**Independent t-test, **Chi-square test*

improved CAT score and BDI focal score at the completion of the 6-month follow-up period, as shown in Table 4.

## Discussion

The primary outcomes of our study showed significantly better efficacy in Group-T compared to Group-D, as a significantly higher number of patients had a reduced number of moderate-severe exacerbations after 6 months of treatment (86.66% vs 53.33% respectively, *P*=0.035). There was a significantly decreased number of overall moderate-severe COPD exacerbations in Group-T compared to Group-D (1.53+0.81 vs 1.13±0.62, respectively, *P*=0.035). Similarly, a significant improvement in post-dose FEV1 (54.5±9.32 Vs 48.6±10.90, *P*=0.028), number of patients with improved CAT score (96.66% Vs 73.33% respectively, *P*=0.011) and number of patients with improved BDI focal score (80% Vs 50% respectively, *P*=0.014) was observed in Group-T compared to Group-D.

The treatment choice for COPD has remained a matter of discussion as trials have shown improvement related to COPD symptoms and lung functions; however, the evidence regarding the reduction in exacerbation with triple inhaler therapies is limited.

A systematic review by Zayed Y et al. showed a significant reduction in COPD exacerbations with triple therapy compared to dual therapy (RR 0.75; *P* < 0.01). Significant improvement in trough FEV1 (*P* < 0.01) and significant decrease in mean SGRQ score (*P* < 0.01) were also observed with triple therapy.[17] The advantage of using a triple regimen with the addition of LAMA in a single inhaler form was clearly apparent

in a meta-analysis done by Zhang L et al., where lung functions, particularly FEV1, were improved to a significant level, in moderate to severe COPD patients.[18]

On the basis of efficacy data observed, triple dose combination in single inhaler formulations has been studied in different studies over the past few years to find some decisive outcomes. In the Trilogy study, the triple combination formulation significantly improved the pre-dose FEV1 ($P$<0.001) and post-dose FEV1 ($P$<0.001) after 26 weeks of treatment. There was also an improvement in the mean TDI focal score compared to the dual combination.[19] The IMPACT study compared the dual therapy of ICS+LABA/ LAMA+LABA with the triple combination of ICS+LABA +LAMA, with the aim of reducing the moderate & severe COPD exacerbation. The results showed a significantly reduced incidence of acute moderate-to-severe COPD with triple combination therapy compared to either ICS+LABA or LABA+LAMA. The reported annual rate of acute exacerbation was 0.95 with triple combination, 1.08 with ICS+LABA combination and 1.39 with LABA+LAMA combination in patients having levels of eosinophil up to 150 cells/ µL−1.[20] The results of Voorham J et al. confirmed that, in patients with at least 2 or more exacerbations during last 1 year, reduced risk of exacerbation (hazard ratio 0.87, 95% CI 0.76–0.99) and acute respiratory events was observed with triple inhalation compared to dual inhalation therapy. The study also reported a lower risk of treatment failure with the triple combination.[21] In contrast to the above mentioned studies, Suissa S found no superior effectiveness of Triple combination in reducing exacerbations (HR 1.08, 95% CI: 1.00-1.16) except for those who were facing multiple exacerbations (HR 0.83, 95% CI: 0.74-0.92) and suggested that triple therapy should be reserved for patients with frequent exacerbations to save them from the possible adverse effects of using a three drug combination.[22]

To collect comprehensive data over the topic, Long H and co-workers conducted a meta-analysis including 25,171 patients from 6 studies and compared the fixed dose combination (FDC) of triple regimen and FDCs of dual regimen. The increase in FEV1 was significantly greater with single-inhaler triple therapy compared to ICS/LABA FDC, with a mean difference of 103.4 ml (95% CI 64.65–142.15). This meta-analysis indicated that single-inhaler triple therapy lowers the risk of all-cause mortality and moderates severe exacerbations in COPD patients. However, it is associated with a higher risk of pneumonia compared to LABA/LAMA FDC.[23] A systemic review by Lai CC et al. evaluated the impact of one-year single-inhaler triple therapy (LABA/LAMA/ICS) versus dual therapies (LABA/LAMA or ICS/LABA) on COPD mortality and reduction of moderate to severe exacerbations. Triple therapy reduced exacerbations compared with dual therapy (RR = 0.76 for LABA/LAMA; RR = 0.84 for ICS/LABA; $P$ < 0.001), but increased the risk of pneumonia (RR = 1.43; $P$ < 0.001). Hence, triple therapy was beneficial for patients, especially with multiple prior exacerbations (HR 0.83).[24]

The results of our study are consistent with previous studies on this topic and show superior efficacy of triple inhaled therapy in reducing the number of moderate-to-severe exacerbations, post-dose FEV1, CAT score, BDI focal score, and other important parameters related to efficacy in COPD patients.

The primary limitation of our research is the small sample size and short duration of patients' follow-up. Future studies with a larger number of patients and a longer duration of follow-up will be helpful to confirm this evidence.

## Conclusion

Triple inhaled inhaler therapy with CS, LABA, and a LAMA is more effective in reducing moderate-severe COPD exacerbations compared to dual inhaled inhaler therapy with a CS and LABA in COPD patients. A multifactorial approach and personalized selection of treatment needs to be adopted on the basis of the patient's clinical findings and the presence of comorbid conditions.

**Acknowledgment:** We are grateful for the cooperation and assistance of the nursing staff in maintaining the patient history and clinical record.

**Conflict of Interest**: The authors declare no conflict of interest

**Grant Support and Financial Disclosure**: None

## REFERENCES


1. Ritchie AI, Baker JR, Parekh TM, Allinson JP, Bhatt SP, Donnelly LE, et al. Update in Chronic Obstructive Pulmonary Disease 2020. American Journal of Respiratory and Critical Care Medicine. 2021; 204: 14-22. doi: 10.1164/rccm.202102-0253UP
2. Erhabor GE, Adeniyi B, Arawomo AO, Akinwalere O, Adetona G, Fagbohun FT, et al. Acute Exacerbation of COPD: Clinical Perspectives and Literature Review. West African Journal of Medicine. 2021; 38: 1129-42
3. Pham HQ, Pham KHT, Ha GH, Pham TT, Nguyen HT, Nguyen THT, et al. Economic Burden of Chronic Obstructive Pulmonary Disease: A Systematic Review. Tuberculosis and respiratory diseases. 2024; 87: 234-51. doi: 10.4046/trd.2023.0100.
4. Khan KS, Jawaid S, Memon UA, Perera T, Khan U, Farwa UE, et al. Management of Chronic Obstructive Pulmonary Disease (COPD) Exacerbations in Hospitalized Patients from Admission to Discharge: A Comprehensive Review of Therapeutic Interventions. Cureus. 2023; 15: e43694. doi: 10.7759/cureus.43694
5. Tamondong-Lachica DR, Skolnik N, Hurst JR, Marchetti N, Rabe AP, Montes de Oca M, et al. GOLD 2023 update: implications for clinical practice. International Journal of Chronic Obstructive Pulmonary Disease. 2023: 745-54. doi: 10.2147/COPD.S404690
6. Agustí A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. American Journal of Respiratory and Critical Care Medicine. 2023; 207: 819-37. doi: 10.1164/rccm.202301-0106PP
7. Bollmeier SG, Hartmann AP. Management of chronic obstructive pulmonary disease: A review focusing on exacerbations. American Journal of Health-System Pharmacy. 2020; 77: 259-68. doi: 10.1093/ajhp/zxz306.
8. Billington CK, Penn RB, Hall IP. $\beta_2$ Agonists. Handbook of Experimental Pharmacology. 2017; 237: 23-40. doi: 10.1007/164_2016_64
9. Casale TB, Foggs MB, Balkissoon RC. Optimizing asthma management: Role of long-acting muscarinic antagonists. The Journal of Allergy and Clinical Immunology. 2022; 150: 557-68. doi: 10.1016/j.jaci.2022.06.015
10. Brusselle G, Price D, Gruffydd-Jones K, Miravitlles M, Keininger DL, Stewart R, et al. The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK. International journal of chronic obstructive pulmonary disease. 2015: 10: 2207-17. doi: 10.2147/COPD.S91694
11. Cazzola M, Rogliani P, Laitano R, Calzetta L, Matera MG. Beyond Dual Bronchodilation – Triple Therapy, When and Why. International Journal of Chronic Obstructive Pulmonary Disease. 2022; 17: 165-80. doi: 10.2147/COPD.S345263
12. Janson C. Treatment with inhaled corticosteroids in chronic obstructive pulmonary disease. Journal of Thoracic Disease. 2020; 12: 1561-9. doi: 10.21037/jtd.2020.02.51
13. Celli BR, Fabbri LM, Aaron SD, Agusti A, Brook R, Criner GJ, et al. An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal. American Journal of Respiratory and Critical Care Medicine. 2021; 204: 1251-8. doi: 10.1164/rccm.202108-1819PP
14. Lin L, Song Q, Cheng W, Liu C, Zhao YY, Duan JX, et al. Comparation of predictive value of CAT and change in CAT in the short term for future exacerbation of chronic obstructive pulmonary disease. Annals of Medicine. 2022; 54: 875-85. doi: 10.1080/07853890.2022.2055134
15. Kon SS, Canavan JL, Jones SE, Nolan CM, Clark AL, Dickson MJ, et al. Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. The Lancet Respiratory Medicine. 2014; 2: 195-203. doi: 10.1016/S2213-2600(14)70001-3
16. Rhee CK, Yoshisue H, Lad R. Fixed-Dose Combinations of Long-Acting Bronchodilators for the Management of COPD: Global and Asian Perspectives. Advances in Therapy. 2019; 36: 495-519. doi: 10.1007/s12325-019-0893-3
17. Zayed Y, Barbarawi M, Kheiri B, Haykal T, Chahine A, Rashdan L, et al. Triple versus dual inhaler therapy in moderate-to-severe COPD: A systematic review and meta-analysis of randomized controlled trials. Clinical Respiratory Journal. 2019; 13: 413-28. doi: 10.1111/crj.13026
18. Zhang L, Wang X, Zhang Y, Chen W. Efficacy and Safety of Single Inhaler Triple Therapy Versus Separate Triple Therapy in Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-analysis. Clinical Therapeutics. 2022; 44: 859-73. doi: 10.1016/j.clinthera.2022.04.004
19. Singh D, Papi A, Corradi M, Pavlišová I, Montagna I, Francisco C, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. Lancet. 2016; 388: 963-73. doi: 10.1016/S0140-6736(16)31354-X
20. Dobler CC. The IMPACT of triple versus dual single-inhaler therapy on exacerbations of COPD. Breathe. 2018; 14: 333-5. doi: 10.1183/20734735.026418
21. Voorham J, Corradi M, Papi A, Vogelmeier CF, Singh D, Fabbri LM, et al. Comparative effectiveness of triple therapy versus dual bronchodilation in COPD. ERJ Open Research. 2019; 5: 00106-2019. doi: 10.1183/23120541.00106-2019
22. Suissa S, Dell'Aniello S, Ernst P. Single-Inhaler Triple versus Dual Bronchodilator Therapy in COPD: Real-World Comparative Effectiveness and Safety. International Journal of Chronic Obstructive Pulmonary Disease. 2022; 17: 1975-86. doi: 10.2147/COPD.S378486
23. Long H, Xu H, Janssens JP, Guo Y. Single-inhaler triple vs single-inhaler dual therapy in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized control trials. Respiratory Research. 2021; 22: 209. doi:10.1186/s12931-021-01794-w
24. Lai CC, Chen CH, Chen KH, Wang CY, Huang TM, Wang YH, et al. The impact of 52-week single inhaler device triple therapy versus dual therapy on the mortality of COPD patients: A systematic review and meta-analysis of randomized controlled trials. Life. 2022; 12: 173. doi: 10.3390/life12020173

**Author Contributions**

**SB:** Conception and design of the work, manuscript writing for methodology design and investigation
**JAK:** Revising, editing, and supervising for intellectual content
**FA:** Validation of data, interpretation, and write-up of results
**HW:** Writing the original draft, proofreading, and approval for final submission
**ZH:** Data acquisition, curation, and statistical analysis