

Comparison of dyspnea score (mMRC) in patients with chronic obstructive pulmonary disease (COPD) using triple versus dual therapy

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ABSTRACT

Background: COPD is associated with long-term dyspnea and exacerbations. This research compared effects of using dual (LABA/LAMA) and triple (LABA/LAMA/ICS) inhaler therapy on dyspnea and exacerbations in COPD patients.

Methods: It was a comparative cohort study that was carried out by the Department of Pulmonology, Khyber Teaching Hospital, Peshawar, from January to June 2026. Consecutive sampling (non-probability) was conducted to enroll 336 COPD patients, although 168 cases took dual and 168 cases took triple therapy. Dyspnea was measured with modified Medical Research Council (mMRC) at baseline and follow up. Exacerbations were noted also. The SPSS version 26 was used in analysis of data through the use of parametric and non-parametric tests and multivariate logistic regression.

Results: Follow-up mMRC scores were lower with triple therapy than dual therapy (1.54 ± 0.94 vs. 2.18 ± 1.02 ; $p < 0.001$). Mean mMRC improvement was greater with triple therapy (1.31 ± 0.76 vs. 0.64 ± 0.72 ; $p < 0.001$). There was an improvement in clinical condition of 81.0% compared to 54.8% of the patients ($p < 0.001$). Total exacerbations were also lower with triple therapy (3.2 ± 1.9 vs. 4.4 ± 2.3 ; $p < 0.001$). Multivariate analysis revealed that triple therapy was still significantly correlated with the clinical improvement (AOR 3.42, 95% CI: 2.10-5.58; $p < 0.001$).

Conclusion: Triple therapy has been linked to higher improvement of dyspnea and reduce exacerbation compared to dual therapy.

Keywords: COPD, Dual therapy, Exacerbation, Triple therapy

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Introduction

COPD is a widespread, avoidable and manageable chronic illness of the lungs and respiratory system. It is manifested by chronic airway respiratory symptoms and permanent airflow blockage due to airway and alveoli abnormalities due to the presence of harmful particles or gases during a prolonged period

of exposure (1). COPD is a gradual illness which is devastating to quality of life and functional capacity. It is as well stringent on the patients, healthcare system and the society. COPD affects approximately 392 million individuals all over the world. It is among the causing factors of morbidity and mortality and is a major contributor to the worldwide disease burden.

Over three million deaths occur every year as a result of COPD therefore, the disease is ranked third as the most common cause of death in the world. Low- and Middle-Income

countries are affected by the disease especially (2, 3).

Pathophysiology COPD is caused by chronic airway inflammation, alterations in the structure of the small airways, hypersecretion of mucus and gradual losses of lung tissue. The changes cause dysfunctional gas exchange and long-term airflow constraints (4). Characteristic of the patients, there is low exercise tolerance, high frequency exacerbations, dyspnea during exercise, sputum liquors, and persistent cough. The exacerbations are severe events related to the evolution of the disease since they contribute to faster worsening of lung functions, rise in the number of hospitalizations, decrease in health related quality of life as well as higher mortality and medical costs (5,6). As such, the primary objectives of COPD treatment are the reduction of symptoms and prevention of exacerbations.

A pharmacological treatment is a significant part of a long-term COPD. The choice of the treatment is determined by the level of symptoms, exacerbation history, as well as by the probability of exacerbation. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) and report 2025 suggests the use of long-acting bronchodilators as the main component of maintenance therapy. Utterly dyspneic patients with recurring episodes of exacerbation despite proper administration of the right bronchodilator therapy might require triple inhaler therapy that incorporates an inhaled corticosteroid (ICS) when the patient has over a large number of blood eosinophils or when the patient experiences frequent episodes of exacerbation (1).

In the last ten years, there have been some significant randomized controlled clinical trials that showed the clinical efficacy of triple inhaler therapy. The patients treated with

triple therapy had fewer moderate to severe exacerbations and an improved health status compared to those with dual bronchodilator therapy in the IMPACT study (7). In line with the evidence, the ETHOS study revealed that triple therapy was less effective in terms of attacks reduction and improved the clinical outcomes among moderate-to-severe COPD patients (8). KRONOS study further found triple therapy to be effective regarding the lung functioning and control of symptoms compared to a dual therapy. These findings comply with the prior guidelines on the escalation of treatment in the right patients (9). Despite all the positive evidence in major multinational clinical studies, treatment outcomes in clinical settings can vary with the outcomes of experiments in controlled research settings (10). Patient-related factors, medication compliance, the environmental exposures, tobacco use, healthcare availability, and socioeconomic status may differ significantly across the countries, especially in the resource-constrained environments (10). High tobacco consumption, biomass fuel and occupational pollutants and rising urban air pollution are the determinants of COPD burden in Pakistan (11,12). Poor disease control and frequent hospitalizations could also be caused by underdiagnosis and lack of access to special respiratory care (11,12).

Although there has been evidence of the effectiveness of triple inhaler therapy, there is limited comparative data on this in Pakistan. Majority of treatment decisions are made using the evidence that supports the epidemiology of the Western population that are varied in terms of health care systems, exposures to the environment and demographics. As a result, the study would investigate the outcomes of treatment in the local population to check whether similar

clinical benefits can be attained in regular clinical practice and to furnish data to support evidence-based treatment choices.

The current research was done in order to compare the efficacy of dual and triple inhaler therapy in influencing the severity of dyspnea and the frequency of exacerbations on COPD patients who visited the pulmonology department. The results can be used to enhance tertiary care hospitals in Pakistan to manage COPD and also give local evidence as to the clinical outcomes of these treatment strategies.

Methods

The research was carried out in the Department of Pulmonology at the Khyber Teaching Hospital, Peshawar, Pakistan, during the month of March up to the month of June 2026. Being a tertiary care teaching hospital, the hospital also attracts referrals to the specialized respiratory care available in the hospital throughout Khyber Pakhtunkhwa and adjacent districts which constituted the population with which the study was done.

The enrollment process was inclusive of non-probability consecutive sampling, which attracted adult COPD patients in who had been prescribed either those who are on dual inhaler or triple inhaler therapy as part of routine care. The necessary sample size was calculated using the Open-Epi Version 3 calculator, 95% confidence level, 80% power and equal allocation (1:1) across arms which gave the baseline of 304 participants, which was subsequently increased to 336 (168 per arm) to accommodate an estimated 10% non-response rate.

The participants who were enrolled were aged 18-60 years, had a COPD diagnosis made by post-bronchodilator spirometric testing (FEV1/FVC ratio less than 0.70) and had full documentation of both baseline and follow-up

visits, which was within the GOLD 2025 criteria. Status of treatment made every participant fall into one of two types, dual therapy, which is based on a long-acting β_2 -agonist (LABA) in combination with a long-acting muscarinic antagonist (LAMA), or triple therapy, which is an extended therapy incorporating an inhaled corticosteroid (ICS) to the same LABA/LAMA combination. Certain criteria were used to exclude Whites with a history of lung cancer or active pulmonary tuberculosis, bronchial asthma, overlapping asthma-COPD syndrome, any other major chronic respiratory disease, or gaps in their healthcare records, or who expressed an unwillingness to take part.

The data collection tool was a proforma specially designed to address this investigation, which captures the age, sex, height, weight, body mass index (BMI), place of residence, education, occupation, socioeconomic bracket, smoking habits and the number of pack-years, COPD duration, comorbid conditions and assigned-treatment. The severity of dyspnea, measured using the mMRC scale, was a twice measured variable at baseline and at the reported follow-up meeting with the change in the measure becoming the main outcome variable of the study. Clinical improvement status of COPD exacerbations logged during the study window made up the secondary outcomes.

Statistical processing was done in the IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test identified whether the continuous variables were normally distributed, and either summarized them as mean $\pm$ SD or as median with interquartile range (IQR); categorical data was summarized using frequencies and percentages. The independent samples t-test and Mann-Whitney U -test were used to conduct the baseline comparison in a group

where the data was normally distributed and non-normally distributed respectively and on groups where the data were categorical Chi-square test and Fisher exact test respectively with the number of cells. Univariate analyses were used to determine independent variables that could predict an improvement in clinical outcomes, and the Enter method was used to include variables with $p < 0.10$ in a multivariate model of binary logistic regression. The dependent variable was clinical improvement (yes/no) which was improvement in mMRC between baseline and follow-up. Treatment group, age, sex, BMI, smoking status, and pack-years, COPD length, baseline mMRC score, and comorbidities were the independent variables. Adjusted odds ratios (AORs), 95% confidence and p-values were provided. The definition of significance in the entire study was two sided p-value whose level was below 0.05.

All participants agreed and signed a written informed consent form after being informed about the procedures of the study at the Institutional Research and Ethical Review Board of Khyber Medical College Peshawar (Approval No. 523/DME/KMC, dated 23 May 2025).

Results

The last sample consisted of 336 patients with COPD, 168 (50.0%) patients were on dual inhaler therapy (LABA/LAMA) and 168 (50.0%) patients were on triple inhaler therapy (LABA/LAMA/ICS). Table 1 shows baseline demographic and clinical characteristics. No statistically significant differences found between the two treatment groups existed in terms of age, sex, BMI, residence, education, socioeconomic status, smoking status, pack-years, COPD duration, or comorbidities (all $p > 0.05$).

Table 1. Baseline demographic and clinical characteristics of study participants according to treatment group (N = 336)

Variable	Dual Therapy (n=168)	Triple Therapy (n=168)	p-value
Age (years), mean $\pm$ SD	47.8 $\pm$ 10.1	48.2 $\pm$ 9.8	0.712
Male sex, n (%)	108 (64.3)	112 (66.7)	
Female	60 (35.7)	56 (33.3)	0.650
BMI (kg/m²), mean $\pm$ SD	26.3 $\pm$ 4.8	26.5 $\pm$ 4.6	0.698
BMI category, n (%)			0.892
Underweight	12 (7.1)	10 (6.0)	
Normal	44 (26.2)	48 (28.6)	
Overweight	72 (42.9)	68 (40.5)	
Obese	40 (23.8)	42 (25.0)	
Residence, n (%)			0.830
Rural	82 (48.8)	84 (50.0)	
Urban	86 (51.2)	84 (50.0)	
Education, n (%)			0.784
Illiterate	28 (16.7)	26 (15.5)	
Primary	42 (25.0)	44 (26.2)	
Secondary	52 (31.0)	48 (28.6)	
Graduate	46 (27.4)	50 (29.8)	
Socioeconomic status, n (%)			0.856
Low	52 (31.0)	50 (29.8)	
Middle	78 (46.4)	82 (48.8)	
High	38 (22.6)	36 (21.4)	
Smoking history, n (%)			0.850
Current smoker	58 (34.5)	54 (32.1)	
Former smoker	40 (23.8)	44 (26.2)	
Never smoker	70 (41.7)	70 (41.7)	
Pack-years, mean $\pm$ SD	14.2 $\pm$ 8.8	13.8 $\pm$ 8.6	0.674
COPD duration (years), mean $\pm$ SD	6.3 $\pm$ 4.2	6.1 $\pm$ 4.0	0.658
Comorbidities, n (%)			0.950
None	60 (35.7)	58 (34.5)	
Hypertension	34 (20.2)	36 (21.4)	
Diabetes mellitus	26 (15.5)	24 (14.3)	
Hypertension + Diabetes	24 (14.3)	26 (15.5)	
Other	24 (14.3)	24 (14.3)	

The main outcome was the variation in the dyspnea level measured by the mMRC scale. Baseline mean of mMRCs among dual and triple therapy groups were similar (2.82 $\pm$ 0.94 and 2.85 $\pm$ 0.92 respectively; $p = 0.768$). The mean score of mMRC was found to be significantly lower at the one month follow up

in the triple therapy group as compared to the dual therapy group (1.540394 vs. 2.180502; $p < 0.001$). The mean improvement in mMRC score was also greater in the triple therapy group (1.31 ± 0.76 vs. 0.64 ± 0.72 ; $p < 0.001$). It

showed a significant clinical improvement in 136 (81.0) patients receiving triple therapy as opposed to 92 (54.8) receiving dual therapy ($p < 0.001$).

Table 2. Comparison of dyspnea outcomes between treatment groups

Parameter	Dual Therapy (n=168)	Triple Therapy (n=168)	Mean Difference / Comparison	p-value
Baseline mMRC score	2.82 ± 0.94	2.85 ± 0.92	-0.03 (95% CI: -0.23 to 0.17)	0.768
Follow-up mMRC score	2.18 ± 1.02	1.54 ± 0.94	0.64 (95% CI: 0.43 to 0.85)	<0.001
Mean mMRC improvement	0.64 ± 0.72	1.31 ± 0.76	-0.67 (95% CI: -0.83 to -0.51)	<0.001
Clinical improvement, n (%)	92 (54.8)	136 (81.0)	26.2 percentage points	<0.001
No clinical improvement, n (%)	76 (45.2)	32 (19.0)	-26.2 percentage points	

The distribution of mMRC grades at one-month follow-up differed significantly between the two treatment groups ($\chi^2=18.42$, $df=4$, $p < 0.001$). Grade 0-1 was observed in 88 (52.4%) patients receiving triple therapy

compared with 50 (29.8%) receiving dual therapy, whereas grade 3-4 was observed in 32 (19.1%) and 58 (34.5%) patients, respectively ($p < 0.001$).

Table 3. Distribution of follow-up mMRC grades according to treatment group

mMRC Grade	Dual Therapy (n=168)	Triple Therapy (n=168)	p-value
Grade 0	10 (6.0)	28 (16.7)	<0.001
Grade 1	40 (23.8)	60 (35.7)	
Grade 2	60 (35.7)	48 (28.6)	
Grade 3	44 (26.2)	28 (16.7)	
Grade 4	14 (8.3)	4 (2.4)	
Overall comparison			
Grade 0-1	50 (29.8)	88 (52.4)	<0.001
Grade 3-4	58 (34.5)	32 (19.1)	<0.001

Overall comparison: $\chi^2 = 18.42$, $df = 4$, $p < 0.001$.

The frequency of COPD exacerbation was determined during the last week, two weeks, and month. The average, exacerbations per group were also significantly reduced in the triple therapy group in all of these three observation periods (all $p < 0.001$). In the

previous week, the triple therapy group was 0.7 ± 0.7 as compared to the dual therapy group at 1.1 ± 0.9 . Over the preceding two weeks, the corresponding values were 1.1 ± 0.9 and 1.6 ± 1.1 , while over the preceding month they were 1.3 ± 1.0 and 1.8 ± 1.2 , respectively (all $p < 0.001$).

Table 4. Comparison of exacerbation frequency between treatment groups

Parameter	Dual Therapy (n=168)	Triple Therapy (n=168)	Mean Difference (95% CI)	p-value
Exacerbations (last week)	1.1 ± 0.9	0.7 ± 0.7	0.4 (0.2–0.6)	<0.001
Exacerbations (last 2 weeks)	1.6 ± 1.1	1.1 ± 0.9	0.5 (0.3–0.7)	<0.001
Exacerbations (last month)	1.8 ± 1.2	1.3 ± 1.0	0.5 (0.3–0.7)	<0.001
Total exacerbations	4.4 ± 2.3	3.2 ± 1.9	1.2 (0.7–1.7)	<0.001

Exacerbation frequency compared using Mann–Whitney U because distribution was non-normal.

Multi-factor logistic regression analysis was conducted in order to determine the variables that independently had any association with clinical improvement (Table 5). Triple therapy was also in direct proportionality related to an increase in odds, relative to dual therapy in terms of clinical improvement (adjusted OR 3.42, 95% CI: 2.105.58; $p < 0.001$). Clinical improvement was inversely related to longer COPD duration (adjusted OR 0.88 or 1-year increase, 95% CI: 0.82–0.94; $p = 0.001$) as did higher baseline mMRC score (adjusted OR 0.62 or 1-unit increase, 95% CI: 0.47–0.94; $p = 0.001$). Clinical improvement was not independently related to age, sex, BMI, smoking status, pack-years, and comorbidities (all $p > 0.05$).

Table 5. Multivariable logistic regression analysis of independent predictors of clinical improvement among patients with COPD

Variable	Adjusted OR	95% CI	p-value
Triple therapy (vs. Dual therapy)	3.42	2.10–5.58	<0.001
Age (per year increase)	0.99	0.96–1.02	0.486
Male sex (vs. Female)	1.12	0.66–1.90	0.672
BMI (per unit increase)	1.03	0.98–1.08	0.256
Smoking status			
Current smoker (vs. Never)	0.76	0.42–1.37	0.356
Former smoker (vs. Never)	0.88	0.48–1.62	0.680
Pack-years (per unit increase)	0.99	0.97–1.02	0.568
COPD duration (per year increase)	0.88	0.82–0.94	<0.001
Baseline mMRC (per unit increase)	0.62	0.47–0.82	0.001
Comorbidities (Present vs. None)	0.72	0.43–1.21	0.214

CI: Confidence interval; OR: Odds ratio. Dependent variable: clinical improvement (yes/no).

Discussion

Dyspnea is a significant symptom of COPD and the factor linked to the decrease of physical activity, worse quality of life, and higher rates of healthcare use (2,3). In this study, baseline mMRC scores were similar in both groups but more dyspnea improvement was seen in patients that received triple therapy in the one month follow up. This finding is consistent with previous clinical studies reporting improved symptom control

and health-related outcomes with triple inhaler therapy compared with dual bronchodilator therapy (9,10,11,12). The potential benefit of triple therapy may reflect the combined bronchodilator effects of LABA and LAMA together with the anti-inflammatory effects of ICS. However, differences in treatment response may also be influenced by factors that were not fully measured in the present study.

COPD exacerbations are an important component of disease burden and are associated with increased healthcare utilization and poorer clinical outcomes (2,8). In this study, exacerbation frequency was lower among patients receiving triple therapy than among those receiving dual therapy during the assessed observation periods. Similar reductions in exacerbation frequency have been reported in randomized studies evaluating triple inhaler therapy (9,10,11,12). A comparatively large sample size with equitable distribution among treatment groups and the use of the validated modified Medical Research Council (mMRC) dyspnea scale to evaluate treatment results are two of the study's strengths (4,5). Current GOLD recommendations also consider escalation to triple therapy in appropriate patients with persistent exacerbations despite dual bronchodilator treatment (1). Nevertheless, treatment selection in routine clinical practice may be influenced by disease severity and other patient characteristics, which should be considered when interpreting the findings of the present observational study.

Strength and limitations of study

The strengths of this study include a relatively large sample size with equal allocation between the two treatment groups, the use of the validated (mMRC) dyspnea scale, and the inclusion of patients from a tertiary-care pulmonology department in Pakistan. The study also provides local comparative data on dual and triple inhaler therapy from a clinical setting where such evidence is limited. Nevertheless, a number of drawbacks need to be taken into account. To begin with, it was a single-center observational study, which could limit the external validity of the study findings and present the risk of unaccounted confounding. Second, the duration of follow-up did not extend beyond one month, which

did not allow evaluating such long-term results as the ability to maintain symptoms control, hospitalization, mortality, and lung function changes. Third, adherence to medication was not assessed systematically, and breathing technique was not evaluated systematically; these might both affect treatment response.

Set against this, probably significant unmeasured variables such as the count of eosinophils in blood, pulmonary rehabilitation, environmental exposures, and other elements of disease management could have influenced the results observed. Nevertheless, observational design, brief follow-up, and lack of systematic evaluation of adherence to medication and technique of inhaler restrict the possibility of coming to causal conclusions. Consequently, the results can only be viewed as affiliations and not demonstrating a causal treatment impact.

Conclusion

Triple inhaler therapy (LABA/LAMA/ICS) as compared to dual inhaler therapy (LABA/LAMA) was found to be more effective in relation to the severity of dyspnea and reduction of COPD exacerbations in the one-month period. Those who responded to triple therapy similarly performed better on mMRC dyspnea scale and a larger proportion of clinical improvement. The correlation between outcome of triple therapy and clinical betterment was significant even when multivariates were adjusted. However, due to the observational nature of the allocation of treatment and the short follow-up time, these results only show an association and are no longer enough to determine a causal effect of treatment.

Conflict of interest

The authors declare no conflict of interest.

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