International Journal of Chronic Obstructive Pulmonary Disease

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ORIGINAL RESEARCH

Real-World Long-Term Outcomes of Triple Therapy Following Hospitalization for Acute Exacerbation of COPD: A Retrospective Cohort Study

Wen-Lin Su[1,2], Chou-Chin Lan[1,2], Mei-Chen Yang[1,2], Chun-Yao Huang[1], Yao-Kuang Wu[1,2]

[1]Division of Pulmonary Medicine, Department of Internal Medicine, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan; [2]School of Medicine, Tzu-Chi University, Hualien, Taiwan

Correspondence: Yao-Kuang Wu, Division of Pulmonary Medicine, Department of Internal Medicine, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, No. 289, Jianguo Road, Xindian Dist, New Taipei City, 232016, Taiwan, Tel +886-2-66289779 ext 5709, Fax +886-2-66289009, Email drbfci@yahoo.com.tw

Purpose: Chronic obstructive pulmonary disease (COPD) exacerbations significantly accelerate disease progression and increase mortality and healthcare utilization. While triple therapy (inhaled corticosteroids/long-acting β_2-agonist/long-acting muscarinic antagonist [ICS/LABA/LAMA]) is commonly prescribed to manage COPD, its long-term real-world effectiveness following hospitalization for acute exacerbation of COPD remains unclear.

Patients and Methods: This retrospective cohort study included 500 patients hospitalized for severe COPD exacerbations at a tertiary hospital (2015–2023). Patients were classified as receiving triple therapy (ICS/LABA/LAMA) during or within 7 days after the index hospitalization or not. Primary outcomes were COPD-related readmission and all-cause mortality within three years; secondary analyses were stratified by prior exacerbation frequency, baseline FEV_1 % predicted, and eosinophil count. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox models, with Kaplan–Meier methods for survival.

Results: Among the study population, 329 patients (65.8%) received triple therapy. Overall, no significant differences were observed in three-year COPD-related readmission rates (adjusted hazard ratio [aHR]: 0.95, 95% confidence interval [CI]: 0.66–1.35) or all-cause mortality (aHR: 0.88, 95% CI: 0.57–1.36) between the groups. However, stratified analyses demonstrated significant benefits of triple therapy in patients with ≥2 exacerbations within one year prior to the index hospitalization (aHR for readmission: 0.14; aHR for mortality: 0.24) and showed numerically lower risks among those with baseline FEV_1 ≥50% predicted (aHR for readmission: 0.57; aHR for mortality: 0.43).

Conclusion: Triple therapy was not associated with improved outcomes in the overall cohort but may be associated with better outcomes in selected high-risk subgroups. These findings should be interpreted with caution given the observational design and potential residual confounding. Further studies are warranted to confirm these findings and refine patient selection for triple therapy.

Keywords: COPD exacerbation, triple therapy, mortality, real-world study, retrospective cohort

Introduction

Chronic obstructive pulmonary disease (COPD) is a global health challenge with profound implications for patient health and healthcare systems.[1] Affecting over 250 million people worldwide, COPD contributes to approximately 3.23 million deaths annually and ranks as the third leading cause of global mortality.[2] The disease's prevalence is expected to rise due to aging populations, increased tobacco use, and ongoing exposure to environmental pollutants.[3] Acute exacerbations of COPD (AECOPD) represent critical events that significantly accelerate disease progression and increase healthcare utilization.[4] These episodes are characterized by up to 20% of patients being readmitted to the hospital within 30 days

https://doi.org/10.2147/COPD.S586308
Received: 10 December 2025
Accepted: 27 April 2026
Published: 14 May 2026

and nearly 50% within a year of an occurrence.[5] The one-year mortality rate following hospitalization for AECOPD ranges from 20% to 40%.[6] This highlights the urgent need for effective management strategies to mitigate these risks.

Triple therapy, comprising inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), and long-acting muscarinic antagonists (LAMA), has emerged as an important strategy in COPD management.[7] According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy, escalation to LABA/LAMA/ICS is recommended for patients with persistent exacerbations despite dual-bronchodilator therapy.[8] Prior randomized controlled trials have demonstrated that triple therapy can reduce exacerbation risk and improve clinical outcomes in selected patients with a high exacerbation burden. However, real-world evidence regarding the long-term effectiveness of triple therapy following hospitalization for acute exacerbation of COPD remains limited.[9,10] In addition, clinical trial populations may not fully represent routine clinical practice, as patients with advanced age, multiple comorbidities, or polypharmacy are often underrepresented.[11,12] Therefore, real-world studies are needed to better evaluate the effectiveness of triple therapy in broader and more representative patient populations.

Accordingly, the present retrospective cohort study aimed to evaluate the long-term impact of triple therapy on exacerbation rates and mortality among patients hospitalized for an AECOPD. By analyzing real-world data, we seek to bridge the knowledge gap between clinical trial results and everyday clinical practice. The findings might offer valuable evidence to inform personalized treatment strategies and improve patient outcomes in this high-risk population.

Methods

Study Design and Population

This retrospective cohort study analyzed patients discharged after hospitalization for a severe AECOPD between January 2015 and November 2023 at Taipei Tzu Chi Hospital, a tertiary medical center in Northern Taiwan. Eligible patients were identified from electronic medical records and were required to be aged ≥18 years, have a confirmed diagnosis of COPD before the index date based on the International Classification of Diseases (ICD) diagnostic codes, and have experienced at least one severe AECOPD requiring hospitalization (the index hospitalization) during the study period. The diagnosis of COPD was identified using ICD-9 codes 491, 492, and 496, or ICD-10 codes J41-J44. Severe AECOPD were defined as a hospitalization or emergency department visit with a primary COPD diagnosis (ICD-10-CM J44.1 or J44.0, ICD-9-CM 491.21 or 491.22) accompanied by prescription records for systemic corticosteroids and/or respiratory antibiotics during the encounter, where moderate exacerbations were defined as outpatient visits for a primary COPD diagnosis with prescriptions for systemic corticosteroids and/or respiratory antibiotics for a duration of 3–14 days.[13–15] In the present study, we focused on severe AECOPD requiring hospitalization; therefore, patients who were evaluated only in the emergency department and discharged within 24 hours without admission were not classified as hospitalized AECOPD cases and were not included in the study cohort.

Exclusion criteria were: a prior diagnosis of another significant respiratory disease (eg., asthma, clinically significant bronchiectasis, or interstitial lung disease) or incomplete clinical data.

Patients were categorized into two groups: (1) Patients in the triple therapy group were those who initiated ICS/LABA/LAMA during the index hospitalization or who started ICS/LABA/LAMA within 7 days after discharge; and (2) patients in the non-triple-therapy group receiving any other inhaled regimen. Data on inhaler use before and after index hospitalization were collected, and patients were included regardless of their maintenance inhaler regimen before the index hospitalization. Patients were contacted within 7 days after discharge for an initial follow-up.

Inhaled therapy followed institutional practice aligned with GOLD recommendations: LABA + LAMA as preferred initial therapy, escalation to LABA + LAMA + ICS if an ICS indication was present, particularly in patients with blood eosinophils ≥ 300 cells/μL; LABA + ICS alone was generally avoided.[16,18]

The patients were followed from the index date until death, loss to follow-up, or the end of the study period (November 30, 2023), whichever occurred first.

Data Collection

Data extraction and verification were performed by trained research staff from the Division of Pulmonary Medicine using the hospital's electronic medical record system, with oversight by the study investigators. Demographic, clinical, and laboratory data were collected at the time of the index admission, including age, sex, smoking status, body mass index (BMI), comorbidities (neuromuscular disease [NMD], chronic lung disease, ischemic heart disease, non-terminal cancer, end-stage renal disease [ESRD], diabetes mellitus, liver disease, autoimmune disease, and hypertension), history of prior exacerbations, and markers of inflammation (eg, C-reactive protein [CRP], white blood cell count [WBC], and neutrophil–lymphocyte ratio [NLR]), bilevel positive airway pressure (BiPAP), along with clinical outcomes and length of stay. Chronic lung disease was defined as the presence of restrictive lung disease (such as pulmonary fibrosis or work-related lung diseases including silicosis or coal worker's pneumoconiosis) or obstructive lung diseases other than COPD (including asthma, bronchiectasis, and cystic fibrosis). We extracted spirometry results obtained within six months before the index date, including both pre- and post-bronchodilator forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC ratio. None of the patients had received systemic corticosteroids within 72 hours of the index admission.

Ethics Statement

The study complies with the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Taipei Tzu Chi Hospital (IRB: 14-IRB028). Given the retrospective design and the use of de-identified medical records, the requirement for informed consent was waived by the ethics committee of IRB.

Outcomes

The two primary outcomes, compared between the triple therapy group and the non-triple therapy group, were (1) time to first COPD-related readmission, defined as readmission for a severe COPD exacerbation, that is, a hospital admission or emergency visit with a primary COPD diagnosis accompanied by systemic corticosteroids and/or respiratory antibiotic prescription records, and (2) overall mortality within three years of discharge.

Secondary outcomes included stratified analyses of these endpoints by prior exacerbation frequency, eosinophil count (obtained at admission during the index hospitalization), and baseline lung function (FEV1% predicted).

Statistical Analysis

For the statistical comparison of patients who underwent triple therapy or not, categorical data are presented as n (%) and performed by chi-squared test or Fisher's exact test, as appropriate. Continuous variables were assessed for normality using the Shapiro–Wilk test, while data with normal distribution are presented as mean ± SD and performed as a t-test, otherwise, data are presented as median and interquartile range (IQR, ie., 25th-75th percentile). For the primary outcomes, Cox proportional hazard (PH) regression models were utilized to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) of the effect of triple therapy for COPD-related readmission and overall mortality within three years. Covariates with p-value < 0.1 were included as adjustment variables. The cumulative incidence curve and overall survival plot were conducted by the Kaplan–Meier method and tested by Gray's test and Log rank test. The duration was calculated from the discharge date to the date of the event (first COPD-related readmission or mortality) that occurred or to the latest follow-up date if the patient was never readmitted due to COPD or survived past three years.

Missing data for covariates were handled by complete-case analysis; variables with missing values are indicated in the tables. No imputation was performed. As this was a retrospective cohort study including all eligible patients during the study period, no formal sample size calculation or power analysis was performed. A two-tailed p-value <0.05 was considered statistically significant. All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Study Population

A total of 500 patients were included. Among them, 329 patients (65.8%) received triple therapy during or within 7 days after discharge from their index hospitalization, while 171 patients (34.2%) did not. The median age of the patients was 78 years, with a predominance of male patients (84.4%). Hypertension was observed in 52.6% of the patients. Prior severe AECOPD in the past 12 months was 0 in 65.4% of patients, 1 in 20.8%, and ≥2 in 13.8% (Table 1).

The patterns of inhaler use before and after the index hospitalization for patients receiving or not receiving triple therapy are summarized in Supplemental Table 1. Before the index hospitalization, 59.6% of patients in the triple therapy group (those who received triple therapy after hospitalization) and 7.6% in the non-triple therapy group were already on triple therapy.

Table 1 Comparison of Baseline Characteristics Between Patients with and without Triple Therapy

Variables	All (N=500)	Triple Therapy (N=329)	Non-Triple Therapy (N=171)	P-value
Male, n (%)	422 (84.4)	271 (82.4)	151 (88.3)	0.083
Age, years	78.0 (69.0–85.0)	77.0 (68.0–83.0)	80.0 (72.0–88.0)	**<0.001**
BMI, kg/m2 (missing=3)	23.3 (20.4–26.3)	22.7 (20.4–26.0)	23.9 (20.6–26.7)	0.070
Smoking status				0.061
Current	109 (21.8)	82 (24.9)	27 (15.8)	
Former	202 (40.4)	129 (39.2)	73 (42.7)	
Never	189 (37.8)	118 (35.9)	71 (41.5)	
Comorbidities, n (%)				
NMD	49 (9.8)	32 (9.7)	17 (9.9)	0.939
Chronic lung disease	55 (11.0)	42 (12.8)	13 (7.6)	0.080
Ischemic heart disease	140 (28.0)	98 (29.8)	42 (24.6)	0.217
Non-terminal cancer	54 (10.8)	38 (11.6)	16 (9.4)	0.453
ESRD	7 (1.4)	6 (1.8)	1 (0.6)	0.431
Diabetes mellitus	103 (20.6)	80 (24.3)	23 (13.5)	**0.004**
Liver disease	9 (1.8)	8 (2.4)	1 (0.6)	0.175
Autoimmune disease	10 (2.0)	7 (2.1)	3 (1.8)	1.000
Hypertension	263 (52.6)	164 (49.8)	99 (57.9)	0.087
Laboratory measures				
CRP, mg/dL (missing=52)	1.9 (0.5–6.8)	1.6 (0.4–5.9)	2.7 (0.7–8.2)	**0.004**
WBC, 103/μL	9.6 (7.1–12.8)	9.7 (7.3–12.5)	9.4 (7.0–13.3)	0.712
Neutrophil, %	77.1 (67.3–84.5)	77.3 (66.7–84.1)	77.0 (68.3–84.6)	0.699
Lymphocyte, %	13.2 (8.0–20.4)	13.5 (8.0–20.5)	13.0 (7.5–19.9)	0.630
Monocyte, %	6.1 (4.7–8.4)	6.0 (4.7–8.4)	6.4 (4.7–8.1)	0.718
Eosinophil, %	1.0 (0.1–2.4)	1.0 (0.2–2.4)	0.9 (0.1–2.2)	0.152
Basophil, %	0.2 (0.1–0.4)	0.2 (0.1–0.5)	0.2 (0.1–0.4)	0.107
Neutrophil count, 103/μL	7.0 (4.9–10.4)	6.8 (5.2–10.4)	7.4 (4.6–10.1)	0.797
Lymphocyte count, 103/μL	1.2 (0.8–1.8)	1.2 (0.8–1.8)	1.2 (0.8–1.7)	0.556
Eosinophil count, cells/μL	93.7 (12.0–221.9)	97.2 (19.4–238.6)	78.9 (8.6–213.7)	0.100
<300	405 (81.0)	259 (78.7)	146 (85.4)	0.072
≥300	95 (19.0)	70 (21.3)	25 (14.6)	
NLR	5.8 (3.3–10.6)	5.8 (3.2–10.2)	6.0 (3.7–11.4)	0.615
<3	110 (22.0)	74 (22.5)	36 (21.1)	0.712
≥3	390 (78.0)	255 (77.5)	135 (78.9)	
Platelet, 103/μL	213.0 (169.5–264.0)	218.0 (176.0–267.0)	204.0 (162.0–253.0)	**0.037**
Hb, g/dL	13.3 ± 2.1	13.5 ± 2.2	12.9 ± 2.0	**0.002**

(*Continued*)

Table 1 (Continued).

Variables	All (N=500)	Triple Therapy (N=329)	Non-Triple Therapy (N=171)	P-value
Respiration				
FEV1, %, predicted	51.0 (39.0–65.0)	49.0 (37.0–62.0)	57.0 (44.0–74.0)	**<0.001**
<50	223 (44.6)	166 (50.5)	57 (33.3)	**<0.001**
≥50	277 (55.4)	163 (49.5)	114 (66.7)	
FVC, %, predicted	74.0 (59.0–90.5)	71.0 (58.0–86.0)	78.0 (62.0–99.0)	**0.003**
FEV1, L	1.1 (0.8–1.5)	1.0 (0.8–1.4)	1.2 (0.9–1.6)	**<0.001**
FVC, L	2.1 ± 0.7	2.1 ± 0.7	2.2 ± 0.8	0.105
FEV1/FVC, %	55.4 (46.3–63.0)	53.0 (45.0–61.6)	59.0 (49.0–65.0)	**<0.001**
BiPAP, %	90 (18.0)	67 (20.4)	23 (13.5)	0.056
RCW	8 (1.6)	5 (1.5)	3 (1.8)	1.000
AECOPD before the index hospitalization within 1 year				**0.012**
0	327 (65.4)	202 (61.4)	125 (73.1)	
1	104 (20.8)	72 (21.9)	32 (18.7)	
2+	69 (13.8)	55 (16.7)	14 (8.2)	

Notes: Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BiPAP, bilevel positive airway pressure; BMI, body mass index; CRP, C-reactive protein; ESRD, end-stage renal disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; Hb, hemoglobin; NMD, neuromuscular disease; NLR, neutrophil-to-lymphocyte ratio; RCW, respiratory care ward; WBC, white blood cell.

Among the 329 patients who received triple therapy after the index hospitalization, 75.4% were prescribed multiple-inhaler triple therapy (MITT) and 24.6% single-inhaler triple therapy (SITT). Among the 171 patients who did not receive triple therapy, 10.5% received LAMA monotherapy, 28.7% received ICS/LABA, and 60.8% received LAMA +LABA (Supplemental Table 1).

Comparisons Between Patients with and without Triple Therapy

Patients receiving triple therapy were generally younger (median: 77.0 vs. 80.0 years, p<0.001) and had higher proportion of diabetes (24.3% vs. 13.5%, p=0.004), lower CRP levels (1.6 vs. 2.7 mg/dL, p=0.004), and higher platelet and hemoglobin (Hb) levels (median: 218.0 vs. 204 103/μL, p=0.0378; mean: 13.5 vs. 12.9, p=0.002, respectively) compared with those not receiving triple therapy. Significant differences were also observed between the triple therapy cohort and the non-triple therapy cohort in respiratory status, including pre-bronchodilator FEV_1% predicted (median: 49.0% vs. 57.0%, $p < 0.001$) and FVC% predicted (median: 71.0% vs. 78.0%, $p = 0.003$), post-bronchodilator FEV_1 (median: 1.0 L vs. 1.2 L, $p < 0.001$), and FEV_1/FVC ratio (median: 53.0% vs. 59.0%, $p < 0.001$) (Table 1).

The length of stay was longer in the triple therapy group (median: 8.0 vs. 7.0 days, p=0.020). However, no significant differences were found in the rate of the first COPD-related readmission within 1 year (17.6% vs. 17.0%, p=0.851) or 3 years (38.3% vs. 35.7%, p=0.565). Mortality rates were slightly lower in the triple therapy group, but the difference did not reach statistical significance (3-year mortality: 17.0% vs. 23.4%, p=0.086) (Table 2).

The cumulative incidence curve of the first COPD-related readmission and overall survival curve for the entire study population indicate no difference for a rise in hospital readmission (p=0.540) and increased mortality (p=0.140) over the 3-year period between the two groups (Figure 1).

The stratified cumulative incidence curve of first COPD-related readmission and overall survival curve found no difference between triple therapy patients and those not receiving triple therapy for hospital readmission in patients who had within 1 year prior to index hospitalization <2 exacerbations (p=0.101) or an FEV1% predicted <50% (p=0.400) (Figure 2A and C). In addition, no difference in survival rate was seen in these two subgroups with or without triple therapy (p=0.245 and 0.775, respectively) (Figure 3A and C). However, triple therapy was associated with a lower risk of hospital readmission due to COPD in the patients with ≥2 exacerbation within 1 year prior of index hospitalization (p=0.009) or FEV1% predicted ≥50% (p=0.039) (Figure 2B and D). Triple therapy was also associated with higher survival in patients with ≥2 exacerbations (p=0.009) or FEV1% predicted ≥50% (p=0.004) (Figure 3B and D).

Table 2 Comparison of Outcomes Between Patients with and without Triple Therapy

Outcome	All (N=500)	Triple Therapy (N=329)	Non-Triple Therapy (N=171)	P-value
Length of stay, day	8.0 (6.0–12.0)	8.0 (6.0–13.0)	7.0 (6.0–12.0)	**0.020**
COPD-related readmission within	242 (48.4)	166 (50.5)	76 (44.4)	0.202
1 year	87 (17.4)	58 (17.6)	29 (17.0)	0.851
3 years	187 (37.4)	126 (38.3)	61 (35.7)	0.565
AECOPD post index hospitalization/per year				0.468
0~0.9	408 (81.6)	266 (80.9)	142 (83.0)	
1~1.9	49 (9.8)	36 (10.9)	13 (7.6)	
≥2	43 (8.6)	27 (8.2)	16 (9.4)	
Mortality	140 (28.0)	83 (25.2)	57 (33.3)	0.056
1 year	17 (3.4)	9 (2.7)	8 (4.7)	0.255
3 years	96 (19.2)	56 (17.0)	40 (23.4)	0.086
Follow-up duration, years	2.7 (1.5–4.6)	2.6 (1.5–4.4)	2.7 (1.5–4.8)	0.518

Notes: Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease.

Factors Associated with COPD-Related Readmission Within Three years

Univariate analysis identified age, BMI, NMD, smoking status, ESRD, CRP, WBC, lymphocyte, monocyte, NLR, platelet count, hemoglobin, respiratory parameters, BiPAP use, and exacerbation frequency within one year before the index hospitalization as significantly associated with readmission risk ($p < 0.1$) (Table 3). Variables meeting this threshold were entered into the multivariable Cox PH model. Due to strong intercorrelations among lymphocyte percentage, NLR, and respiratory parameters (Spearman's $\rho > 0.7$; Supplemental Table 2), NLR and FEV_1 (L) were retained to address multicollinearity in the final model.

After adjusting for relevant covariates, triple therapy was not associated with a significant reduction in COPD-related readmission risk (adjusted HR: 0.95, 95% CI: 0.66–1.35, $p = 0.764$). NMD (adjusted HR: 2.46, 95% CI: 1.61–3.77, $p < 0.001$) and ESRD (adjusted HR: 5.89, 95% CI: 2.38–14.59, $p < 0.001$) remained independently associated with higher readmission risk (Table 3).

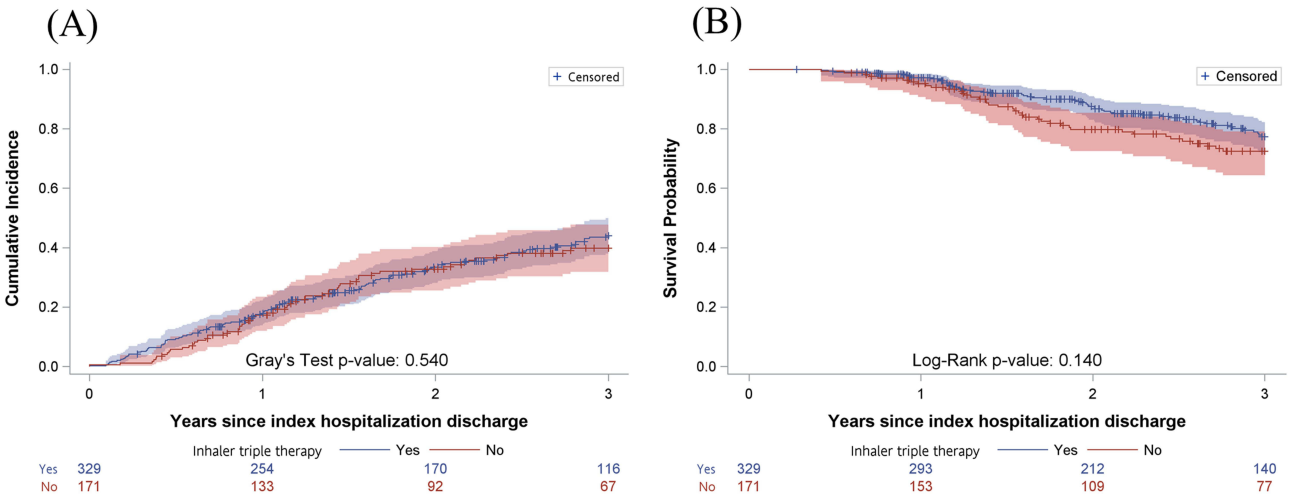

Figure 1 (**A**) The cumulative incidence curve for first COPD-related readmission and (**B**) classified by treatment in patients with COPD and severe exacerbations post-hospitalization.

https://doi.org/10.2147/COPD.S586308

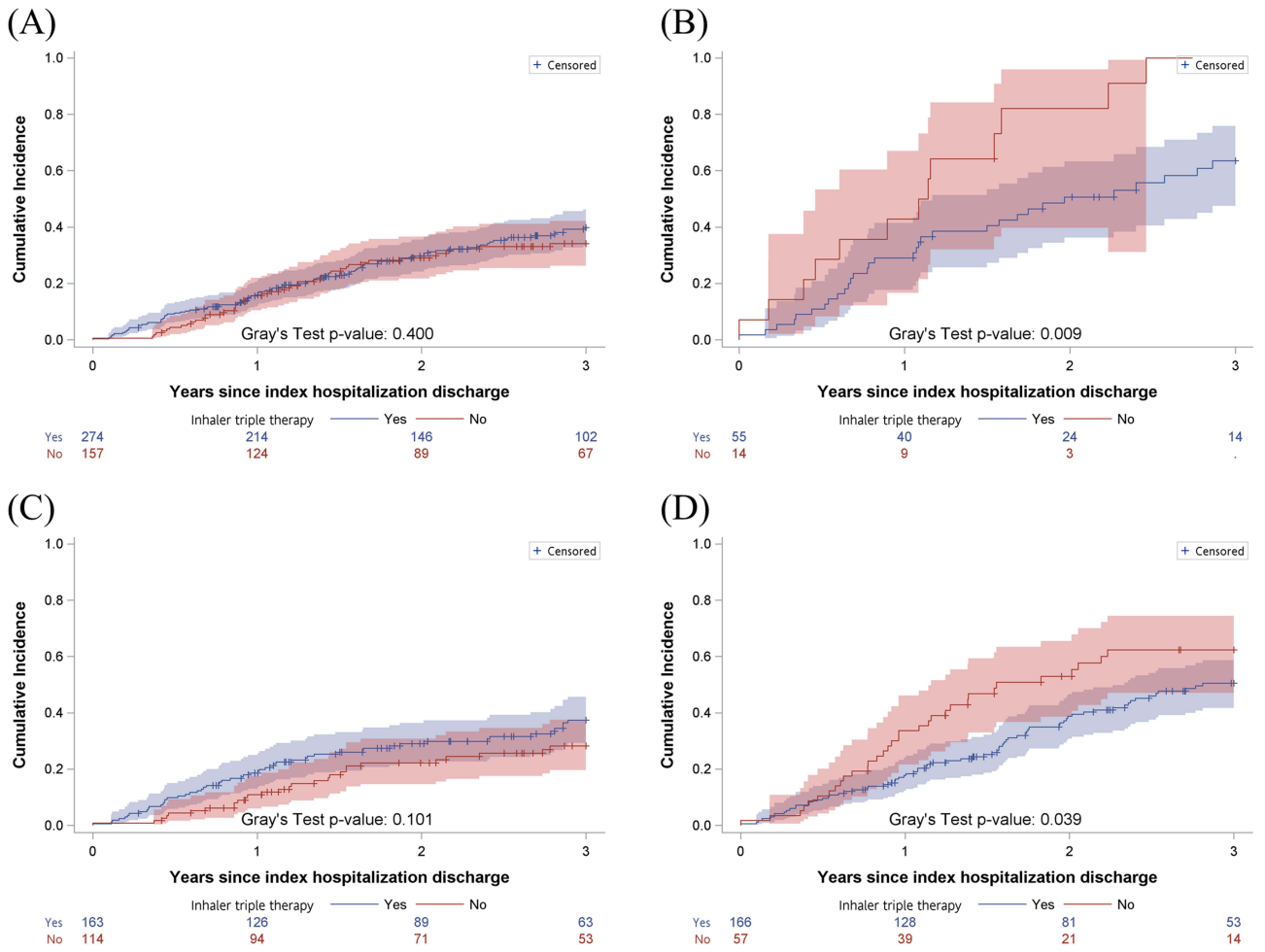

Figure 2 The cumulative incidence curve for first COPD-related readmission was classified by treatment in the subgroups (**A**) <2 exacerbations, (**B**) ≥2 exacerbations, (**C**) FEV1% predicted <50%, (**D**) FEV1% predicted ≥50%.

Factors Associated with Overall Mortality

Table 4 shows factors associated with overall mortality after the index hospitalization. In the multivariable model, higher age (aHR 1.04, 95% CI 1.01–1.06, p = 0.002) was associated with increased mortality, whereas higher BMI (aHR 0.94, 95% CI 0.89–0.99, p = 0.017) and higher hemoglobin (aHR 0.86, 95% CI 0.77–0.96, p = 0.007) were associated with lower mortality risk. The presence of NMD (aHR 3.30, 95% CI 1.98–5.49, p < 0.001) and ≥2 exacerbations in the prior year (aHR 2.01, 95% CI 1.20–3.37, p = 0.008) also predicted higher mortality. Triple therapy use was not significantly associated with mortality risk (aHR 0.88, 95% CI 0.57–1.36, p = 0.556) (Table 4).

Stratified Analyses by Eosinophil Count, AE, NLR, FEV1

Table 5 shows that, when stratified by eosinophil count, NLR, history of AECOPD, and FEV_1% predicted, inhaler triple therapy was not significantly associated with COPD-related readmission or overall mortality in most subgroups. The only exception was in patients with ≥2 prior AEs, where triple therapy was linked to a substantially lower risk of both readmission (aHR 0.14, 95% CI 0.05–0.44, p = 0.001) and mortality (aHR 0.24, 95% CI 0.07–0.78, p = 0.018) (Table 5).

Discussion

This retrospective cohort study evaluated the real-world long-term outcomes of triple therapy (ICS/LABA/LAMA) in patients hospitalized for COPD exacerbations, a high-risk population that is often underrepresented in randomized

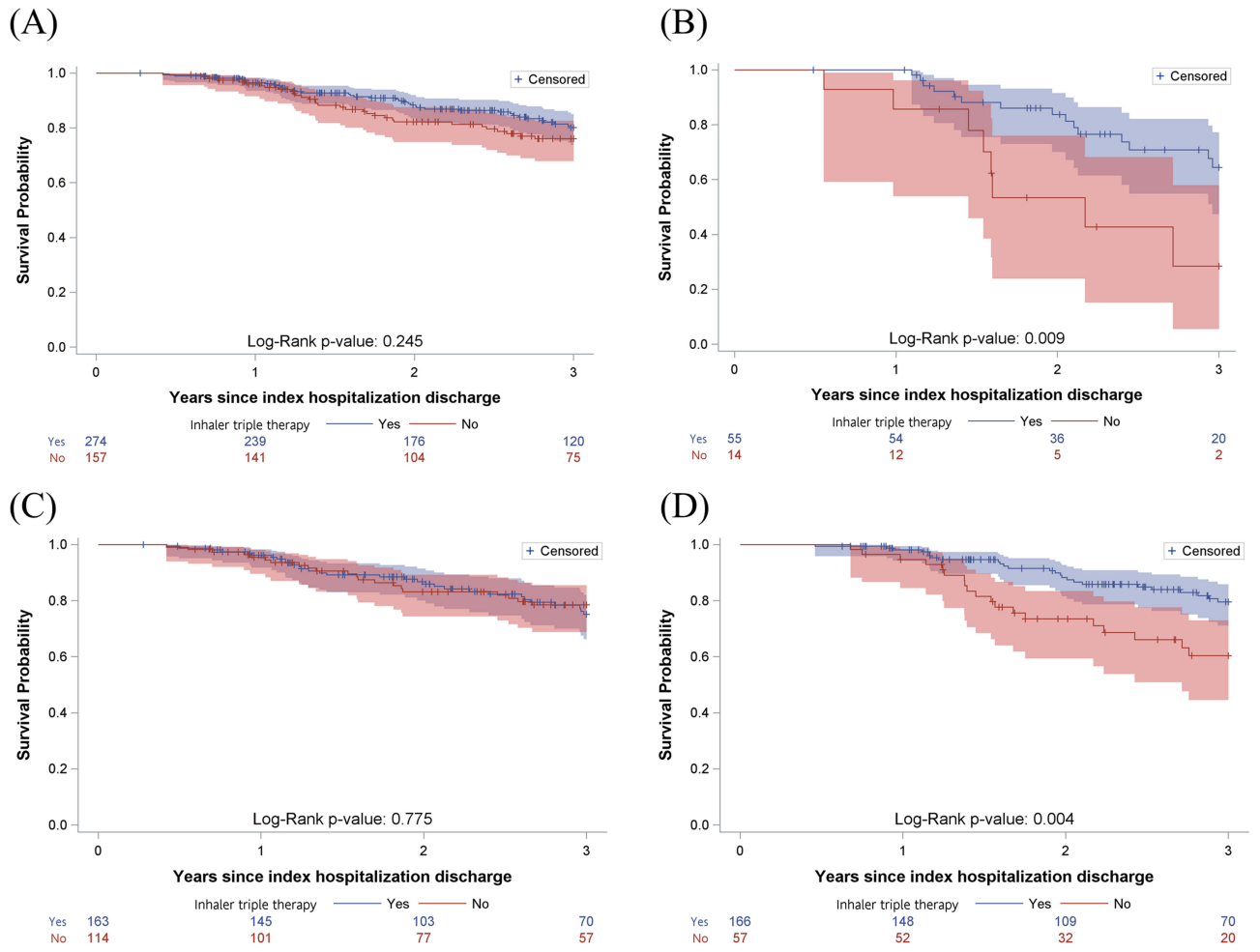

Figure 3 The overall survival curve was classified by treatment in the subgroups (**A**) <2 exacerbations, (**B**) ≥2 exacerbations, (**C**) FEV1% predicted < 50%; (**D**) FEV1% predicted ≥50%.

controlled trials. No significant differences in three-year COPD-related readmission or all-cause mortality were observed between patients who received triple therapy and those who did not. However, stratified analyses suggested that triple therapy may be associated with lower risks of COPD-related readmission and mortality in certain subgroups. These findings should be interpreted with caution given the observational design, potential residual confounding, and non-random treatment allocation. Overall, the results suggest that the effects of triple therapy may vary across patient subgroups and highlight the need for further studies to clarify which patients may benefit most.

Notably, eosinophil-based stratification did not demonstrate clear associations with outcomes in our cohort. The lack of a clear association between eosinophil-based stratification and outcomes in our study may have several explanations. First, eosinophil counts were measured during AECOPD, which may not accurately reflect the patient's baseline inflammatory phenotype. Second, prior or early exposure to systemic corticosteroids may have suppressed eosinophil levels, thereby attenuating potential associations. Third, the relatively small sample size in the higher eosinophil subgroup (eg, ≥300 cells/μL) may have limited statistical power to detect meaningful differences. Therefore, these findings should be interpreted with caution.

Three major randomized controlled studies have investigated the efficacy of triple therapy in patients with COPD.[16,18,19] The ETHOS trial was a 52-week Phase 3 study that evaluated triple therapy using two doses of ICS in patients with moderate-to-very severe COPD (N=8509) who had at least one exacerbation within the prior year.[18] They compared the ICS/LABA/LAMA therapy (budesonide/formoterol/glycopyrrolate) to a "control" group who received one

Table 3 Factors Associated with COPD-Related Readmission

Variables	Crude HR (95% CI)	P-value	Adjusted HR* (95% CI)	P-value
Inhaler triple therapy	1.10 (0.81–1.49)	0.541	0.95 (0.66–1.35)	0.764
Male vs Female	1.19 (0.79–1.80)	0.406		
Age, years	1.01 (0.99–1.03)	0.064	1.01 (0.99–1.02)	0.461
BMI, kg/m2 (missing=3)	0.94 (0.91–0.98)	**0.001**	0.96 (0.92–1.00)	**0.032**
Smoking (vs Never)				
Current	1.12 (0.75–1.68)	0.579	1.10 (0.69–1.76)	0.692
Former	1.47 (1.06–2.03)	**0.021**	1.39 (0.97–1.99)	0.075
Comorbidities				
NMD	2.26 (1.53–3.35)	**<0.001**	2.46 (1.61–3.77)	**<0.001**
Chronic lung disease	0.96 (0.61–1.53)	0.876		
Ischemic heart disease	1.09 (0.79–1.49)	0.609		
Non-terminal cancer	0.78 (0.47–1.30)	0.336		
ESRD	4.58 (2.02–10.36)	**<0.001**	5.89 (2.38–14.59)	**<0.001**
Diabetes mellitus	1.06 (0.74–1.50)	0.760		
Liver disease	1.07 (0.34–3.34)	0.913		
Autoimmune disease	NA	-		
Hypertension	1.18 (0.88–1.57)	0.271		
Laboratory measures				
CRP, mg/dL (missing=52)	0.97 (0.95–1.001)	0.056	0.97 (0.94–1.00)	**0.033**
WBC,103/μL	1.04 (1.01–1.07)	**0.012**	1.03 (0.99–1.07)	0.146
Neutrophil, %	1.01 (0.99–1.02)	0.263		
Lymphocyte, %	0.98 (0.97–0.999)	**0.036**		
Monocyte, %	0.94 (0.89–0.99)	**0.017**	1.00 (0.94–1.06)	0.930
Eosinophil, %	1.003 (0.96–1.05)	0.893		
Basophil, %	1.02 (0.64–1.62)	0.947		
NLR	1.01 (1.003–1.02)	**0.006**	1.01 (1.00–1.02)	0.112
Platelet, 103/μL	5.83 (1.52–22.29)	**0.010**	4.39 (0.71–27.17)	0.111
Hb, g/dL	0.92 (0.86–0.99)	**0.025**	1.00 (0.92–1.10)	0.936
Respiration				
FEV1, %, predicted	0.988 (0.981–0.996)	**0.002**		
FVC, %, predicted	0.992 (0.986–0.998)	**0.009**		
FEV1, L	0.52 (0.37–0.73)	**<0.001**	0.59 (0.38–0.92)	**0.021**
FVC, L	0.77 (0.63–0.94)	**0.009**		
FEV1/FVC, %	0.98 (0.97–0.99)	**0.006**	1.00 (0.98–1.02)	0.853
BiPAP, %	1.37 (0.97–1.93)	0.075		
RCW	NA	-		
AECOPD before the index hospitalization within 1 year (vs 0)				
1	1.11 (0.76–1.61)	0.592	1.16 (0.78–1.72)	0.477
2+	2.45 (1.73–3.48)	**<0.001**	2.57 (1.72–3.85)	**<0.001**

Notes: Bold values indicate statistical significance ($p < 0.05$). NA means no event occurred in a subgroup. *Adjusted for covariates with $p < 0.1$ in the univariate analysis.
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BiPAP, bilevel positive airway pressure; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ESRD, end-stage renal disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; Hb, hemoglobin; HR, hazard ratio; NMD, neuromuscular disease; NLR, neutrophil-to-lymphocyte ratio; RCW, respiratory care ward; WBC, white blood cell.

of 2 dual therapies (ie, glycopyrrolate/formoterol or budesonide/formoterol). The triple therapy assessed two different ICS doses (ie, 320 μg of 160 μg of budesonide). The study found that the triple therapy resulted in a 13% to 25% lower rate (p values ≤0.003) of moderate to severe COPD exacerbations compared with the dual therapies.

The IMPACT trial was a randomized controlled study involving 10,355 patients with COPD that compared 52 weeks of once daily dosing of the ICS/LABA/LAMA combination of fluticasone furoate/vilanterol/umeclidinium with either the ICS/LABA combination fluticasone/vilanterol or LABA/LAMA combination of vilanterol/umeclidinium.[16] The primary

Table 4 Factors Associated with Overall Mortality

Variables	Crude HR (95% CI)	P-value	Adjusted HR* (95% CI)	P-value
Inhaler triple therapy	0.74 (0.49–1.11)	0.141	0.88 (0.57–1.36)	0.556
Male vs Female	1.87 (0.94–3.71)	0.075	1.30 (0.63–2.67)	0.476
Age, years	1.06 (1.03–1.08)	**<0.001**	1.04 (1.01–1.06)	**0.002**
BMI, kg/m2 (missing=3)	0.93 (0.89–0.98)	**0.004**	0.94 (0.89–0.99)	**0.017**
Smoking (vs Never)				
Current	0.79 (0.43–1.45)	0.442	1.06 (0.54–2.06)	0.867
Former	1.41 (0.91–2.20)	0.124	1.48 (0.94–2.35)	0.094
Comorbidities				
NMD	3.25 (2.00–5.27)	**<0.001**	3.30 (1.98–5.49)	**<0.001**
Chronic lung disease	1.18 (0.64–2.16)	0.596		
Ischemic heart disease	1.28 (0.84–1.96)	0.249		
Non-terminal cancer	1.45 (0.81–2.60)	0.216		
ESRD	2.46 (0.60–10.03)	0.208		
Diabetes mellitus	0.75 (0.44–1.29)	0.298		
Liver disease	0.67 (0.09–4.82)	0.693		
Autoimmune disease	NA	-		
Hypertension	1.40 (0.93–2.11)	0.104		
Laboratory measures				
CRP, mg/dL (missing=52)	0.99 (0.96–1.03)	0.626		
WBC, 103/μL	1.03 (0.99–1.07)	0.200		
Neutrophil, %	1.02 (0.999–1.04)	0.062		
Lymphocyte, %	0.97 (0.95–0.998)	**0.035**	0.99 (0.96–1.01)	0.329
Monocyte, %	0.93 (0.86–1.004)	0.064	0.95 (0.88–1.02)	0.143
Eosinophil, %	1.02 (0.96–1.08)	0.607		
Basophil, %	1.45 (0.80–2.60)	0.218		
NLR	1.01 (0.997–1.02)	0.126		
Platelet, 103/μL	4.95 (0.69–35.31)	0.111		
Hb, g/dL	0.79 (0.72–0.87)	**<0.001**	0.86 (0.77–0.96)	**0.007**
Respiration				
FEV1, %, predicted	1.000 (0.99–1.01)	0.925		
FVC, %, predicted	1.001 (0.99–1.01)	0.884		
FEV1, L	0.70 (0.44–1.11)	0.128		
FVC, L	0.84 (0.64–1.10)	0.206		
FEV1/FVC, %	0.99 (0.98–1.01)	0.506		
BiPAP, %	1.28 (0.79–2.07)	0.324		
RCW	NA	-		
AECOPD before the index hospitalization within 1 year (vs 0)				
1	1.28 (0.78–2.12)	0.326	1.19 (0.71–1.99)	0.514
2+	2.25 (1.38–3.69)	**0.001**	2.01 (1.20–3.37)	**0.008**

Notes: Bold values indicate statistical significance ($p < 0.05$). NA means no event occurred in a subgroup. *Adjusted for covariates with $p < 0.1$ in the univariate analysis.
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BiPAP, bilevel positive airway pressure; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ESRD, end-stage renal disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; Hb, hemoglobin; HR, hazard ratio; NMD, neuromuscular disease; NLR, neutrophil-to-lymphocyte ratio; RCW, respiratory care ward; WBC, white blood cell.

outcome was the rate of moderate or severe COPD exacerbations. Similar to the ETHOS study, they found that the triple combination resulted in a 15% to 25% reduction in the rate of moderate or severe exacerbation per year compared with the dual therapy (p values < 0.001). They also found that the triple therapy resulted in a lower rate of hospitalization due to COPD than the vilanterol/umeclidinium dual therapy.

The 52-week TRIBUTE trial investigated the efficacy of the triple ICS/LABA/LAMA therapy beclomethasone dipropionate, formoterol fumarate, and glycopyrronium compared with the dual-bronchodilator therapy indacaterol

Table 5 Comparison of Inhaler Triple Therapy versus No Triple Therapy for COPD-Related Readmission and Overall Mortality, Stratified by Eosinophil Count, NLR, History of AECOPD, and FEV_1% Predicted

Subgroup	Triple Therapy			Non-Triple Therapy			Adjusted HR	P-value
	Total	Event	%	Total	Event	%	(95% CI)*	
First COPD-related readmission								
Eosinophil count, cells/μL								
<300	228	87	38.2%	131	47	35.9%	1.00 (0.68–1.47)	0.993
≥300	65	27	41.5%	22	6	27.3%	0.80 (0.27–2.37)	0.682
NLR								
<3	65	26	40.0%	33	10	30.3%	0.95 (0.42–2.15)	0.902
≥3	228	88	38.6%	120	43	35.8%	0.95 (0.63–1.41)	0.782
AECOPD a								
0~1	245	85	34.7%	140	41	29.3%	1.05 (0.70–1.57)	0.809
2+	48	29	60.4%	13	12	92.3%	0.14 (0.05–0.44)	**0.001**
FEV1, %, predicted								
<50	145	47	32.4%	102	24	23.5%	1.08 (0.64–1.84)	0.767
≥50	148	67	45.3%	51	29	56.9%	0.69 (0.43–1.11)	0.128
Overall mortality								
Eosinophil count, cells/μL								
<300	257	42	16.3%	145	31	21.4%	0.89 (0.54–1.45)	0.633
≥300	70	14	20.0%	25	8	32.0%	0.85 (0.31–2.34)	0.753
NLR								
<3	74	11	14.9%	36	5	13.9%	1.09 (0.28–4.26)	0.898
≥3	253	45	17.8%	134	34	25.4%	0.92 (0.57–1.49)	0.743
AECOPD a								
0~1	272	41	15.1%	156	31	19.9%	1.03 (0.64–1.68)	0.895
2+	55	15	27.3%	14	8	57.1%	0.24 (0.07–0.78)	**0.018**
FEV1, %, predicted								
<50	162	31	19.1%	113	20	17.7%	1.22 (0.66–2.25)	0.532
≥50	165	25	15.2%	57	19	33.3%	0.62 (0.33–1.17)	0.138

Notes: *Adjusted for covariates with p<0.1 in the univariate analysis, except the stratified variable. An AECOPD before the index hospitalization within 1 year. Bold values indicate statistical significance ($p < 0.05$).

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; NLR, neutrophil-to-lymphocyte ratio; FEV1, forced expiratory volume in 1 second.

plus glycopyrronium in terms of the rate of moderate-to-severe COPD exacerbations in symptomatic COPD patients (N=1532) that.[19] Included patients had severe or very severe airflow limitations and a history of exacerbations despite maintenance therapy. The triple therapy was associated with a significant reduction in the rate of moderate-to-severe exacerbations compared with the dual therapy (p=0.043).

A meta-analysis reported no increased risk of pneumonia with triple therapy compared with dual therapy.[20] In contrast, other studies have suggested a potential increase in pneumonia risk despite clinical benefits.[21,22] However, pneumonia outcomes were not assessed in the present study, and therefore the relevance of these findings to our cohort remains uncertain.

The mortality benefit of triple therapy observed in the three large clinical studies differs from our findings. Although the absolute risk difference of 6.4% may be clinically relevant in this high-risk population, the present study was not powered to detect modest differences in mortality, and the confidence intervals remain wide. Therefore, these findings should be interpreted with caution and considered hypothesis-generating rather than conclusive evidence of a mortality benefit. Another possible explanation is the distribution of ICS-naïve and ICS-exposed patients in our study. In the IMPACT and ETHOS studies, the proportion of ICS-naïve patients was 33% and 20%, respectively. In contrast, our study included a higher proportion of ICS-naïve subjects (43%). Subgroup analyses of ICS-naïve patients in the IMPACT and

ETHOS trials found no significant difference in exacerbation risk or mortality between triple and dual therapies, suggesting that the observed benefits of triple therapy were primarily driven by patients with prior ICS exposure.[20] This may explain why we did not observe a significant mortality difference in our study, since a large proportion of our study population consisted of ICS-naïve patients. Additionally, variations in primary outcomes may have played a role, as prior trials focused on reducing moderate-to-severe exacerbations, whereas our study specifically examined severe exacerbations requiring hospitalization.

Our findings suggest that COPD patients may not be a homogeneous group with respect to treatment response. However, given the relatively small subgroup sizes and multiple comparisons, these observations should be interpreted with caution and considered exploratory and hypothesis-generating. Further studies are needed to clarify whether specific patient subgroups derive differential benefit from triple therapy. Although certain subgroups appeared to show more favorable outcomes, these observations remain uncertain and may reflect underlying differences in disease severity or inflammatory patterns.[23] This is consistent with prior studies, including systematic reviews and meta-analyses, which suggest that the effectiveness of triple therapy may vary according to exacerbation history, disease severity, and blood eosinophil levels.[20] Overall, the triple therapy's effectiveness was influenced by exacerbation history, disease severity, and blood eosinophil levels, suggesting its use should be tailored to specific patient characteristics. Notably, the observed association in patients with FEV_1 ≥50% appears inconsistent with current GOLD recommendations, which generally support escalation to triple therapy in patients with more severe airflow limitation. One possible explanation is that FEV_1 alone may not fully reflect exacerbation risk or underlying inflammatory burden. Patients with relatively preserved lung function may still experience frequent exacerbations or have distinct inflammatory phenotypes that respond to ICS-containing therapy. In addition, treatment decisions in real-world practice may be influenced by clinical factors beyond spirometric severity. Therefore, this observation should be interpreted with caution and considered exploratory.

Similarly, a meta-analysis of 60 randomized controlled trials found that triple therapy was associated with a reduced risk of all-cause mortality in COPD patients; however, predictors of this association included medication factors and patient characteristics, among which eosinophil counts of ≥200/iL.[23] For example, previous studies have reported potential benefits of triple therapy in patients with frequent exacerbations (≥2) and higher eosinophil counts (≥300 cells/μL).[21] However, these findings, including ours, should be interpreted cautiously and require further validation. Overall, the available evidence highlights the need for individualized treatment strategies while emphasizing the uncertainty of subgroup-specific effects.

In our cohort, 84% of patients were male. This marked male predominance is consistent with previous hospital-based studies of severe COPD and AECOPD in Asian populations, where men constitute 60–90% of hospitalized cases, largely reflecting higher smoking rates and occupational exposures among older men.[24,25] However, contemporary global data indicate that the burden of COPD among women is increasing.[26] Therefore, our findings are most generalizable to predominantly male, smoking-related COPD populations in East Asia, and caution is warranted when extrapolating these results to female patients or settings with a more balanced sex distribution.

It is also important to acknowledge that the GOLD recommendations for inhaled pharmacologic therapy evolved during the study period. Earlier GOLD reports allowed relatively broad use of ICS/LABA and triple therapy in high-risk patients, whereas more recent updates (from 2017 onwards) have prioritized LABA/LAMA combinations as first-line maintenance therapy and reserved ICS-containing regimens, including triple therapy, for selected patients with frequent exacerbations and/or elevated blood eosinophil counts.[27–29] These evolving recommendations, together with the increasing availability of single-inhaler triple combinations, may have contributed to temporal changes in prescribing patterns and to the concentration of more severe or exacerbation-prone patients in the triple-therapy group, further limiting causal interpretation of our observational findings.[29]

Strength and Limitation

The strengths of this research include its substantial sample size of 500 COPD patients, comprehensive data collection spanning from 2015 to 2023, and detailed analysis of multiple clinical parameters including baseline characteristics, respiratory functions, and long-term outcomes. In addition, the findings reflect the use of treatment in a real-world setting.

However, several limitations should be acknowledged. First, the observational nature of this study precludes definitive conclusions regarding causal relationships between triple therapy and patient outcomes. Second, potential selection bias may exist due to differences in baseline characteristics between groups; patients who received triple therapy differed in age, comorbidities, baseline lung function, inflammatory profiles, and prior inhaler use compared with those who did not. In addition, the comparator group was heterogeneous, comprising LAMA monotherapy, LABA/LAMA, and LABA/ICS regimens, which have different expected effects on exacerbation risk and mortality. This heterogeneity may have diluted treatment effects and limited direct comparability between groups. As a result, the observed associations should be interpreted with caution, as the choice of comparator may have influenced the estimated treatment effects. Third, given the retrospective design, treatment decisions were made according to clinical judgment and evolving GOLD recommendations rather than through randomized allocation, which may have introduced bias. Temporal changes in guideline recommendations and prescribing patterns during the study period may have further influenced treatment allocation. Fourth, patients receiving triple therapy may differ systematically from those receiving other regimens due to clinical decision-making, introducing potential confounding by indication. Although multivariable Cox regression was applied to adjust for measured covariates, residual confounding cannot be excluded. Fifth, the limited sample size and heterogeneity of treatment regimens in the comparator group restricted the use of more advanced statistical techniques, such as propensity score matching or inverse probability weighting, as these approaches may have resulted in substantial loss of sample size or unstable estimates. In addition, the heterogeneity of the comparator group, including LAMA monotherapy, LABA/LAMA, and LABA/ICS regimens, may have further limited comparability and influenced the estimated treatment effects. Although multivariable adjustment was performed, it may not have fully accounted for residual confounding. Sixth, the sample size may have been insufficient to detect small or moderate differences in outcomes, particularly in subgroup analyses, which may have limited statistical power. As a result, negative findings should be interpreted with caution. Seventh, data on other pharmacologic interventions (eg, phosphodiesterase inhibitors, theophylline, long-term macrolide therapy) and non-pharmacologic measures (eg, pulmonary rehabilitation) were not systematically collected, potentially leading to unmeasured confounding. Eighth, relevant cardiovascular comorbidities, including arrhythmias, heart failure, and valvular heart disease, were not captured in the dataset and may have influenced outcomes. In addition, although Gray's test was used to compare cumulative incidence functions, competing-risk regression models (eg, Fine–Gray models) were not applied in multivariable analyses. Therefore, the potential impact of competing risks, particularly mortality, may not have been fully accounted for. Further, both single-inhaler and multiple-inhaler triple therapy were included in this study, and differences in adherence between these approaches may have influenced outcomes. Finally, although subgroup analyses were performed, the mechanisms underlying the observed associations in patients with multiple prior exacerbations remain unclear, and these findings should be interpreted with caution. Therefore, the results of this study should be considered associative rather than causal or comparative effectiveness evidence.

Conclusion

In this retrospective cohort study, triple therapy (ICS/LABA/LAMA) showed no significant impact on overall COPD exacerbation-related hospital readmission rates or mortality within three years following the indexed hospitalization for COPD exacerbations. However, stratified analyses suggested possible benefits in selected high-risk subgroups; however, these findings require cautious interpretation and further validation. These findings underscore the importance of personalized treatment approaches in managing COPD, where triple therapy may be most beneficial for targeted populations rather than as a universal strategy. Further prospective studies are warranted to validate these subgroup-specific effects and guide clinical decision-making in real-world settings.

Data Sharing Statement

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

No funding source for this study.

Disclosure

The authors report no conflicts of interest in this work.

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