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Evaluation of comparative efficacy of Umeclidinium/Vilanterol versus other bronchodilators in the management of chronic obstructive pulmonary disease: a systematic review and meta-analysis of RCTs

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Abstract

Background UMEC/VI administered via a combination inhaler is associated with a clinically significant improvement in lung function and health-related quality of life in patients with mild-to-moderate COPD. However, their efficacy compared to other bronchodilator mono or dual therapies still remains unclear.

Objective The objective of this research was to evaluate the therapeutic efficacy of UMEC/VI dual and UMEC/VI/FF triple therapies versus alternative bronchodilator regimens in COPD patients.

Methods A systematic search was conducted using four electronic databases (PubMed, EMBASE, Scopus, and Cochrane Library) to select publications published in peer-reviewed journals written in English. The odds ratio (OR) and risk ratio (RR) was calculated, along with their 95% confidence intervals. We assessed heterogeneity using Cochrane Q and I [2] statistics and the appropriate *p*-value. The analysis used RevMan 5.4.

Results The current meta-analysis includes 31,814 COPD patients from 17 RCTs. The meta-analysis results demonstrate that the combination of LABA and LAMA provides additive bronchodilation and improved lung function in COPD patients. We found that UMEC/VI dual therapy significantly improved FEV1 (OR 1.98 [95% CI 1.70–2.30]), TDI values (OR 1.97 [95% CI 1.72–2.26]), and reduced SGRQ total scores (OR 1.99 [95% CI 1.71–2.32]), with fewer drug-related adverse events (RR 0.58 [95% CI 0.53–0.64]). Similarly, UMEC/VI/FF triple therapy also showed similar benefits, with significant improvements in FEV1 (OR 1.93 [95% CI 1.73–2.15]), TDI values (OR 2.37 [95% CI 2.15–2.61]), and reduced SGRQ total scores (OR 1.83 [95% CI 1.63–2.05]), and fewer drug-related adverse events (RR 0.53 [95% CI 0.49–0.58]).

Conclusion This systematic review and meta-analysis concludes that UMEC and VI combinations are an efficacious treatment option for symptomatic COPD patients.

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Keywords Chronic obstructive pulmonary disease (COPD), Bronchodilators, Umeclidinium/Vilanterol (UMEC/VI), Indacaterol/glycopyrrolate (IND/GLY), Tiotropium/olodaterol (TIO/OLO), Salmeterol/Fluticasone propionate (SAL/FP), Fluticasone furoate (FF), Long-acting muscarinic antagonists (LAMA), Long acting beta2-agonists (LABA)

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive and debilitating respiratory condition characterized by airflow limitation, inflammation, and significant morbidity and mortality worldwide [1]. Smoking is the leading cause of chronic obstructive pulmonary disease (COPD), responsible for approximately 75% of COPD deaths [2]. Bronchodilators are the cornerstone of COPD management, aiming to improve lung function, symptoms, and quality of life [3]. Umeclidinium/Vilanterol (UMEC/VI) is a combination of Umeclidinium bromide (UMEC), a long-acting muscarinic antagonist (LAMA), and Vilanterol tridentate (VI), a long-acting beta2-adrenergic agonist (LABA), approved for COPD treatment including chronic bronchitis and emphysema [4–6]. UMEC/VI combines the bronchodilatory effects of both UMEC and VI, resulting in dual bronchodilation through simultaneous relaxation of airway smooth muscle and decreased airway resistance, sustained bronchodilation for up to 24 h, improved lung function, and a reduction in symptoms such as dyspnea, wheezing, and coughing [7–10]. Previous studies reported that the combination of UMEC and VI provided sustained relief from bronchospasm and improved lung function. For instance, Maqsood et al. (2019) [11] reported in their systematic review and meta-analysis that a once-daily dose of UMEC/VI administered via a combination inhaler is associated with a clinically significant improvement in lung function and health-related quality of life in patients with mild-to-moderate COPD. Similarly, Horita et al. (2017) [12] and Fukada et al. (2023) [13] also reported in their meta-analysis that the combination of UMEC/VI has fewer exacerbations, a larger improvement of lung functions, a lower risk of pneumonia, and a more frequent improvement in quality of life. Furthermore, Cazzola et al. (2018) [14] conducted a systematic review and meta-analysis, which revealed that patients receiving single long-acting bronchodilator therapy or LABA/LAMA combination therapy, yet still experiencing exacerbations and having blood eosinophil counts of 300 cells/L, may derive benefits from ICS/LABA/LAMA combination therapy. Additionally, numerous studies have suggested the potential advantages of adding Fluticasone as a potent corticosteroid along with UMEC and VI in the UMEC/VI/FF triple therapy for the management of COPD [15–17]. However, their efficacy compared to other bronchodilator mono or dual therapies still remains unclear. Therefore, this systematic review and meta-analysis aims to comprehensively evaluate the therapeutic efficacy of UMEC/VI dual therapy and UMEC/VI/FF triple therapy, compared to monotherapeutic and dual therapeutic regimens employing alternative bronchodilators, including LAMAs (tiotropium, glycopyrrolate) and LABAs (salmeterol, formoterol, indacaterol, fluticasone furoate), in patients with COPD.By synthesizing evidence from relevant randomized controlled trials (RCTs) [18–34] selected as per the pre-specified inclusion-exclusion criteria, this study endeavors to provide a robust assessment of UMEC/VI's efficacy and update the treatment recommendations for COPD patients.

Objective

This objective of study is to evaluate the therapeutic efficacy of UMEC/VI dual and UMEC/VI/FF triple therapies versus alternative bronchodilator regimens in COPD patients."

Materials and methods

Search strategy and selection criteria

This systematic review and meta-analysis were conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [35] and AMSTAR (Assessing the Methodological Quality of Systematic Reviews) [36] guidelines, ensuring a rigorous and transparent methodology. A comprehensive review of RCTs was performed, applying pre-specified inclusion and exclusion criteria to evaluate the comparative efficacy of UMEC/VI dual and UMEC/VI/FF triple therapies versus alternative bronchodilator regimens in patients with COPD. A comprehensive literature search was performed across multiple scientific databases, including Embase, PubMed, Scopus, and Cochrane CENTRAL, to identify relevant randomized controlled trials (RCTs) published up to June 30, 2024. The search terms used were: "Chronic obstructive pulmonary disease", "COPD", "Bronchodilators", "Umeclidinium", "Vilanterol", "Umeclidinium/Vilanterol", "UMEC/VI", "Indacaterol/glycopyrrolate", "IND/GLY", "Tiotropium/olodaterol", "TIO/OLO", "Placebo", "PBO", "Salmeterol/Fluticasone propionate", "SAL/FP", "Fluticasone furoate", "FF", "GFFMDI", "Glycopyrronium/formoterol fumarate dihydrate", "Long-acting muscarinic antagonists", "LAMA", "Long acting beta2-agonists", "LABA", "Forced expiratory volume in 1 s", "FEV_1", "Dual inhaler

therapy;", "Triple inhaler therapy", "Monotherapy", "Smoking history", "Severity of COPD", "Forced vital capacity", "FVC", "SGRQ total score", "St George's Respiratory Questionnaire total score", "TDI", "Transitional dyspnoea Index", "Randomized controlled trial", "RCT", "Systematic review", "meta-analysis". Following the PICOS framework [37], keywords were identified and assessed for agreement in both Medline and EMBASE databases. The specified keywords were applied to the Title-Abstract-Keyword field in Scopus, while the Cochrane database was searched using the terms "chronic obstructive pulmonary disease," "Umeclidinium," and "Vilanterol."

The PICOS criteria were defined as follows:

- P: Patients with COPD.
- I: UMEC/VI dual therapy or UMEC/VI/FF triple therapy.
- C: Control group treated with other bronchodilators such as indacaterol/glycopyrrolate, tiotropium/olodaterol, Placebo, Salmeterol/Fluticasone propionate, Fluticasone furoate.
- O: Primary clinical outcomes, including change in FEV1, St George's Respiratory Questionnaire total score, Transitional dyspnoea Index, and drug-related adverse events.

The search was restricted to randomized controlled trials (RCTs). Additional articles were identified through backward and forward citation tracking of previous meta-analyses and included studies. The complete search strategy is outlined in Table 1. Two reviewers independently evaluated the titles, abstracts, and full texts of potential articles, with discrepancies resolved through discussion and consultation with the senior author if necessary."

Study selection and data extraction

This systematic review and meta-analysis included RCTs that compared the efficacy of UMEC/VI dual and UMEC/VI/FF triple therapies with alternative bronchodilator regimens in COPD patients. No restrictions were placed on publication year or language.

Inclusion criteria: Studies were included if they met the following criteria: Study design: RCT, patients with COPD, participants ≥ 18 years old, reported primary outcomes: FEV1 change, St. George's Respiratory Questionnaire total score, Transitional Dyspnea Index, and drug-related adverse events and full-text availability with sufficient data for a 2 × 2 table.

Exclusion criteria: Studies that did not meet the inclusion criteria were excluded, including: Observational studies (case series, case-control, and cohort studies), review articles and expert commentary, preclinical and animal studies and clinical trials involving children and adolescents under 18 years old.

Two researchers independently extracted data from included studies using a standardized form, collecting information on study characteristics, patient demographics, and outcomes. The extracted information includes the study ID and year, journal of publication, Study name, the total number of participants, age of participants, gender (M/F), inclusion criteria, study duration, control, intervention, number of participants in the intervention/control arm, severe or very severe COPD (%), current smokers (%), and primary outcomes. Authors were contacted for supplementary data when necessary."

Risk of bias assessment of included studies

A systematic risk of bias assessment was conducted utilizing a standardized questionnaire to evaluate the methodological quality of the included RCTs. Two investigators independently appraised the risk of bias in each study using the Cochrane Risk of Bias Tool, Version 2 (RoB 2) [38], which encompass five distinct domains: randomization process, intervention adherence, missing outcome data, outcome measurement, and outcome reporting. To ensure objectivity, a third reviewer served as an arbiter to resolve any discrepancies. The risk of bias was subsequently categorized as "uncertain", "high", or "low". Furthermore, small-study effects and publication bias were evaluated using a comparison-adjusted funnel plot [39], and the statistical significance of any bias was confirmed via Egger's test [40], performed using MedCalc software [41].

Statistical analysis

The Review Manager (RevMan) software, version 5.4 [42], was utilized to conduct a comprehensive meta-analysis of the continuous and dichotomous outcomes. For each included study, odds ratios (ORs), risk ratios (RRs) and corresponding 95% confidence intervals (CIs) [43] were calculated to quantify the effect size of binary outcomes. The DerSimonian-Laird method [44] was employed to estimate ORs using 2 × 2 contingency tables, and forest plots [45] were constructed to visualize the impact of various outcome determinants. Heterogeneity was assessed using the I [2] statistic [46] and $\chi 2$ test [47], with accompanying p-values [48]. Given the variability in study settings, a random-effects model was adopted. Statistical significance was defined as a p-value < 0.05.

Table 1 Database search strategy

Database	Search strategy
Scopus	#1 "Chronic obstructive pulmonary disease" OR "COPD" OR "Bronchodilators" OR "Umeclidinium" OR "Vilanterol" OR "Umeclidinium/Vilanterol" OR "UMEC/VI" OR "Indacaterol/glycopyrrolate" OR "IND/GLY" OR "Tiotropium/olodaterol" OR "TIO/OLO" OR "Placebo" OR "PBO" OR "Salmeterol/Fluticasone propionate" OR "SAL/FP" OR "Fluticasone furoate" OR "FF" OR "GFFMDI", OR "Glycopyrronium/formoterol fumarate dihydrate", OR "Long-acting muscarinic antagonists" OR "LAMA" OR "Long acting beta2-agonists" OR "LABA". #2 "Forced expiratory volume in 1 s" OR "FEV_1" OR "Dual inhaler therapy;" OR "Triple inhaler therapy" OR "Monotherapy" OR "Smoking history" OR "Severity of COPD" OR "Forced vital capacity" OR "FVC" OR "SGRQ total score" OR "St George's Respiratory Questionnaire total score" OR "TDI" OR "Transitional dyspnoea Index" "Randomized controlled trial" OR "RCT" OR "Systematic review" OR "meta-analysis". #3 #1 AND #2
PubMed	#1 "Chronic obstructive pulmonary disease" OR "COPD" [MeSH Terms]# OR "Bronchodilators" [All Fields] OR "Umeclidinium/Vilanterol" [MeSH terms] OR "Vilanterol" [All fields] OR "Umeclidinium" [All Fields] OR "UMEC/VI" [All Fields] OR "Indacaterol/glycopyrrolate" [All fields] OR "IND/GLY" [All fields] OR "Tiotropium/olodaterol" [All fields] OR "TIO/OLO" [All fields] OR "Placebo" [All fields] OR "PBO" [All fields] OR "Salmeterol/Fluticasone propionate" [All fields] OR "SAL/FP" [All fields] OR "Fluticasone furoate" [All fields] OR "FF" [All fields] OR "GFFMDI" [All fields] OR "Glycopyrronium/formoterol fumarate dihydrate" [All fields] OR "Long-acting muscarinic antagonists" [All fields] OR "LAMA" [All fields] OR "Long-acting beta2 antagonists" [All fields] OR "LABA" [All fields]. #2 "Forced expiratory volume in 1 s" [MeSH Terms] OR "FEV_1" [All Fields] OR "Dual inhaler therapy" [All Fields] OR "Triple inhaler therapy" [All Fields] OR "Monotherapy" [All Fields] OR "Smoking history" [All Fields] OR "Severity of COPD" [All Fields] OR "Forced vital capacity" [All Fields] OR "FVC" [All Fields] OR "SGRQ total score" [All Fields] OR "St George's Respiratory Questionnaire total score" [All Fields] OR "TDI" [All Fields] OR "Transitional dyspnoea Index" [All Fields] OR "RCT" [All Fields] OR "systematic review" [All Fields] OR "meta-analysis" [All Fields] #3 #1 AND #2
Embase	"Chronic obstructive pulmonary disease"/ exp$ OR "COPD"/ exp OR "Bronchodilators"/exp OR "Umeclidinium/Vilanterol"/exp OR "Vilanterol"/exp OR "Umeclidinium"/exp OR "UMEC/VI"/exp OR "Indacaterol/glycopyrrolate" exp OR "IND/GLY"/exp OR "Tiotropium/olodaterol"/exp OR "TIO/OLO"/exp OR "Placebo"/exp OR "PBO"/exp OR "Salmeterol/Fluticasone propionate" exp OR "SAL/FP"/exp OR "Fluticasone furoate" OR "FF"/exp OR "GFFMDI"/exp OR "Glycopyrronium/formoterol fumarate dihydrate"/exp OR "Long-acting muscarinic antagonists"/exp OR "LAMA"/exp OR "Long-acting beta2 antagonists" exp OR "LABA"/exp #2 "Forced expiratory volume in 1 s"/ exp OR "FEV_1" / exp OR "Dual inhaler therapy"/exp OR "Triple inhaler therapy"/exp OR "Monotherapy"/exp OR "Smoking history"/exp OR "Severity of COPD"/exp OR "Forced vital capacity"/exp OR "FVC"/exp OR "SGRQ total score"/exp OR "St George's Respiratory Questionnaire total score"/exp OR "TDI"/exp OR "Transitional dyspnoea Index"/exp OR " Randomized controlled trial"/exp OR " RCT" /exp OR "Systematic review"/exp OR "meta-analysis"/exp #3 #1 AND #2
Cochrane library	#1 (Chronic obstructive pulmonary disease): ti, ab, kw@ OR (COPD): ti, ab, kw OR (Bronchodilators): ti, ab, kw OR (Umeclidinium/Vilanterol) ti, ab, kw OR (Vilanterol): ti, ab, kw OR (Umeclidinium): ti, ab, kw OR (UMEC/VI): ti, ab, kw OR (Indacaterol/glycopyrrolate): ti, ab, kw OR (IND/GLY): ti, ab, kw OR (Tiotropium/olodaterol): ti, ab, kw OR (TIO/OLO): ti, ab, kw OR (Placebo): ti, ab, kw OR (PBO): ti, ab, kw OR (Salmeterol/Fluticasone propionate): ti, ab, kw OR (SAL/FP): ti, ab, kw OR (Fluticasone furoate): ti, ab, kw OR (FF): ti, ab, kw OR (GFFMDI)): ti, ab, kw OR (Glycopyrronium/formoterol fumarate dihydrate)): ti, ab, kw OR (Long-acting muscarinic antagonists): ti, ab, kw OR (LAMA): ti, ab, kw OR (Long-acting beta2 antagonists): ti, ab, kw OR (LABA): ti, ab, kw (Word variations have been searched) #2 (Forced expiratory volume in 1 s): ti, ab, kw OR (FEV_1): ti, ab, kw OR (Dual inhaler therapy): ti, ab, kw OR (Triple inhaler therapy): ti, ab, kw OR (Monotherapy): ti, ab, kw OR (Smoking history): ti, ab, kw OR (Severity of COPD): ti, ab, kw OR (Forced vital capacity): ti, ab, kw OR (FVC): ti, ab, kw OR (SGRQ total score): ti, ab, kw OR (St George's Respiratory Questionnaire total score): ti, ab, kw OR (TDI): ti, ab, kw OR (Transitional dyspnoea Index): ti, ab, kw OR (Randomized controlled trials): ti, ab, kw OR (RCT): ti, ab, kw OR (Systematic review): ti, ab, kw OR (meta-analysis): ti, ab, kw (Word variations have been searched) #3 #1 AND #2

MeSH terms: Medical Subject Headings; $ exp: explosion in Emtree- searching of selected subject terms and related subjects; @ ti, ab, kw: either title or abstract or keyword fields

Results

Study selection outcomes

A comprehensive literature search was conducted across multiple databases, yielding 284 studies that met the inclusion criteria outlined in the PICOS paradigm. A total of 182 articles were selected for consideration, while 102 papers were omitted due to duplicate content. Following further screening, 86 papers were subsequently assessed for eligibility. However, 65 studies were excluded due to invalid titles and abstracts, and 31 papers were excluded due to the unavailability of full-text papers. Later, when the inclusion-exclusion criteria were applied, it was found that 69 studies were ineligible and were therefore excluded on the primary basis of lacking sufficient data to generate 2×2 tables or lacking required primary outcomes. Finally, this meta-analysis included 17 RCTs that satisfied the predetermined inclusion-exclusion criteria, as shown in Fig. 1. The included studies comprise a total of 31,184 participants who are 18 years of age or older. 11 of the 15 included studies compare the effectiveness of UMEC/VI dual therapy in comparison to dual or monotherapies of other bronchodilators [18, 21–24, 26, 28–32], and the remaining four studies compare

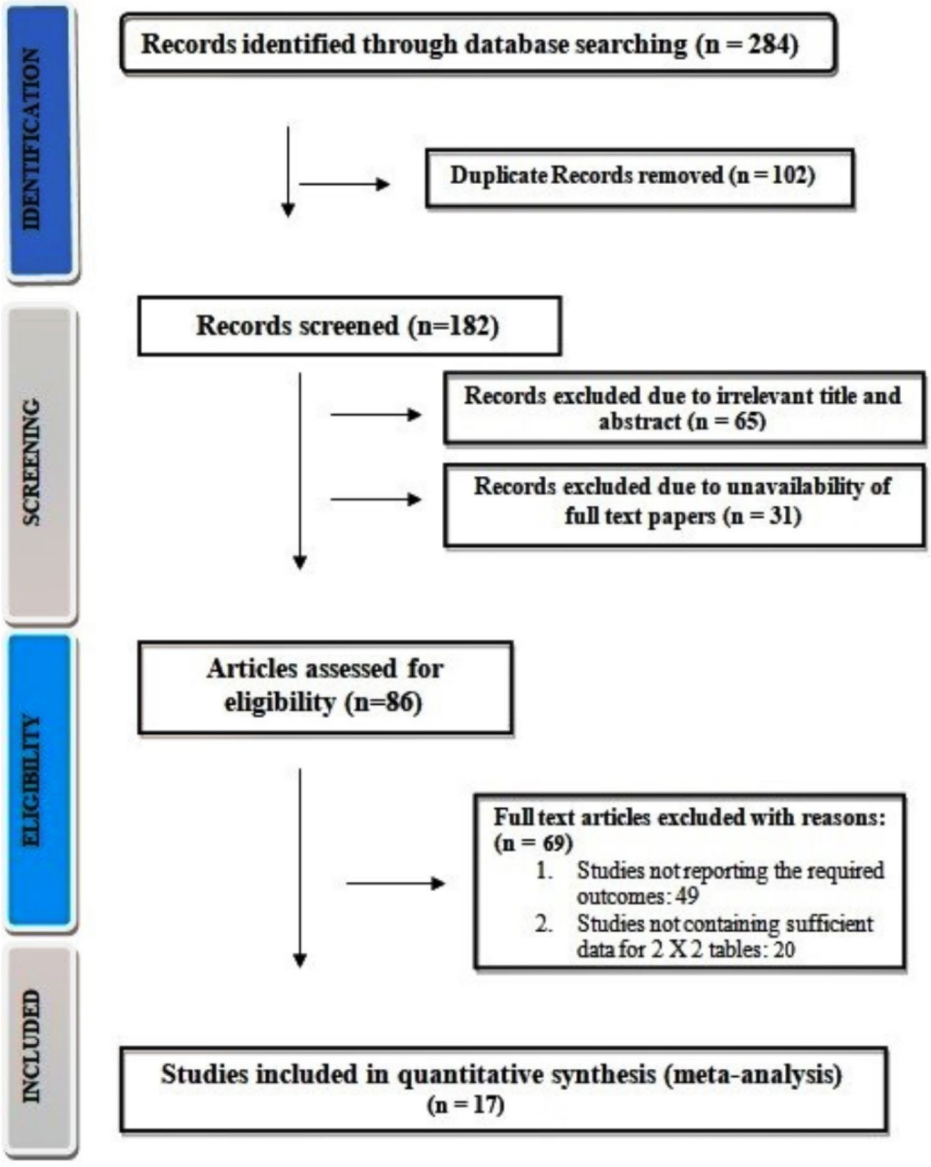

Fig. 1 PRISMA Study flow diagram

the effectiveness of UMEC/VI/FF triple therapy in comparison to dual or monotherapies of other bronchodilators [19, 20, 26, 28] for treatment of COPD. The demographic characteristics of the articles included in this meta-analysis are detailed in Table 2. The content presents study ID and year, journal of publication, study name, the total number of participants, age of participants, gender (M/F), inclusion criteria, study duration, control, intervention, number of participants in the intervention/control arm, severe or very severe COPD (%), current smokers (%), and primary outcomes. Furthermore, we retrieved event data for the 2×2 table from the aforementioned studies to conduct a meta-analysis.

Risk of bias assessment of included RCTs

A rigorous risk of bias assessment was performed to evaluate the methodological quality of each included study, utilizing a pre-established questionnaire (Table 3). The results of this evaluation indicate a low risk of bias across the majority of studies, as illustrated by the summary plot (Fig. 2) and traffic light plot (Fig. 3). Specifically, 13 out of 15 randomized controlled trials (RCTs) exhibited a low risk of bias, while two studies (Kalberg et al. [25] and Maltais et al. [31]) demonstrated a moderate risk of bias due to deviations from intended interventions. In contrast, two RCTs (Decramer et al. [22] and Maleki Yazdi et al. [29]) showed a high risk of bias, attributed to biases

Table 2 Characteristics of the included RCTs

Study ID and year	Journal of publication	Study name	Total number of participants	Age of participants	Gender (M/F)	Inclusion criteria	Study duration	Control	Intervention	Number of participants in Intervention/control arm	Severe or very severe COPD (%)	Current smokers (%)	Primary outcomes
Alcazar et al. [18]	Pulmonary therapy	NCT02799784	292	64.4	175/117	Age ≥ 40 years; diagnosis of COPD (ATS/ERS definition), pre- and post albuterol/salbutamol FEV1/FVC ratio\0.70 smoking history of ≥ 10 pack-years	8 weeks	TIO/OLO	UMEC/VI	147/145	41.2	53	FEV_1, SGRQTS, TDI
Bansal et al., 2021 [19]	Primary care respiratory medicine	FULFIL, 207,626	770	65.9	540/230	Age ≥ 40 years; diagnosis of COPD (ATS/ERS definition), pre- and post albuterol/salbutamol FEV1/FVC ratio\0.70 smoking history of ≥ 10 pack-years	12 weeks	TIO 18	FF/UMEC/VI 100/62.5/25	387/383	46	60.0	FEV_1, SGRQTS, TDI
Bremner et al., 2018 [20]	Respiratory research	GSK study CTT200812, NCT02729051	1055	66.7	785/270	Age ≥ 40 years; diagnosis of COPD (ATS/ERS definition), pre- and post albuterol/salbutamol FEV1/FVC ratio\0.70 smoking history of ≥ 10 pack-years	24 weeks	Budesonide/Formoterol	FF/UMEC/VI 100/62.5/25	527/528	41.0	54.0	FEV_1, SGRQTS, TDI
Celli et al., 2014 [21]	Chest	NCT01313637	811	63.1	535/276	Age ≥ 40 years; diagnosis of COPD (ATS/ERS definition), pre- and post albuterol/salbutamol FEV1/FVC ratio\0.70 smoking history of ≥ 10 pack-years	24 weeks	PBO 125	UMEC/VI 125/25	407/404	44.0	53.0	FEV_1, SGRQTS, TDI
Decramer et al., 2014 [22]	The Lancet respiratory medicine	NCT01316900, NCT01316913	2332	62.5	1754/578	Age ≥ 40 years; diagnosis of COPD (ATS/ERS definition), pre- and post albuterol/salbutamol FEV1/FVC ratio\0.70 smoking history of ≥ 10 pack-years	24 weeks	TIO 18	UMEC/ VI 125/ 25	1141/1191	40.0	45.0	FEV_1, SGRQTS, TDI
Donohue et al., 2015 [23]	Respiratory medicine	DB2114951, NCT01879410	706	63.2	367/339	Age ≥ 40 years; diagnosis of COPD (ATS/ERS definition), pre- and post albuterol/salbutamol FEV1/FVC ratio\0.70 smoking history of ≥ 10 pack-years	12 weeks	SAL/FP 50/250	UMEC/VI 62.5/25	353/353	50.0	51.0	FEV_1, SGRQTS, TDI
Feldman et al. 2017 [24]	Advances in therapy	GSK 204,990, NCT02799784	463	64.4	278/185	Age ≥ 40 years; diagnosis of COPD (ATS/ERS definition), pre- and post albuterol/salbutamol FEV1/FVC ratio\0.70 smoking history of ≥ 10 pack-years	8 weeks	TIO/OLO 5/5	UMEC/VI 62.5/25	236/227	50.0	53	FEV_1, SGRQTS, TDI
Kalberg, et al. 2016 [25]	Drugs in R & D	GSK 11,696, NCT02257385	961	64.0	711/250	Age ≥ 40 years; established COPD (in accordance with the ATS/ERS criteria); pre- and post-bronchodilator FEV1/FVC ratio\0.7 smoking history of ≥ 10 pack-years	12 weeks	TIO 18 + IND 150	UMEC/VI 62.5/25	482/479	56.0	41.0	FEV_1, SGRQTS, TDI
Kato et al., 2019 [26]	International journal of chronic obstructive pulmonary disease	IMPACT, NCT02164513	10,355	65	5550/2735	Age ≥ 40 years; diagnosis of COPD (according to the GOLD 2015 criteria); moderate-to-severe airflow limitation; smoking history of ≥ 10 pack-years	52 weeks	FF/VI 100/25	FF/UMEC/VI 100/62.5/25	5151/5204	40	55	FEV_1, SGRQTS, TDI
Kerwin et al., 2017 [27]	Lung	A2350, NCT02487498	712	64.1	428/357	Age ≥ 40 years; diagnosis of COPD (according to the GOLD 2015 criteria); moderate-to-severe airflow limitation; smoking history of ≥ 10 pack-years	12 weeks	IND/GLY 27.5/15.6	UMEC/VI 62.5/25 µg	357/355	36	56.9	FEV_1, SGRQTS, TDI
Lipson et al., 2018 [28]	The New England Journal of medicine	IMPACT, NCT02164513	8285	63.5	5485/2800	Age ≥ 40 years; diagnosis of COPD (according to the GOLD 2015 criteria); moderate-to-severe airflow limitation; smoking history of ≥ 10 pack-years	52 weeks	FF 100	FF/UMEC/VI 100/62.5/25	4151/4134	65	50	FEV_1, SGRQTS, TDI

Table 2 (continued)

Study ID and year	Journal of publication	Study name	Total number of participants	Age of participants	Gender (M/F)	Inclusion criteria	Study duration	Control	Intervention	Number of participants in Intervention/control arm	Severe or very severe COPD (%)	Current smokers (%)	Primary outcomes
Maleki yazdi et al. 2014 [29]	Respiratory medicine	ZEP117115, NCT01777334	905	61.9	309/145	Age ≥ 40 years; diagnosed with COPD, postsalbutamol FEV1 B 70% and post-salbutamol FEV1/FVC ratio\0.7. Smoking history of ≥ 10 pack-years	24 Weeks	Tiotropium 18 mcg	UMEC/VI 62.5/25 mcg	454/451	60	59.0	FEV_1, SGRQTS, TDI
Maltais et al. 2019 [30]	Advances in therapy	NCT03162055	1159	62.5	754/405	Age ≥ 40 years; diagnosed with COPD, postsalbutamol FEV1 B 70% and post-salbutamol FEV1/FVC ratio\0.7. Smoking history of ≥ 10 pack-years	24 Weeks	GFF MDI	UV DPI	560/559	66	48	FEV_1, SGRQTS, TDI
Maltais et al. 2019 [31]	Respiratory research	EMAX, NCT03034915	1400	64.6	855/545	Age ≥ 40 years; diagnosis of COPD (ATS/ERS definition), pre- and post-salbutamol FEV1/FVC ratio\0.7, Smoking history of ≥ 10 pack years	24 Weeks	salmeterol 50 µg	UMEC/VI 62.5/25 µg	717/683	36	49	FEV_1, SGRQTS, TDI
Riley et al., 2018 [32]	ERJ Open research	GSK 201,317, NCT02275052	396	60.7	209/156	Age ≥ 40 years; diagnosis of COPD (ATS/ERS definition), pre- and post-salbutamol FEV1/FVC ratio\0.7, Smoking history of ≥ 10 pack-years	12 weeks	PBO	UMEC/VI 62.5/25	198/198	46.0	64.0	FEV_1, SGRQTS, TDI
Siler et al., 2016 [33]	International Journal of Chronic Obstructive Pulmonary Disease	201,211, NCT02152605	496	64.1	288/208	Age ≥ 40 years; diagnosis of COPD (ATS/ERS definition), pre- and post-salbutamol FEV1/FVC ratio\0.7, Smoking history of ≥ 10 pack years	12 weeks	PBO	UMEC/VI 62.5/25	248/248	55.0	64	FEV_1, SGRQTS, TDI
Singh et al., 2015 [34]	BMC Pulmonary medicine	DB2116134, NCT01822899	716	61.8	380/336	Age ≥ 40 years; diagnosis of COPD (ATS/ERS definition), pre- and post-salbutamol FEV1/FVC ratio\0.7, Smoking history of ≥ 10 pack-years	12 weeks	SAL/FP 50/500	UMEC/VI 62.5/25	358/358	46.0	57.0	FEV_1, SGRQTS, TDI

FEV_1: Forced expiratory volume in 1 s, FVC: Forced vital capacity of the lungs, UMEC/VI: Umeclidinium/Vilanterol, IND/GLY: indacaterol/glycopyrrolate, TIO/OLO: tiotropium/olodaterol, PBO: Placebo, SAL/FP: Salmeterol/Fluticasone propionate, FF: Fluticasone furoate, GFFMDI: glycopyrronium/formoterol fumarate dihydrate, UV DPI: umeclidinium/vilanterol dry powder inhaler, SGRQTS: St George's Respiratory Questionnaire total score, TDI: Transitional dyspnoea Index

Table 3 Risk Assessment of included studies

Study ID and Year	Alcazar et al., 2018	Bansal et al., 2021 [19]	Bremner et al., 2018 [20]	Celli et al., 2014 [21]	Decramer et al., 2014 [22]	Donohue et al., 2015 [23]	Feldman et al. 2017 [24]	Kalberg, et al. 2016 [25]	Kato et al., 2019 [26]	Kerwin et al., 2017 [27]	Lipson et al., 2018 [28]	Maleki yazdi et al. 2014 [29]	Maltais et al. 2019 [30]	Maltais et al. 2019 [31]	Riley et al., 2018 [32]	Siler et al., 2016 [33]	Singh et al., 2015 [34]
Was a consecutive or random sample of patients enrolled?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Did the study avoid inappropriate exclusions?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Did all patients receive the same reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were all patients included in the analysis?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Was the sample frame appropriate to address the target population?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were study participants sampled in an appropriate way?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the study subjects and the setting described in detail?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were valid methods used for the identification of the condition?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the condition measured in a standard, reliable way for all participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

 # Y: yes; N: No

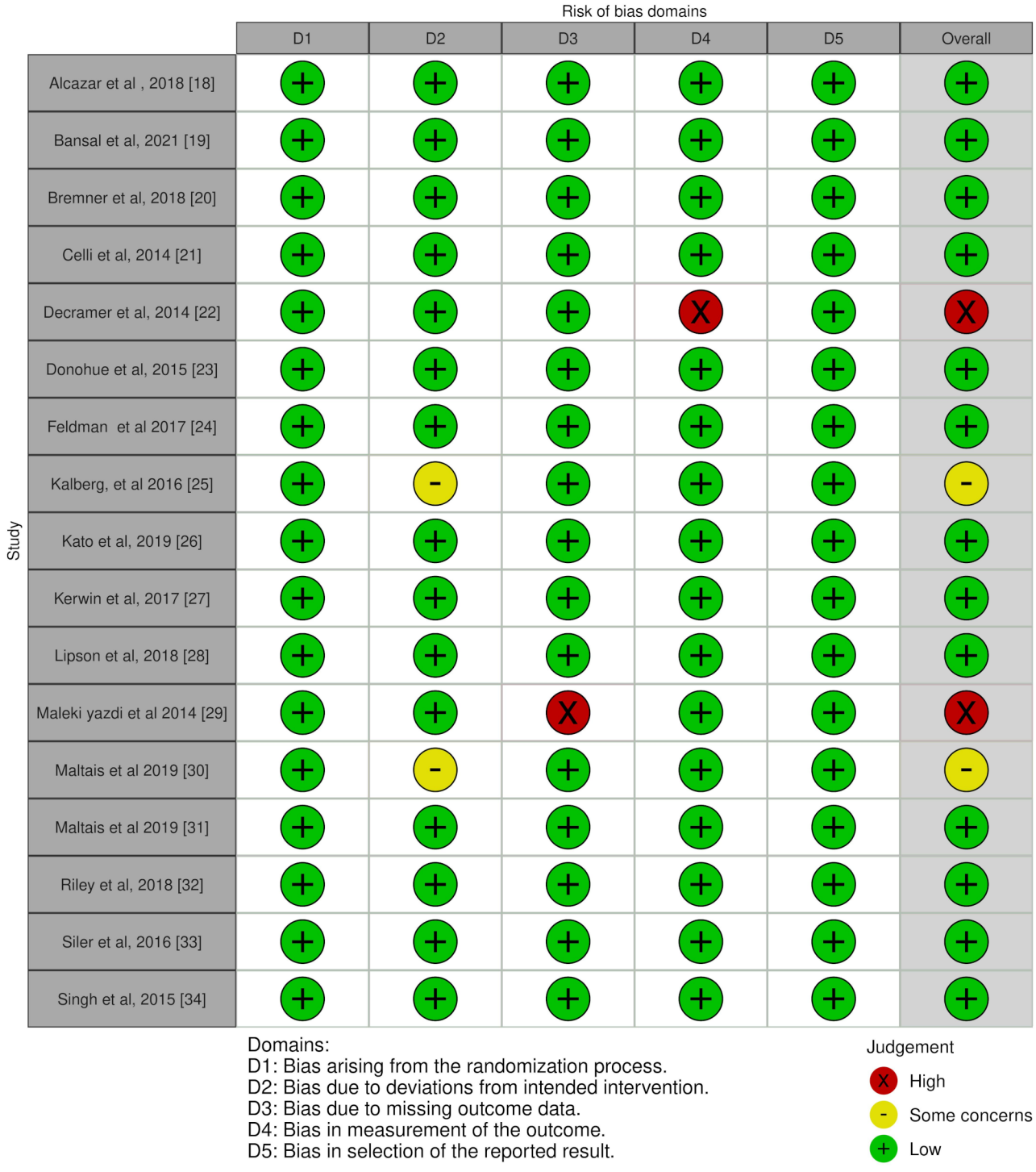

Fig. 2 Risk of Bias summary plot

in outcome measurement and missing outcome data, respectively.

Findings derived from the statistical investigation

In all, 31,814 COPD patients from 17 RCTS were included in the current meta-analysis to evaluate the efficacy ofUMEC/VI dual and UMEC/VI/FF triple therapies versus alternative bronchodilator regimens in patients with COPD. Following conclusions were obtained from the statistical analysis of the primary study outcome:

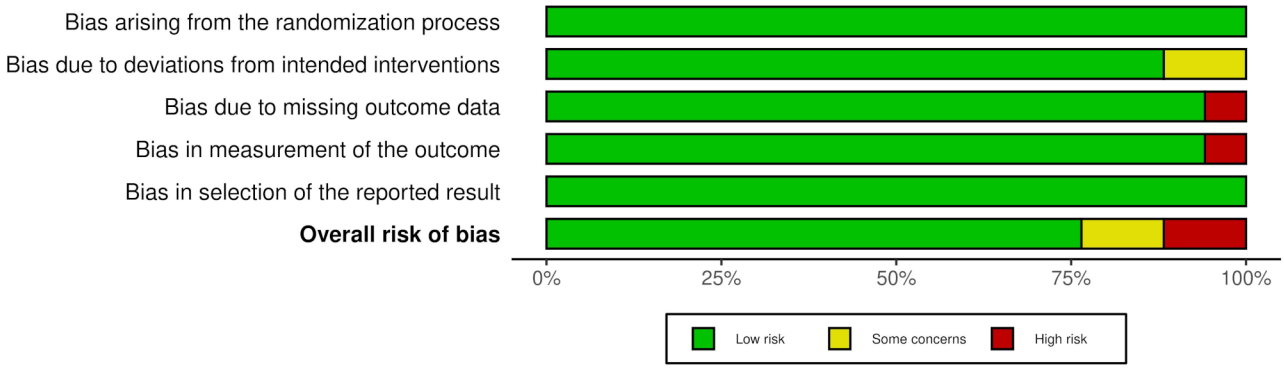

Fig. 3 Traffic light plot for assessment of Risk of Bias

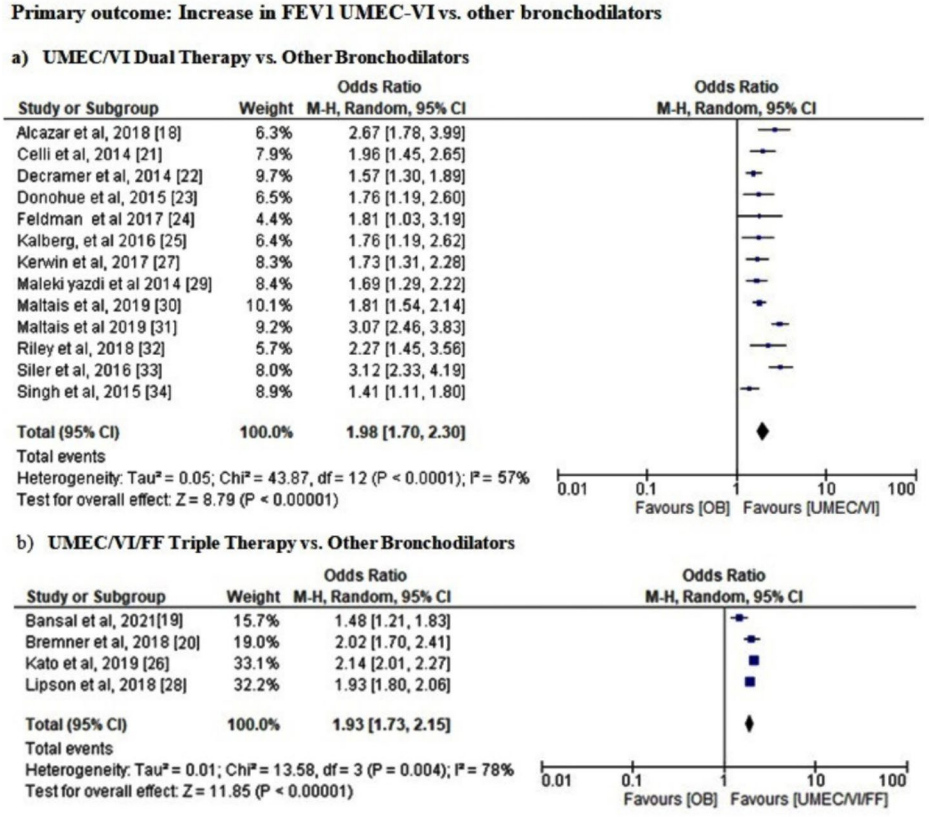

Fig. 4 Forest plot for increase in FEV1 UMEC-VI vs. other bronchodilators

Odds ratio for increase in FEV1 values

We used event data from the included studies to compute the odds ratio (OR) of the increase in FEV1 in the intervention group of COPD patients using either UMEC/VI dual therapy or UMEC/VI/FF triple therapy, compared to the control group of COPD patients using alternative bronchodilator regimens. The members of both intervention groups (UMEC/VI dual therapy or UMEC/VI/FF triple therapy) have a higher likelihood of an increase in FEV1 values as compared to the control group, as evident by their ORs > 1 (Fig. 4). The OR value for UMEC/VI dual therapy was 1.98 [95% CI 1.70 to 2.30] and a tau [2] value of 0.05, $chi^2 = 43.87$, df = 12, Z = 8.79, $I^2 = 57\%$, and $p < 0.001$ (Fig. 4A). The OR value for UMEC/VI/FF triple therapy was 1.93 [95% CI 1.73 to 2.15] and a tau [2] value of 0.01, $chi^2 = 13.58$, df = 3, Z = 11.85, $I^2 = 78\%$, and $p < 0.001$ (Fig. 4B). Furthermore, the symmetrical funnel plots (Fig. 5) for both intervention groups and a statistically insignificant Egger's test p statistic ($p = 0.232$ for UMEC/VI dual therapy and $p = 0.331$ for UMEC/VI/FF triple therapy), which are greater than the predefined significance limit of 0.05; demonstrate a minimal possibility of publication bias.

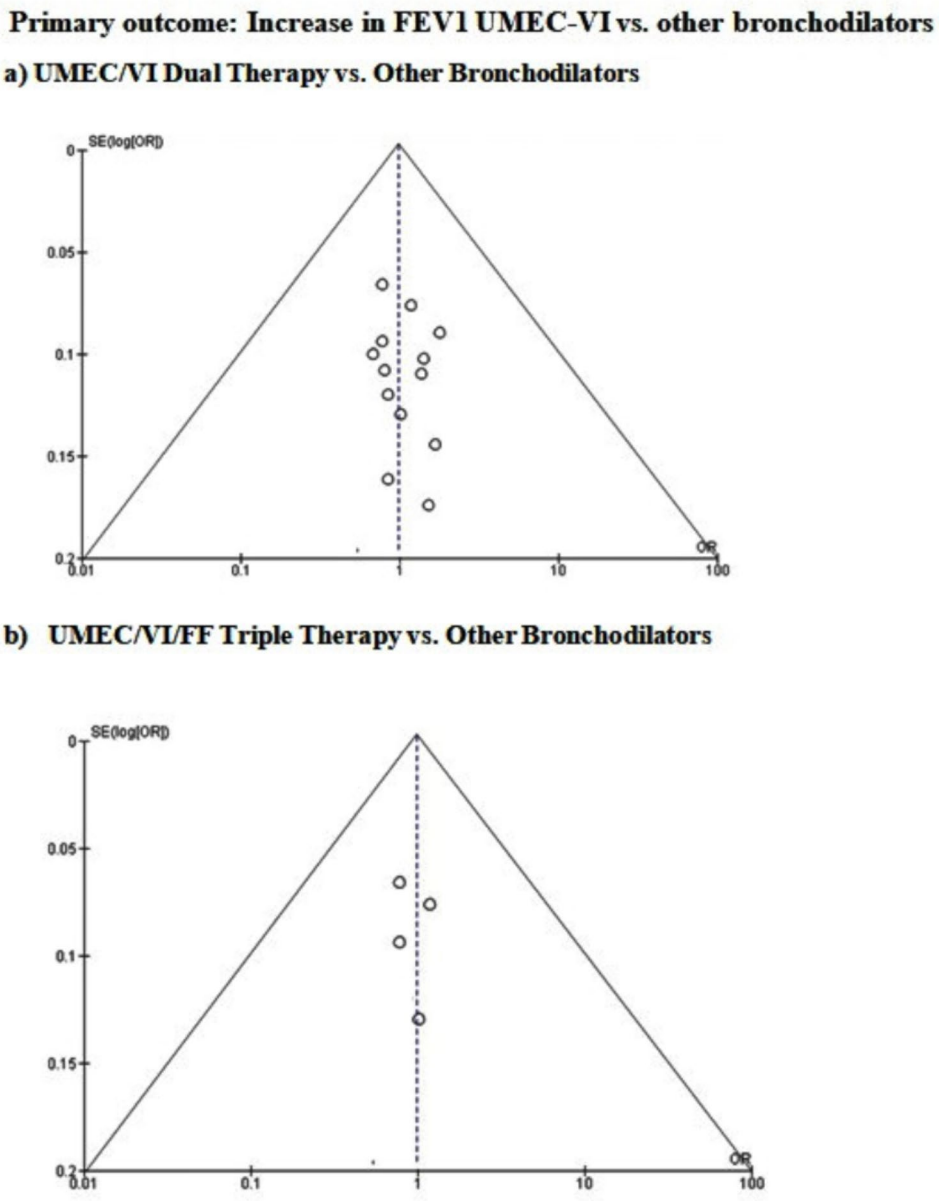

Fig. 5 Funnel plot for increase in FEV1 UMEC-VI vs. other bronchodilators

Odds ratios for decrease in SGRQ total score

The OR of the decrease in SGRQ total score in the intervention group of COPD patients who were treated with either UMEC/VI dual therapy or UMEC/VI/FF triple therapy was calculated using event data from the included studies. The control group of COPD patients who were treated with alternative bronchodilator regimens was used as the control group. The ORs of the members of both intervention groups (UMEC/VI dual therapy or UMEC/VI/FF triple therapy) are greater than 1, indicating a greater probability of a decrease in SGRQ total score values compared to the control group (Fig. 6). The OR value for UMEC/VI dual therapy was 1.99 (95% CI 1.71 to 2.32), with a tau [2] value of 0.04, $chi^2 = 27.34$, df = 11, Z = 8.91, $I^2 = 60\%$, and $p < 0.001$(Fig. 6A). For the UMEC/VI/FF triple therapy, the OR value was 1.83 (95% CI 1.63 to 2.05), with a tau [2] value of 0.01, $chi^2 = 12.90$, df = 3, Z = 10.24, $I^2 = 77\%$, and $p < 0.001$(Fig. 6B). Additionally, the symmetrical funnel plots (Fig. 7) for both intervention groups and a statistically insignificant Egger's test p statistic ($p = 0.281$ for UMEC/VI dual therapy and $p = 0.121$ for UMEC/VI/FF triple therapy) are indicative of a minimal possibility of publication bias, given that they exceed the predefined significance threshold of 0.05.

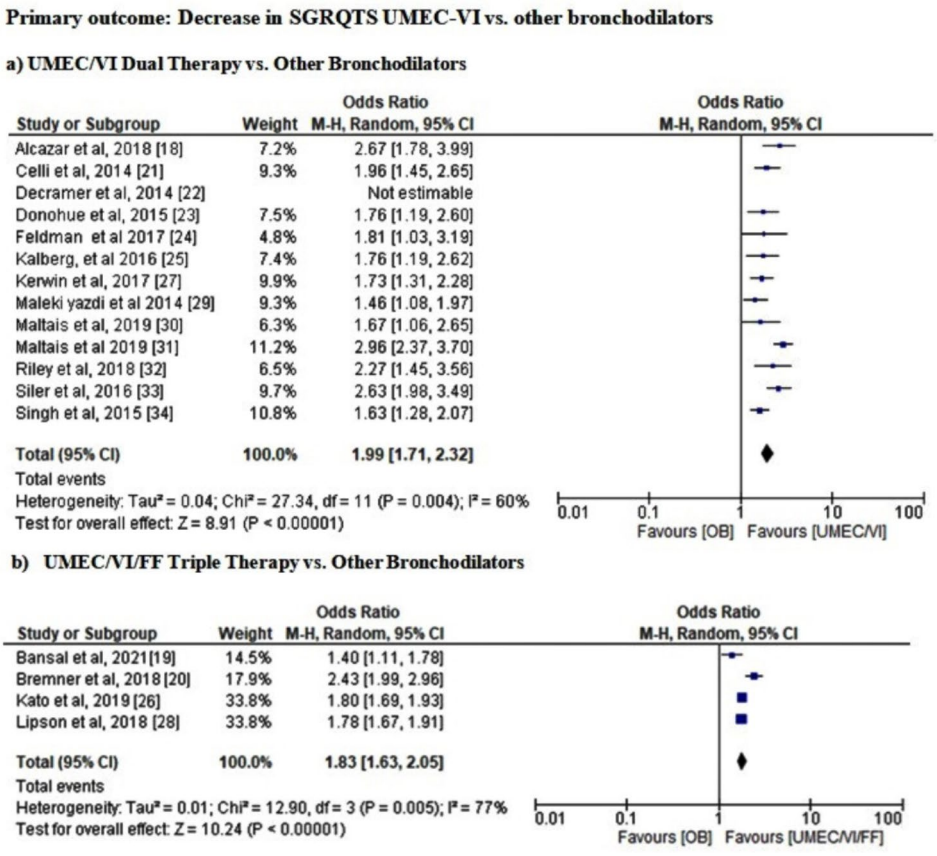

Fig. 6 Forest plot for decrease in SGRQTS UMEC-VI vs. other bronchodilators

Odds ratios for increase in TDI value

The likelihood of increase in TDI values was assessed in COPD patients treated with either UMEC/VI dual therapy or UMEC/VI/FF triple therapy, compared to those receiving alternative bronchodilator regimensutilizing the event data from the included studies.The individuals in both intervention groups (UMEC/VI dual therapy or UMEC/VI/FF triple therapy) are more likely to experience an increase in TDI values compared to the control group, as indicated by their ORs being more than 1 (Fig. 8). The OR for UMEC/VI dual therapy was 1.97 (95% CI 1.72 to 2.26), with a tau [2] value of 0.03, $chi^2 = 24.96$, df = 12, Z = 9.70, $I^2 = 52\%$, and $p < 0.001$(Fig. 8A). For the UMEC/VI/FF triple therapy, the OR value was 2.37 (95% CI 2.15 to 2.61), with a tau [2] value of 0.00, $chi^2 = 6.47$, df = 3, Z = 17.36, $I^2 = 54\%$, and $p < 0.001$(Fig. 8B). In addition, the symmetrical funnel plots (Fig. 9) for both intervention groups and the statistically insignificant Egger's test p statistic ($p = 0.296$ for UMEC/VI dual therapy and $p = 0.158$ for UMEC/VI/FF triple therapy), which exceed the predefined significance limit of 0.05, indicate a low likelihood of publication bias.

Risk ratios for drug related adverse events

The risk of adverse events associated with UMEC/VI dual therapy and UMEC/VI/FF triple therapy was evaluated in patients with COPD, compared to the alternative bronchodilator regimens. The analysis revealed a low risk of adverse events in both intervention groups, as evidenced by RRs value less than 1 (Fig. 10). The RR for UMEC/VI dual therapy was 0.58 (95% CI 0.53–0.64), with a tau [2] value of 0.00, $chi^2 = 9.96$, df = 12, Z = 11.46, $I^2 = 52\%$, and $p < 0.001$(Fig. 10A). For the UMEC/VI/FF triple therapy, the RR was 0.53 (95% CI 0.49 to 0.58), with a tau [2] value of 0.00, $chi^2 = 3.14$, df = 3, Z = 13.33, $I^2 = 54\%$, and $p < 0.001$(Fig. 10B). The symmetry of the funnel plots (Fig. 11) and the non-significant Egger's test p-statistic ($p = 0.199$ for UMEC/VI dual therapy and $p = 0.168$ for UMEC/VI/FF triple therapy) suggest a low risk of publication bias.

Discussion

The present study evaluated the therapeutic efficacy of UMEC/VI dual therapy and UMEC/VI/FF triple therapies compared to alternative bronchodilator regimens in patients with COPD. COPD is a chronic and debilitating lung disease marked by persistent inflammation, irreversible airflow obstruction, and progressive

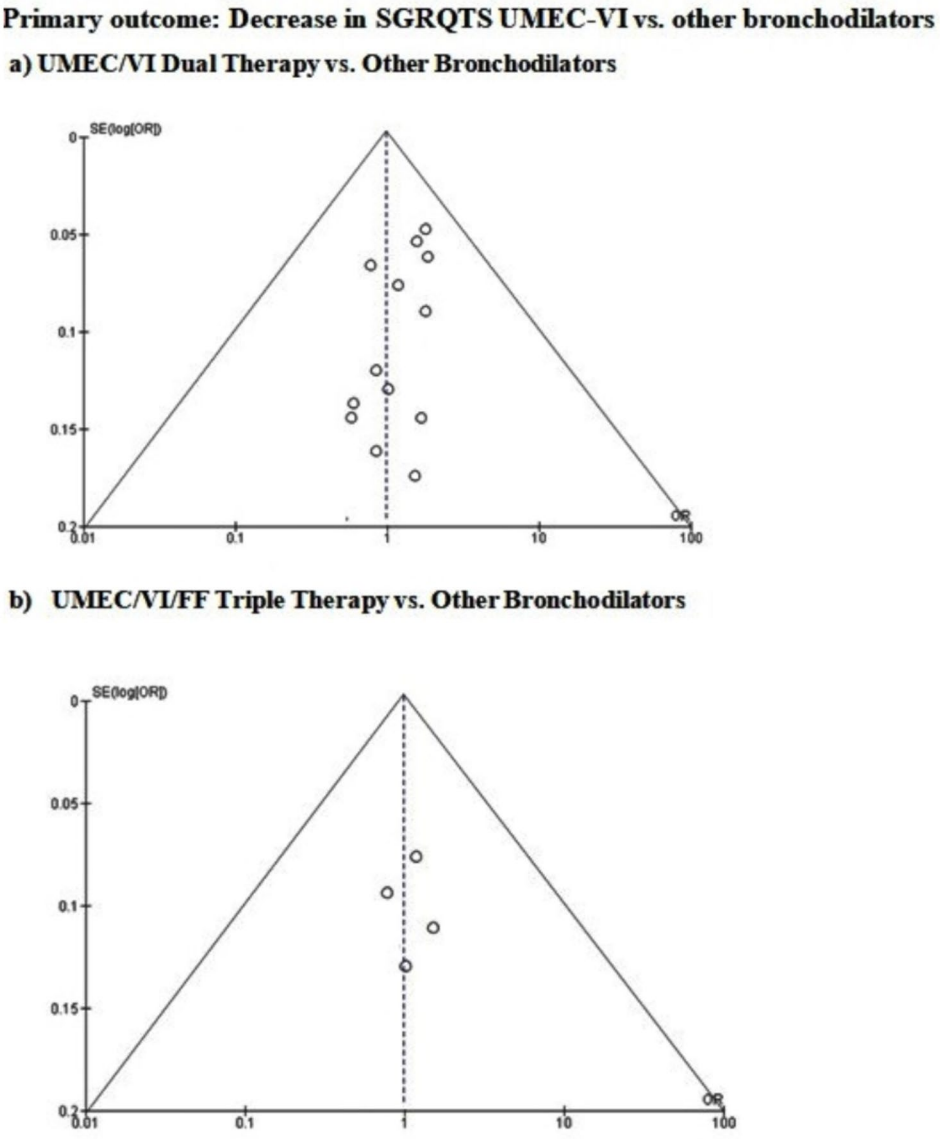

Fig. 7 Funnel plot for decrease in SGRQTS UMEC-VI vs. other bronchodilators

decline in lung function [49, 50]. Prolonged exposure to noxious stimuli, including cigarette smoke, drives the inflammatory response and subsequent lung damage. Prompt diagnosis and treatment are essential to slow disease progression and enhance quality of life for individuals with COPD [51, 52]. Our findings suggest that both UMEC/VI dual and UMEC/VI/FF triple therapies are associated with improved lung function and reduced symptoms in COPD patients. In COPD, UMEC/VIL and UMEC/VIL/FF combinations enhance the efficacy of VI/FF by providing additional bronchodilation and anti-inflammatory effects. UMEC (a muscarinic antagonist) and VIL (a long-acting β2 agonist) work synergistically with VI/FF to improve lung function and symptom control [55]. Drug umeclidinium (LAMA) works by blocking the action of acetylcholine on muscarinic receptors in the airways, leading to bronchodilation and improved lung function. This mechanism is particularly beneficial in COPD patients, who exhibit increased cholinergic tone and airway hyperresponsiveness [53, 54]. While, vilanterol (LABA) involves binding to beta2-adrenergic receptors in the airways, leading to bronchodilation and relaxation of airway smooth muscle. This is achieved through the activation of adenylate cyclase, increasing intracellular cAMP levels, and subsequent relaxation of airway smooth muscle [56, 57]. The addition of FF, an inhaled corticosteroid, to UMEC/VI dual therapy provides anti-inflammatory effects, reducing airway inflammation and improving lung function [58, 59].

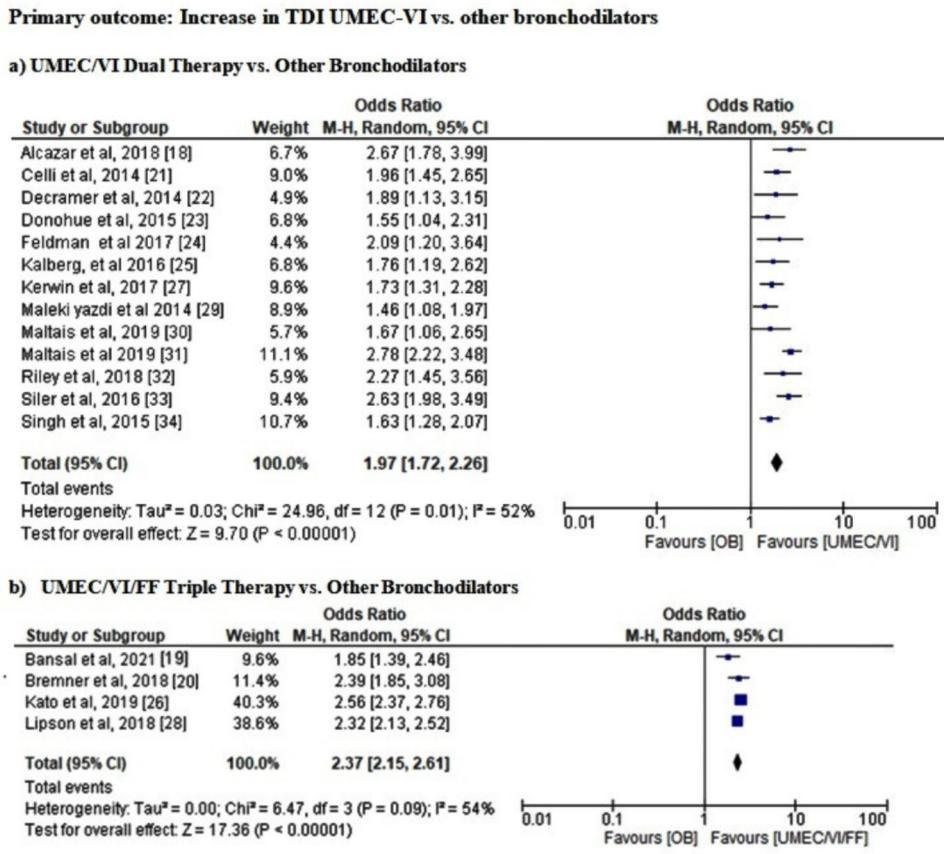

Fig. 8 Forest plot for increase in TDI UMEC-VI vs. other bronchodilators

Previous studies demonstrate the efficacy of UMEC/VI dual therapy and triple therapy of UMEC/VI/FF in improving lung function and reducing symptoms in COPD patients. Research indicates that in individuals with severe chronic obstructive pulmonary disease (COPD), the use of triple therapy effectively targets bronchodilation and airway inflammation [60, 61]. In their 2018 Network Meta-Analysis, Ismaila et al. [62] examined 69 studies to compare the effectiveness of Umeclidinium/Vilanterol with other bronchodilators for treating Chronic Obstructive Pulmonary Disease (COPD). The results showed that UMEC/VI led to significant improvements in lung function (treatment difference of 100 ml), which were considered clinically meaningful. Additionally, at the 12-week mark, UMEC/VI demonstrated statistically significant improvements in trough FEV1 compared to all other dual therapies. The researchers determined that administering UMEC/VI to individuals with COPD may enhance their pulmonary function and overall quality of life to a greater extent than other bronchodilators. In their subgroup analysis of the Spain cohort in the IMPACT study, Marin et al. [63] (2020) found that the exposure-adjusted rate of on-treatment moderate/severe COPD exacerbations per year was 1.31 for FF/UMEC/VI, compared to 1.43 for FF/VI and 1.57 for UMEC/VI. The study found no additional negative effects and determined that patients who had triple therapy with FF/UMEC/VI had a decreased risk of exacerbations, adjusted for exposure, compared to those who received FF/VI and UMEC/VI. The UMEC/VIL combination provides additive bronchodilation by targeting different pathways to relax airway smooth muscles. UMEC, a long-acting muscarinic antagonist (LAMA), inhibits acetylcholine action on muscarinic receptors, while VIL, a long-acting β2 agonist (LABA), stimulates β2 receptors. The UMEC/VIL/FF combination adds anti-inflammatory effects, reducing airway inflammation and improving lung function. FF, an inhaled corticosteroid (ICS), enhances the bronchodilatory effects of UMEC and VIL by reducing airway inflammation and hyperresponsiveness. This triple combination provides comprehensive management of COPD, addressing both bronchodilation and anti-inflammatory aspects.

Our study findings align with previous research, demonstrating that the combination of LABA and LAMA provides additive bronchodilation and improved lung function in COPD patients. Specifically, we found that UMEC/VI dual therapy significantly

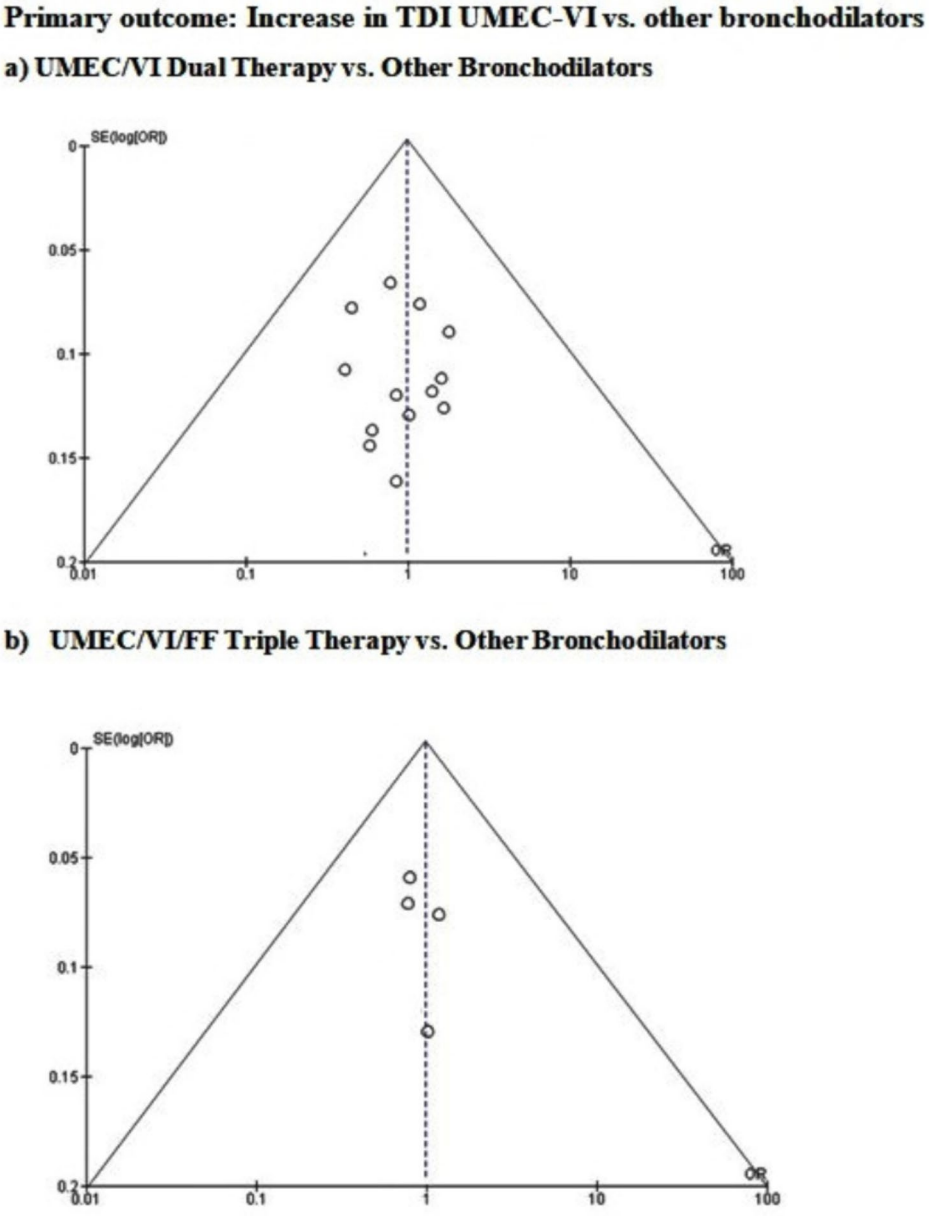

Fig. 9 Funnel plot for increase in TDI UMEC-VI vs. other bronchodilators

improved FEV1 (OR 1.98 [95% CI 1.70–2.30]), TDI values (OR 1.97 [95% CI 1.72–2.26]), and reduced SGRQ total scores (OR 1.99 [95% CI 1.71–2.32]), with fewer drug-related adverse events (RR 0.58 [95% CI 0.53–0.64]). Similarly, UMEC/VI/FF triple therapy showed similar benefits, with significant improvements in FEV1 (OR 1.93 [95% CI 1.73–2.15]), TDI values (OR 2.37 [95% CI 2.15–2.61]), and reduced SGRQ total scores (OR 1.83 [95% CI 1.63–2.05]), and fewer drug-related adverse events (RR 0.53 [95% CI 0.49–0.58]). These results support the use of UMEC/VI dual and UMEC/VI/FF triple therapies as effective treatment options for COPD patients, offering improved lung function, reduced symptoms, and a favorable safety profile. However, the study's limited duration and lack of subgroup analyses by age, sex, and disease severity across various patients necessitate further investigation to address these knowledge gaps.

Limitations

This study emphasizes the use of specific search criteria, including Medical Subject Headings (MeSH) terms and keywords (e.g., "Chronic Obstructive Pulmonary Disease," "Umeclidinium," "Vilanterol") and Boolean operators to search relevant studies investigating the efficacy of UMEC/VI combinations in COPD

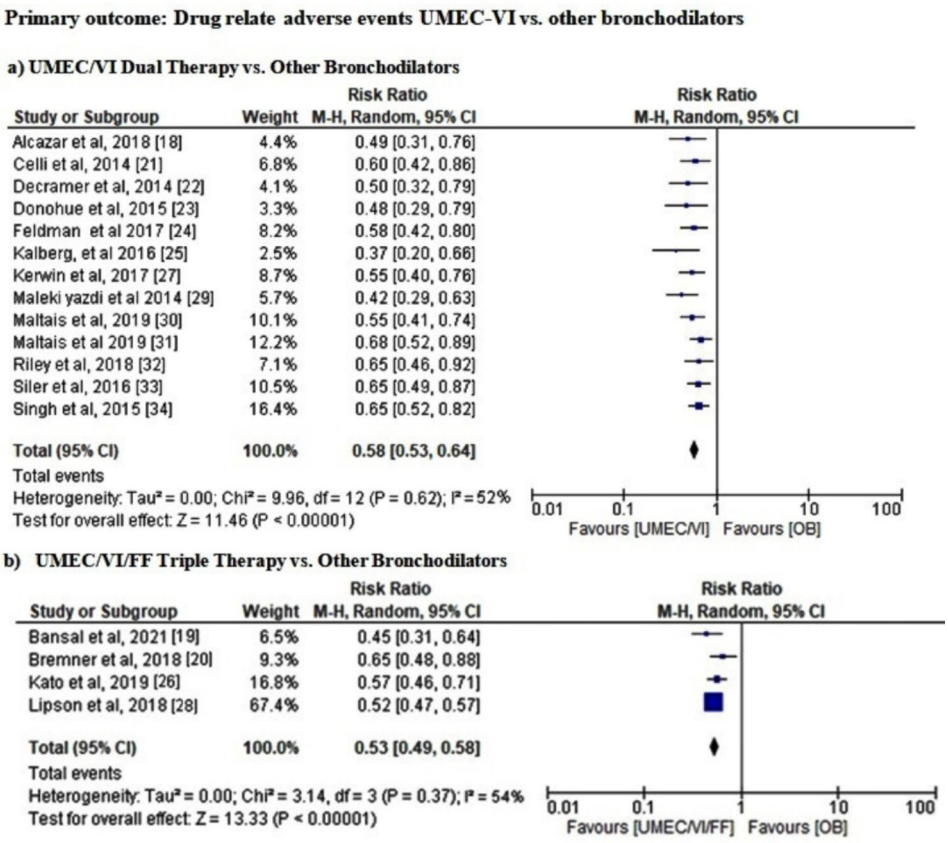

Fig. 10 Forest plot for drug relate adverse events UMEC-VI vs. other bronchodilators

management across multiple databases. Nevertheless, it is imperative to delineate specific limitations. First of all, it is imperative to recognize the potential selection bias in our analysis as a result of excluding a substantial amount of research. Secondly, the present meta-analysis comprises a mere seventeen papers, which exhibit notable heterogeneity and variation. Furthermore, this investigation did not consider critical risk factors for COPD, such as age, comorbidities (e.g., diabetes, hypertension), and immunocompromised status, nor did it explore potential pharmacokinetic and pharmacodynamic interactions between UMEC and VI, which could potentially impact treatment outcomes. Moreover, there were a limited number of participants included in each subgroup and the majority of the included studies had a relatively short duration of less than 52 weeks. Therefore, it is imperative to conduct further research with a larger sample size and extended follow-up periods that considers these risk factors in order to determine the efficacy of UMEC and VI combinations for treating symptomatic COPD patients.

Conclusion

Our meta-analysis demonstrated that patients receiving UMEC/VI therapy exhibited significant improvements in lung function, as evidenced by increased FEV1 values, enhanced quality of life (assessed by St George's Respiratory Questionnaire total score), and alleviated dyspnea (measured by transitional dyspnea index), compared to those treated with alternative LAMA/LABA monotherapies or dual therapies. Notably, both UMEC/VI dual therapy and UMEC/VI/FF triple therapy conferred improved lung function, better quality of life, reduced reliance on rescue medications, and decreased frequency of moderate to severe COPD exacerbations with fewer drug related adverse effects as compared to other bronchodilators. These findings suggest that UMEC and VI combinations may be a more efficacious treatment option for symptomatic COPD patients.However, the conclusion is limited by the scarcity of studies and short trial duration, necessitating further research.

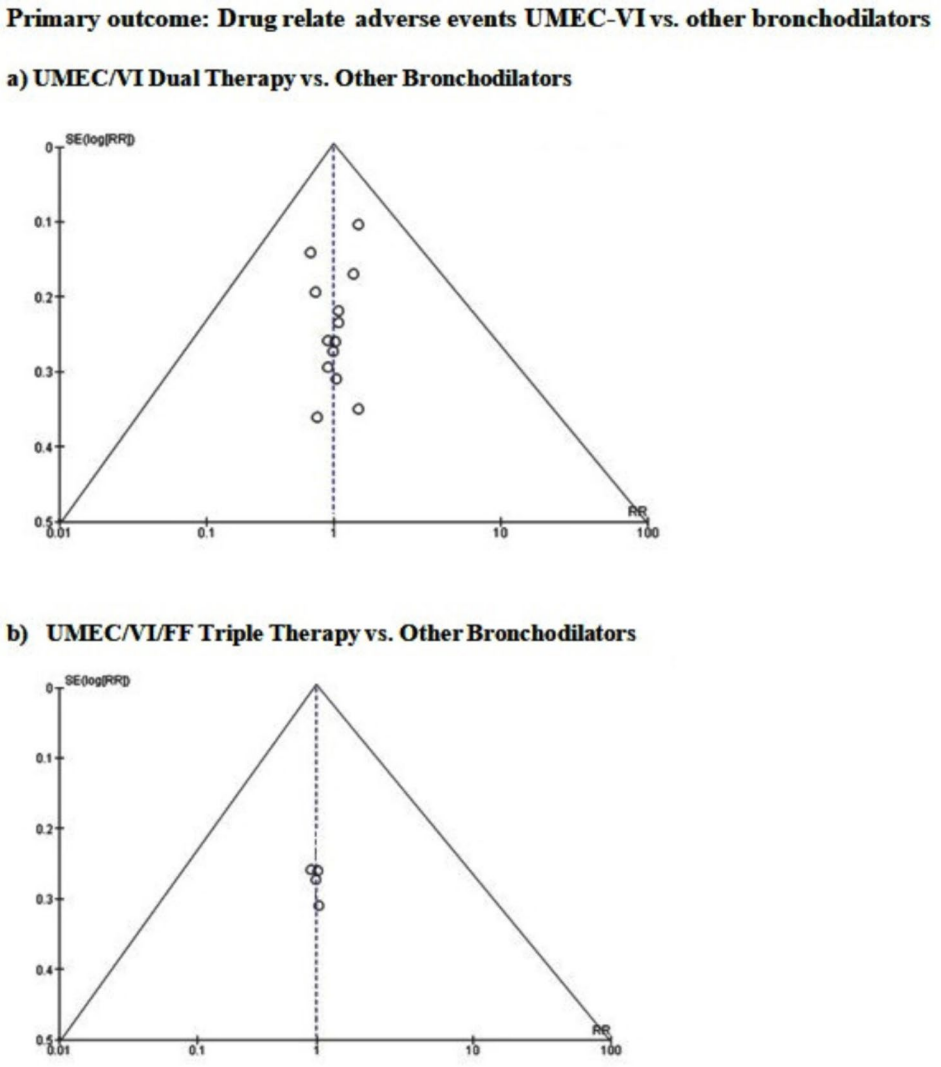

Fig. 11 Funnel plot for drug relate adverse events UMEC-VI vs. other bronchodilators

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-024-03445-4.

Supplementary Material 1

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None.

Author contributions
Conceptualization: HZ; Methodology: JL; Validation: HZ and JL; Formal analysis: FG; Data Curation: YG; Writing - LZ; Writing - Review & Editing: HZ.

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None Received.

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable as the study is totally based on the published literature.

Clinical trial number
Not applicable.

Patient consent for publication
N/A.

Competing interests
The authors declare no competing interests.

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