Efficacy and safety of ensifentrine, a novel phosphodiesterase 3 and 4 inhibitor, in chronic obstructive pulmonary disease: A systematic review and meta-analysis

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Review

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ABSTRACT

Background: We evaluated the efficacy and safety of Ensifentrine in COPD via a systematic review and meta-analysis of randomized controlled trials (RCTs).

Methods: We performed a detailed literature search on Medline (via PubMed), Scopus, Google Scholar, and Cochrane on the basis of pre-specified eligibility criteria. We used Review Manager to calculate pooled mean differences (MD) and 95% Confidence Interval (CI) using a random effects model. The Cochrane's Risk of Bias 2 (RoB-2) tool was used to assess the risk of bias in the included RCTs.

Results: A total of 4 studies, consisting of 2020 patients, were included in the meta-analysis. The mean age ranged from 62.5 years to 65.5 years in the included studies. All the included studies were at low risk of bias. Ensifentrine 3 mg dose significantly improved the mean peak Forced Expiratory Volume-1 (FEV-1), morning trough FEV-1, TDI score, ERS score, and SGRQ-C score as compared to the placebo, yielding a pooled MD of 149.76 (95% CI, 127.9 to 171.6), 43.93 (95% CI, 23.82 to 64.05), 0.92 (95% CI, 0.64 to 1.21, −1.20 (95% CI, −1.99 to −0.40), and −1.92 (95% CI, −3.24 to −0.59), respectively.

Conclusion: Ensifentrine is associated with improvements in outcomes related to COPD symptoms such as peak FEV-1, morning trough FEV-1 and TDI in the patients suffering from this chronic disease. It is also associated with improved quality of life as seen by E-RS score and SGRQ-C score.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) ranks as the third most prevalent cause of global mortality and the seventh most common cause of poor health worldwide [1]. It is a group of progressive lung diseases characterized by airway obstruction and persistent respiratory symptoms [2,3], adversely impacting one's quality of life and increasing the risk of premature death [4]. Despite being preventable and treatable [5], COPD stands as one of the major causes of unplanned hospitalization and readmission worldwide [6]. Thus, in October 2014, COPD was added to the list of diseases that the Hospital Readmission Reduction Program (HRRP) was designed to target by the Centers for Medicaid & Medicare Services (CMS) [7]. Current medications are unable to stop the progression of the disease or address the hallmark characteristics of this disease [8,9]. Consequently, it is evident that there is a necessity for conducting research based on evidence for emerging drugs that provide

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significant symptom relief and decrease exacerbations, one of which includes phosphodiesterase inhibitors (PDEIs) [10]. Phosphodiesterases are a group of enzymes that increase the metabolism of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) and, thus, regulate cell functions [11]. PDEIs function by inhibiting these enzymes, thus preventing the breakdown of cAMP and cGMP and increasing their intracellular levels [11].

Given that inflammation plays a significant role in the pathophysiology of COPD, phosphodiesterase 4 inhibitors (PDE4Is) are anticipated to reduce inflammation in COPD patients effectively. Furthermore, in individuals with severe COPD, they can prevent exacerbation [12], while PDE3 inhibitors contribute to the relaxation of airway smooth muscles and bronchodilation [9]. Ensifentrine is a novel inhaled selective dual inhibitor of PDE3 and PDE4 which affects ciliary function in bronchial epithelia, bronchodilation, and airway inflammation [10]. Currently, there are no PDE3 and PDE4 inhibitors that have been approved for the treatment of COPD; therefore, ensifentrine is the first of its kind that has shown significant bronchodilation, reduction in residual volumes, improvement in COPD symptoms and quality of life in patients [10]. Despite the presence of several clinical trials investigating the efficacy and safety of ensifentrine in COPD [13–15], to the best of our knowledge, no meta-analysis on this topic has to date been performed. In view of consistent evidence of ensifentrine demonstrating the amelioration of COPD characteristics among the treated population, the results of available studies were pooled in order to generate an aggregated result, enhancing the generalizability and reliability of conclusions regarding ensifentrine's usage in the COPD population. Thus, for the first time we conducted a systematic review and meta-analysis, evaluating the efficacy and safety of ensifentrine in COPD patients.

2. Methods

We used the Cochrane Handbook for Systematic Reviews of Interventions to conduct this systematic review and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [16]. This review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the identifier CRD42023484769. This study did not require ethical approval since we conducted analysis using pre-existing published data.

2.1. Eligibility criteria

The inclusion criteria were as follows: (i) randomized controlled trials (RCTs); (ii) patients diagnosed with COPD; (iii) the intervention of interest was any dose of ensifentrine being compared with placebo; (iv) studies reporting outcomes related to lung functions and/or quality of life of patients.

The exclusion criteria were as follows: (i) non-RCTs; (ii) patients with asthma; (iii) abstracts, correspondence, conference presentations, research-in-progress studies, review articles, non-experimental and preclinical studies.

2.2. Information sources

We searched the following databases and international registers from inception till November 2023, with no language restrictions: MEDLINE (via PubMed), the Cochrane Central Register of Controlled Trials (via The Cochrane Library), Scopus, Google Scholar, and the Clinical Trials Registry Platform portal. We screened the reference lists of the included articles and relevant systematic reviews to further expand our search for potentially eligible studies. A search strategy with keywords and Medical Subject Headings (MeSH) terms pertaining to ensifentrine and COPD was used. The detailed search strategy utilized for each database is available in Supplementary Table S1.

2.3. Selection process

Mendeley Desktop 1.19.8 (Mendeley Ltd., Amsterdam, The Netherlands) was employed for the deduplication and screening of all the articles retrieved through our online search. After deduplication, two authors independently completed the first phase of screening titles and abstracts. The remaining articles were then subjected to comprehensive full-text screening by the same authors. Any disagreements between them were resolved by a third reviewer.

2.4. Data collection process and data items

After the process of study selection and screening, we extracted data by three reviewers into an Excel spreadsheet to ensure consistency of data extraction. Relevant data items extracted included trial name, year of publication, study design, location, post-bronchodilator FEV-1 %, smoking history, treatment details, lung function outcomes, quality of life outcomes, and adverse events data.

The outcomes of interest included mean peak FEV-1, morning trough FEV-1, and COPD exacerbations, which determined the lung function. FEV-1 is the forced expiratory volume in 1 s, defined as the volume of air exhaled in the first second during forced exhalation after maximal inspiration. Other outcomes included Evaluating Respiratory Symptoms (E-RS) evaluation, St. George's Respiratory Questionnaire (SGRQ), and Transition Dyspnea Index (TDI) for the assessment of severity of respiratory symptoms and dyspnea, impact on overall health, daily life, and perceived well-being of COPD patients. Safety outcomes included worsening of COPD symptoms, hypertension, diarrhea, and incidence of any serious adverse event.

2.5. Risk of bias assessment

We used the Cochrane Risk of Bias tool for randomized trials (RoB 2.0) to assess the risk of bias in the included RCTs [17], which evaluates bias in the following 5 domains: (i) the randomization process; (ii) deviations from intended interventions; (iii) missing outcome data; (iv) measurement of the outcome, and (v) selection of the reported result. Two authors independently rated the risk of bias for each included study as low, high, or some concerns. We utilized a third reviewer to resolve any disagreement between them.

2.6. Data synthesis

Review Manager (RevMan, version 5.4; The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analysis. The random effects model was used to calculate the mean difference (MD) and their corresponding 95% confidence intervals (95% CI). We used the random-effects model because of the estimated heterogeneity of the true effect sizes. For each synthesis, the I^2 index and the chi-square test were used for the assessment of heterogeneity, and a P value of 0.1 was considered critical for the heterogeneity of the included studies. We presented the meta-analysis in forest plots for each outcome. Subgroup analysis was performed for different doses of ensifentrine, while sensitivity analysis was conducted wherever significant heterogeneity was observed in the results. For outcomes with less than 10 studies, Doi plots were constructed, and the Luis Furuya-Kanamori (LFK) index was used to assess publication bias using MetaXL version 5.3 (EpiGear International Pty, Sunrise Beach, Queensland, Australia). The LFK index has greater sensitivity and power than the Egger test and, hence, is suitable for a lower number of studies [18].

2.7. Certainty of evidence assessment

For evaluation of the certainty of the evidence, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used, and the quality of evidence of the pooled estimates

was judged as high, moderate, low, or very low according to the GRADE Working Group [19,20].

3. Results

3.1. Study selection and characteristics of included studies

After screening, a total of 4 RCTs were included in the systematic review and meta-analysis [13–15]. Fig. 1 shows the detailed selection process in a PRISMA flowchart. The study characteristics of individual studies are shown in Table 1 and Table 2. Our systematic review and meta-analysis comprised a total of 2202 patients, with 164 patients taking a 0.75 mg dose of ensifentrine, 162 patients taking a 1.5 mg dose of ensifentrine, 1139 patients taking a 3 mg dose of ensifentrine, and 737 patients taking placebo. Among the participants taking ensifentrine, 600 were males and 865 were females. All studies reported the outcomes of interest for a 3 mg dose of ensifentrine. Ferguson et al. [13] and Singh et al. [15] reported outcomes of interest for 1.5 mg dose and 0.75 mg dose of ensifentrine. All studies enrolled patients with certain proportions of smokers in the intervention arm and others having a smoking history. Among the 1465 patients in the intervention arm, 812 patients are current smokers. The smoking history reported as mean pack-years across all studies ranged from 41.1 to 52.5. The mean age of participants in the intervention arms ranged from 62.5 years to 65.5 years. The baseline post-bronchodilator FEV-1 reported as % predicted in the included studies ranged from 48.9% to 56%. Ferguson et al. [13] used concomitant once-daily tiotropium in addition to ensifentrine and Singh et al. [15] used concomitant corticosteroids. Anzueto et al. [14] included patients with maintenance therapy consisting of either long-acting beta-2 agonists or long-acting muscarinic antagonists, with or without inhaled corticosteroids.

3.2. Risk of bias assessment

The quality of the assessment is presented in Supplementary Figures F6 and F7. Of the 4 reports, 3 were judged to be at low risk of bias in all domains as determined by the RoB2 tool. One study [13] was reported to have some concerns with respect to the measurement of outcomes and selection of the reported results.

3.3. Mean peak FEV-1

Mean Peak FEV-1 was reported by all studies included in this review at a 3 mg dose. The analysis yielded a pooled mean difference of 149.76 mL (95% CI, 127.9 to 171.6; p-value <0.0001; $I^2 = 0\%$; Fig. 2) for the 3 mg dose favoring the ensifentrine group. There was no evidence of publication bias as determined by the shape of doi plots, which showed no asymmetry (LFK index = 0.92), as shown in Supplementary Figure F1. The quality of evidence as determined by GRADE was ranked to be high (Table 3). 2 trials reported the Mean Peak FEV-1 for 1.5 mg dose and 0.75 mg dose. The analysis yielded a pooled mean difference of 130.96 mL (95% CI, 80.4 to 181.5; p-value <0.0001; $I^2 = 0\%$; Fig. 2) for the 1.5 mg dose favoring the ensifentrine group. The quality of evidence was ranked as moderate as determined by GRADE (Table 3). The

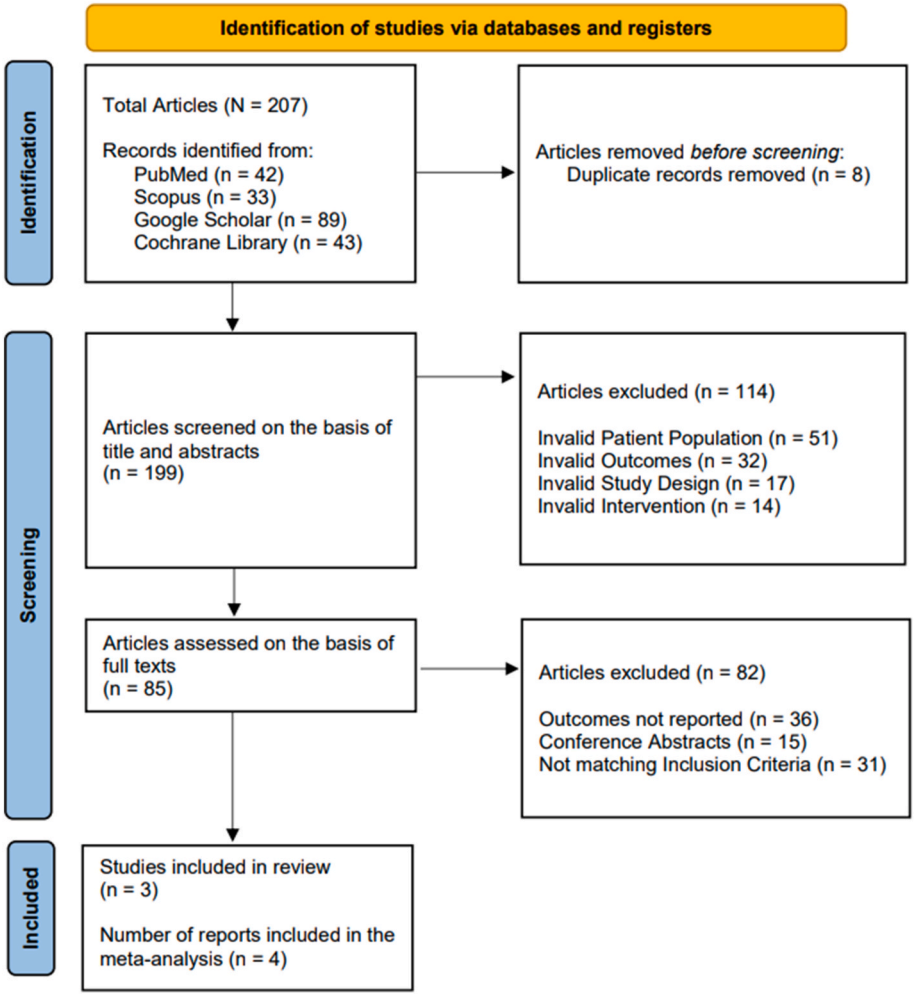

Fig. 1. PRISMA flowchart.

Table 1
Characteristics of the included studies.

First Author	Year	Location	Study Design	Follow-up Duration	Intervention	Control	Population
Ferguson et al.	2021	USA	RCT	4 weeks	Tiotropium 2.5 mcg, two puffs + nebulized 0.75, 1.5, or 3 mg ensifentrine BID	Placebo	Symptomatic patients with a pre-dose FEV1 of 30–70% and a modified medical research council (mMRC) dyspnea scale score ≥2 after 2 weeks of daily treatment with tiotropium
Singh et al.	2020	Bulgaria, Czechia, Germany, Poland, Romania, and UK	RCT	4 weeks	Inhaled corticosteroids + inhale twice daily nebulized ensifentrine 0.75, 1.5, or 3 mg	Placebo	40–75 years, COPD diagnosed, post-bronchodilator FEV1 40–80% predicted normal, FEV1/FVC <0.7, ⩾2 modified medical research council dyspnea scale score (43), smoking history ⩾10 pack-years
Anzueto et al. (Enhance 1)	2023	USA, Russian federation, Bulgaria, Czechia, Poland, UK, Slovakia, Romania, Germany, Hungary, Greece, Republic of Korea	RCT	24 weeks, 48 weeks	Twice-daily ensifentrine 3 mg over 24 weeks via a standard jet nebulizer (PARI)	Placebo	40–80 years, COPD diagnosed, post-bronchodilator FEV1 30–70% predicted normal, FEV1/FVC <0.7, ⩾2 modified medical research council dyspnea scale score (43), smoking history ⩾10 pack-years
Anzueto et al. (Enhance 2)	2023	USA, Bulgaria, Denmark, Canada, Belgium, Estonia, Hungary, Poland, Slovakia, Spain	RCT	24 weeks	Twice-daily ensifentrine 3 mg over 24 weeks via a standard jet nebulizer (PARI)	Placebo	40–80 years, COPD diagnosed, post-bronchodilator FEV1 30–70% predicted normal, FEV1/FVC <0.7, ⩾2 modified medical research council dyspnea scale score (43), smoking history ⩾10 pack-years

analysis yielded a pooled mean difference of 119.18 mL (95% CI, 65.3 to 173.1; p-value <0.0001; $I^2 = 11\%$; Fig. 2) for the 0.75 mg dose favoring the ensifentrine group. The quality of evidence was ranked as moderate as determined by GRADE (Table 3).

3.4. Morning trough FEV-1

Morning trough FEV-1 was reported by all studies included in this review for a 3 mg dose. The analysis yielded a pooled mean difference of 43.93 mL (95% CI, 23.82 to 64.05; p-value <0.0001; $I^2 = 0\%$; Fig. 3) for the 3 mg dose favoring the ensifentrine group. We did not see asymmetry in the doi plot (LFK index = −0.80), suggesting no evidence of publication bias, as shown in Supplementary Figure F2. The quality of evidence was ranked to be high as determined by GRADE (Table 3). 2 trials were reported morning through FEV-1 for 1.5 mg dose and 0.75 mg dose. The analysis yielded a non-significant pooled mean difference of 9.45 mL (95% CI, −36.5 to 55.4; p-value = 0.69; $I^2 = 0\%$; Fig. 3) for the 1.5 mg dose. The quality of evidence was ranked to be moderate as determined by GRADE (Table 3). The analysis yielded a non-significant pooled mean difference of 11.00 mL (95% CI, −36.04 to 58.04; p-value = 0.65; $I^2 = 7\%$; Fig. 3) for 0.75 mg dose. The quality of evidence was ranked to be low, as determined by GRADE, due to some concerns about inconsistency and imprecision (Table 3).

3.5. COPD exacerbation

Ensifentrine 3 mg dose was associated with a significantly reduced hazard of developing a COPD exacerbation as compared to placebo with a pooled HR of 0.60 (95% CI, 0.44 to 0.81; p-value = 0.0008, $I^2 = 0\%$, Fig. 4). Doi plot asymmetry indicated a significant publication bias (LFK index = 1.93) as shown in Supplementary Figure F16. The quality of evidence was moderate as shown in GRADE evaluation in Table 3.

3.6. Transition Dyspnea Index (TDI) score

The TDI score was reported by all studies included in this review for a 3 mg dose. The analysis yielded a pooled mean difference of 0.92 (95% CI, 0.64 to 1.21; p-value <0.0001; $I^2 = 0\%$; Fig. 5) for the 3 mg dose favoring the ensifentrine group. We observed minor asymmetry in the doi plot (LFK index = −1.63), suggesting some evidence of publication bias, as shown in Supplementary Figure F3. The quality of evidence was ranked as moderate as determined by GRADE (Table 3). 2 trials reported TDI scores for 1.5 mg dose and 0.75 mg dose. The analysis yielded a non-significant pooled mean difference of 0.97 (95% CI, −0.34 to 2.29; p-value = 0.15; $I^2 = 74\%$; Fig. 5) for the 1.5 mg dose. The quality of evidence was ranked to be low as determined by GRADE (Table 3). The analysis yielded a non-significant pooled mean difference of 0.49 (95% CI, −1.07 to 2.05; p-value = 0.54; $I^2 = 81\%$; Fig. 4) for 0.75 mg dose. The quality of evidence was ranked as low as determined by GRADE (Table 3).

3.7. Evaluating Respiratory Symptoms (E-RS) score

The E-RS score was reported by all studies included in this review for a 3 mg dose. The analysis yielded a pooled mean difference of −1.20 (95% CI, −1.99 to −0.40; p-value = 0.003; $I^2 = 39\%$; Fig. 6) for the 3 mg dose favoring the ensifentrine group. We observed major asymmetry in the doi plot (LFK index = 3.64), suggesting strong evidence of publication bias, as shown in Supplementary Figure F4. The quality of evidence was ranked to be moderate as determined by GRADE (Table 3). 2 studies reported E-RS scores for 1.5 mg dose and 0.75 mg dose. The analysis yielded a pooled mean difference of −1.74 (95% CI, −3.21 to −0.27; p-value = 0.02; $I^2 = 65\%$; Fig. 6) for the 1.5 mg dose favoring the ensifentrine group. The quality of evidence was ranked to be low as determined by GRADE (Table 3). The analysis yielded a non-significant pooled mean difference of −1.33 (95% CI, −3.19 to 0.53; p-value = 0.16; $I^2 = 78\%$; Fig. 5) for 0.75 mg dose. The quality of evidence was ranked to be low as determined by GRADE (Table 3).

3.8. St. George's Respiratory Questionnaire-COPD (SGRQ-C) score

The SGRQ-C score was reported by all studies included in this review for a 3 mg dose. The analysis yielded a pooled mean difference of −1.92 (95% CI, −3.24 to −0.59; p-value = 0.005; $I^2 = 4\%$; Fig. 7) for the 3 mg dose favoring the ensifentrine group. We did not observe asymmetry in the doi plot (LFK index = −0.51), suggesting no evidence of publication bias, as shown in Supplementary Figure F5. The quality of evidence was ranked as high as determined by GRADE (Table 3). 2 trials reported SGRQ-C scores for 1.5 mg dose and 0.75 mg dose. The analysis yielded a pooled mean difference of −3.81 (95% CI, −6.38 to −1.24; p-value = 0.04; $I^2 = 0\%$; Fig. 7) for the 1.5 mg dose favoring the ensifentrine group. The quality of evidence was ranked to be moderate as determined by GRADE (Table 3). The analysis yielded a non-significant pooled mean difference of −2.26 (95% CI, −4.87 to 0.35; p-value = 0.09; $I^2 = 0\%$; Fig. 7) for 0.75 mg dose. The quality of evidence was ranked to be moderate as determined by GRADE (Table 3).

Table 2
Baseline characteristics of patients in the included studies.

Author	Year	Total Participants				Mean Age (Years)				Gender (%)				Current smokers (%)				Smoking history pack-years (Mean)				Post-bronchodilator FEV1 % predicted			
		0.75 mg	1.5 mg	3 mg	Placebo	0.75 mg	1.5 mg	3 mg	Placebo	0.75 mg	1.5 mg	3 mg	Placebo	0.75 mg	1.5 mg	3 mg	Placebo	0.75 mg	1.5 mg	3 mg	Placebo	0.75 mg	1.5 mg	3 mg	Placebo
Ferguson et al.	2021	83	81	82	84	65.5 (8.43)	63.8 (7.71)	64.5 (7.92)	63.6 (8.41)	M = 44.6 F = 55.4	M = 37 F = 63	M = 45.1 F = 54.9	M = 47.6 F = 52.4	59	51.9	52.4	63.1	52.5	50.5	51	52.5	50.9	49.9	50.4	48.9
Singh et al.	2020	81	81	82	79	63.6 (7.05)	63.4 (6.40)	62.5 (6.51)	63.5 (6.44)	M = 68 F = 32	M = 57 F = 43	M = 55 F = 45	M = 63 F = 38	61	49	57	54	44.7	43.7	41.8	43.3	56	56	55.6	56
Anzueto et al. (Enhance 1)	2023			477	283			65.1	64.9			M = 57.4 F = 42.6	M = 59 F = 41			56.2	57.6			41.1	41.8			52.9	51.7
Anzueto et al. (Enhance 2)	2023			498	291			65	65.3			M = 49 F = 51	M = 47.4 F = 52.6			55.4	55			42.7	41.9			50.8	50.4

3.9. Adverse events

Table 4 summarizes the adverse events reported in the included studies. Pooled risk ratios revealed a non-significant result for reported hypertension, diarrhea, and COPD for a 3 mg dose of ensifentrine in the included studies. Analysis revealed a non-significant pooled risk ratio of 1.11 (95% CI, 0.48 to 2.54; p-value = 0.81; I^2 = 16%; Supplementary Figure F8) for COPD reported as an adverse event in the included studies. The Doi plot revealed major asymmetry (LFK index = 2.61), showing evidence of publication bias as shown in Supplementary Figure F12. A non-significant pooled risk ratio of 0.72 (95% CI, 0.30 to 1.73; p-value = 0.46; I^2 = 33%; Supplementary Figure F9) was observed for hypertension reported as an adverse event in the included studies. The doi plot revealed no asymmetry (LFK index = 0.69), showing no evidence of publication bias, as shown in Supplementary Figure F13. A non-significant pooled risk ratio of 1.53 (95% CI, 0.49 to 4.73; p-value = 0.46; I^2 = 0%; Supplementary Figure F10) was observed for diarrhea reported as an adverse event in the included studies. The doi plot revealed no asymmetry (LFK index = −0.20), showing no evidence of publication bias as shown in Supplementary Figure F14. Compared to placebo, ensifentrine (3 mg) was not associated with serious adverse events, with a pooled RR of 1.01 (95% CI, 0.69 to 1.48; p-value = 0.97; I^2 = 0%; Supplementary Figure F11). There was significant asymmetry of the doi plot (LFK index = 3.38) indicating the presence of publication bias (Supplementary Figure F15).

4. Discussion

The findings presented in our meta-analysis supported the argument that ensifentrine showed significant efficacy for COPD patients as compared to placebo. The pooled results showed an appreciable benefit in terms of mean peak FEV-1 values for 3 mg, 1.5 mg, and 0.75 mg doses of ensifentrine. A statistically significant benefit in terms of morning trough FEV-1 was reported in the pooled results for a 3 mg dose of ensifentrine. Additionally, ensifentrine significantly decreased the hazard of COPD exacerbations. In terms of the TDI score, a statistically significant benefit was reported in the pooled results for a 3 mg dose of ensifentrine. The pooled results for the E-RS score and SGRQ-C score reported a statistically significant benefit for a 3 mg dose of ensifentrine. For 1.5 mg and 0.75 mg doses of ensifentrine, nonsignificant results were reported for the TDI score, E-RS score, and SGRQ-C score.

Despite its decreasing trend, COPD continues to be a substantial public health concern and a major cause of death [21]. The worldwide prevalence of COPD in 2019 was estimated to be 212.3 million cases, resulting in 3.3 million deaths and 74.4 million Disability-Associated Life Years [21]. Individuals diagnosed with COPD have an increased susceptibility to the development of cardiovascular disease, lung carcinoma, and several other conditions [22]. Despite the fact that it worsens with time and there is no absolute cure for COPD, it is still manageable. The majority of patients with COPD may improve their quality of life and control their symptoms with the help of medical professionals who know how to treat the disease [23]. Smoking cessation, oxygen therapy, oral prophylactic antibiotic therapy, pulmonary rehabilitation, the use of bronchodilators (inhalers), anticholinergic inhalers, mucolytics, corticosteroids, and phosphodiesterase inhibitors are quite common for the treatment and management of COPD [2,24,25].

The current landscape of COPD pharmacotherapy options varies more in terms of inhalation devices offered than in terms of pharmacological properties and clinical outcomes [26]. While there are inhaled maintenance medications that have the potential to impact FEV-1 decrease and mortality, it has been challenging to establish a concrete impact on the course of the disease [26,27]. On top of that, there is a lack of data on how COPD medicine impacts lung function and clinical outcomes. There is currently no medication that may stop the remodeling of the airways and encourage the regeneration of the lungs. Additionally, the inflammation of the airways in COPD is not very responsive to

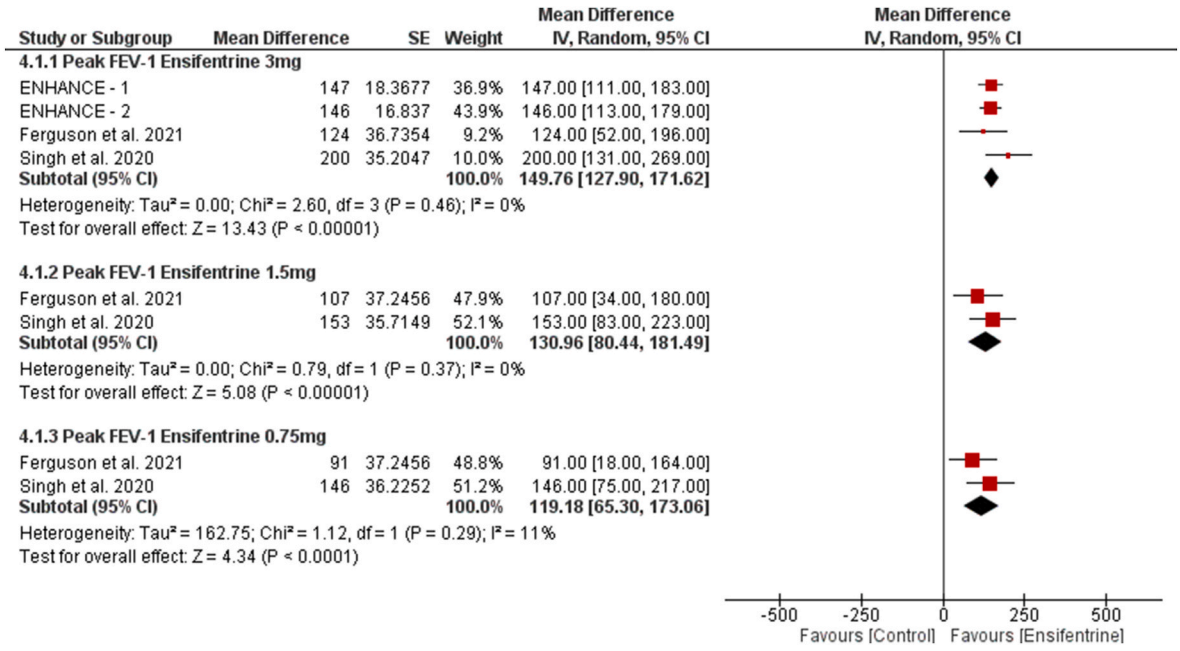

Fig. 2. Pooled results showing mean peak FEV-1.

Table 3
Grading of recommendations assessment, development, and evaluation (GRADE) summary of findings.

Outcome	No. Of participants (studies)	Effect estimate (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of Evidence (GRADE)
Peak FEV-1 (3 mg dose)	1139 (4)	MD = 149.8 (127.9–171.6)	Not serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊕ HIGH
Peak FEV-1 (1.5 mg dose)	162 (2)	MD = 130.96 (80.4–181.5)	Not serious	Not serious	Not serious	Serious	–	⊕⊕⊕⊖ MODERATE
Peak FEV-1 (0.75 mg dose)	162 (2)	MD = 119.2 (65.3–173.1)	Not serious	Not serious	Not serious	Serious	–	⊕⊕⊕⊖ MODERATE
Morning trough FEV-1 (3 mg dose)	1139 (4)	MD = 43.93 (23.8–64.1)	Not serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊕ HIGH
Morning trough FEV-1 (1.5 mg dose)	162 (2)	MD = 9.45 (−36.5 to 55.4)	Not serious	Not serious	Not serious	Serious	–	⊕⊕⊕⊖ MODERATE
Morning trough FEV-1 (0.75 mg dose)	162 (2)	MD = 11.00 (−36.04 to 58.04)	Not serious	Serious	Not serious	Serious	–	⊕⊕⊖⊖ LOW
COPD exacerbation (3 mg Dose)	975 (2)	HR = 0.60 (0.44–0.81)	Not serious	Not serious	Not serious	Not serious	Suspected	⊕⊕⊕⊖ MODERATE
Transition dyspnea index score (3 mg dose)	1139 (4)	MD = 0.92 (0.64–1.21)	Not serious	Not serious	Not serious	Not serious	Suspected	⊕⊕⊕⊖ MODERATE
Transition dyspnea index score (1.5 mg dose)	162 (2)	MD = 0.97 (−0.34 to 2.29)	Not serious	Serious	Not serious	Serious	–	⊕⊕⊖⊖ LOW
Transition dyspnea index score (0.75 mg dose)	162 (2)	MD = 0.49 (−1.07 to 2.05)	Not serious	Serious	Not serious	Serious	–	⊕⊕⊖⊖ LOW
ERS questionnaire score (3 mg dose)	1139 (4)	MD = −1.20 (−1.99 to −0.40)	Not serious	Not serious	Not serious	Not serious	Suspected	⊕⊕⊕⊖ MODERATE
ERS questionnaire score (1.5 mg dose)	162 (2)	MD = −1.74 (−3.21 to −0.27)	Not serious	Serious	Not serious	Serious	–	⊕⊕⊖⊖ LOW
ERS questionnaire score (0.75 mg dose)	162 (2)	MD = −1.33 (−3.19 to 0.53)	Not serious	Not serious	Not serious	Serious	–	⊕⊕⊖⊖ LOW
SGRQ-C score (3 mg dose)	1139 (4)	MD = −1.92 (−3.24 to −0.59)	Not serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊕ HIGH
SGRQ-C score (1.5 mg dose)	162 (2)	MD = −3.81 (−6.38 to −1.24)	Not serious	Not serious	Not serious	Serious	–	⊕⊕⊕⊖ MODERATE
SGRQ-C score (0.75 mg dose)	162 (2)	MD = −2.26 (−4.87 to 0.35)	Not serious	Not serious	Not serious	Serious	–	⊕⊕⊕⊖ MODERATE

CI, confidence interval; MD, Mean Difference; ERS, Evaluating Respiratory Symptoms; SGRQ-C, St. George's Respiratory Questionnaire-COPD.

current treatments, such as corticosteroids [26,28,29].

PDEI levels modulate a variety of cellular processes; for example, PDE3 inhibition relaxes airway smooth muscle, and PDE4 inhibition reduces inflammation [9–12]. Inhibiting both PDE3 and PDE4 simultaneously may have complementary (or perhaps complementary and synergistic) effects on anti-inflammatory and bronchodilator properties, according to the available data [30,31]. Ensifentrine (RPL554) is a newly developed compound that effectively inhibits both PDE3 and PDE4 enzymes [10]. It is specifically intended to reduce airway inflammation, widen the bronchial tubes, and enhance the frequency of ciliary beating in the cells lining the bronchial tubes [10]. Considering the overwhelmingly positive evidence towards the use of such

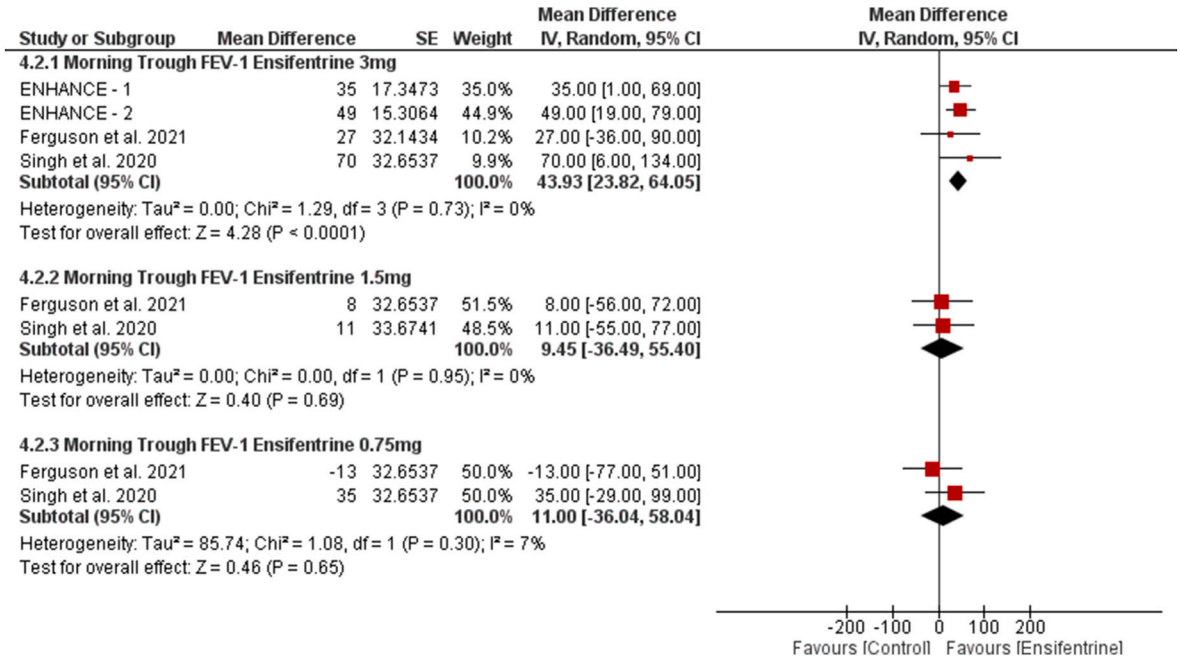

Fig. 3. Pooled results showing morning trough FEV-1.

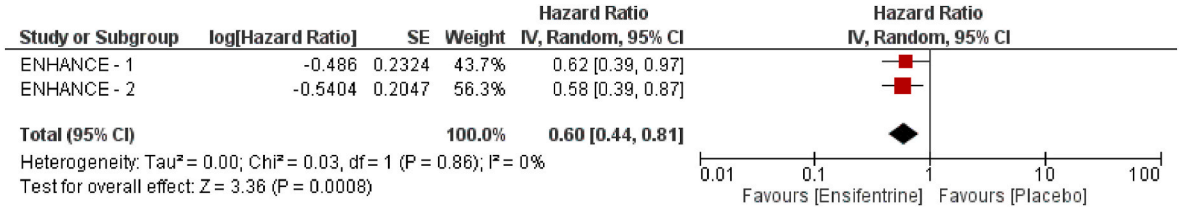

Fig. 4. Forest plot showing pooled analysis of COPD Exacerbation.

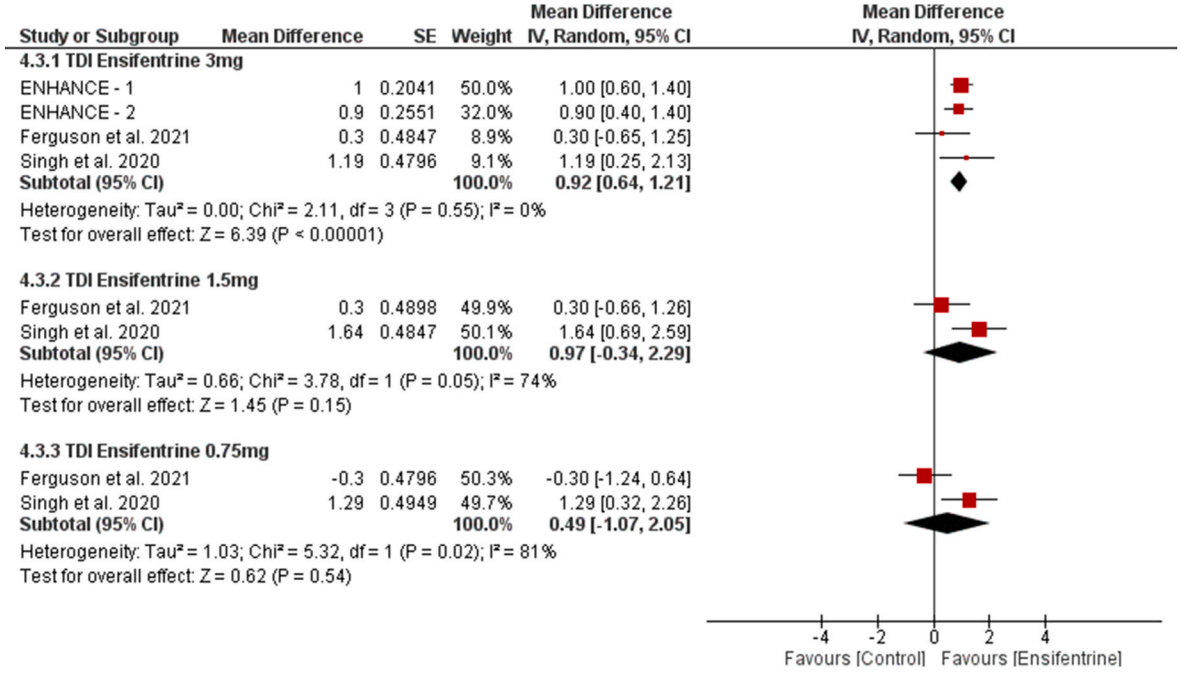

Fig. 5. Pooled results showing Transition Dyspnea Index (TDI) Score.

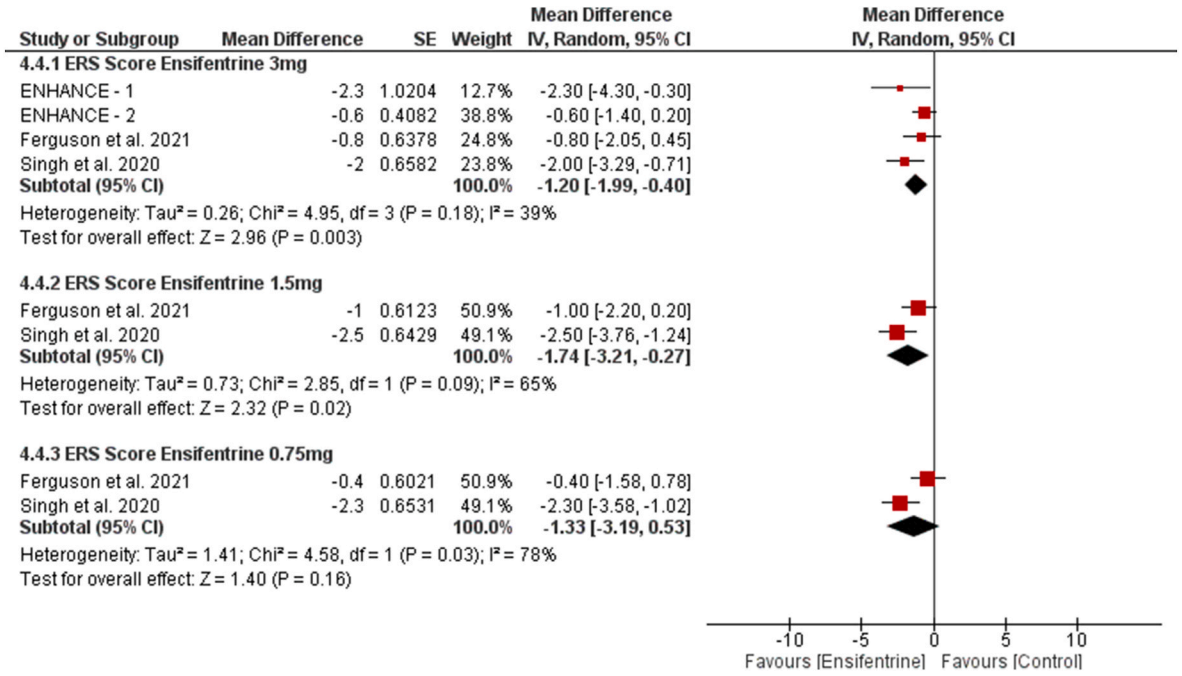

Fig. 6. Pooled results showing Evaluating Respiratory Symptoms (E-RS) score.

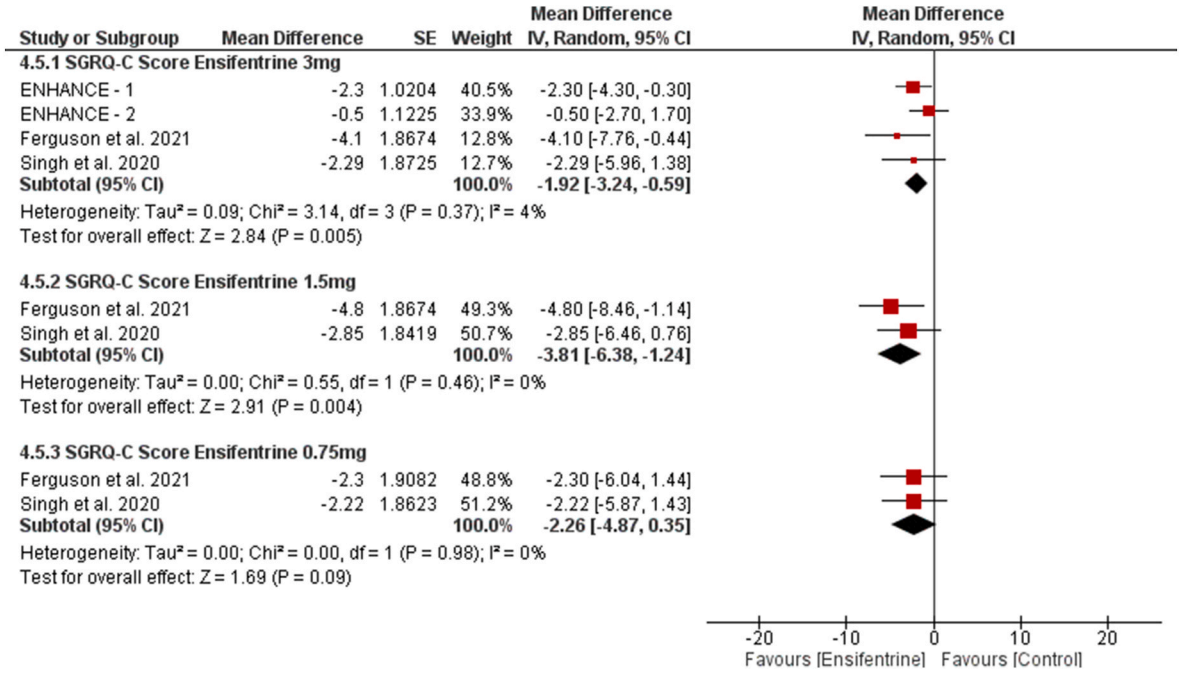

Fig. 7. Pooled results showing St. George's Respiratory Questionnaire-COPD (SGRQ-C) score.

medications, we performed the first meta-analysis and systematic review that evaluates the efficacy of ensifentrine in COPD.

Like any drug, it is also important to consider the side effects of ensifentrine. Ensifentrine did not have a clinically significant impact on heart rate, PR intervals, or QRS intervals. Both 3 mg and 9 mg doses of ensifentrine were tolerated well in persons who were in good health [32]. No serious adverse events (AEs) associated with ensifentrine have been seen, including those affecting the cardiovascular or gastrointestinal systems, even at dosages of 6 mg BID for a duration of 4 weeks [10]. We also analyzed the most common reported AEs, such as hypertension, diarrhea and COPD but none of them showed any significant association with ensifentrine. Additionally, ensifentrine was not significantly associated with serious adverse events in our analysis either, which indicates its desirable safety and tolerability profile among the patients.

The results of our analysis yield several important clinical implications. Ensifentrine demonstrated improved lung function ultimately increasing patient health status. Additionally, it was significantly associated with superior TDI, ER-S, and SGRQ-C scores, indicating better patient perception towards their dyspnea symptoms, leading to quality of life enhancements. Furthermore, the desirable safety and tolerability profile indicated its feasibility as a long-term pharmacological therapy for COPD. However, all of these improvements are only significant for 3

Table 4
Adverse events reported in included studies.

Study	Year	Sample size		Diarrhea				Hypertension				COPD				Serious AEs	
		Ensifentrine group	Control Group	0.75 mg	1.5 mg	3 mg	Placebo	0.75 mg	1.5 mg	3 mg	Placebo	0.75 mg	1.5 mg	3 mg	Placebo	3 mg	Placebo
Anzueto et al. (Enhance 1)	2023	477	283			2	2			12	4			7	6	32	19
Anzueto et al. (Enhance 2)	2023	498	291			8	2			5	1			11	5	28	17
Ferguson GT et al.	2021	246	84	1	0	1	0	1	1	0	0	2	0	3	0	2	0
Singh et al.	2020	82	79	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	3	3
Combined effects RR (95% CI)						1.53 (0.49–4.73)				0.72 (0.30–1.73)				1.11 (0.48–2.54)		1.01 (0.69–1.48)	
Heterogeneity						0 %				33 %				16 %		0%	
LFX index						−0.20				0.69				2.61		3.38	

RR = Risk Ratio; LFK index = Luis Furuya-Kanamori Index; AEs = Adverse Events.

mg dose of ensifentrine.

Like any meta-analysis, our review has its own strengths and limitations. Potential strengths include the fact that evidence in terms of efficacy and quality of life outcomes was thoroughly assessed using randomized controlled trials, and the results were evaluated using the GRADE working group guidelines. The high to moderate quality of evidence for the ensifentrine 3 mg dose, coupled with significant findings, constitutes an important strength of our meta-analysis. However, the low statistical power for the multiple outcomes constitutes an important limitation that calls for future large-scale clinical trials with diverse population groups. More importantly, all the included RCTs were limited to a single center, which might diminish the generalizability of our findings to a broader, global, and a diversified patient population. The moderate to low quality of evidence as determined by the GRADE evaluation for the outcomes assessed for ensifentrine 1.5 mg dose and 0.75 mg dose, coupled with non-significant results, decrease the overall robustness of our findings for these dosages. Furthermore, we only considered published articles that might constitute publication bias, as negative findings might not be published. The included studies had patients with similar baseline characteristics, which resulted in negligible heterogeneity, thereby constituting a strength of our meta-analysis. The minor heterogeneity may have resulted from a difference in follow-up duration, which ranged from 4 to 12 weeks across all included studies. Furthermore, the limited follow-up duration is insufficient to properly assess all the associated adverse effects and efficacy endpoints, especially in terms of concluding the long-term impact and safety of ensifentrine therapy. Lastly, we could not account for the differences in follow-up duration or concomitant therapy in the assessment of the certainty of evidence.

Future trials should aim to assess the limitations of our review, particularly the lack of confidence in the efficacy and quality of life outcomes for 1.5 mg and 0.75 mg doses of ensifentrine. More importantly, high-powered clinical trials should aim to assess the dose-ranging response of ensifentrine for patients with COPD. Furthermore, the evaluation of outcomes should be done in comparison to standard therapies currently available for COPD, in order to employ a better understanding of the comparative efficacy and safety of ensifentrine.

Authors contributions

EF made substantial contributions to the conception of the work. OUR made significant contributions to the data analysis and interpretation. EF, OUR, and ZAN made significant contributions to the design of the work and the interpretation of data. UA, RIK drafted the original manuscript. MOL and other authors substantially contributed to the revision of the manuscript drafts. All authors have approved the submitted version of the manuscript and agreed to be accountable for any part of the work.

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Declaration of competing interest

The authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resinv.2024.12.012.

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