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SYSTEMATIC REVIEW

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Automatically titrating oxygen system versus constant flow oxygen system during exercise in patients with COPD: a systematic review and meta-analysis

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Abstract

Background Hypoxemia is a common symptom among patients with chronic obstructive pulmonary disease (COPD). The constant flow oxygen system (CFOS) is often insufficient to correct this symptom. The automatically titrating oxygen system (ATOS), a new oxygen therapy mode, remains undetermined in its ability to improve exercise performance more effectively than CFOS in COPD patients. The main objective of this meta-analysis was to explore this issue.

Methods We conducted a thorough search of randomized controlled trials (RCTs) in PubMed, Embase, Web of Science (from inception to 1 November 2024). Study selection, data extraction, and risk of bias assessment were performed independently by two authors. Data synthesis was conducted using Stata software (Version 17.0). The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system was utilized to rate evidence quality.

Results Five eligible studies ($n=120$) were included. Compared to CFOS, ATOS was more effective in extending the distance (MD = 180.28 m, 95%CI:133.03 to 227.52) and duration (MD = 237.63 s, 95%CI: 181.18 to 294.07) of endurance shuttle walking test (ESWT). Besides, ATOS could better prolong the percentage time of sustaining targeted SpO_2 (92%-96%) (MD = 29.43%,95%CI:21.15 to 37.71) and relieve dyspnea at isotime (MD = -1.65, 95%CI -3.19 to -0.11) during ESWT.

Discussion ATOS may have more advantages in improving exercise tolerance, sustaining targeted SpO_2, and ameliorating dyspnea during exercise in COPD patients.

Clinical trial registration The review was registered with PROSPERO (The website is https://www.crd.york.ac.uk/prosp ero/, and the ID is CRD 42024574955) and we didn't make a protocol.

Keywords Constant flow oxygen system, Automatically titrating oxygen system, Chronic obstructive pulmonary disease, Endurance shuttle walking test, Meta-analysis

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Background

Chronic obstructive pulmonary disease (COPD), a widespread and debilitating respiratory disorder characterized by persistent airflow limitation, is a major contributor to premature death and disability [1]. Hypoxemia, a common symptom in COPD patients, leads to various consequences such as decreased exercise tolerance [2]. While many COPD patients do not exhibit chronic respiratory insufficiency at rest, their oxygen demands increase significantly during exercise, resulting in exercise-induced desaturation (EID) and exertional hypoxemia [3]. Oxygen therapy is an effective strategy to maintain oxygen saturation above 90% under resting conditions [4]. It has been reported to delay muscle fatigue, improve respiratory mechanics, alleviate dyspnea, and enhance exercise capacity [5]. However, despite evidence that higher oxygen flows in constant flow oxygen systems (CFOS) are associated with better outcomes [6–8], clinicians remain hesitant to recommend higher oxygen flows during exercise, especially for patients with resting hypercapnia. This reluctance stems from concerns about potential adverse effects, such as further CO_2 retention, absorptive atelectasis [9, 10], and damage to the central nervous system [11].

Given such a dilemma, there is an urgent need for innovative oxygen delivery strategy to to meet the varying oxygen demands of COPD patients during exercise [11]. The Automatically titrating oxygen system (ATOS) is emerged as a promising solution [12, 13], which is based on a closed-loop circuit and can adjust oxygen flow according to the patient's real-time and the targeted SpO_2 preset by the physician [5]. Previous studies have suggested that ATOS is associated with a higher percentage of time spent within the targeted SpO2 and reduced hospital stays [12]. However, its superiority over CFOS in COPD patients remains a topic of ongoing debate. While some preliminary studies have shown that ATOS can reduce hypoxemia time [14–17], alleviate symptoms of dyspnea at isotime [15, 16], and improve exercise endurance in stable COPD during a single bout of exercise [14–16, 18], others didn't report significant improvement in dyspnea and exercise capacity [14, 17].

To address this knowledge gap, we conducted this systematic review and meta-analysis to figure out whether ATOS is more effective than CFOS in improving exercise capacity, correcting hypoxemia, and relieving dyspnea in patients with COPD during a single bout of exercise session. By integrating existing evidence, we aimed to provide a comprehensive understanding of the acute benefits of ATOS and offer guidance for clinical practice and future research directions in oxygen therapy management for COPD patients, with or without chronic respiratory insufficiency.

Methods

We conducted this systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19] (see Additional file 1).

Search strategy

We performed a comprehensive literature search in PubMed, Embase, and Web of Science from inception to 1 November 2024, restricting the language to English. Additionally, we manually reviewed references from relevant studies and systematic reviews to ensure no pertinent studies were overlooked. The search keywords included "chronic obstructive pulmonary disease," "COPD," "oxygen therapy," "automated titration oxygen system," "closed-loop," "constant flow oxygen system," "randomized controlled trial," "controlled clinical trial," "randomized," and "random" (see Additional files 2–4 for details).

Eligibility criteria

We screened studies in according with the PICOS (participants, interventions, comparators, outcomes and study design) criteria.

Participants: Patients with a confirmed diagnosis of COPD, regardless of gender, age, or disease severity [20]. *If studies included patients with other diseases, COPD patients were analyzed separately.*

Interventions Automated oxygen delivery systems that adjust flow rates using a closed-loop algorithm based on measured versus target SpO2 during endurance shuttle walking tests (ESWT) [13].

Comparators Constant flow oxygen systems delivering a fixed flow rate during ESWT.

Outcomes The primary outcomes were the distance and duration of endurance of ESWT. Secondary outcomes included dyspnea at isotime (assessed by the Borg scale) and the percentage of time maintaining target SpO2 during ESWT.

Study design Studies were included if they were randomized controlled trials (RCTs) or randomized crossover controlled trails.

Study selection

Two reviewers (Peijian Wang and Jing Wang) independently screened studies in three stages: (1) importing search results into EndNote (X9 version) and removing duplicates, (2) screening titles and abstracts, and (3)

reviewing full texts for eligibility. Disagreements were resolved by a third reviewer (Siyuan Wang). If multiple studies originated from the same cohort, we selected the one with the largest sample size.

Data extraction and management

Two reviewers (Peijian Wang and Jing Wang) independently extracted data on study characteristics, participant demographics, intervention details, and outcomes. A third reviewer (Siyuan Wang) resolved any discrepancies. For multi-arm trials, only data comparing ATOS and CFOS were extracted. Missing data were obtained from authors when possible; otherwise, they were estimated based on available data [21].

Risk of bias assessment

The risk of bias was assessed independently by two reviewers (Peijian Wang, Jing Wang) using the Cochrane risk of bias 2.0 tool [22].

Data analysis

We analyzed data using StataMP (version 17.0) with the generic inverse variance method. Effect sizes were reported as mean differences (MDs) with 95% confidence intervals (CIs), calculated from study means and standard errors (SEs). If SEs were unavailable, they were estimated from standard deviations, CIs, interquartile ranges, or *p*-values [21, 23]. Mean scores and SEs were also approximated from study figures using PlotDigitizer (www.plotdigitizer.com) when necessary.

Heterogeneity was assessed using the I^2 statistic, with $I.^2 > 50\%$ indicating significant heterogeneity. Random-effects models were used for significant heterogeneity; otherwise, fixed-effects models were applied [24]. For primary outcomes with heterogeneity, meta-regression analysis was conducted to identify sources of heterogeneity. Sensitivity analysis evaluated result stability, and publication bias was assessed using Egger's test [25]

Evidence quality assessment

We conducted the quality of evidence assessment for primary outcomes with the GRADEpro (http://www.gradepro.org/). The quality assessment of RCTs began with a high rating and was then adjusted according to predefined criteria. Evidence quality started as high for RCTs and was adjusted based on predefined criteria, such as risk of bias, inconsistency, and imprecision [26].

Results

Study selection and characteristics

Our comprehensive literature search identified 569 potentially eligible records. After removing duplicates and screening titles and abstracts, 22 studies remained. Following full-text assessment, 5 studies were included in this meta-analysis [14–18] (see Fig. 1 for the study selection process).

These studies involved a total of 120 stable COPD patients, with sample sizes ranging from 10 to 50. Three studies included patients receiving long-term oxygen therapy (LTOT) [15, 16, 18], while one study excluded LTOT patients [17]. The walking speed during ESWT was set at 75% to 85% of peak VO2, estimated from the incremental shuttle walking test (ISWT). Two studies included patients with severe hypoxemia [15, 18], and two included patients with moderate hypoxemia [16, 17]. Basic study characteristics are summarized in Table 1.

Risk of bias assessment

Five studies reported the change in the duration of ESWT. Among them, 4 studies were evaluated as having a low risk of bias, while 1 study was considered as having some concerns, as "selection of reported result" was not described clearly (details in Additional files 5–6).

Primary outcomes

Duration of ESWT

All five studies, including 120 patients, compared the disparities in ESWT duration regarding ATOS and CFOS for COPD patients [14–18]. The outcome showed that ATOS could significantly improve the duration of ESWT (MD = 237.63.43 s, 95%CI:181.18 to 294.07, Fig. 2), exceeding the minimal clinical importance difference (MCID) (MCID = 65 s, 95CI:45 to 65) [27]. No significant heterogeneity existed among the studies ($I^2 = 40.5\%$, $p = 0.151$). Sensitivity analysis confirmed the stability of the results (Fig. 3), and Egger's test indicated no publication bias ($p = 0.129$).

Distance of ESWT

Four studies (110 patients) compared the effect of ATOS and CFOS on the ESWT distance for COPD patients [15–18]. ATOS significantly increased walking distance (MD = 180.28 m, 95% CI: 133.03 to 227.52, Fig. 4), surpassing the MCID (95 m, 95% CI: 60 to 115) [27]. Besides, there was no significant heterogeneity among these studies ($I^2 = 0.0\%$, $p = 0.891$), and sensitivity analysis confirmed result stability (Fig. 5). Egger's test also showed no publication bias ($p = 0.354$).

Secondary outcomes

Percentage of time within targeted SpO_2

Four studies (70 patients) compared the ability of ATOS and CFOS to maintain target SpO_2 during ESWT [14–17]. ATOS significantly prolonged the percentage of time maintaining target SpO_2 (MD = 29.43%, 95% CI: 21.15 to 37.71, $I^2 = 46.9\%$, $p = 0.130$) (Fig. 6).

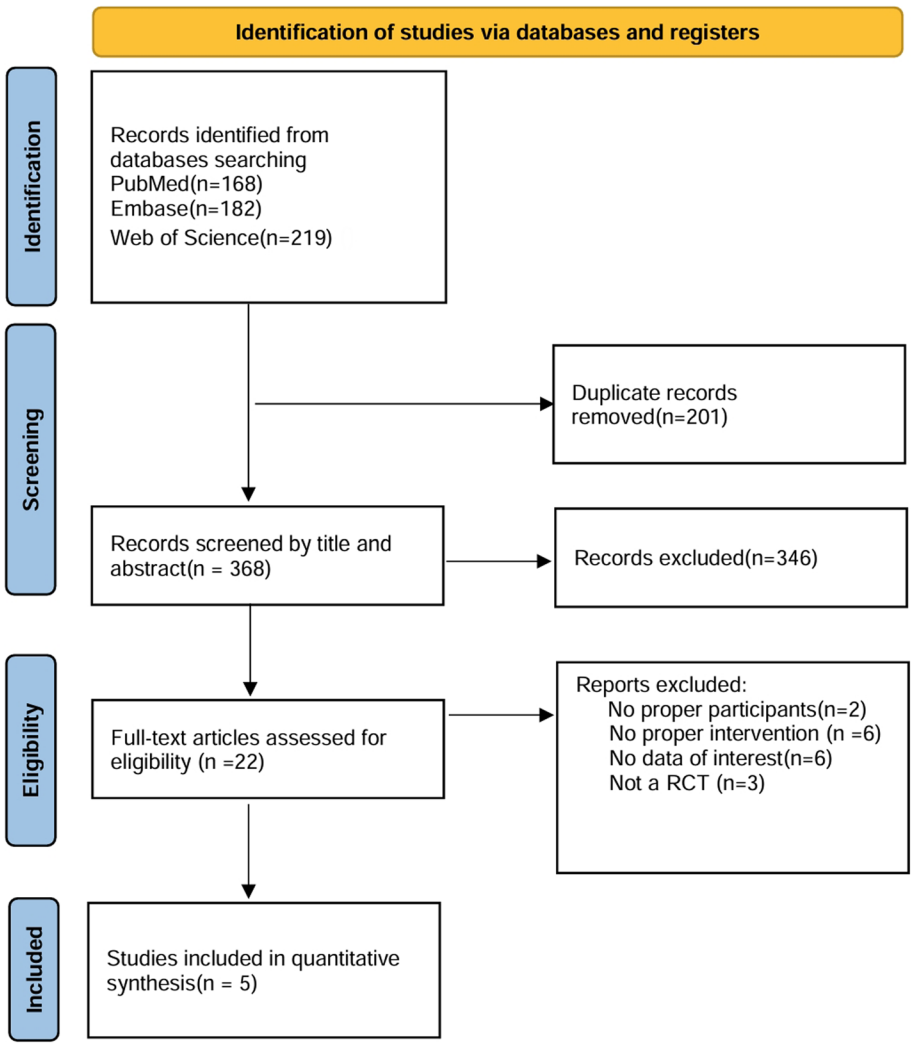

Fig. 1 Study flow diagram

Dyspnea at isotime

Three studies (55 participants) dyspnea at isotime [14–16]. Pooled analysis showed significant improvement with ATOS (MD = -1.65, 95% CI: -3.19 to -0.11), although significant heterogeneity was observed ($I^2 = 83.7\%$, *p=0.002*) (Fig. 7).

Evidence quality assessment

Primary outcomes were rated as "moderate quality" due to small sample sizes in most studies. The GRADE evidence profile is presented in Table 2.

Discussion

CFOS has been proven to have a certain efficacy in correcting hypoxemia. However, in clinical application, since it cannot quickly make dynamic adjustments to the oxygen flow according to different exercise intensities, it causes difficulties for COPD patients with hypoxemia to receive PR effectively. ATOS, as a new modality of oxygen therapy, has caught attention of clinicians. To our knowledge, this systematic review is the first to integrate all available studies to compare the acute effects of two oxygen therapy modalities on COPD patients in single bout of exercise. It may assist clinicians in formulating more reasonable oxygen therapy regimens during exercise, thereby enhancing the safety during exercise and improving the quality of life of those patients.

The ESWT is a reliable field-based test for assessing endurance capacity in COPD patients [28]. Compared to the 6-min walk test (6MWT), ESWT is more sensitive in detecting functional improvements after treatment, as it imposes a predefined walking speed (75%-85% of estimated VO_2 peak) that minimizes the influence of patient motivation and pacing ability [29]. The average exercise

Table 1 Basic characteristics of the included studies

Study	Location	Sample size(M/F)	Age(years)	GOLD stage (II/III/IV)	FEV_1/FVC(%)	LTOT(L/min)	P_aO_2 (mmHg)	Speed (% of peak VO_2)	SpO_2-targeted in ATOS	O_2 flow rate during ESWT(L/min)		Outcomes
										CFOS	ATOS	
Schneeberger et al. (2023) [18]	Germany	50(27/23)	66(59,70)	0/23/27	45.8(40.8,53.7)	1.75(1.0,2.9)	54.7(51.0, 57.7)	85%	>92%	3.0(3.0,4.0)	4.5(3.2,6.1)	Duration and distance of ESWT
Kofod et al (2021) [15]	Demark	33(12/21)	72.7(6.5)	NA	43(35,48)	1.6(0.9)	<55	75%	90-94%	1.6(0.9)	7.9(3.1)	Duration and distance of ESWT; Percentage of time within targeted SpO_2; Dyspnoea at isotime
Vivodtzev et al (2019) [16]	France	12	65(10)	0/4/8	50(15)	1.9(1.0)	62.0(6.4)	85%	>94%	3.1(1.2)	5.4(2.7)	Duration and distance of ESWT; Percentage of time within targeted SpO_2; Dyspnoea at isotime
Vezina et al (2024) [14]	Canada	10(6/4)	68±8.5	NA	25.5(3.9)	NA	NA	85%	92-96%	2.1(0.4)	6.9(2.9)	Duration of ESWT; Percentage of time within target SpO_2; Dyspnoea at isotime
Lellouche et al (2016) [17]	France	16(13/3)	69(2)	5/8/3	35(7)	No one receive LTOT	72(10)	85%	92-96%	2	2.9(1.7)	Duration and distance of ESWT; Percentage of time within targeted SpO_2; Dyspnoea at isotime

Data are presented as mean (SD) or median (interquartile range)

Abbreviations: *M* Male, *F* Female, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *FEV_1* Forced expiratory volume in 1 second, *FVC* Forced vital capacity, *PaO_2* Partial pressure of oxygen, *peak VO_2* Peak oxygen consumption, *SpO_2* Percutaneous oxygen saturation, *ATOS* Automatically titrating oxygen system, *CFOS* Constant flow oxygen system, *ISWT* Incremental shuttle walking test, *ESWT* Endurance shuttle walking test, *LTOT* Long-term oxygen therapy

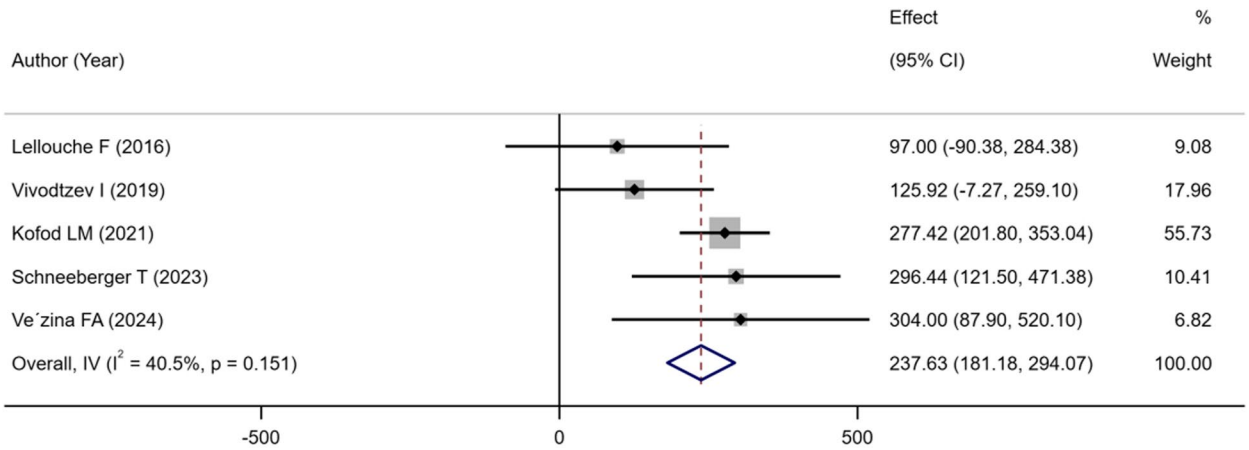

Fig. 2 Forest plot of comparing the effect of ATOS and CFOS on the duration of ESWT. ATOS automatically titrating oxygen systems, CFOS constant flow oxygen system, ESWT endurance shuttle walking test, CI confidence interval

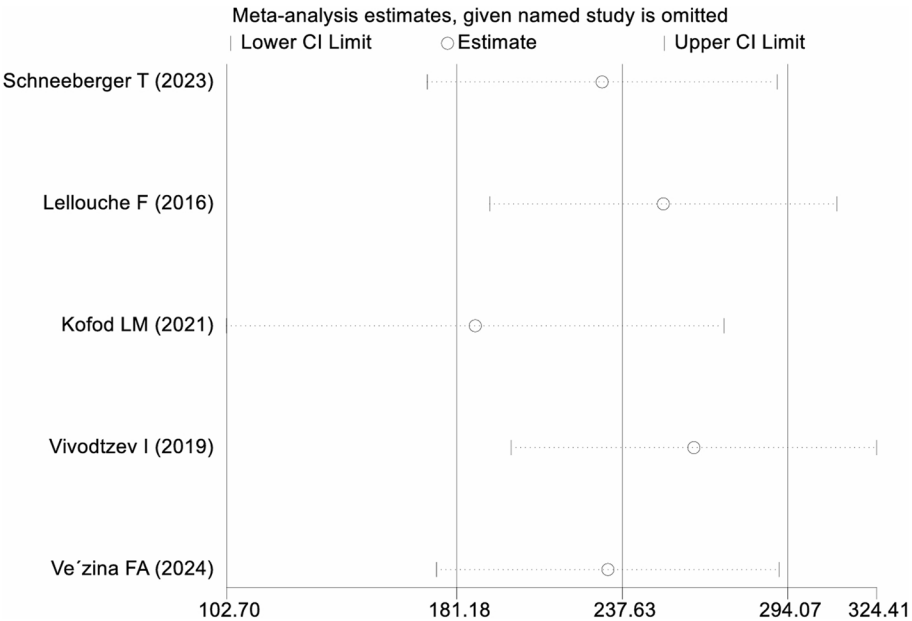

Fig. 3 Sensitivity analysis of comparing the effect of ATOS and CFOS on the duration of ESWT. ATOS automatically titrating oxygen system, CFOS constant flow oxygen system, ESWT endurance shuttle walking text, CI confidence interval

duration in our included studies exceeded 9 min, allowing clear differentiation between ATOS and CFOS based on SpO_2 curves [30, 31].

Our meta-analysis revealed that ATOS significantly improved exercise performance in COPD patients during a single bout of exercise, likely due to several factors:

1. Improved muscle oxygenation: ATOS has a maximum output capacity of up to 20 L/min, which is significantly higher than the typical flow rates of CFOS (1.6–3.1 L/min). This higher flow rate allows for more effective oxygen diffusion and improving limb oxygenation [32].Besides, One of the key features of ATOS is its ability to dynamically adjust the oxygen flow rate in real-time based on the patient's SpO_2 levels. This closed-loop system ensures that patients maintain a target SpO_2 range (92%–96%) throughout exercise. Enhanced muscle oxygenation can delay the onset of anaerobic metabolism, reduce muscle fatigue, and ultimately improve exercise endurance. Studies showed that higher skeletal muscle mitochondrial oxidative capacity is associated with

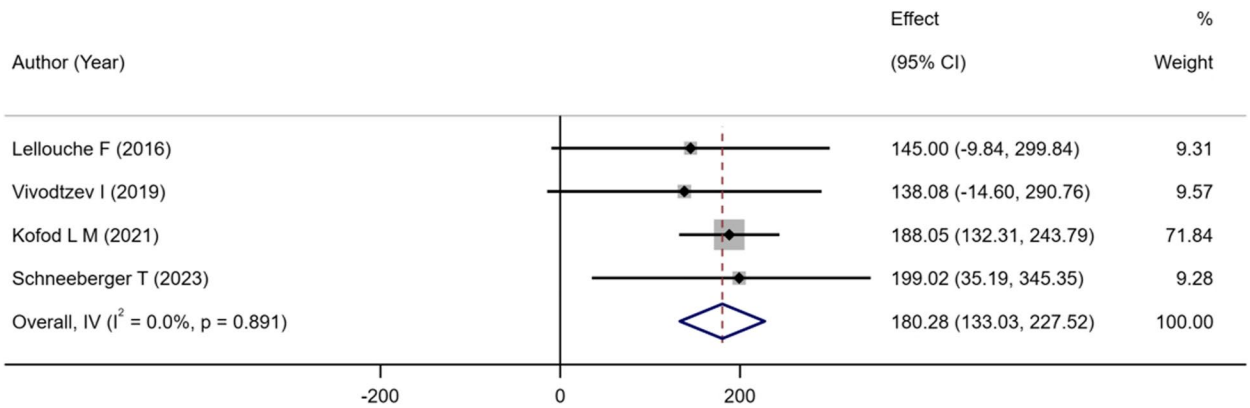

Fig. 4 Forest plot of comparing the effect of ATOS and CFOS on the distance of ESWT. ATOS automatically titrating oxygen system, CFOS constant flow oxygen system, ESWT endurance shuttle walking test, CI confidence interval

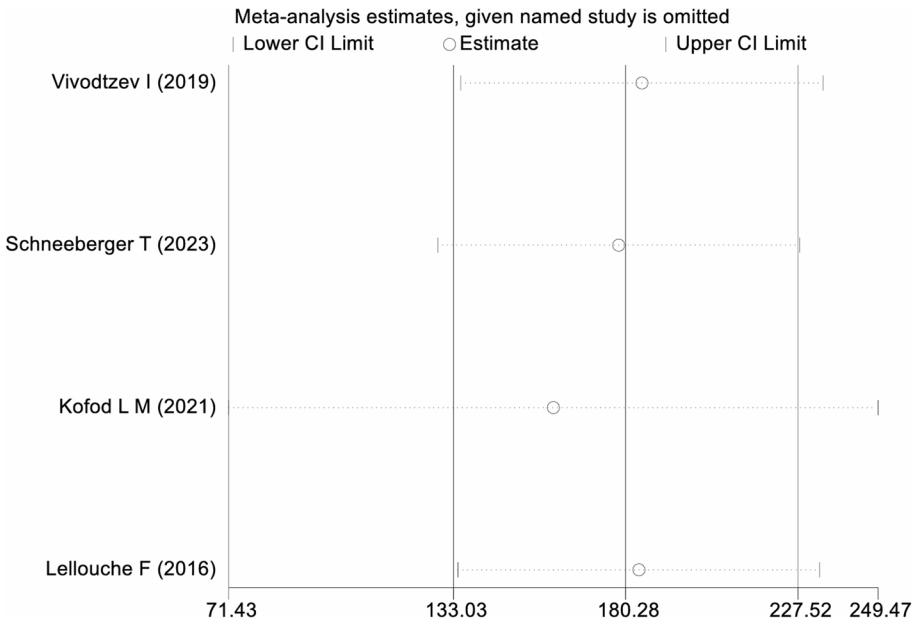

Fig. 5 Sensitivity analysis of comparing the effect of ATOS and CFOS on the distance of ESWT. ATOS automatically titrating oxygen system, ESWT endurance shuttle walking test, CI confidence interval

improved metabolic flexibility and delayed anaerobic metabolism onset [33, 34]. Enhanced oxygen delivery to muscles allows for more efficient aerobic metabolism, which in turn reduces the accumulation of metabolic by-products such as lactate, thereby alleviating muscle fatigue. Additionally, improved mitochondrial function in skeletal muscles has been shown to enhance exercise endurance by maintaining aerobic energy production and reducing acute fatigue.

2. Psychological and Motivational Factors: Some studies showed that ATOS may also have positive psychological effects. CODP patients using ATOS may experience reduced anxiety and increased confidence in their ability to exercise without significant dyspnea. This psychological boost can further enhance exercise tolerance and overall quality of life [35].

It is worth noting that although the secondary outcomes suggested that ATOS may be able to reduce dyspnea, the significant heterogeneity ($I^2 = 82\%$) reminds us to interpret the results with caution.

Limitations and Future Directions

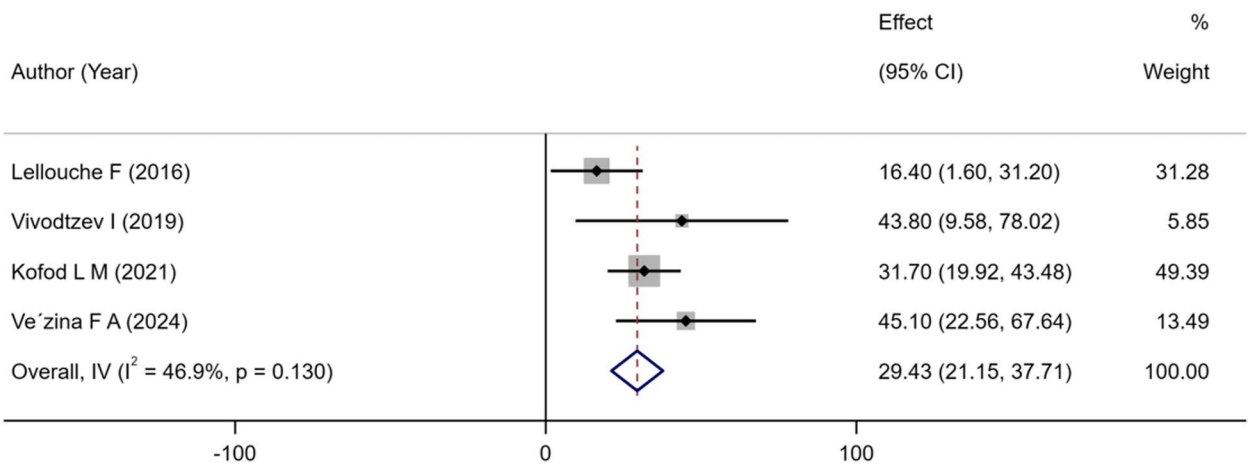

Fig. 6 Forest plot of comparing the effect of ATOS and CFOS on the percentage time within targeted SpO_2 during ESWT, ATOS automatically titrating oxygen system, CFOS constant oxygen flow system, ESWT endurance shuttle walking test, SpO2 oxygen saturation, CI confidence interval

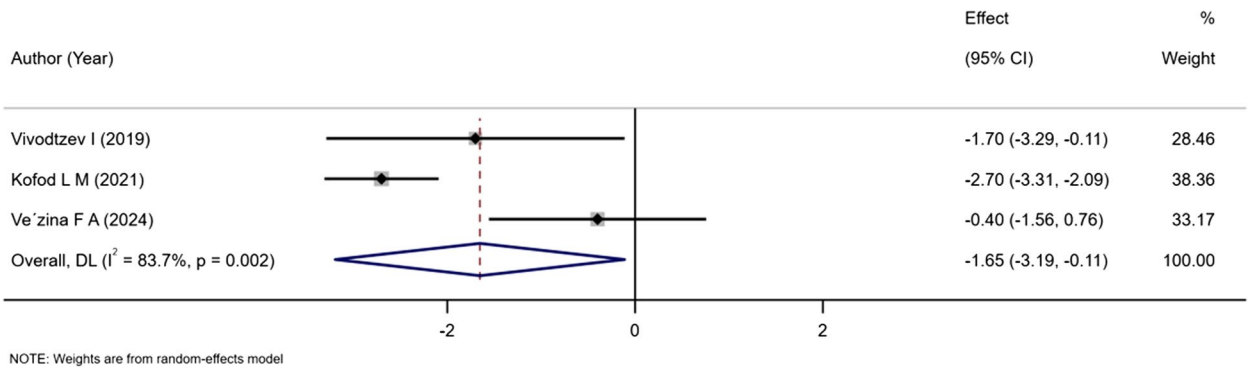

Fig. 7 Forest plot of comparing the effect of ATOS and CFOS on the dyspnea at isotime during ESWT. ATOS automatically titrating oxygen system, CFOS constant flow oxygen system, ESWT endurance shuttle walking test, CI confidence interval

Limitations and future directions

Despite the demonstrated acute benefits of ATOS in improving exercise capacity and maintaining target SpO2 levels in single bout of exercise, our analysis identified several limitations. First, there is significant heterogeneity in the baseline characteristics of the included patients. Specifically, some studies enrolled COPD patients with CRI, while others focused solely on those with EID. Future studies should aim to investigate these distinct patient groups separately to provide more targeted and conclusive results. Second, the included studies primarily assessed immediate effects of the interventions. Given the chronic nature of COPD, it is crucial for future research to explore the long-term effects of different oxygen therapy modalities on patient outcomes.

Additionally, the complexity of ATOS devices, which rely on advanced sensors and algorithms, may limit their widespread adoption due to increased costs and maintenance challenges. Delays in oxygen flow adjustment during rapid changes in patient conditions could lead to brief desaturations, particularly in high-risk patients. Furthermore, the reliability of pulse oximetry sensors, which are essential for ATOS functionality, can be compromised by movement artifacts or weak signals, resulting in inaccurate SpO2 readings [36, 37]. Future research should focus on improving sensor technology and optimizing algorithms to enhance the reliability and responsiveness of ATOS.

Conclusions

Our study demonstrates that ATOS offers advantages in improving exercise tolerance, maintaining target SpO2 levels, and alleviating dyspnea in COPD patients in single bout of exercise. However, the inclusion of patients with varying degrees of hypoxemia requires cautious interpretation of our results. While ATOS shows promise in optimizing oxygen therapy for COPD patients, its complexity, cost, and potential response delays must be considered. Future research should focus on improving

Table 2 Quality of evidence for primary outcomes in patients with COPD

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ATOS	CFOS	Relative (95% CI)	Absolute (95% CI)		
Duration of ESWT												
5	Randomized cross-over controlled trial	not serious	not serious	not serious	serious[a]	none	120	120	-	MD 258.43 higher (206.73 higher to 310.14 higher)	⨁⨁⨁◯ Moderate[a]	Critical
Distance of ESWT												
4	Randomized cross-over controlled trial	not serious	not serious	not serious	serious[a]	none	110	110	-	MD 180.28 higher (132.03 higher to 227.52 higher)	⨁⨁⨁◯ Moderate[a]	Critical

CI Confidence interval, *ATOS* Automatically titrating oxygen system, *ESWT* Endurance shuttle walking test, *CFOS* Constant flow oxygen system, *MD* Mean difference

[a] Small sample size

sensor technology and optimizing algorithms to enhance the reliability and responsiveness of ATOS.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03594-0.

Additional file 1.

Additional file 2.

Additional file 3.

Additional file 4.

Additional file 5.

Additional file 6.

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Authors' contributions
Peijian Wang and Siyuan Wang conceived this study. Jing Wang and Lijun Ge searched the literature. Peijian Wang Beiyao Gao conducted statistical analysis and connected the authors. Peijian Wang and Jing Wang conducted the studies selection, data extraction, and evaluation of the risk of bias. Peijian Wang and Jing Wang drafted the manuscript. Lang Jiang revised the manuscript. All authors read and approved the final manuscript.

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Data availability
The authors declare that all data supporting the findings of this study are available within the supplementary information files. Furthermore , we make a statement in the section of "Ethics approval and consent to participate" that this systematic review does not require ethical approval because all of the included studies have been published before and our review did not involve the patients' privacy.

Declarations

Ethics approval and consent to participate
This review does not require ethical approval because the included studies are published data and do not involve the patients' privacy.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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