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Systematic Review & Meta-Analysis

Triple Inhaler Therapy Outperforms Dual Therapy in Moderate to Severe COPD: A Meta-Analysis of 11,477 Patients from 4 Randomized Controlled Trials Shows Improved Lung Function, Reduced Exacerbations, and Comparable Safety Profile

Chabib Fachry Albab[1*], Almas Talida Habibah[2], Wulandhari[3], Faiq Murteza[3], Achmad Fayyad Mas'udi[4]

[1] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga/ dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[2] Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga/ dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[3] Faculty of Medicine, Universitas of Sebelas Maret, Central Java, Indonesia
[4] Faculty of Medicine, Universitas Airlangga, East Java, Indonesia

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CORRESPONDING AUTHOR*
Chabib Fachry Albab
fachryalbab55@gmail.com
Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga/ dr. Soetomo General Academic Hospital, Surabaya, Indonesia

KEYWORDS
Triple Inhaler Therapy; Dual Inhaler Therapy; Chronic Obstructive Pulmonary Disease; Symptom Control; FEV1

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) continues to be one of the most prevalent health conditions globally. Treatment strategies for COPD are often tailored to disease severity, beginning with single therapy and advancing to dual or triple therapy as needed. However, limited randomized controlled trials (RCTs) have explored the comparative impact of dual and triple inhaler therapies on clinical outcomes and exacerbation frequencies. Our meta-analysis aims to evaluate the effectiveness and safety of triple and double medication in moderate and severe COPD patients.

Material and Methods: A comprehensive exploration of databases was conducted to identify RCTs comparing triple and dual inhaler therapies. For binary outcomes, the pooled RR or OR was calculated; we also used weighted MD to analyze continuous outcomes, both with high CI (95%).

Results: The meta-analysis included four RCTs involving 13,574 patients, of whom 67.92% were male. Triple inhaler therapy proves lung function improvements significantly, evidenced by an increase in FEV1 (MD: 0.06; 95% CI: 0.01–0.11; p=0.02). It showed significant association with a exacerbations reduction in both moderate and severe one (RR: 0.76; 95% CI: 0.72–0.81; p<0.000001). No notable differences in adverse events were observed between combination of triple and double medication (OR: 0.99; 95% CI: 0.90–1.10; p=0.85).

Conclusion: Triple inhaler medication proves more effective than double medication in moderate and severe COPD patients, enhancing lung function and lowering exacerbation rates without a significant increase in adverse effects.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) continues to be one of the highest prevalent health conditions and remains the fourth prime cause of mortality globally [1,2]. As a non-communicable disease, COPD often shows significant rates of morbidity and mortality [3]. COPD condition is a progressive airflow restriction that is often irreversible [1,4]. COPD patients frequently experienced the following symptoms include dyspnea, persistent cough, and sputum formation [5–7].

Recently, COPD is a significant global health challenge, with bronchodilators being the cornerstone of its management [3,8]. To alleviate symptoms, treatment often starts with monotherapy and could continue to combination of double medication and triple medication, including inhaled corticosteroids (ICS), long-acting beta-2-agonists (LABA), and long-acting muscarinic antagonists (LAMA). The medication approach to COPD escalates as concerns to patient's needs and disease severity [3,9].

Initially, ICS combined with LABA were widely used for high risk of exacerbations patients [10]. However, the emergence of LAMAs demonstrated similar benefits while raising concerns about ICS-related pneumonia risks. As a result, treatment guidelines evolved, emphasizing double bronchodilator medication (LABA/LAMA) over ICS-containing regimens [11]. Current guidelines from GOLD recommend combination of LABA+ICS+LAMA of triple medication used only for severe symptoms and frequent exacerbations patients despite dual therapy [12].

Current evidence on triple therapy, including LABA/LAMA/ICS for COPD, primarily compares its efficacy to LABA/ICS or LAMA monotherapy, but more studies are still needed to provide a more relevant comparison to LABA/LAMA dual therapy [13,14]. Some patients may be on triple therapy unnecessarily, exposing them to the risks of long-term ICS use without added benefits [11,15]. ICS can be safely withdrawn without increasing exacerbation risk, although researchers still need to reveal clear guidelines for ICS withdrawal [16,17]. Personalized treatment approaches, including patient phenotyping and biomarkers like blood eosinophils, can help in identifying those who truly gain benefit from ICS, although the elevated eosinophils threshold still remains unknown [18,19].

Recent clinical trials have provided significant insights into the effectiveness of various inhaled drug combinations for treating COPD, leading to changes in treatment guidelines [20]. Evidence suggests that LABA/LAMA combinations are generally greater to LABA/ICS in performing bronchodilation, demonstrating their effectiveness in improving lung function to finally prevent exacerbations [21,22]. Others support the advantage of fixed triple medication (ICS/LAMA/LABA) over LABA/ICS in frequent exacerbations patients, improving lung function, symptom control and quality of life [23-25]. However, questions remain about whether adding ICS to LABA/LAMA offers additional benefits for exacerbation reduction [26].

Additional studies are required to better define criteria for treatment escalation, reveal whom are intending to benefit from ICS, and assess the safety of triple medication in managing COPD symptoms [27]. Numerous studies explored the role of dual and triple inhaler medication, focusing on their impact on clinical outcomes and exacerbation rates. Consequently, a meta-analysis was performed by our team to assess the effectiveness and safety of triple versus dual-inhaler therapy in individuals with moderate to severe COPD.

MATERIAL AND METHODS

This paper adhered to the PRISMA 2020 and relied on data from previously published studies, thereby obviating the requirement for ethical approval. The protocol for this study was officially registered in PROSPERO under the identifier CRD42023439652. A comprehensive search was performed on June 1, 2023, using PubMed and ScienceDirect to identify appropriate randomized controlled trials (RCTs).

Inclusion criteria encompassed studies involving adults aged 18 and above with a follow-up period of at least one year, while non-English publications, review articles, and studies with inadequate data were excluded. Key data, including demographic information, treatment specifics, changes in FEV1, symptom improvement, exacerbation rates, and adverse events, were independently extracted. The Cochrane RoB-2 tool was employed to evaluate the risk of bias, and the GRADE framework was performed to analyze the quality of evidence. Review Manager 5.4.1 was used to perform a meta-analysis to assess both safety (adverse events) and efficacy (exacerbation rates, symptom control, and FEV1 changes), with pooled odds ratios and rate ratios calculated. Publication bias was evaluated using Begg's funnel plots.

RESULTS

A systematic search of online databases identified 933 studies for evaluation, with no additional studies found through manual searches. After screening, this study includes four RCTs evaluating the differences between double medications and combination of triple medication in moderate to severe symptoms patients with COPD (Fig.1). The analysis involved 11,477 patients, consisted of 67.9% male patients with most populations in age around 65.2 years old. The combination of triple medication group included 5,747 patients, while the double medication group comprised 5,730 patients. Table 1 showed the demographic characteristics of participants.

All studies' quality was assessed using the RoB-2 for randomized clinical trials. All studies exhibited a strong selection process, with study populations represent both effectiveness and safety of triple medication and double medication in COPD patient experiencing moderate to severe symptoms (Fig.8).

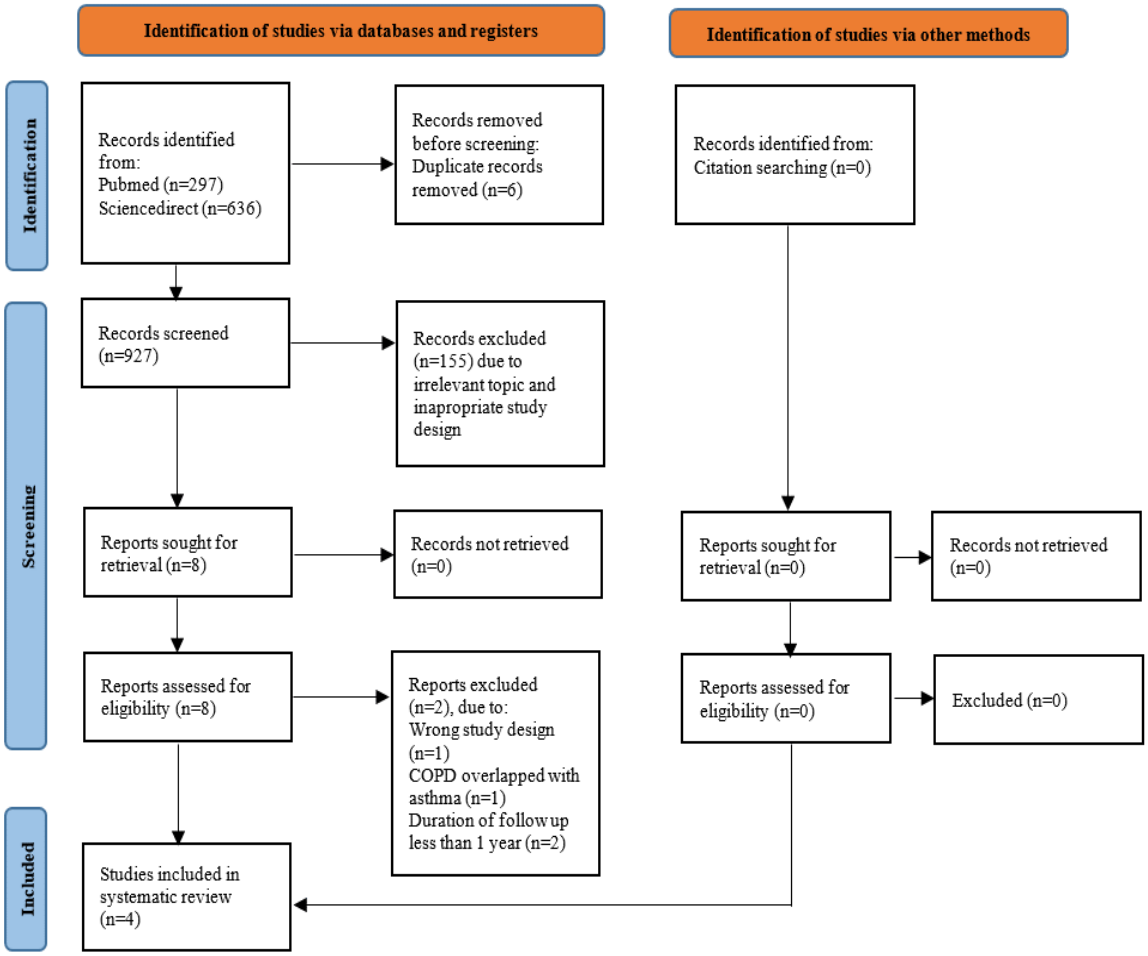


Fig.1. PRISMA Flowchart of the Literature Selection

Adverse events were evaluated across the four included studies, involving 11,477 participants. The analysis of long-term adverse events revealed that no significant differences between triple medication and double medication were found (OR:0.99; 95% CI:0.90–1.10; p=0.85). The analysis was illustrated in Figure 2. Due to the low heterogeneity, this study used a fixed-effects model (p=0.14).

A meta-analysis was performed using four studies to assess the RR for exacerbations of moderate and severe COPD over the last number of year. Pooled results revealed an exacerbation rates reduction with triple medication compared to double medication (RR:0.76; 95% CI:0.72–0.81; p<0.000001) statistically significant, as shown in Figure 3. Due to the low heterogeneity, we employed a fixed-effects model (p=0.55).

An analysis of changes in FEV1 from baseline was carried out across three of the included studies, involving 11,182 patients. The pooled results demonstrated a significant difference in FEV1 changes (MD:0.06; 95% CI:0.01–0.11; p=0.02). The results were illustrated in **Fig.4**. Due to the high heterogeneity, this study utilized a random-effects model (p<0.000001).

DISCUSSION

This meta-analysis highlighted key findings on triple inhaler therapy for COPD. Triple therapy demonstrated a significant enhancement in lung function, evidenced by a mean difference (MD) of 0.06 (p=0.02), outperforming dual therapies in absolute FEV1 changes. The results were supported by Singh et al., who found that triple therapy resulted in enhanced lung function and superior patient-reported outcomes compared to alternative treatments [31]. Moreover, triple therapy showed a reduction in moderate-to-severe COPD exacerbations, with Singh et al. reporting low exacerbation rates during a year follow-up period, even among patients who had a history of prior exacerbations [31].

Safety profiles were similar between triple and dual therapies. Although triple therapy offers advantages such as reducing exacerbations, enhancing lung function, and improving quality of life, its use should be carefully considered. It is particularly appropriate for those who experience recurrent exacerbations or have uncontrolled symptoms even with dual therapy [29-32]. However, some patients still experience exacerbations even with triple therapy, including ICS+LABA+LAMA [33]. GOLD guidelines recommend stepping down to dual bronchodilation if ICS provides no significant benefit, though clear protocols for ICS withdrawal are lacking [12]. Studies like INSTEAD and WISDOM suggest ICS withdrawal may be feasible for some patients, despite potential temporary lung function decline [34,35]. Further research, such as the SUNSET trial, is needed to refine ICS withdrawal strategies [36].

Extended use of ICS is linked to risk of pneumonia and other adverse effects, underscoring the importance of meticulous patient selection [37]. Biomarkers such as blood eosinophil counts are useful in identifying patients who intend to gain benefit from treatment regimens that include ICS [18,38]. Combination therapies involving LABA/ICS have proven to be more effective than monotherapy in reducing the occurrence of symptom exacerbations requiring systemic steroids [39,40]. According to guidelines such as GesEPOC, triple therapy is recommended for threatening patients, especially those diagnosed with asthma-COPD overlap, emphysema, or chronic bronchitis [41].

Patients exhibiting elevated blood eosinophil levels tend to have a more favorable response to LABA/ICS and triple therapy, highlighting the critical role of this biomarker in determining the appropriate use of ICS [19,38]. Personalized treatment approaches, based on patient phenotypes and exacerbation history, are increasingly emphasized [38]. This meta-analysis has limitations, including variability in medications across studies and a lack of direct comparisons between specific regimens. The decision to initiate triple therapy should be individualized, weighing benefits against risks.

CONCLUSION

Triple inhaler therapy demonstrated greater efficacy compared to dual inhaler therapy in individuals with moderate to severe COPD. It was linked to significant improvements in lung function and a reduction in COPD exacerbations. However, no notable difference of adverse events was observed between triple and dual inhaler therapies. Further research is recommended to evaluate triple therapy's potential association with cardiovascular events, pneumonia risk, and its enhanced effectiveness across different COPD severity stages, particularly when considering patients' exacerbation history and age-specific subgroups.

In conclusion, targeted interventions and consistent preventive practices are key to combating this disease. Continued research and community education are essential to enhance the implementation and adherence to these measures, ultimately aiming to reduce and eradicate filariasis in endemic areas.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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Table 1. Demographics of Included Studies

Author, Year of Publication	Country	Studies Group	Sample Size (n)	Male (%)	Mean Age (SD)	BMI (kg/m^2)	History of Smoker (%)	Follow Up Duration (weeks)
Lipson et al, 2018 [29]	UK	Triple therapy	4151	67	65.3 (8.2)	26.6	65	52
		ICS/LABA	4134	66	65.3 (8.3)	26.7	66	
		LABA/LAMA	2070	68	65.2 (8.3)	26.6	65	
Papi et al, 2018 [30]	Italy	Triple therapy	764	72	64.4 (7.7)	25.7	54	52
		LABA/LAMA	768	72	64.4 (7.7)	26.6	57	
Singh et al, 2016 [31]	UK	Triple therapy	687	74	63.3 (7.9)	26.3	53	52
		ICS/LABA	680	77	63.8 (8.2)	26.4	53	
Aaron et al, 2007 [32]	Canada	Triple therapy	145	57.9	67.5 (8.9)	27.8	67.6	52
		LABA/LAMA	148	57.4	67.6 (8.2)	27.2	75.7	

Table 2. Results of Studies

Author, Year of Publication	Studies Group	FEV1 (L)		Number of Exacerbation (%)	One Exacerbation (%)	One or More Exacerbation (%)	Two or More Exacerbation (%)	Adverse Events (n)
		Baseline	Changes					
Lipson et al, 2018 [29]	Triple therapy	1.274 (1.265-1.282)	0.094 (0.086-0.102)	<1	45	NA	55	450
	ICS/LABA	1.177 (1.168-1.185)	-0.003 (-0.012-0.006)		46		54	430
	LABA/LAMA	1.220 (1.208-1.232)	0.04 (0.028-0.052)		45		55	
Papi et al, 2018 [30]	Triple therapy	1.07 (0.31)		NA	80	100	20	490
	LABA/LAMA	1.07 (0.31)			82	100	18	516
Singh et al, 2016 [31]	Triple therapy	1.096 (0.381)	0.071 (0.05-0.093)	NA	NA	NA	NA	368
	ICS/LABA	1.094 (0.393)	0.008 (-0.014-0.03)					379
Aaron et al, 2007 [32]	Triple therapy	1.12 (0.41)		NA	NA	NA	NA	44
	LABA/LAMA	1.08 (0.43)						32

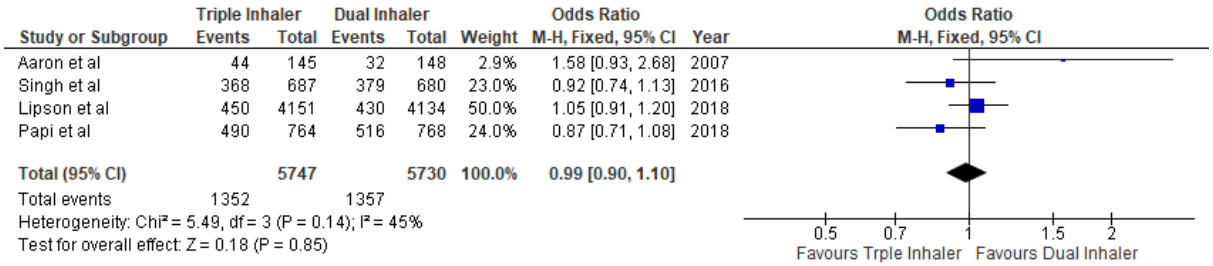


Fig.2. Forest Plot for Any Adverse Events in Moderate to Severe COPD

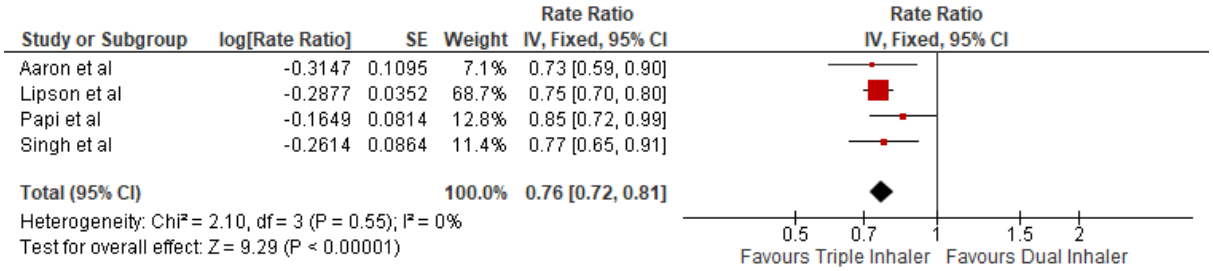


Fig.3. Forest Plot for Moderate to Severe COPD Exacerbation in the Last One Year

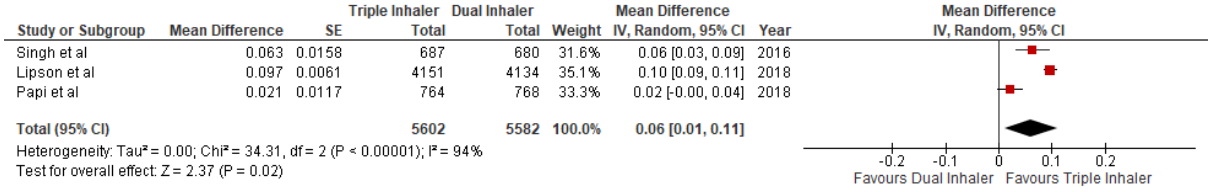


Fig.4. Forest Plot for FEV1 Changes in Moderate to Severe COPD

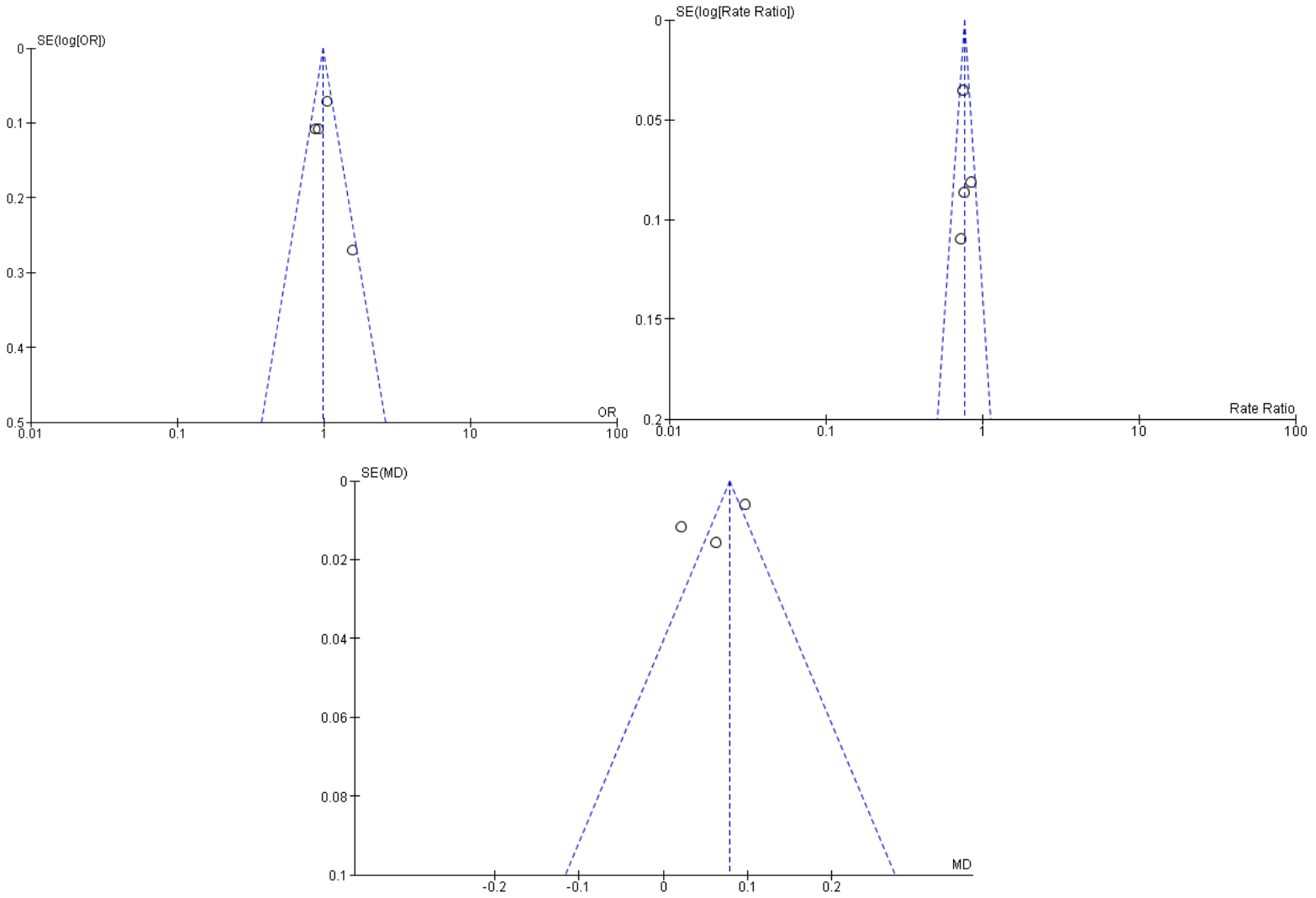


Fig.5. A. Funnel Plot for any Adverse Events in Moderate to Severe COPD; B. Funnel Plot for Moderate to Severe COPD Exacerbation in the Last One Year; C. Funnel Plot for FEV1 Changes in Moderate to Severe COPD

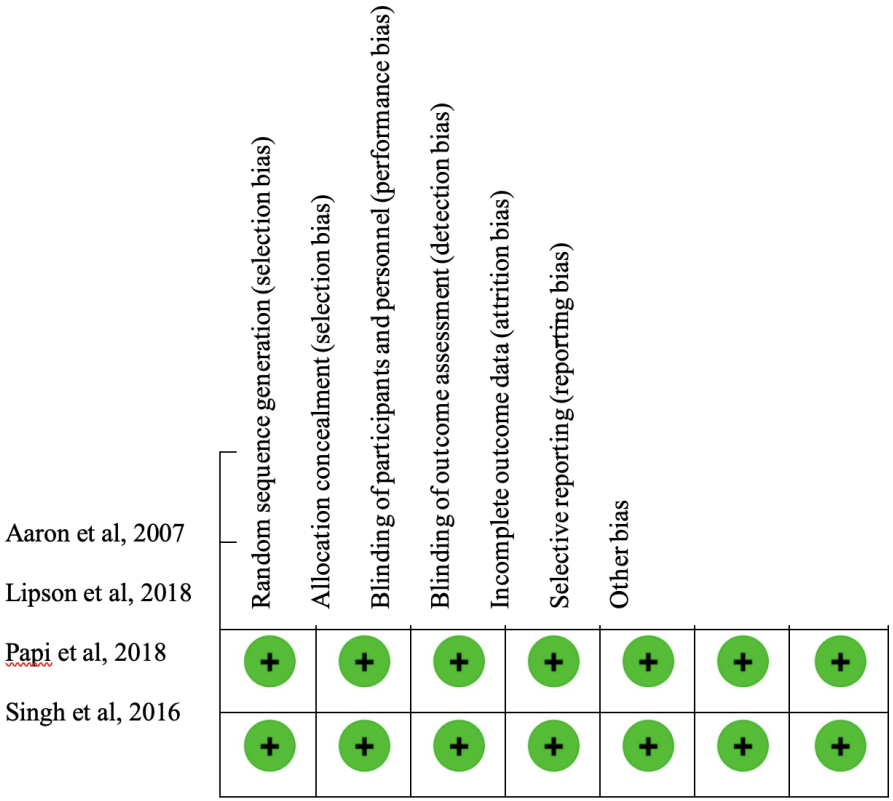


Fig.8. Risk of Bias Assessment for Each Studies included