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Comparison of clinical features and outcomes for asthma-COPD overlap syndrome *vs.* COPD patients: a systematic review and meta-analysis

X.-L. ZHOU[1], L.-Y. ZHAO[2]

[1]Department of Respiratory Medicine, Traditional Chinese Medical Hospital of Zhuji, Zhuji, Province of Zhejiang, P.R. China
[2]Department of Geriatrics, Traditional Chinese Medical Hospital of Zhuji, Zhuji, Province of Zhejiang, P.R. China

Abstract. – OBJECTIVE: The aim of this study was to review evidence to determine whether "pure" chronic obstructive pulmonary disease (COPD) patients without a history of asthma differ in the clinical characteristics, severity of airflow limitation, and clinical outcomes compared to patients with Asthma-COPD Overlap Syndrome (ACOS).

MATERIALS AND METHODS: An electronic search was performed in the MEDLINE, EMBASE, SCOPUS and Web of Science databases to identify comparing the clinical characteristics and outcomes between ACOS and "pure" COPD. The included studies were subjected to meta-analysis and risk of bias assessment using ROBINS-E tool. Eleven observational studies were included.

RESULTS: The results of the meta-analysis showed increased expression of lung function parameters like forced expiration volume (FEV) at 1 sec{mean difference (MD) 2.36; 95% CI [0.05,4.66] ; p=0.004; I^2= 72%} and clinical symptoms in terms of fever {Relative Risk (RR) 0.34, p<0.0001}, wheezing {RR 0.39, p<0.0001} and dyspnea {RR 0.53, p<0.0001}. The comorbidities associated with ACOS patients were similar to that found in patients with "pure" COPD. Interestingly, higher body mass index (BMI) was found in patients with ACOS (MD -0.73 95% CI [-1.06, -0.41], p<0.0001.

CONCLUSIONS: The result showed higher risk in onset of frequent acute exacerbations, severe exacerbations requiring hospitalization and higher number of exacerbations experienced per year in ACOS patients. Within the limitations of the review, ACOS can be regarded as separate entity of co-existence which is classically associated with higher BMI, worsened lung function parameters and exacerbations with a varing degree of clinical symptoms.

Key Words:
Chronic obstructive pulmonary disease, Asthma-COPD overlap syndrome, Meta-analysis.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a form of chronic inflammatory lung disease which is characterized by airflow limitation due to abnormalities of the airway or alveolus[1]. The disease is strongly associated with smoking, rather than patients with allergy, or occupational hazards[2]. The total number of cigarette pack years, as well as smoking frequency is considered to be risk factors for the development of COPD[3]. The disease is also associated with substantial morbidity and mortality; and hence is a recognized public health problem. COPD differs from other restrictive airway diseases like asthma, by being more progressive and persistent, superseded by excessive cough and sputum production, and demonstrating acute exacerbations[4]. Unlike COPD, asthmatic patients respond to bronchodilators immediately as the airway limitation is immediately reversible[5].

The diagnosis of obstructive lung diseases is often misleading as the clinical features of COPD and asthma often co-exist. The Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) released a consensus statement on the Asthma-COPD Overlap Syndrome (ACOS) in 2014, wherein ACOS was defined as an unique entity characterized primarily by chronic airflow limitation with several features usually associated with asthma and COPD together[6]. In contrast to patients suffering from COPD alone, individuals diagnosed with ACOS are known to have a different clinical phenotype, an array of co-morbidities and are also characterized by frequent exacerbations, dyspnea and wheezing[7]. Considering the overlapping symptomatology,

Corresponding Author: Liying Zhao, MD; e-mail: zjzhaoliying@163.com

it is often difficult to clearly differentiate the clinical characteristics of ACOS from COPD in clinical practice.

To date, several investigations in literature have compared clinical features and outcomes of ACOS and COPD patients. Nielsen et al[8] in a systematic review of eleven observational studies concluded that symptoms observed were severe in ACOS patients and presented with more acute exacerbation compared to patients suffering from asthma or COPD alone. They also reported that by virtue of the greater disease severity, an increased morbidity rate was observed in ACOS patients. Further, as compared to COPD-only patients, the ACOS patients were found to have lower forced expiration volume at 1 second (FEV_1) % predicted and FEV/FVC (forced vital capacity) ratio regardless of lower mean lifetime tobacco exposure; however, the authors did not perform a quantitative analysis to justify the same[8].

The differences in the diagnosis and understanding between ACOS and "pure" COPD have always been challenging and have raised concerns among the researchers. ACOS was diagnosed on the basis of included six criteria, three of which are major (persistent airflow limitation, tobacco smoking and previous asthma or bronchodilator reversibility >400 mL at FEV_1) and three minor (history of atopy or rhinitis, and at least two positive bronchodilator tests)[9]. The Spanish guidelines for COPD and for asthma proposed another definition of ACOS stating that patients must present with a concomitant diagnosis of both diseases or show a bronchodilator reversibility >400 mL at FEV_1[10]. The clinical characteristics and the outcomes are also overlapping and reported inconsistently throughout the literature. A clear demarcation between ACOS and "pure" COPD is difficult to assess with a variety of evidence with different diagnostic criteria. This review is an attempt to quantitatively express the events and risk associated in terms of clinical characteristics and outcomes associated with ACOS and "pure" COPD.

To our knowledge, no meta-analysis has been conducted to date to compare the clinical characteristics of patients suffering from "pure" COPD and ACOS. The aim of this study is to review evidence to determine whether COPD patients without a history of asthma differ in the clinical characteristics, severity of airflow limitation, and clinical outcomes compared to patients with ACOS.

Materials and Methods

This review was performed according to preferred reporting of systematic reviews and meta-analysis (PRISMA) guidelines.

Search Strategy

The search was performed both in literature databases and COPD related journals. An electronic search was carried out in MEDLINE, EMBASE, SCOPUS and Web of Science databases using the keywords combined with 'AND' & 'OR'. The last electronic search was conducted on 31 July 2020. The search string used was as follows: (((“Asthma”[MeSH Terms]) AND ((((“COPD”[MeSH Terms]) OR (“chronic obstructive pulmonary disease”[MeSH Terms])) OR (OLD)) OR (Obstructive Lung Disease))) AND (((Overlap Syndrome) OR (ACOS)) OR (Overlap phenotype))) AND (((((Clinical characteristics) OR (Clinical Features)) OR (Clinical Outcomes)) OR (Clinical Symptoms)) OR (Clinical Phenotype)). We further screened the last ten year databases of COPD related journals like American Journal of Respiratory and Critical Care Medicine; International Journal of COPD, European Respiratory Journal; BMC Pulmonary Medicine and Journal of COPD. The bibliography of the previous systematic review and potentially eligible observational studies were thoroughly checked for any additional studies available for inclusion.

Selection Criteria

All types of studies comparing clinical features and outcomes of ACOS and "pure" COPD were included in this review. Non-English language studies, studies not reporting relevant clinical characteristics and outcome data or those with sample size less than 10 were excluded.

Study Selection

The selection of the studies was carried out by two independent reviewers. The search records were imported into citation manager software (EndNote v7.0, Clarivate Analytics, NY, USA). The duplicates from the records were merged and removed in order to get a pool of studies to choose from. All studies were subjected to title and abstract screening to narrow down the selection to potentially eligible articles. These screened articles were assessed by retrieving the full texts and carefully analyzing them against the selection criteria. The two reviewers selected the included articles independently. The studies

with full text assessments, once tagged excluded were listed with detail reasons stated for their exclusion.

Data Extraction

Two independent reviewers separately retrieved the data from the full texts of included study using Excel spread sheet (Microsoft, Redmond, WA, USA). All relevant information pertaining to study design, sample size, demographic characteristics, diagnosis criteria for ACOS and "pure" COPD, associated co-morbidities, clinical characteristics and outcomes were extracted. Any information, if found missing or unclear, the corresponding authors were contacted to provide clarifications.

The primary outcomes assessed were FEV_1 and FVC. Other clinical symptoms like fever, cough, sputum, wheezing and dyspnea among the groups were also recorded. The co-morbidities associated like hypertension (HTN), diabetes mellitus (DM), heart failure (HF), allergy, allergic rhinitis, atopic dermatitis and chronic bronchitis and prognostic parameters like acute exacerbations, severe exacerbations requiring hospitalizations, and other mortality related parameters like development of pneumonia and cardio-pulmonary arrest were also extracted from the included studies.

Data Synthesis

Both qualitative and quantitative analyses were carried out in the review. The data from different studies were to be combined by a meta-analysis only when at least two studies reported the same outcome in a similar unit of analysis. If a meta-analysis could not be performed for a given outcome, then a descriptive analysis was performed. Risk ratio (RR) was assessed for dichotomous data and mean difference (MD) was assessed for continuous data. The RRs and MD were combined using meta-analysis using random effect models. Heterogeneity was assessed using the I^2 statistic. Publication bias was not assessed as less than 10 studies were included in each meta-analysis.

Risk of Bias Assessment

Risks of Bias were assessed by two independent reviewers for all the included reports using ROBINS-E (Risk Of Bias In Non-randomized Studies - of Exposures) tool[11]. The following seven domains were graded for each study as high, unclear or low risk of bias: bias due to confounding; bias in selection of participants into the study; bias in classification of exposures; bias due to departures from intended exposures; bias due to missing data; bias in measurement of outcomes; bias in selection of reported result. Based on the domains, the studies were categorized as low risk of bias if all domains were at low risk except one or less domains were at unclear risk; high risk of bias if one or more domains were at high risk; or medium risk of bias if two or more domains were unclear. The publication bias among the included studies was assessed by visualizing funnel scatter plots of corresponding forest plots of primary outcomes and employing Egger's linear regression test.

Results

A total of 877 unique articles were identified from the literature search. A total of eleven studies[12-22] were included in this systematic review and meta-analysis. The detail for the study selection process along with reason for exclusion for excluded studies is provided in Figure 1.

This review analysed data from 43,362 patients with 25,286 diagnosed with "pure" COPD and 10,085 diagnosed with ACOS. The included studies were conducted in various countries like Vietnam, Korea, Latin America, France, Spain, Taiwan, and few other European nations. The diagnostic criteria used to clearly distinguish between "pure" COPD and ACOS are listed in Table I. The included studies reported a variation

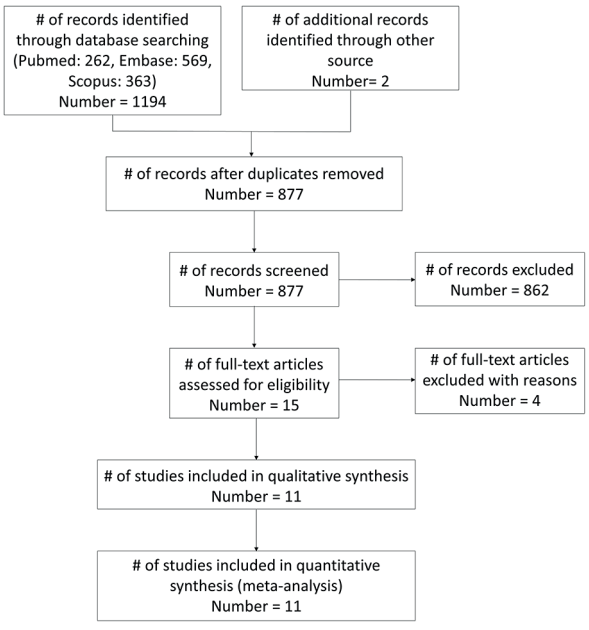

Figure 1. Study selection process.

Table I. Diagnostic criteria for ACOS and COPD among the included studies.

Author	Type of study	N° of patients	Country	Diagnostic criteria	
				COPD	ACOS
Duong-Quy et al[12] 2018	Cohort	209	Vietnam	Report of a previous doctor diagnosis of COPD based on GINA guidelines or GOLD guidelines	Chronic respiratory had been diagnosed as ACOS if they had at least one of the asthma features associated with at least one of the COPD features. With an increase of FEV_1 > 12% and 400 ml from baseline after BD (marked or high reversibility) in subjects who had chronic respiratory symptoms.
Park et al[13] 2017	Cohort	1504	Korean	Pulmonary function test with a post-BD $FEV_1/FVC < 0.7$ at the first visit	Positive response to a bronchodilator (an increase in forced expiratory volume in 1 second [FEV_1] of 12% and 200 mL)
Montes de Oca et al[14] 2017	Cohort	1540	Argentina, Colombia, Venezuela and Uruguay	Post-bronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) < 0.70	Above with both asthma criteria separately: (A) a ratio of post-bronchodilator FEV^1/FVC < 0.70 plus prior medical diagnosis of asthma; (B) a ratio of post-bronchodilator $FEV_1/FVC < 0.70$ and wheezing in the last 12 months plus reversibility (post-bronchodilator increase in FEV1 or FVC of 200 mL and 12%).
Caillaud et al[15] 2017	Cohort	998	France	NR	Reported a physician diagnosis of asthma before the age of 40 years
Cosio et al[16] 2016	Cohort	831	Spain	Smoking history ≥ 10 pack-years and a postbronchodilator $FEV_1/FVC < 0.7$ after 400 mg of inhaled salbutamol	GINA/GOLD report
Chung et al[17] 2015	Cohort	25659	Taiwan	International Classification of Disease Diagnoses, Ninth Revision of Clinical Modification (ICD-9-CM)	International Classification of Disease Diagnoses, Ninth Revision of Clinical Modification (ICD-9-CM)

Continued

Table I *(Continued)*. Diagnostic criteria for ACOS and COPD among the included studies.

Author	Type of study	N° of patients	Country	Diagnostic criteria	
				COPD	ACOS
de Marco et al[18] 2015	Cohort	6984	European	Chronic airflow symptoms (shortness of breath after strenuous activity, dyspnoea (trouble with breathing) or chronic bronchitis (having cough or phlegm on most days for as long as 3 months each year for ≥ 2 years)); or 2) a history of active smoking (≥ 10 pack-years), or occupational exposure to vapours, dust, gas or fumes	Both current asthma and COPD
Hardin et al[19] 2014	Cross-sectional Cohort	3570	NR	GOLD guideline	GINA/GOLD report
Menezes et al[20] 2014	Cohort	767	Brazil, Chile, Mexico, Colombia and Argentina	Based on the ratio of the post-BD $FEV_1/FVC < 0.70$	The combination of CPOD and asthma
Miravitlles et al[21] 2013	Cohort	385	Spain	Post-bronchodilator FEV_1/FVC	The combination of CPOD and asthma ratio of < 0.70
Hardin et al[22] 2011	Cross-sectional Cohort	915	NR	GOLD guideline	GINA/GOLD report

GINA- Global initiative for asthma, GOLD- global initiative for chronic obstructive lung disease , BD- bronchodialator, FEV_1- forced expiration volume at 1 second, FVC- forced vital capacity, COPD- chronic obstructive pulmonary disease, ACOS – Asthma- COPD overlap syndrome NR- not reported.

in diagnostic criteria. Few of the studies used the GINA/GOLD criteria for the diagnosis of ACOS and "pure" COPD, while one study used International Classification of Disease Diagnoses, Ninth Revision of Clinical Modification (ICD-9-CM) for their diagnosis. The rest of the studies defined their own diagnostic criteria based on previous history of asthma, definite lung function values and smoking status.

The demographic characteristics of enrolled patients are listed in Table II. The risk factors like age, pack years, current smoking status and body mass index (BMI) were recorded from all included studies, wherever available, for both the groups. Data of lung function parameters as provided by the included studies is presented in Table III. The meta-analysis was carried out for most of the parameters except prognostic parameters like mortality related parameters such as development of pneumonia and cardio-pulmonary arrest. Only Chung et al[17] reported the development of pneumonia and cardiopulmonary arrest after five years and found it to be 16.80% and 0.58% respectively for ACOS patients compared to 10.21% and 0.53% for "pure" COPD patients.

Clinical Symptoms

The clinical symptoms like fever {RR 0.34, $p<0.0001$}, wheezing {RR 0.39, $p<0.0001$} and dyspnea {RR 0.53, $p<0.0001$} were found to be significantly associated with ACOS than "pure" COPD with relatively significant risk ratio in favour of ACOS (Figure 2). Cough and sputum/phlegm was found prevalent in both the groups; however, no significant difference ($p>0.05$) was observed among ACOS and "pure" COPD.

Co-morbidities

Hypertension, diabetes mellitus, heart failure, allergy, allergic rhinitis, atopic dermatitis and chronic bronchitis were found to be associated co-morbidities with both "pure" COPD and ACOS. A subgroup analysis with all reported co-morbidities was carried out to find no significant difference in association of these co-morbidities was found between both groups, except for allergy showing more association with ACOS RR 0.26, 95% CI [010,0.64], $p=0.004$ (Figure 3). It was seen that the mean difference in BMI between the two groups was found significantly

Table II. Demographic characteristics of ACOS and COPD patients among included studies.

Author	Study groups	N° of patients per group	Demographics characteristics					
			Sex		Age	Pack-year	Current smoker (%)	BMI body mass (index)
			Male	Female				
Duong-Quy	CPOD "pure"	74	NR	NR	59 ± 13	37 ± 12	54 (72.9)	20.3 ± 3.5
et al[12] 2018	ACOS	59	NR	NR	52 ± 14	31 ± 16	22 (37.2)	21.7 ± 2.8
Park	CPOD "pure"	1281	1160	121	71.6 ± 7.7	44 ± 25.5	323 (25.2)	22.7 ± 3.4
et al[13] 2017	ACOS	223	213	10	71 ± 7.7	45.1 ± 24.9	73 (32.9)	23.2 ± 3.3
Montes de Oca	CPOD "pure"	274	150	124	67.3 ± 9.4	44.3 ± 28.9	109 (40.2)	NR
et al[14] 2017	ACOS	35	23	12	65.2 ± 8.6	48.9 ± 37.7	14 (40)	NR
Caillaud	CPOD "pure"	869	673	196	NR	NR	255 (29.3)	NR
et al[15] 2017	ACOS	129	89	40	NR	NR	31 (24)	NR
Cosio	CPOD "pure"	706	588	118	67.8 ± 8.9	56.6 ± 28.7	196 (27.8)	29.1 ± 5.5
et al[16] 2016	ACOS	125	102	23	66.5 ± 8.7	53.2 ± 26.2	44 (35.2)	27.8 ± 5.5
Chung	CPOD "pure"	17088	9728	7360	63.6 ± 13.7	NR	NR	NR
et al[17] 2015	ACOS	8571	4879	3692	63.8 ± 13.6	NR	NR	NR
de Marco	CPOD "pure"	166	87	79	36 ± 6.5	NR	85 (51.5)	NR
et al[18] 2015	ACOS	218	114	104	NR	NR	77 (35.1)	NR
Hardin	CPOD "pure"	3120	1785	1335	64 ± 8.4	54.2 ± 27.8	NR	27.9 ± 6.1
et al[19] 2014	ACOS	450	198	252	60 ± 8.7	45.7 ± 25.1	NR	28.8 ± 6.9
Menezes	CPOD "pure"	594	282	312	64.3 ± 12.1	20 ± 28.4	223 (37.5)	26.8 ± 5.1
et al[20] 2014	ACOS	89	41	48	60.4 ± 11.3	19.3 ± 25.6	29 (32.6)	27.5 ± 5.3
Miravitlles	CPOD "pure"	318	241	77	64.1 ± 9.9	43.1 ± 26.4	121 (38.1)	27.8 ± 4.8
et al[21] 2013	ACOS	67	30	37	63.8 ± 11.4	27.5 ± 20.4	11 (16.4)	29.1 ± 4.5
Hardin	CPOD "pure"	796	423	373	64.7 ± 8.2	55.1 ± 27.3	270 (34.2)	27.8 ± 6
et al[22] 2011	ACOS	119	61	58	61.3 ± 8.9	43.7 ± 20.7	46 (38.7)	28.1 ± 6.7

COPD- Chronic obstructive pulmonary disease, ACOS – asthma- COPD overlap syndrome, NR- not reported.

Table III. Lung function parameters of ACOS and COPD patients among included studies.

Author	Study groups	N° of patients per group	Lung function parameters		
			FEV_1 %	FVC %	FEV_1/FVC %
Duong-Quy et al[12] 2018	CPOD "pure"	74	72 ± 18	NR	63 ± 7
	ACOS	59	69 ± 15	NR	66 ± 7
Park et al[13] 2017	CPOD "pure"	1281	55.1 ± 17.9	80.6 ± 17.5	48.2 ± 12.1
	ACOS	223	52.7 ± 14.5	81.1 ± 17.6	46.6 ± 9.5
Montes de Oca et al[14] 2017	CPOD "pure"	274	64.7 ± 21.1	79 ± 18.8	NR
	ACOS	35	58.8 ± 18.6	76.3 ± 17.7	NR
Caillaud et al[15] 2017	CPOD "pure"	869	NR	NR	NR
	ACOS	129	NR	NR	NR
Cosio et al[16] 2016	CPOD "pure"	706	59.3 ± 20.7	85.6 ± 23.3	52.2 ± 11.5
	ACOS	125	61.2 ± 18.1	84.9 ± 18.5	54.8 ± 10.9
Chung et al[17] 2015	CPOD "pure"	17088	NR	NR	NR
	ACOS	8571	NR	NR	NR
de Marco et al[18] 2015	CPOD "pure"	166	NR	NR	NR
	ACOS	218	NR	NR	NR
Hardin et al[19] 2014	CPOD "pure"	3120	50.3 ± 18	NR	0.49 ± 0.13*
	ACOS	450	50.3 ± 17.9	NR	0.51 ± 0.13*
Menezes et al[20] 2014	CPOD "pure"	594	82 ± 19.2	100.6 ± 18.7	62.7 ± 8
	ACOS	89	72.1 ± 18.9	96.6 ± 21.3	58.5 ± 9.5
Miravitlles et al[21] 2013	CPOD "pure"	318	75.6 ± 18.1	88.1 ± 18.3	62.1 ± 7.2
	ACOS	67	72.7 ± 17.7	86.9 ± 19.8	60.6 ± 7.1
Hardin et al[22] 2011	CPOD "pure"	796	49.4 ± 18.4	76.6 ± 17.9	0.48 ± 0.13*
	ACOS	119	49.2 ± 17.5	78.3 ± 17.3	0.48 ± 0.12*

FEV_1- Forced expiration volume at 1 second, FVC- forced vital capacity, COPD- chronic obstructive pulmonary disease, ACOS – Asthma- COPD overlap syndrome, NR – not reported.

associated risk with ACOS than "pure" COPD with MD -0.73 95% CI [-1.06,-0.41], $p<0.0001$ (Figure 4).

Lung Function

Eight studies[12-14,16,19-22] reported data on FEV_1%. Our meta-analysis demonstrated significantly higher FEV_1% in patients suffering from "pure" COPD compared to ACOS with a mean difference (MD) of 2.36; 95% CI [0.05,4.66] ; $p=0.004$; $I^2= 72\%$ (Figure 5). Data from six studies[13,14,16,20-22] were pooled for comparing FVC%. Pooled analysis indicated no statistically significant difference between the two groups for FVC% ($p=0.73$) (Figure 6).

Smoking Status

No significant difference was observed in the pack years ($p=0.12$) and currents smokers ($p=0.24$) among the ACOS and "pure" COPD patients (Figures 7 and 8).

Exacerbations

Six studies[13,14,17,19-21] were analysed to find ACOS patients to have higher risk in onset of frequent acute exacerbations than that of "pure" COPD patients with RR 0.41 95%CI [0.21,0.82], $p=0.01$ (Figure 9). Similarly, it also showed higher risk for ACOS patients in onset of severe exacerbations requiring hospitalization with RR 0.59 95%CI [0.42,0.81], $p=0.001$ (Figure 10). Only three studies[14,19,20] reported the number of exacerbations in a year and showed a MD of -0.26 95%CI [-0.38,-0.14] ; $p<0.0001$, which was highly significant showing more number of exacerbations for ACOS patients than "pure" COPD patients (Figure 11).

Risk of Bias Assessment

Five trials[12,14,15,18,22] had low risk of bias and rest of six studies[13,16,17,19-21] were assessed to have moderate risk. None of them were found to be high risk (Figure 12). Four studies[12,18,19,22] were found to have not matched or adjusted for confounding factors like age, gender, and pack years etc. Most of the studies recorded an unclear assessment for assessing bias on classification or departures from intended exposures. However, the overall risks of the studies were moderate to low, showing good quality of evidence. The publication bias among the included studies was assessed by

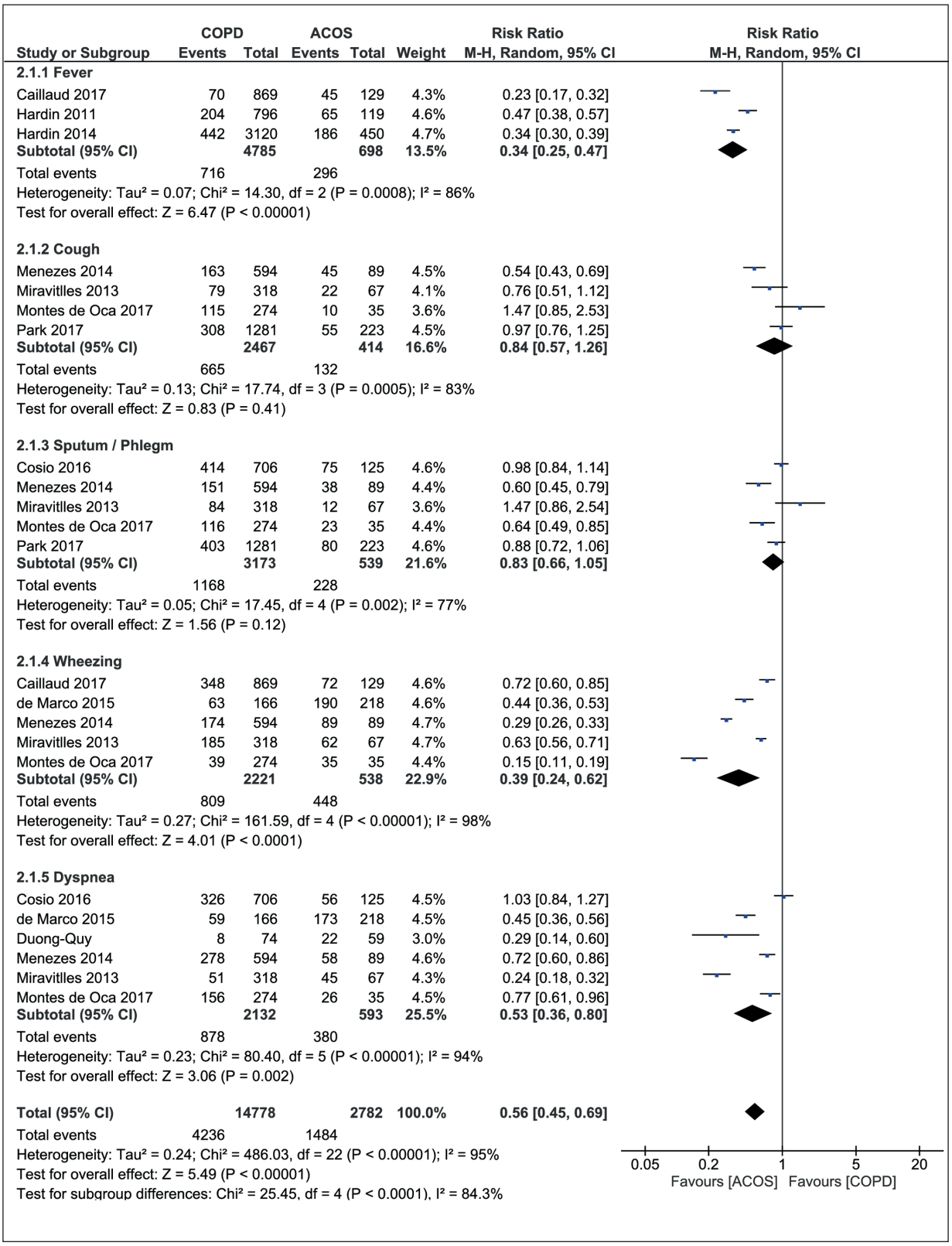

Figure 2. Forest plot showing subgroup comparison of all symptoms associated with COPD and ACOS.

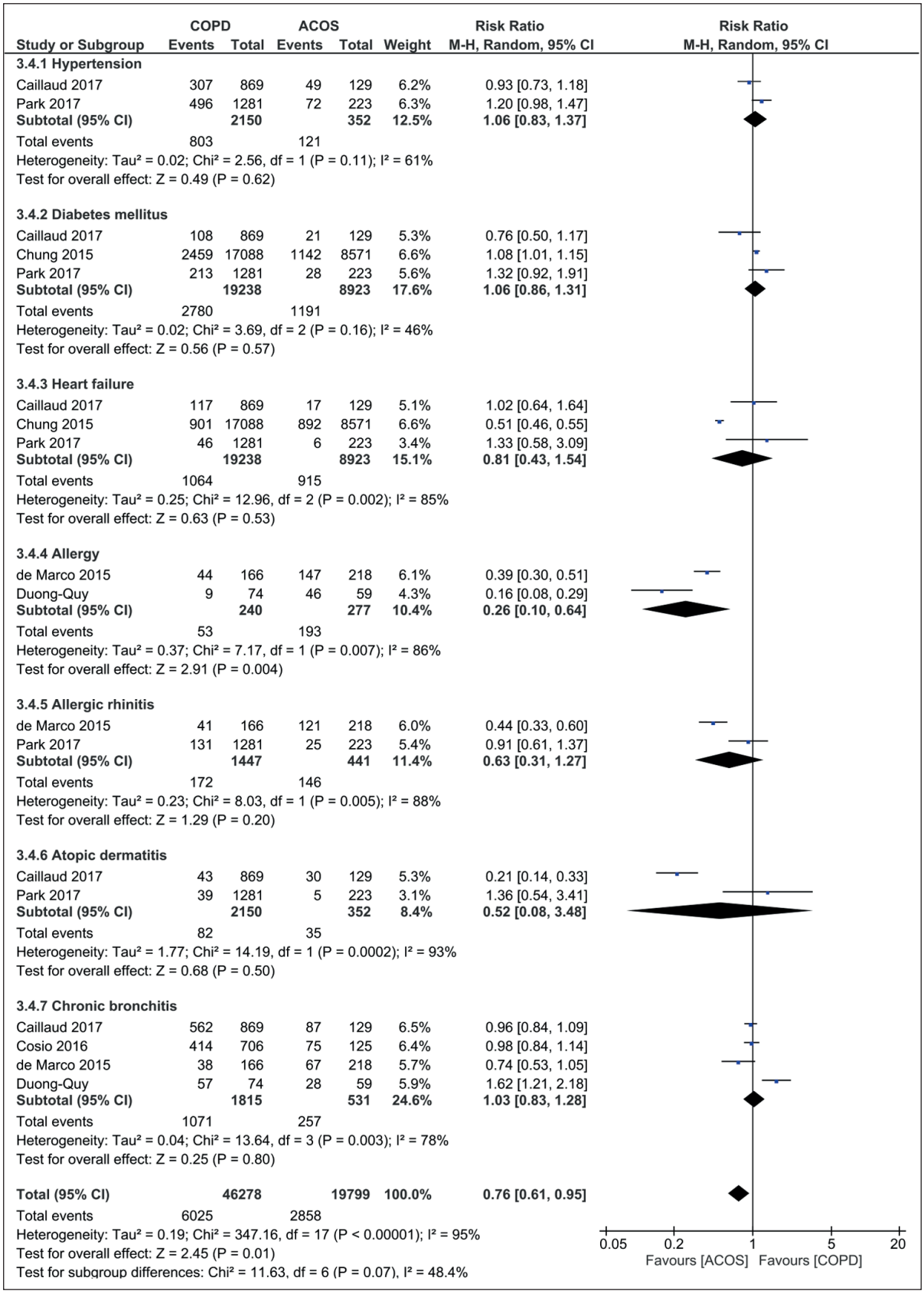

Figure 3. Forest plot showing subgroup comparison of all co-morbidities associated with COPD and ACOS.

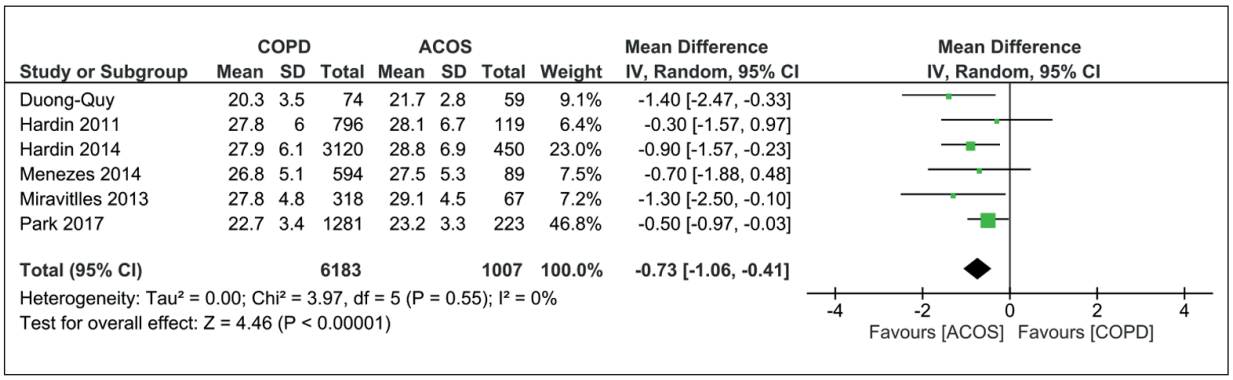

Figure 4. Forest plot showing comparison of BMI between COPD and ACOS.

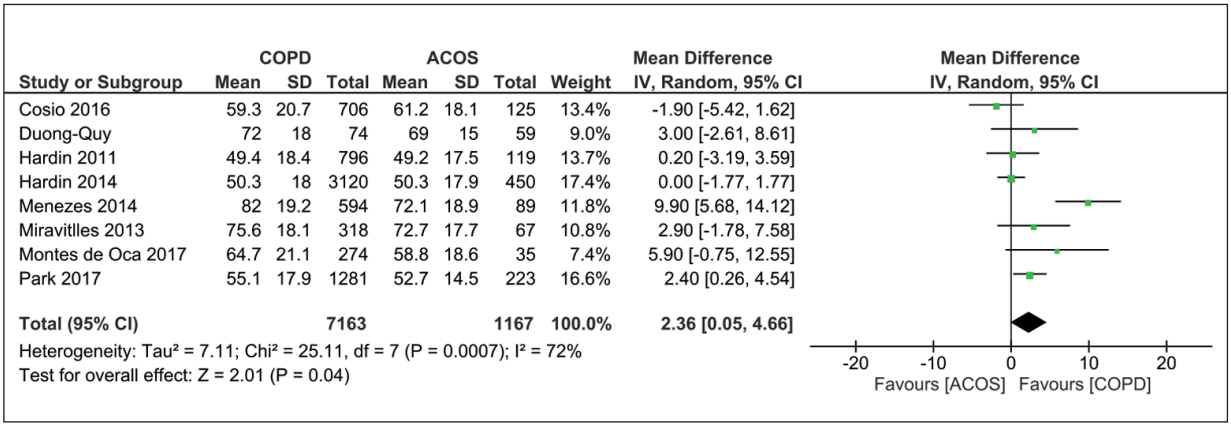

Figure 5. Forest plot showing comparison of FEV_1 % between COPD and ACOS.

visualizing funnel scatter plots of corresponding forest plots of primary outcomes and employing Egger's linear regression test. The value considered in this test was the regression of effect size on its standard error weighted by inverse variance. Considering the primary outcome FEV_1 and FVC, the bias was found to be 1.223 (95% CI =-20.119 to 10.134), p=0.338 and 0.5678 (95% CI = -2.336 to 5.335), p<0.05 suggesting low publication bias.

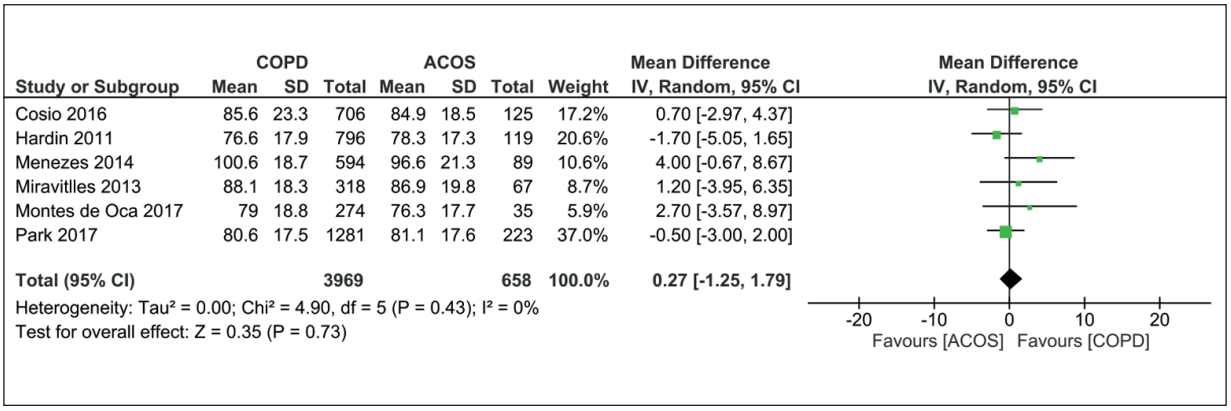

Figure 6. Forest plot showing comparison of FVC % between COPD and ACOS.

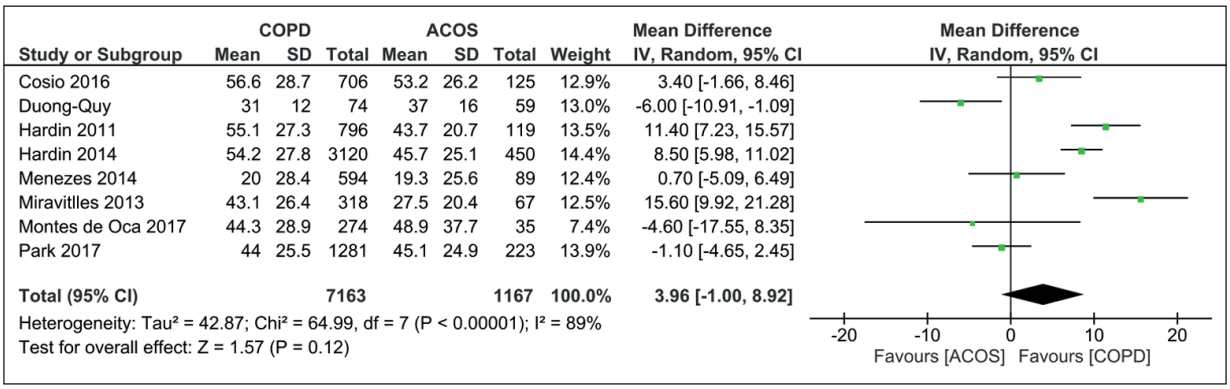

Figure 7. Forest plot showing comparison of pack years between COPD and ACOS.

Discussion

The objective of this present review was to determine whether COPD patients without a history of asthma differ in the clinical characteristics, severity of airflow limitation, and clinical outcomes compared to patients with ACOS. Eleven studies[12-22] with moderate to low risk of bias

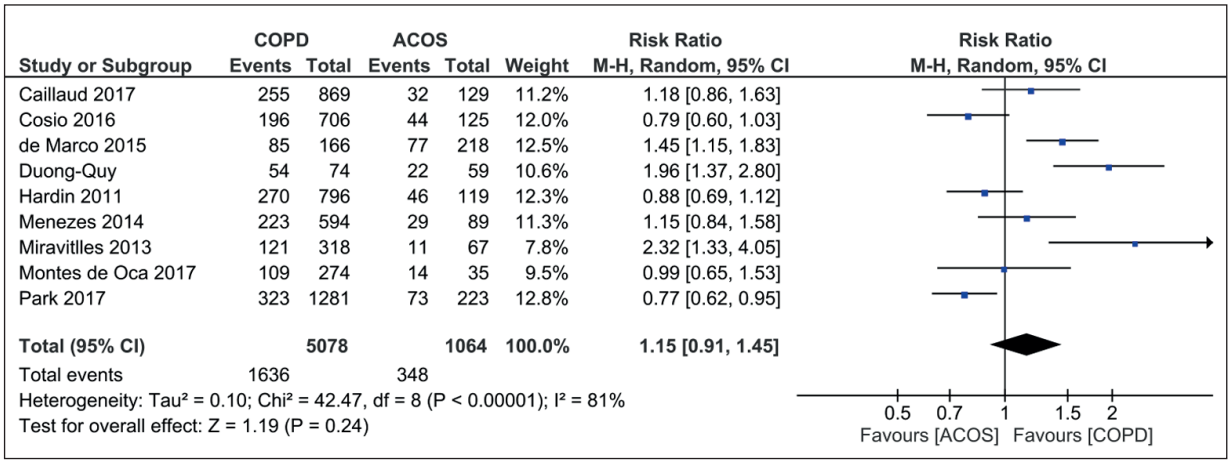

Figure 8. Forest plot showing comparison of current smokers between COPD and ACOS.

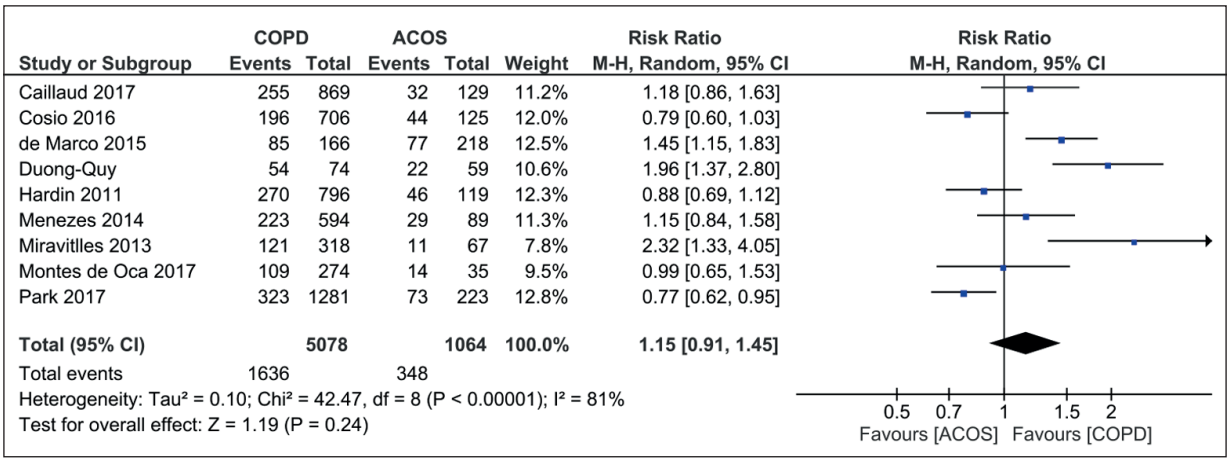

Figure 8. Forest plot showing comparison of current smokers between COPD and ACOS.

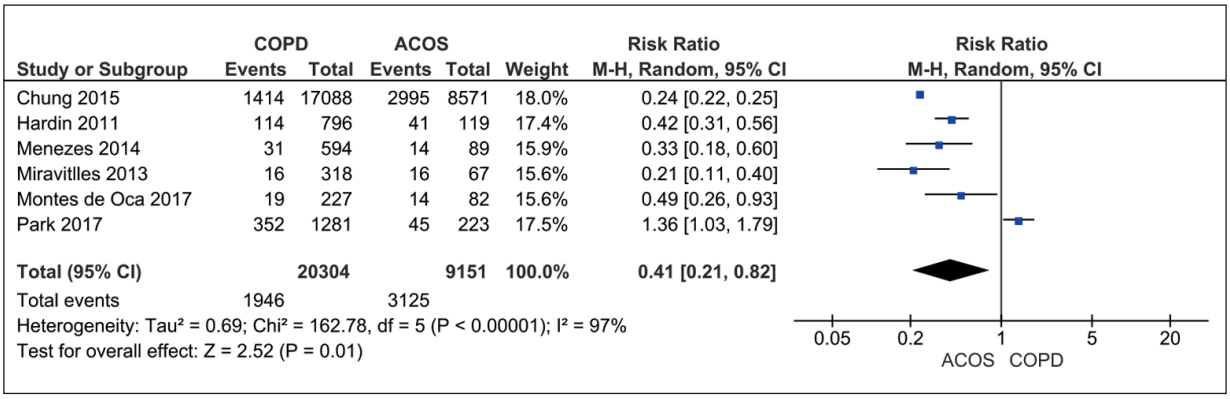

Figure 9. Forest plot showing comparison of frequent acute exacerbations between COPD and ACOS.

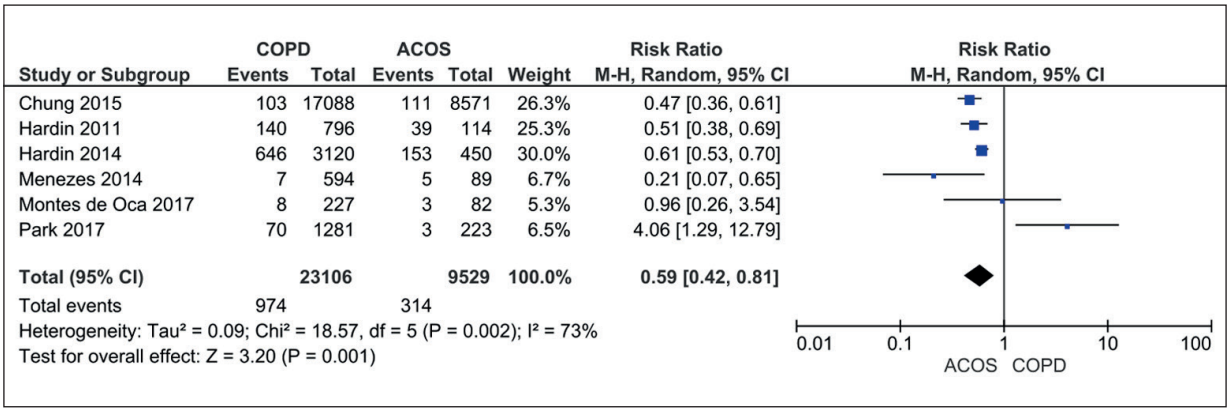

Figure 10. Forest plot showing comparison of severe exacerbations requiring hospitalization between COPD and ACOS.

were assessed in this present review to analyse the clinical characteristics and outcomes, along with some lung function parameters to assess the severity of airflow limitation. The results of the present review were quiet interesting, showing the direct possible link of higher BMI patients associated with ACOS group, showing more predilection. Moreover, the patients with ACOS presented with fever, wheezing and dyspnea more frequently than "pure" COPD patients. The lung function was rather worsened and ACOS patients showed lower FEV_1, compared to "pure" COPD patients. However, no significant difference was observed with co-morbidities associated between the two groups.

The patients suffering from ACOS were found to be associated with increased BMI; however, no difference in association of current smoking

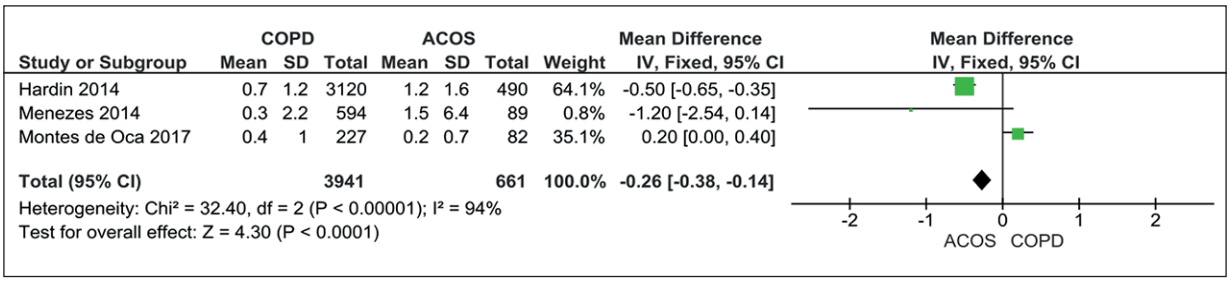

Figure 11. Forest plot showing comparison of number of exacerbations in a year between COPD and ACOS.

Number	Year	Bias due to confounding	Bias in selection of participants	Bias in classification of exposure	Bias due to departures from intended exposures	Bias due to missing data	Bias in selection of reported result	Overall risk
1	Duong-Quy S et al. 2018	Unclear	Low	Low	Low	Low	Low	**Low**
2	Park HJ et al. 2017	Low	Low	Unclear	Unclear	Low	Low	**Moderate**
3	Montes de Oca M et al. 2017	Low	Low	Low	Unclear	Low	Low	**Low**
4	Caillaud D et al. 2017	Low	Low	Low	Low	Low	Low	**Low**
5	Cosio BG et al. 2016	Low	Low	Unclear	Unclear	Low	Low	**Moderate**
6	Chung WS et al. 2015	Low	Unclear	Unclear	Low	Low	Low	**Moderate**
7	de Marco R et al. 2015	Unclear	Low	Low	Low	Low	Low	**Low**
8	Hardin M et al. 2014	Unclear	Low	Unclear	Unclear	Unclear	Low	**Moderate**
9	Menezes AMB et al. 2014	Low	Low	Unclear	Unclear	Low	Low	**Moderate**
10	Miravitlles M et al. 2013	Low	Low	Unclear	Unclear	Low	Low	**Moderate**
11	Hardin M et al. 2011	Unclear	Low	Low	Low	Low	Low	**Low**

Figure 12. Risk of bias assessment by ROBINS-E tool.

status and pack years was found between patients of "pure" COPD and ACOS. Moreover, the mean age group distributions throughout the cohorts in both groups were equal ranging from 50-80 years. These risk factors are often found to be associated with onset of obstructive lung diseases. According to a study, the prevalence of COPD was found lower among former smokers who quit ≥10 years earlier compared with current smokers[23]. It also confirmed that COPD prevalence increased with prolonged smoking duration i.e., pack years. Our meta-results correspond to this study in assessment of current smokers being more in "pure" COPD group.

FEV measures the amount of exhaled air and is assessed during the first (FEV_1), second (FEV_2), and/or third seconds (FEV_3) of the forced breath[24]. Most of the included researches in this review recorded FEV_1. On the other hand, FVC is the total amount of air exhaled during the FEV test. The ratio FEV_1/FVC measures the amount of air a person can forcefully exhale from the lungs

during spirometry[25]. The diagnosis of COPD is based on the FEV_1 value. The value less than 70% indicates airflow limitation. FEV_1 is influenced by the age, gender, and ethnicity, and is best considered as a percentage of the predicted normal value[26]. The meta-analysis was attempted to consider comparison of FEV_1 and FVC among both groups; however FEV_1/FVC was reported as ratio in few studies[19,22] and as percentages in the rest of the studies, making an attempt for meta-analysis difficult for all reported trials. The results for FEV_1 our meta-analysis showed better FEV_1 for patients with "pure" COPD than ACOS. The expiration air volume would be low for ACOS group due to more progressive airway limitation as the patients are diagnosed with previous history of asthma[27]. However, the same did not influence the difference in FVC.

Analysis of the clinical symptoms demonstrated that fever, wheezing and dyspnea to be significantly more prevalent in ACOS group than "pure" COPD. However, the observations were found to have high heterogeneity. Inclusion of a limited number of studies reporting all clinical symptoms along with the high heterogeneity prevents us from drawing strong conclusions on the difference in symptomatology between the ACOS and COPD. Also, the method of assessment of clinical symptoms varied across the studies. The fact that Cosio et al[16] only assessed dyspnea as an affirmative response to clinical questions rather than utilizing the Medical Research Council (MRC) dyspnea scale[28]. This may at least partly explain its non-significant results. The fever was seen to be likely associated in higher side for ACOS patients showing the severity of symptoms in these patients. The possible severe airway limitation due to history of asthma with worsened FEV_1 showed wheezing to be more common for ACOS patients[29].

Asthma as a condition is diagnosed at a comparably younger age and would therefore have less associated co-morbidities as compared to COPD[30]. Co-morbidities associated with COPD might be confounded with smoking frequency, and pack years. The number of current smokers being higher in the "pure" COPD compared to ACOS-group patients with in around six of the included studies[12,16,19-22] out of eight assessing the smoking status, could be a possible confounding in not showing differences for most of the clinical symptoms and characteristics. Moreover, the co-morbidities like HTN, DM, and chronic bronchitis are mostly prevalent among the elderly, and common in patients suffering from COPD[31]. In all the included studies, the age distribution of the patients was on the higher side and the diagnosis of the ACOS was made from the same COPD cohort. This may be a reason that no statistically significant difference was found in any co-morbidities between the two groups in our meta-analysis.

The diagnostic criteria for the diagnosis of ACOS across the eleven included trials (Table I) were varied. Most of the studies followed the GINA and GOLD guidelines for their diagnosis[32]. The fundamental rule employed for classifying a patient with ACOS were based on physiology, a specific inclusion criterion with a certain parameter or smoking history, or just by identifying a patient from COPD cohort with a history of asthma. This could be a possible limitation of this review. The other limitation of the review includes failure in assessment of selection of participants, which was only marked unclear during risk of bias assessment. There may also be a chance of possibly hand picking up of severely compromised patients with terminal symptoms like dyspnea and wheezing to be selected under ACOS. This may limit clear expression for clinical characteristics of ACOS.

This is the first attempt of its kind to compare the clinical characteristics of patients suffering from "pure" COPD and ACOS and demonstrate the severity of airway limitation, clinical characteristics and outcomes by meta-plots. The results expressed in these meta-analyses would definitely help clinicians judiciously identify the patients suffering from ACOS and may render improved standard of care when present with serious co-morbidities.

Conclusions

Within the limitations of this review, particularly related to heterogenous diagnostic criteria of ACOS among the included studies, the results indicate higher FEV_1 among the lung function parameters assessed and strongly associated with clinical symptoms like fever, wheezing and dyspnea, when compared to patients with "pure" COPD. The co-morbidities associated with ACOS patients are similar to that found in patients with "pure" COPD. ACOS patients also showed significantly higher onset of acute and severe exacerbations. We suggest future high-quality evidence like prospective longitudinal and cross-sectional studies with more standardized outcome measurements among ACOS patients.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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

Authors' Contribution
XZ conceived and designed the study. XZ and LZ collected the data and performed the literature search. XZ was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

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