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Hadi AR Hadi Khafaji * and Asim Cheema

Department of Adult Cardiology, Saint Michael's Hospital, Toronto University, Canada

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***Corresponding author:** Hadi AR Hadi Khafaji, Department of Adult Cardiology, Saint Michael's Hospital, Toronto University, Canada, E-mail: hadi968@hotmail.com; hadiarhadi@yahoo.com

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Review Article

Heart failure and chronic obstructive airway disease as combined comorbidities. Meta-analysis and Review

Abstract

Background: The existence of COPD and heart failure in elderly population adds additional morbidity and mortality risk than if those with only one of the two comorbidities. The aim of the current meta-analysis was to explore the effect of COPD on heart failure patient in terms of all-cause mortality, cardiac mortality and recurrent heart failure hospitalization.

Methods and results: A comprehensive search of PubMed, MEDLINE, Embase and Cochrane was conducted until August 2017. The total standardized mean difference, with 95% (CI), was estimated for fixed and random effects models to present "pooled effect" for continuous outcomes (mean ± standard deviation or median ± interquartile range) & categorical outcomes (Odds risk OR). Statistical heterogeneity among studies was assessed with Cochran's Q test and the I^2 statistic. A total of 15 observational studies were analyzed. COPD and heart failure patients have higher: short term (in hospital, 1-3 months) (*P=0.009, 0.0006* respectively), long term all-cause mortality (1& 2-5 years) (*P=0.00001, 0.04* respectively), long term cardiac mortality (P=0.02) and more frequent hospitalization for heart failure (P=0.002). GOLD stage II-IV COPD had higher long-term all-cause mortality (P<0.0001) but not long-term cardiac mortality (P=NS). Beta blockers treatments appear to decrease all-cause mortality in COPD with heart failure (P <0.0001).

Conclusion: Heart failure patients with COPD have frequent heart failure hospitalization, higher long-term cardiac mortality, short- and long-term all-cause mortality that is more evident in advanced stage of COPD. Beta blockers use appear to be safe and decrease mortality in these patients.

Introduction

The co-occurrence of Heart Failure (HF) and Chronic Obstructive Pulmonary Disease (COPD) that share common clinical presentation and risk factors is common in the elderly population, such overlap makes the diagnosis of COPD in HF and vice versa challenging [1,2].

The existence of these clinical syndromes in elderly population adds additional morbidity and mortality risk than if those with only one of these diseases [3]. Furthermore, it will add dilemma to recognition of each when these disorders exist and leads to over diagnosis of heart failure in COPD patient or under diagnosis of COPD in heart failure patients [4]. Treatment interaction, the more complex issue is that the treatment of one may adversely affect the other [5], as bronchodilator may cause tachycardia and may precipitate heart failure furthermore beta blockers and diuretics may adversely affect COPD.

The above 2 clinical presentation has not analyzed systematically, with the presence of only observational studies that supply both cardiologist and internist with inconsistent information. We choose to systematically analyze the available research article, so we can reach final conclusion about the morbidity and mortality interaction between these conditions when heart failure patient with COPD presented with acute exacerbation.

The aim of the current meta-analysis was to explore the effect of COPD on heart failure patient in term of short- and long-term all-cause mortality and cardiac mortality and the effect of COPD on recurrent heart failure hospitalization.

Methods

Search strategy & data collection

A comprehensive search of PubMed, MEDLINE, Embase and Cochrane was conducted until August 2017, using combination of keywords; heart failure, COPD, all-cause mortality, cardiac mortality recurrent heart failure hospitalization. Along with available studies electronic search was done for abstracts, conference proceedings, unpublished and observational

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studies. References cited in the studies were reviewed for additional information. The flow diagram shown in Figure 1, the search strategy yields 15 observational studies that met the study criteria.

Criteria for study selection and qualitative assessment

The inclusion and exclusion criteria for the studies in the current meta-analysis are shown in Figure 2. Data regarding publication status, study design, patient-related characteristics, treatment regimens, outcome methods and results was extracted according to the standard protocol independently by 2 individual researchers. Any conflicts or incongruities were resolved by mutual agreement.

Clinical end points studied

The clinical endpoints that were analyzed in this meta-analysis are short- and long-term all-cause mortality, early and late cardiac mortality in all COPD patient and in subgroups as per COPD GOLD stages, recurrent heart failure hospitalization and the effect of B blocker treatment on all-cause mortality.

Statistical analysis

Review manager 5.3 (The Nordic Cochrane Centre, The Cochran Collaboration, Copenhagen, Denmark) was used for the analysis. The total standardized mean difference (SMD), with 95% confidence interval (CI), was estimated for fixed and random effects models to present "pooled effect" for continuous outcomes (mean ± standard deviation or median ± interquartile range) & categorical outcomes (Odds risk OR). Statistical heterogeneity among studies was assessed with Cochran's Q test and the I2 statistic. The studies were considered statistical heterogeneous if p <0.05 and I^2 ≥ 50% [6,7]. A random effect model was used for analysis to determine the heterogeneity, and fixed effect model was used in case of homogeneity. Statistical significance value was set at 0.05. Processing of the data and reporting of results were performed according to accepted principles of systemic review and meta-analysis. In order to assess potential publication bias, or "small-study effect", we used the funnel plot, which provides a good visual evaluation of sampling bias.

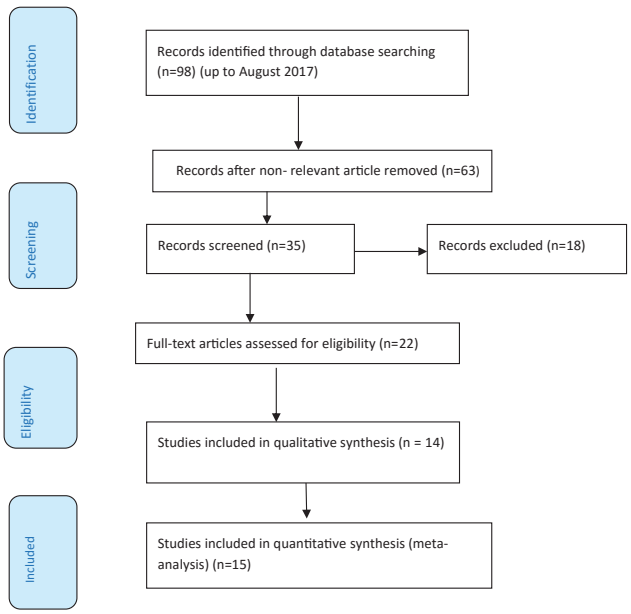

Figure 1: Flow diagram of study selection process.

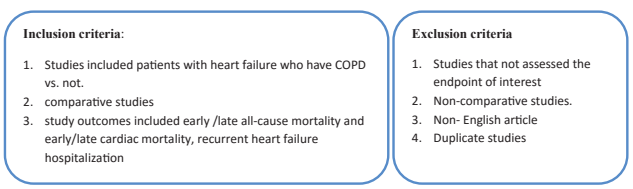

Figure 2: Inclusion/Exclusion Criteria.

Results

A total of 15 observational studies [8-22], were identified, the baseline clinical characteristics of the patients included are shown in Table 1, Males were the predominant gender in these studies with the mean age shown being above 65 years of age with similar rate of CAD hypertension and dyslipidemia.

Patients with COPD and heart failure have higher short term (in-hospital, 1-3 months) (*P=0.009, 0.0006* respectively, and long-term mortality (1 year, 2-5 years) (*P=0.00001* for both) with moderate heterogeneity between the included studies) Figure 3.

The short-term cardiac mortality appears to be non-significantly (*P=0.07*) higher in COPD patients while the long-term cardiac mortality appears to be significantly higher (*P=0.02*) in COPD patient with heart failure with moderate heterogeneity between the included studies Figure 4.

COPD patient with heart failure have more frequent hospitalization for heart failure (*P=0.002*) with mild heterogeneity between the included studies Figure 5.

The heterogeneity of all the variable analyzed is shown in Funnel plots in Figure 6.

Patient with advanced stage [11,13,19], of COPD i.e. GOLD stage II-IV when compared to GOLD 0-I and non-COPD had higher long-term all-cause mortality (P<*0.0001*) [11,19], but not long-term cardiac mortality (P=NS). Figure 7 A,B.

Beta blockers treatments appear to decrease all-cause mortality [8,10,11], in COPD with heart failure as it does with non-COPD with heart failure (P <0.0001) Figure 7 C.

The multivariate analysis of the all-cause mortality predictors was shown in Table 2. The age, diabetes, COPD stage, low ejection fraction, and impaired renal function were the most frequent predictors in the included studies.

Discussion

Heart failure and COPD as combined comorbidities presents a great diagnostics and therapeutic challenges, because both conditions share features such as; presentation in advanced age, common symptoms of dyspnea and smoking as a risk

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Table 1: Baseline clinical characteristics of the included studies.

Author	Study design/ period	Patients COPD vs. Non COPD	Age COPD vs. Non COPD	Male COPD vs. Non COPD	DM COPD vs. No COPD	Hypertension COPD vs. Non COPD	Dyslipidemia COPD vs. Non COPD	History of CAD COPD vs. Non COPD	Smoking History COPD vs. Non COPD
Rothnie KJ 2015 / UK	Retrospective Observational 2003-2013	34019 vs. 266142	> 60 years 77% vs. 66%	62% vs. 67%	16 % vs. 15%	45% vs. 44.3%	27% vs. 28%	22% vs. 16%	43% vs. 34%
Polikutina OM 2015/Russia	Retrospective study from Jan – Dec 2008	65 vs. 464	67 (56 -75) vs. 62.5 (55 -72)	75% vs. 63%	14% vs. 20%	NR	NR	34% vs. 26%	54% vs. 41%
Andell P 2014 / Sweden	Retrospective analysis SWEDEHEART registry 2005-2010	4867 vs. 76324	75± 9 vs. 70± 13	54%vs. 64%	20% vs. 19%	32% vs. 20%	NR	14% vs. 8%	33% vs. 22%
Campo G 2013 / Italy	Retrospective analysis of REAL registry 2003-2009	2032 vs. 9086	70 ±12 vs. 65±13	66% vs. 74%	22% vs. 21%	70% vs. 61%	47 % vs. 48 %	17% vs. 14%	24% vs. 27%
Lazzeri C 2013/ / Italy	Prospective 2005-2009	71 vs. 747	74 (69–81) vs. 67 (58–76)	66% vs. 73%	34% vs. 27 %	63% vs. 53%	NR	21% vs. 13%	76% vs. 62%
Sung PH 2013/ Taiwan	Prospective observational 2002-2011	124 vs. 1430	68.5 ± 9.9 vs. 60.9 ± 12.6	85% vs. 81%	32% vs. 36%	55% vs. 56%	39% vs. 42%	4.8% vs. 4.4%	37% vs. 35%
Enriquez JR 2013 / USA	Retrospective analysis of ACTION registry-GWTG 2008-2010	22624 vs. 136266	68 vs. 63	58% vs. 66%	39% vs. 29%	82% vs. 71%	67% vs. 59%	36% vs. 23%	46% vs. 34%
Stefan MS 2012 / USA	Retrospective analysis WHA study	1080 vs. 5210	74 vs.70	52% vs. 57 %	37% vs. 32%	73% vs. 69%	NR	NR	27% vs. 20%
Quint JK 2011 / UK*	Retrospective Observational 2003-2008 MINAP and GPRD records	968 vs. 7097	NR	NR	NR	NR	NR	NR	NR
Hadi A 2010 6 Middle Eastern countries	Retrospective analysis of prospectively collected data GulfRACE registry 2007	434 vs. 7733	64 vs. 55	NR	48% vs. 40%	64% vs. 49%	39% vs 31%	34.8% vs. 23.8%	39% vs. 36%
Dziewierz A 2010/ Poland	Retrospective analysis of prospectively collected data Krakow ACS registry 2005 & 2006	81 vs. 633	71.8 ± 10.7 vs. 67.9 ± 12.9	62% vs. 60%	23% vs.23%	76% vs. 71%	37% vs. 47%	35% vs. 29%	41% vs. 32%
Bursi F 2010 /USA	Retrospective study Rochester Epidemiology Project 1979-2007	415 vs. 3023	73 ± 11 vs. 67 ± 15	59% vs. 57%	23% vs. 21%	68% vs. 57%	43% vs. 39%	NR	35% vs. 26%
Wakabayashi K 2010/USA	Prospective study 1999-2008	365 vs. 2884	66.2± 13.6 vs. 60.7± 13.8	59% vs. 68%	36% vs. 29%	87% vs. 80%	85% vs. 83%	NR	40% vs. 37%
Hawkins NM 2009 /Multinational	Retrospective analysis of VALIANT trial in 24 countries	1258 vs. 13445	68.1 ± 9.9 vs. 64.5 ± 11.9	71% vs. 68%	26% vs. 23%	58% vs. 55%	36% vs. 29%	40% vs. 27%	42% vs. 31%
Rha SW 2009 /Korea*	Retrospective analysis of KAMIR registry 2005-2007	192 vs. 192	71.74 ± 9.97 vs. 63.04 ± 12.66	NR	NR	NR	NR	NR	28.4% vs. 14.8%
Salisbury AC 2007 / USA	Retrospective analysis PREMIER registry 2003-2004	387 vs. 2094	64.5 ± 12.4 vs. 60.1 ± 13	62 % vs. 68%	37% vs. 27%	68% vs. 63%	50% vs. 49%	30% vs. 20%	38% vs. 33%
Kjoller K 2003 /Denmark	Retrospective analysis of TRACE study.1990-1992	765 vs. 5904	70.5 vs. 68.2	68% vs. 67%	11% vs. 11%	18% vs. 23%	NR	25% vs. 23%	60% vs. 50%
Behar S 1992/ Israel	Retrospective analysis of SPRINT study 1981-1983	406 vs. 5433	66.8 ± 9.7 vs. 62.7± 10.8	79% vs. 73%	16% vs. 21%	37% vs. 40%	NR	29% vs. 24%	44% vs. 31%

CAD; Coronary Artery Disease, COPD; Chronic Obstructive Pulmonary Disease, DM; Diabetes Mellitus, NR; Not Registered. * : This study published in abstract form, ACTION; Acute Coronary Treatment and Intervention Outcomes Network, GulfRACE; Gulf Registry of Acute Coronary Events, Krakow Registry ACS; Acute Coronary Syndromes, KAMIR; Korea Acute Myocardial Infarction Registry, MINAP; Myocardial Ischemia National Audit Project, PREMIER : Prospective Registry Evaluating Myocardial Infarction: Event and Recovery , REAL : REgistro AngioPlastiche dell'Emilia Romagna, SWEDENHEART: Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies, SPRINT : Secondary Prevention Re-infarction Israeli Nifidipine Trial, TRACE : TRAndolapril Cardiac Evaluation, VALIANT; VALsartan In Acute myocardial infarction Trial, WHA; Worchester Heart Attack study.

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Table 2: Multivariate analysis of the all cause death predictors in the included studies.

Study	Mortality	Variable	Adjusted OR/ HR	95% C.I.	P value
Khafaji H 2015	In hospital	STEMI	OR 2.25	1.57 – 3.23	0.001
		VHD	OR 1.59	1.12 – 2.25	0.009
		Stroke	OR 1.71	1.13 – 2.60	0.01
	Long term	Age	OR 1.04	1.03 – 1.05	0.001
		CKD	OR 1.53	1.19 – 1.96	0.001
		LVEF≥35	OR 0.74	0.60 – 0.91	0.005
		LVEF <35	OR 1.35	1.10 – 1.67	0.005
Yoshihisa A 2014	Long term	Age	HR 1.067	1.023–1.114	0.003
		Anemia	HR 2.689	1.064–6.794	0.037
		COPD GOLD II	HR 2.645	1.012–7.632	0.036
Arnaudis B 2012	Long term	COPD GOLD I	HR2.274	(1.218–4.245)	0.010
		COPD GOLD II	HR 2.813	(1.029–7.687)	0.044
		ICD/ CRT	HR1.767	(0.997–3.133)	0.051
De Blois J 2010	Long term	Age	HR 1.022	1.015-1.028	<0.001
		CKD	HR 1.003	1.002-1.004	<0.001
		COPD GOLD II	HR 1.188	1.015-1.391	0.03
		NYHA Class III/IV	HR 1.464	1.286-1.667	<0.001
		Diabetes	HR 1.389	1.204-1.601	<0.001
Lainscak M 2009	Long term	COPD	HR1.38	(1.04–1.83)	
Rusinaru D 2008	Long term	LVEF≥35	HR 1.74	1.22–2.49	0.002
		LVEF <35	HR 1.48	1.03–2.14	0.035
Staszewsky L 2007	Long term	age	HR 1.38	(1.14-1.67)	0.0008
		Male			
		CAD			
		Diabetes			
		LVEF	HR1.25	(1.03-1.52)	0.0215
Macchia A 2007	Long term	Age	HR1.06	(1.04–1.08)	0.0001
		Diabetes	HR 1.44	(1.12–1.84)	0.005
		PVD	HR 1.74	(1.19–2.55)	0.004
		Stroke	HR1.48	(1.03–2.14)	0.036
		COPD	HR1.42	(1.09–1.86)	0.010

factor, in addition to that, treatment of one condition may affects the other [1]. Unfortunately, this issue has not been studied systematically in randomized stream and even forgotten in major clinical trials. To the best of our knowledge this the first meta-analysis that explored the impact of COPD in heart failure patient. The absence of randomized trial makes the final result biased in many aspects. As we can see from the current analysis, few conclusions have been withdrawn:

***First*:** The presence of COPD adds an increased risk of both short and long term all-cause and long-term cardiac mortality in period of the follow up of the included studies which appear to be satisfactory in most of the studies that reach up to 5 years.

Second: Heart failure exacerbation on the background of COPD may be explained by many mechanisms; the low-grade inflammation, underuse of β-blockers, and adverse CV effects of bronchodilators [14,15]. The increased hospitalization rates in patients with HF and COPD may also be related to improvement in HF prognosis with contemporary therapies i.e. increase heart failure population. Alternatively, the improved survival of patients with HF and COPD, there is a larger population at risk for hospitalization.

Third: The severity of COPD appears to be directly proportional to the heart failure all-cause mortality and cardiac mortality and it appear that heart failure patient with advanced COPD i.e. GOLD stage ≥ II die from non-cardiac causes that related to associated comorbidities like diabetes and renal failure and advanced age as shown the mortality predictors in Table 2, though the mortality predictors were assessed only in few studies.

Fourth: Treatment of HF as per heart failure guidelines, necessitate the addition of beta blockers even in COPD patients, because there is no evidence that HF should be treated differently in patients with this comorbidity. B-Blockers are strongly recommended in all patients with systolic HF, including those with coexistent COPD [23-25], with cardio-selective b-blockers as the default [26,27]. The result from the current analysis showed that treatment with B blocker had mortality benefit though this issue has been assessed in 3 studies [8,10,11], only, but still it gives the preliminary idea that beta blockers are safe in the patients subset, though we are unable to analyze the beta blocker selectivity as this issue has not been investigated in the included studies and despite concerns regarding β blockers in patients with HF with COPD, there was no evidence that β-blocker selectivity was associated with differences in outcomes for patients with HF with COPD versus those without as in OPTIMIZE-HF registry sub-analysis [28]. The available evidence suggests that COPD patients treated with cardio selective beta-blockers has no significant short-term impact on airway function or COPD exacerbations. However, the trials were small and of short duration. Given their substantiated benefit in conditions such as heart failure,

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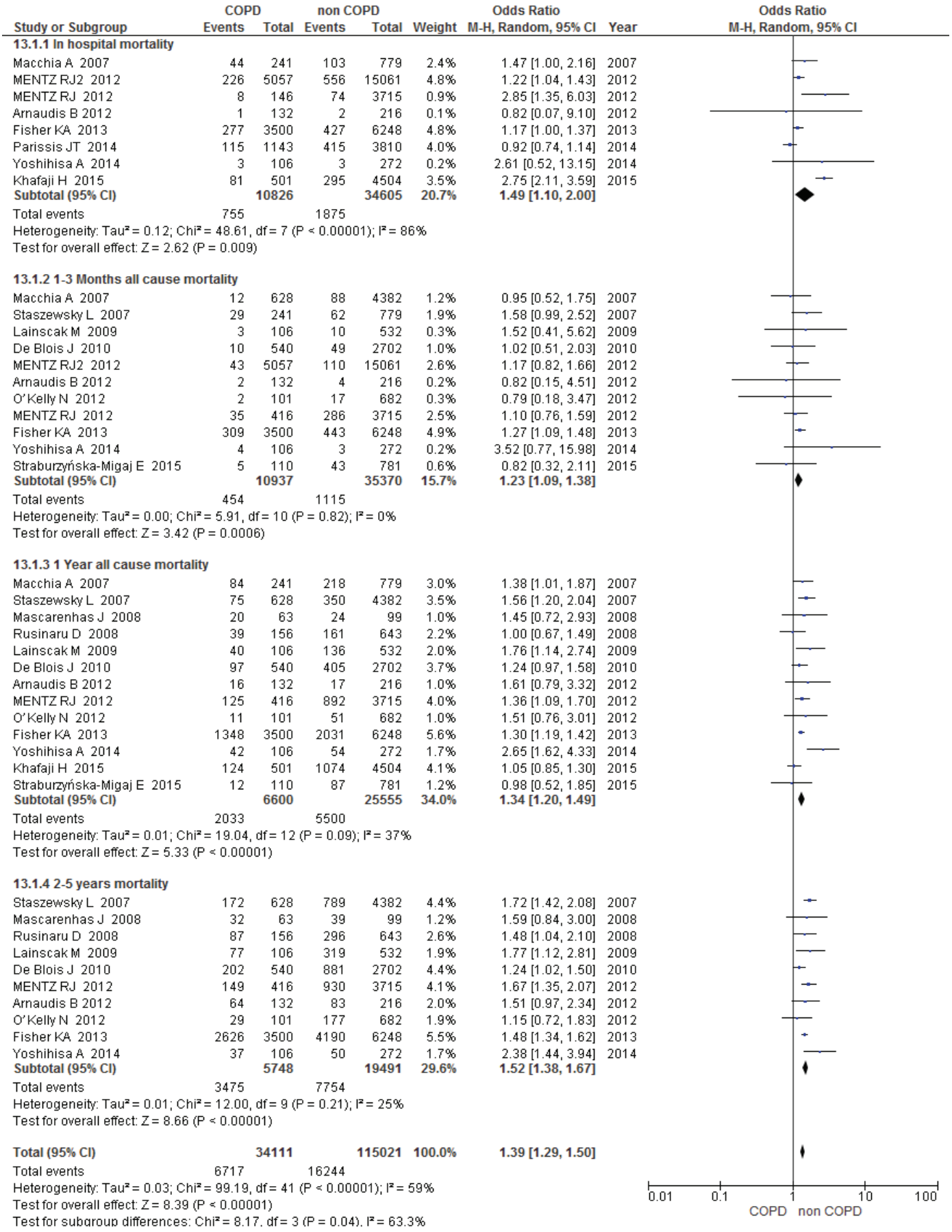

Figure 3: Forest plot of short and long term all-cause mortality in the included studies.

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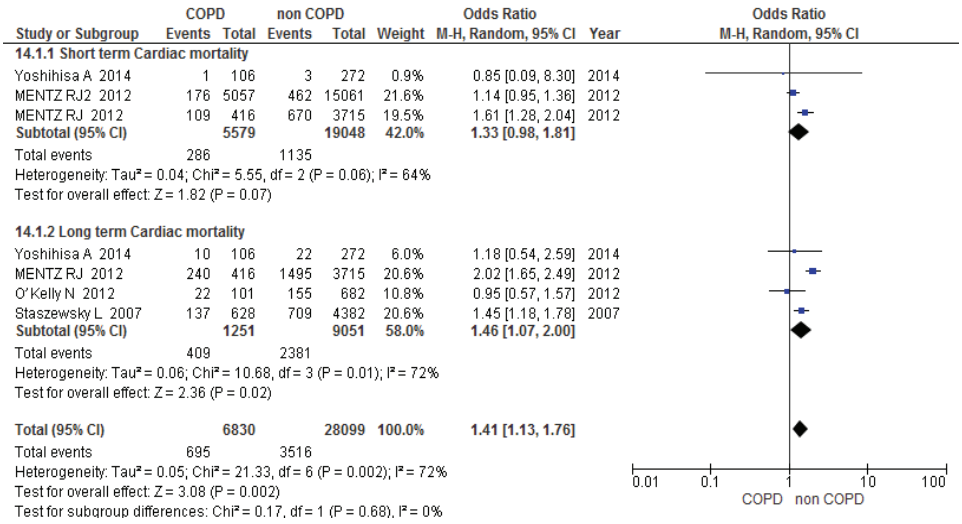

Figure 4: Forest plot of short and long term cardiac mortality in the included studies.

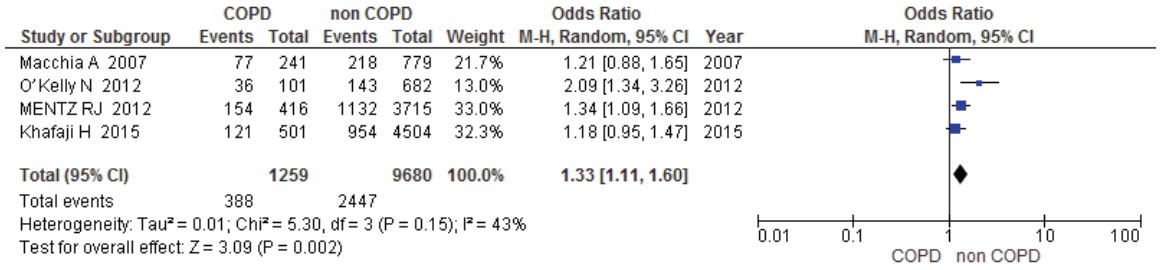

Figure 5: Forest plot for recurrent heart failure hospitalization in the included studies.

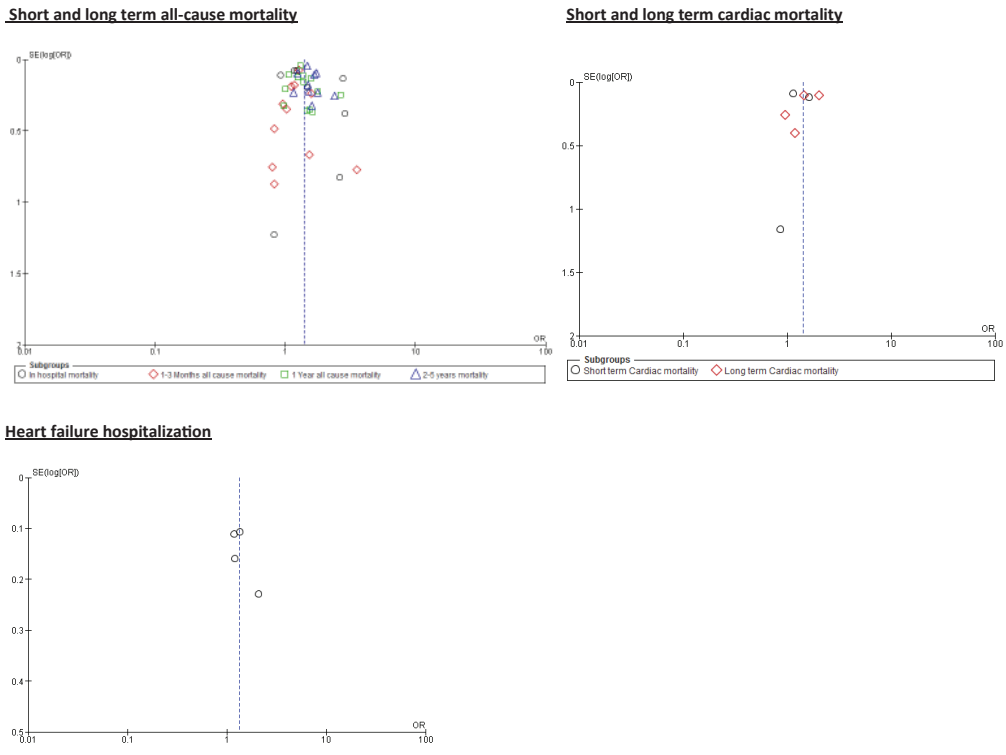

Figure 6: Funnel plots.

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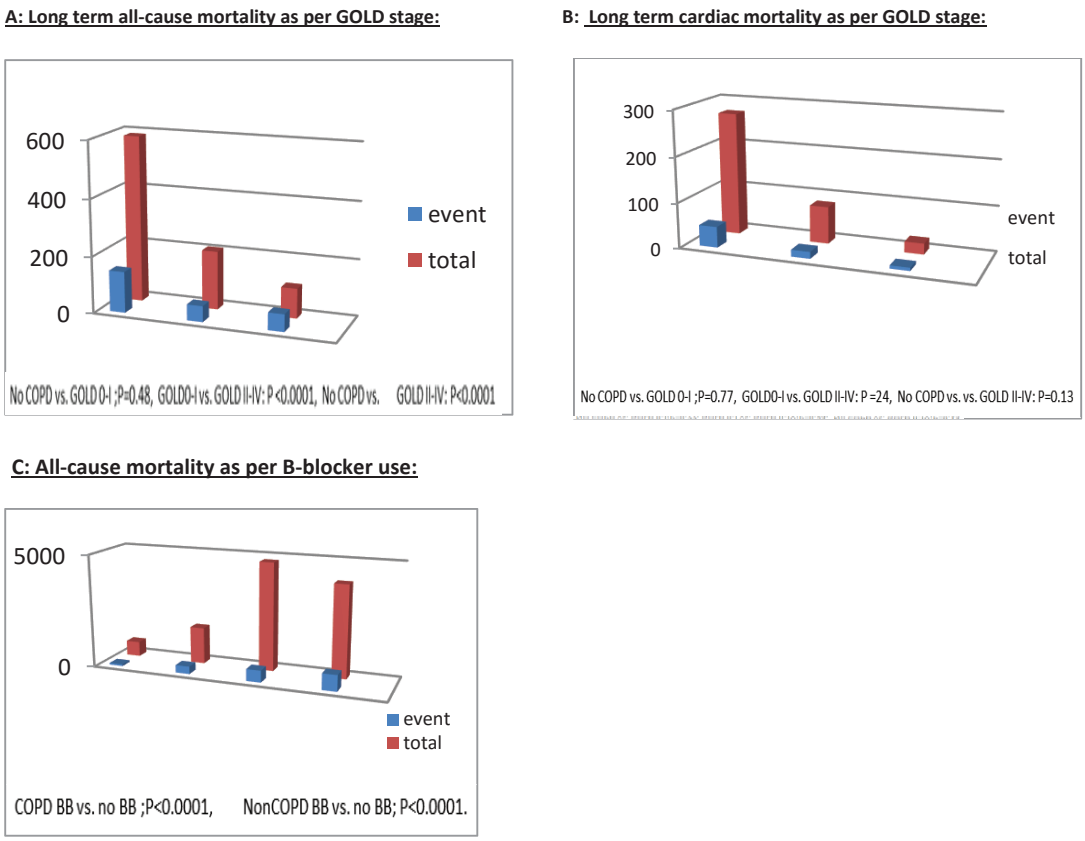

Figure 7: Funnel plots.

coronary artery disease and hypertension, cardio selective beta-blockers should be considered for patients with COPD, but administered with careful monitoring since data concerning long term administration and their effects during exacerbations is not available on wide scale.

Fifth: The mortality predictors in this patient's population are variable but there are common predictors as shown in Table 1, these predictors appear to be the combination of mortality risk factors of COPD and HF, such as age, diabetes, chronic kidney disease, low ejection fraction, in addition to well-known other factors like liver disease, low systolic blood pressure, lower serum sodium, lower admission weight, and depression. The use of statins and beta-blockers at discharge was associated with significantly decreased mortality as shown in retrospective analysis of OPTIMIZE-HF registry in patient without COPD [29].

Strength and limitations

The strength of this research is that it is the first meta-analysis done in this field of heart failure patients with COPD who presented acutely or chronically. The current meta-analysis result was extracted from observational studies most of which are retrospective analysis of major heart failure registries that can result in publication bias. In addition, the definition and staging of COPD was not available in many studies and that patient were considered to have COPD as per medical record and no spirometry done in these studies (only one prospective study included), the low number of patients included explore the need for large study that can achieve statistical power. The conclusion regarding B blockers in heat failure patient with COPD need to be interpreted carefully as this include relatively small number of patients from few retrospective studies though one of which was retrospective analysis of major heart failure registry, again necessitate the need for a large randomized controlled trial in this field.

Conclusion

Heart failure patient with COPD appear to have more frequent heart failure hospitalization, higher long-term cardiac mortality, short- and long-term all-cause mortality and this more apparent in advanced stages of COPD reflect the synergistic effect of both comorbidities. Beta blockers use appear to be safe as it decreases mortality in these patients.

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