International Journal of Research and Review
Volume 11; Issue: 10; October 2024
Website: www.ijrrjournal.com
Review Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Prevalence of Chronic Obstructive Pulmonary Disease Exacerbation with Heart Failure Comorbid: A Systematic Review and Meta-Analysis

La Ode Muhammad Nazar Ghazali Yusuf[1], Muhammad Ilyas[1], Faisal Yunus[1], Nirwana Fitriani Walenna[2], Edward Pandu Wiriansyah[1], Sitti Nurisyah[1], Erwin Arief[1]

[1]Pulmonology and Respiratory Medicine Department, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
[2]Anatomy Department, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

Corresponding Author: La Ode Muhammad Nazar Ghazali Yusuf

DOI: https://doi.org/10.52403/ijrr.20241014

ABSTRACT

Heart Failure (HF) is one of the comorbidities in Chronic Obstructive Pulmonary Disease (COPD), associated with the incidence of respiratory tract infections which is a risk factor for COPD exacerbations. Eleven studies conducted in the meta-analysis. Pooled prevalence of COPD exacerbations with HF comorbidity was 29,43 % (95%CI:17,68%- 42,92%) and statistical heterogenity among the eleven studies was significant (I^2 = 99,95%. Q = 191,96 p=<0,001). Eight studies were based in Europe, two studies in Americas and one study in Asia. Prevalence of COPD exacerbations with HF comorbidity based on WHO region subgroup analysis found European region 31,44% (95%CI: 17,87%-46,58%), America's region 32,92% (95%CI: 12,61%-55,73%) and the Western Pacific region 10,86% (95%CI:10,03%- 13,21%) with significant statistical heterogeneity (I^2 = 99,94%, Q = 191,96, p= <0,001). The age of exacerbating COPD patients with comorbid heart failure was above 70 years and there were differences in gender characteristics based on the two studies that reported. Statins reduce the incidence of COPD exacerbations. Differences in the risk of COPD exacerbation receiving Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker (ACEi/ARB) therapy. The most common comorbid cardiovascular disease apart from heart failure are atrial fibrillation and ischemic heart disease. As a conclusion, the pooled prevalence of COPD exacerbations with heart failure comorbid in this systematic review and meta-analysis was 29.43% (95% CI:17.68%-42.92%).

Keywords: COPD exacerbation, Heart Failure, prevalence

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a pulmonary disease that can be characterized by persistent airflow resistance and is generally progressive, associated with excessive chronic inflammatory responses in the airways and pulmonary parenchyma due to harmful gases or particles. The characteristics of airflow barriers in COPD are caused by a combination of small airway obstruction (bronchioloitis obstruction) and parenchymal damage (emphysema) that varies in each individual due to chronic inflammation that causes loss of connection of the alveoli and small airways as well as a decrease in the elasticity of pulmonary recoil.[1]

The Asia Pacific COPD Round Table Group

estimated the number of moderate to severe COPD patients in Asia Pacific countries in 2006 to reach 56.6 million people with a prevalence of 6.3%.[2,3] Among the comorbidity conditions seen in people with chronic obstructive pulmonary disease (COPD), cardiovascular disease (PKV) is generally considered the most major comorbidities, such as, heart failure, ischemic heart disease, atrial fibrillation and hypertension.[2,4] Increased awareness of the role of other risk factors for COPD, particularly those affecting its basic history, has led to the realization that COPD and PKV have a closer relationship mechanically than previously thought. [4]

The diagnosis and management of heart failure was significantly delayed in patients with COPD compared to patients without COPD. [5] A tudi investigated the effects of cardiovascular drugs in patients with COPD with respect to survival, with mixed results, however, studies examining the effects on the risk of EXACERBATION COPD were less common. One observational study found that the use of *angiotensin receptor blockers* (ARBs) was associated with fewer exacerbation events than the use of *ACE inhibitors* (ACEi).[6]

A systematic review of BB use on exacerbation risk concluded that most evidence supports no change or reduction in the risk of exacerbation in BB users compared to non-users in patients with COPD with, or at risk of, cardiovascular disease. The long-term effect of heart failure drugs on the risk of exacerbation in patients with COPD with heart failure has not been assessed.[7] Therefore, this article aims to provide an overview of the prevalence of copd exacerbation with comorbid heart failure based on a systematic review and meta-analysis approach.

METHODS

Identify Research Questions

The research questions asked in this systematic review use *the Population in Question, Exposure, Comparator* and *Outcome methods. Population* is COPD exacerbation, *Exposure* is Heart Failure, *Comparator* is absent. *Outcome* is the prevalence of COPD exacerbation with comorbid heart failure.

Protocol Drafting

Preparation of a systematic review protocol using the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) method which will be registered in the *Prospective Register of Systematic Reviews* (PROSPERO).

Search Strategy

Search for research articles on *the PubMed* electronic database that have been published from 2015 to the present that use English using a special combination *of Medical subject Heading* (MeSH Term) and a series of keywords including *COPD*, exacerbation, *Heart failure*, *prevalence.* MeSH Term will be combined using the *Boolean logic Operator*: AND, OR.

Data Extraction

Data extraction using *Microsoft Exel* containing general information formats (first author, year and place), design studies, total samples (exacerbation COPD and exacerbation COPD with comorbid heart failure), subgroup analysis (study time period and WHO region) age, sex, smoking, infection, COPD degrees, ACEi therapy, ARB therapy, Beta Bloker therapy, statin therapy and comorbid cardiovascular disease if data are available.

Assessment of Article Quality and Risk of Bias

Bias risk assessment of research journals and articles using *the Newcastle Ottawa Sc*ale (NOS) criteria for cohort studies.

Study population

The study population was adults aged ≥ 35 who were diagnosed with exacerbated COPD with comorbid Heart Failure.

Inclusion Criteria and Research Exclusion

Inclusion Criteria: Cohort study research

design (retrospective or prospective and both) The year of literature publication after 2015 to 2021, Articles containing the keywords *COPD, exacerbation* and *Heart Failure,* Articles or journals in the form of *full paper* that can be accessed in full, the article reported *prevalence rate* of COPD exacerbation with comorbid heart failure. When not mentioned, data is available that allows to calculate *the prevalence rate*, The study population was patients with COPD and Heart failure. Exclusion Criteria: Articles or journals with research designs other than cohort studies.

Data Synthesis and Analysis

The results of the study selection were combined and analyzed using MetaXL software as per the statistical guidelines in *The Cochrane Handbook for Systematic Reviews of Interventions*. The risk of bias between studies is illustrated by a *plot funnel diagram.* The results of the meta-analysis of the selected studies are presented with *a forest plot.*

Data presentation

The first reviewer (NG) performs a systematic article search using the search strategy step on PubMed's electronic data base. Furthermore, the second reviewer (NW) reviews the references of the selected articles to identify relevance to this systematic review that the search strategy may have missed. The two reviewers (NG and NW) then classified the article as included and excluded based on inclusion and exclusion criteria. Articles categorized as included were included in the review and assessed for the quality of the study using the New Castle Ottawa Scale (NOS) by both reviewers (NG and NW). Articles categorized as excluded by reviewers are subsequently excluded. The full manuscript for all titles that have been assessed for study quality is then downloaded for further review with meta-analysis. The flow in accordance with PRISMA 2020 is presented in figure 1.

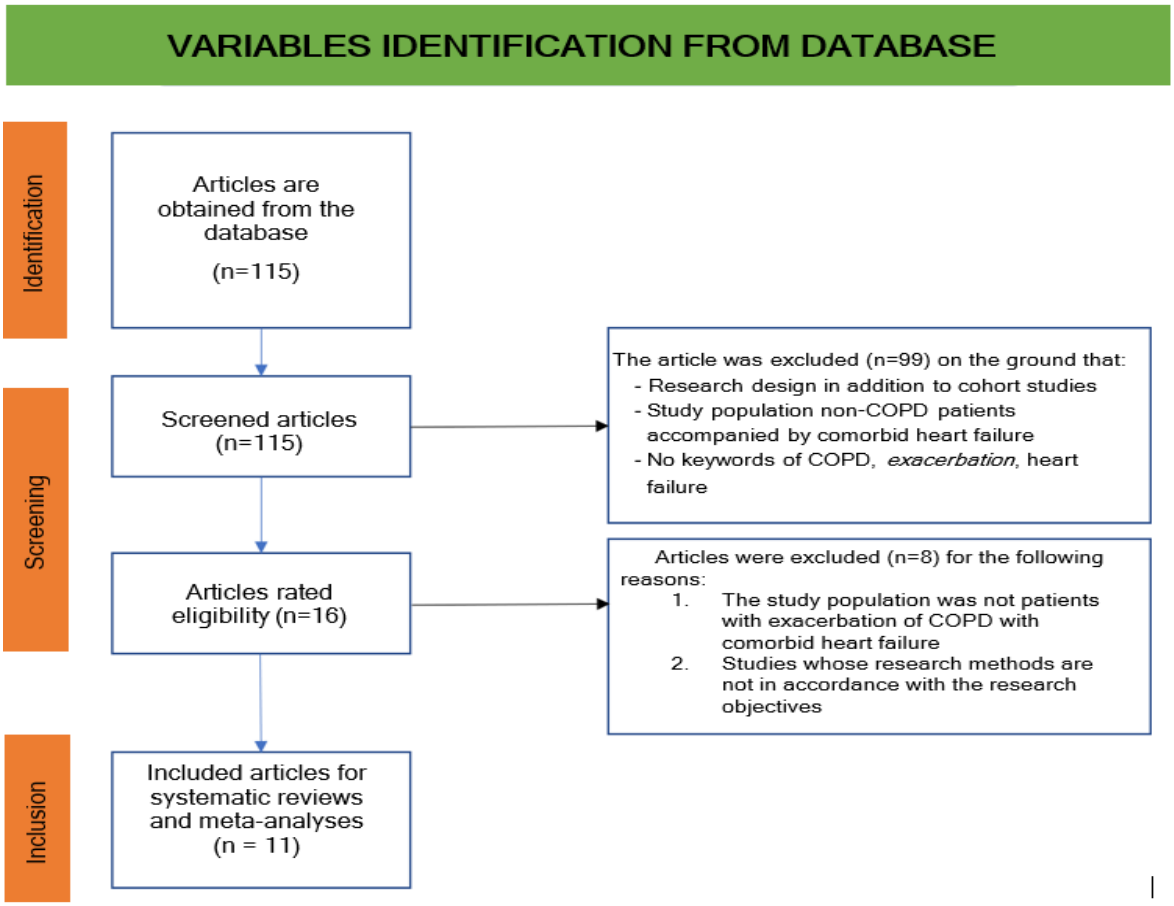

Figure 1. PRISMA flow

RESULTS

Study Characteristics

A total of 11 articles were conducted systematic review (Genao et al,2015; Janson et al,2020; Westerik et al,2017; Rasmussen et al,2020; Spece et al, 2018; Hoiseth et al, 2016; Marcun et al,2016; Santibanez et al,2016; Kim et al,2021; Rusinowicz,2017; and Germini et al 2018). Nine of the 11 articles are studies with retrospective design. Meanwhile, exacerbation COPD with comorbid heart failure also varied in each study of 19-23423 cases. Characteristics of COPD exacerbation with comorbid heart failure from the eleventh study are shown in table 1.

Two studies, namely by Hoseth et al (2016) and Marcun et al (2016) showed the age of COPD patients who experienced exacerbations with comorbid heart failure above the age of 35 years. The study conducted by Hoseth et al (2016) average exacerbated COPD patients with comorbid heart failure aged 79.6 years (mean SD±5.9). Marcun et al 2016 also reported the average age of patients was 75 years.

Two of the eleven articles showing the sex characteristics of exacerbated COPD with comorbid heart failure were Hoseth et al (2016) who reported more exacerbated COPD patients with comorbid heart failure in women than men (n=10.53% vs n=9.47%) while from Marcun et al (2016) reported more exacerbated COPD patients with comorbid heart failure in men than women (n=17, 77% vs n=5.23%). The rest of the article does not show sex characteristics in exacerbation COPD populations with comorbid heart failure.

Table 1. Population characteristics of COPD exacerbation with heart failure comorbid

No	Penulis,tahun	Total populasi PPOK eksaserbasi	Total populasi PPOK eksaserbasi dengan komorbid gagal jantung	Karakteristik PPOK eksaserbasi dengan komorbid Gagal jantung				
				Usia (±mean)	Jenis Kelamin		ACEi/ARB	Statin
					Laki-laki (%)	Perempuan (%)		
1	Genao L,2015	52741	23423	NA	NA	NA	NA	NA
2	janson C, 2020	51247	7876	NA	NA	NA	NA	NA
3	Westerik J, 2017	14603	1048	NA	NA	NA	NA	NA
4	Rasmussen D, 2020	5829	3610	NA	NA	NA	NA	NA
5	Spece L, 2018	2391	548	NA	NA	NA	NA	NA
6	Hoiseth AD, 2016	103	19	79.6 (5.9)	9(47)	10(53)	6(32)	9(47)
7	Marcun R, 2016	116	22	75±10	17(77)	5(23)	17(77)	6(27)
8	Santibanez M, 2016	148	58	NA	NA	NA	NA	NA
9	Kim Y, 2021	1555	180	NA	NA	NA	NA	NA
10	Rusinowicz T,2017	152	121	NA	NA	NA	NA	NA
11	Germini F, 2018	4396	1162	NA	NA	NA	NA	NA

NA: *not available*, ACEi: *Angiotensin Converting Enzim inhibitor*, ARB: *Angiotensin Receptor Bloker*

Two of the eleven articles showing the characteristics of ACEi/ARB therapy of exacerbated COPD patients with comorbid heart failure were Hoseth et al (2016) who reported 6 patients using ACEi/ARB therapy (32%) while from marcun et al (2016) reported more using ACEi/ARB therapy as many as 17 patients (77%).

Two of the eleven articles showing the characteristics of Statin therapy in exacerbated COPD patients with comorbid heart failure were Hoseth et al (2016) who reported 9 patients using ACEi/ARB therapy (47%) while from marcun et al (2016) reported 6 patients using statin therapy (27%).

Atrial fibrillation is another of the most reported comorbid cardiovascular diseases

namely by Westerik et al (2017) (7.1%,1044/14603), Rasmussen et al (2020) (22.5%, 2449/5829), Genao et al (2015) (25.8%, 13612/52741), Hoiseth et al (2016) (37%, 7/19), Marcun et al (2016) (50%, 11/22), Santibanez et al (2016) (49/148) followed By Ischemic Heart Disease reported by Janson et al (2020) (14.2%, 7253/51247), Santibanez et al (2016) (37/148), Kim et al (2021) (18.2%, 283/1555) then coronary artery disease was reported by Spece et al (2018) (30%,728/2391) and Germini (2018) (22.6%, 995/4396).

Meta-analysis in the eleventh study found pooled prevalents of COPD exacerbation with comorbid heart failure was 29.43 % (95%CI:17.68%- 42.92%) and statistical heterogeneity among the eleven meaningful studies (I2 = 99.95%. Q = 191.96 p=<0.001). The results of the analysis are presented in figure 2.

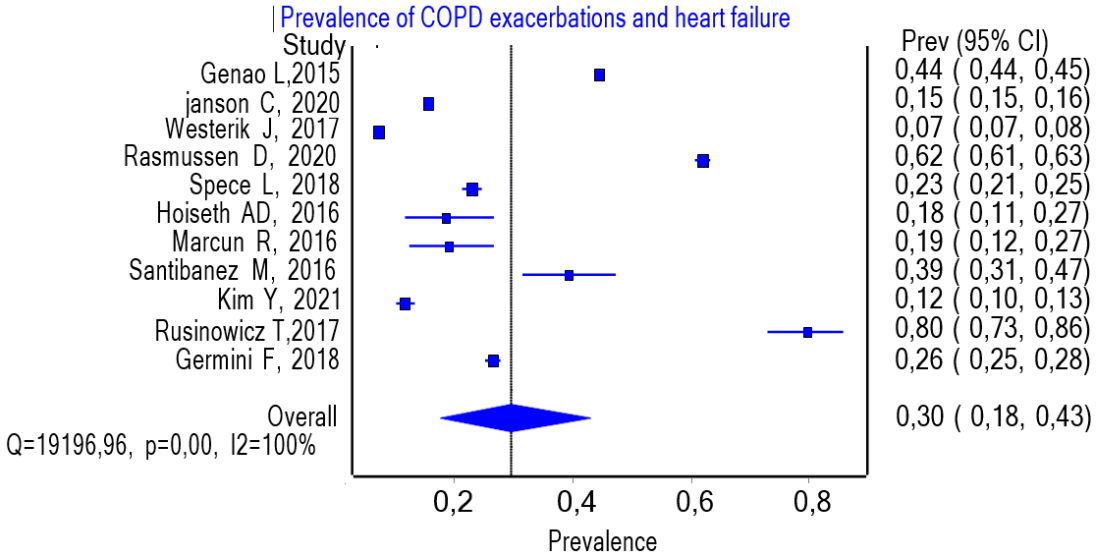

Figure 2. Forest plot Prevalent COPD exacerbation with comorbid heart failure

Sub-group analysis

Prevalence of COPD Exacerbations and Heart Failure based on Study Period

The study time period was obtained from all eleven articles, the longest study by Rasmussen et al from 2003 to 2015, Kim et al from 2003 to 2015 and Rusinowicz et al from 2004 to 2016 for 12 years each Furthermore, the study by janson et al for 9 years (2006-2015) then Spece et al for 6 years (2005-2011) then Genao et al for 4 years (2006-2010), then marcun et al for 2 years (2009-2011) and Westerik et al (2012-2013), Hoiseth et al (2009-2010), Santibanez et al (2011-2012), Germini et al (2014) for 1 year each. The results of the analysis and forest plot are presented in table 2 and figure 3. The subgroup meta-analysis based on the study period obtained the prevalence of exacerbation COPD based on the subgroup of the 5-year ≤ study period was 24.21% (95%CI: 6.18%- 46.12%) and the prevalence in the 5-year > study was 36.31% (95%CI:13.08%- 61.91%). The statistical heterogeneity of subgroups is very meaningful (I^2 = 99.94%, Q = 191.96, p=<0.001.

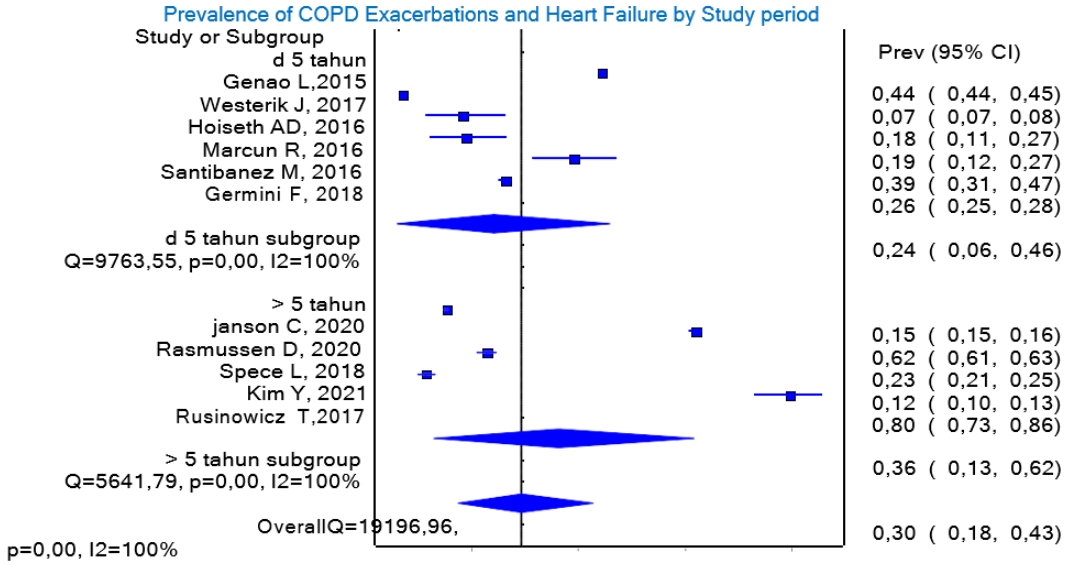

Figure 3. Forest plot subgroup period of study

Prevalence of COPD Exacerbations and Heart Failure by World Health Organization Region

Based on the World Health Organization (WHO) Region, eight of the eleven studies were conducted in Europe (Janson et al (2020), Westerik et al (2017), Rasmussen et al (2020), Hoiseth et al (2016), Marcun et al (2016), Santibanez et al (2016), Rusinowicz et al (2017) and Germini et al (2018). Two studies in the Americas region and one study in the western pacific region. Subgroup meta-analysis based on WHO region obtained prevalent COPD exacerbation with comorbid heart failure based on WHO subgroup Europe region 31.44% (95%CI: 17.87%-46.58%), American subgroup region 32.92% (95%CI: 12.61%-55.73%) and western pacific region subgroup 10.86% (95%CI:10.03%- 13.21%). The statistical heterogeneity of subgroups is very meaningful (I2 = 99.94%, Q = 191.96. p= <0.001). This result is depicted in table 3 and figure 4.

Table 2. Prevalence of COPD Exacerbations and Heart failure based on Study Period

Studi or subgroup	Prevalence	95%CI	Weight (%)
≤ 5 years			
Genao L,2015	44,41%	43,98%-44,83%	9,21%
Westerik J, 2017	7,17%	6,76%-7,61%	9,21%
Hoiseth AD, 2016	18,44%	11,48%-26,57%	8,81%
Marcun R, 2016	18,96%	12,31%-26,65%	8,85%
Santibanez M, 2016	39,18%	31,45%-47,21%	8,93%
Germini F, 2018	26,43%	25,13%-27,74%	9,21%
≤ 5 years subgroup	24,21%	6,18%-46,12%	54,24%
> 5 years			
janson C, 2020	15,36%	15,05%-15,68%	9,21%
Rasmussen D, 2020	61,93%	60,68%-63,17%	9,21%
Spece L, 2018	22,91%	21,25%-24,62%	9,19%
Kim Y, 2021	11,57%	10,03%-13,21%	9,18%
Rusinowicz T,2017	79,61%	72,81%-85,66%	8,94%
> 5 years subgroup	36,31%	13,08%-61,91%	45,75%
Pooled	29,54%	17,68%-42,92%	100%
Statistics			
I-squared	99,94%	99,94%-99,95%	
Cochran's Q	191,96		
Chi2, p	<0,001		

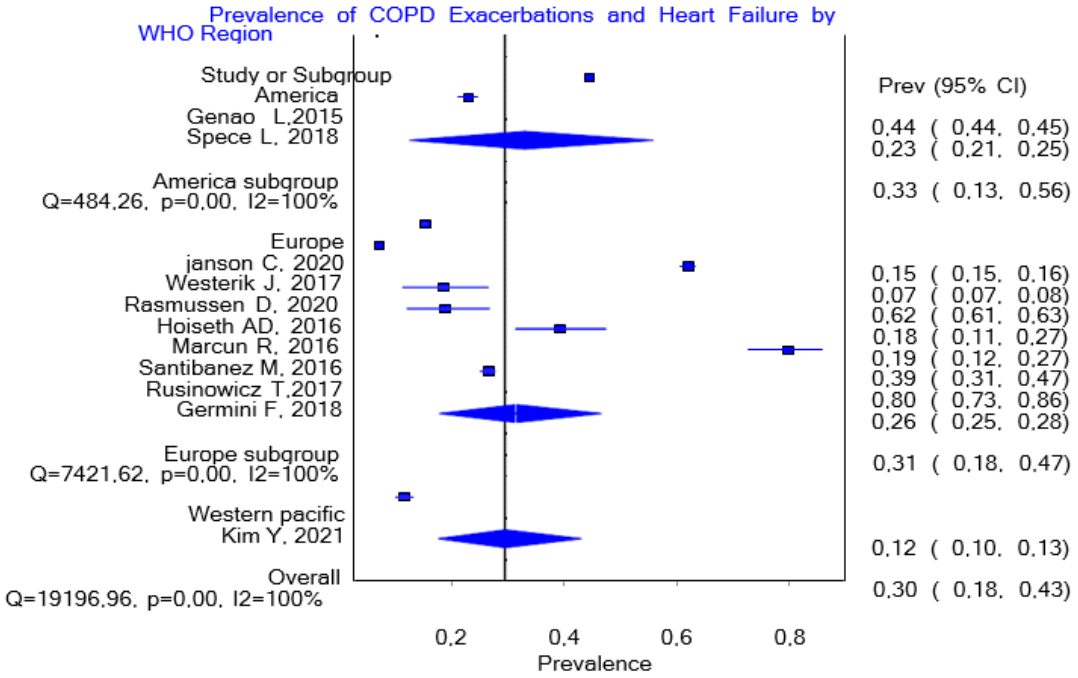

Figure 4. Forest plot subgroup WHO region

Prevalence of COPD Exacerbations and Heart Failure based on Research Design

Nine out of eleven studies with retrospective design (Genao, 2015; Janson et al, 2020; Westerik et al, 2017; Rasmussen et al, 2020; Spece et al, 2018; Santibanez et al, 2016; Kim et al, 2021; Rusinowicz et al, 2017 and Germini et al, 2018). Research conducted by Hoiseth et al,2016 and Marcun et al,2016 with prospective study design. The subgroup meta-analysis based on the study design obtained the prevalence of exacerbation COPD based on the prospective cohort research design was 18.41% (95%CI:13.94%-24.32%) and the retrospective cohort subgroup was 32.13%(95%CI:18.62%-47.14%). The statistical heterogeneity of subgroups is very meaningful (I2 =99.94%, Q = 191.96, p=<0.001). This result is depicted in table 4 and figure 5.

Table 3. Prevalence of COPD Exacerbations and Heart failure based on WHO regions

Studi or subgroup	Prevalence	CI 95%	Weight (%)
America			
Genao L,2015	44,41%	43,98%-44,83%	9,21%
Spece L, 2018	22,91%	21,25%-24,62%	9,19%
America subgroup	32,92%	12,61%-55,73%	18,41%
Europe			
janson C, 2020	15,36%	15,05%-15,68%	9,21%
Westerik J, 2017	7,17%	6,76%-7,61%	9,21%
Rasmussen D, 2020	61,93%	60,68%-63,17%	9,21%
Hoiseth AD, 2016	18,44%	11,48%-26,57%	8,81%
Marcun R, 2016	18,96%	12,31%-26,65%	8,85%
Santibanez M, 2016	39,18%	31,45%-47,21%	8,93%
Rusinowicz T,2017	79,61%	72,81%-85,66%	8,94%
Germini F, 2018	26,43%	25,13%-27,74%	9,21%
Europe subgroup	31,44%	17,87%-46,58%	72,39%
Western pacific			
Kim Y, 2021	11,57%	10,03%-13,21%	9,18%
Western pacific subgroup	10,86%	10,03%-13,21%	9,18%
Pooled	29,54%	17,68%-42,92%	100%

Statistics			
I-squared	99,94%	99,94%-99,95%	
Cochran's Q	19,196		
Chi2, p	<0,001		

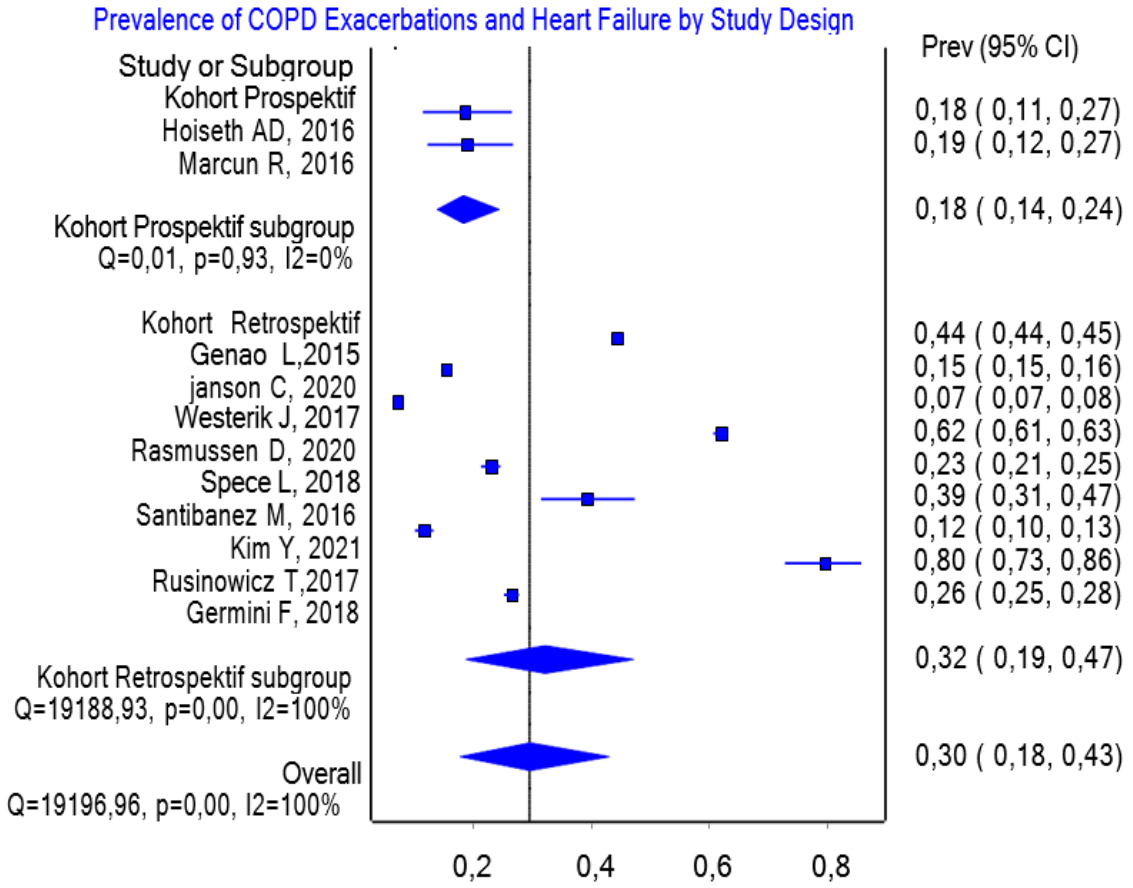

Figure 5. Forest plot research design subgroup

DISCUSSION

This study is the first systematic review and meta-analysis study of the prevalent of COPD exacerbation with comorbid heart failure. 115 articles were obtained from the database using search keywords which were then excluded as many as 104 articles on the grounds of research design other than cohort studies, the study population was not a patient with COPD and heart failure, and there are no keywords COPD, *exacerbation*, *Heart failure*, the study population is not an exacerbation COPD patient accompanied by comorbid heart failure, studies whose research methods are not in accordance with the research objectives and NOS < 6, so that 11 studies which the meta-analysis performed.

Pooled prevalent of COPD exacerbation with comorbid heart failure was in this study was 29.43 % (95%CI:17.68%-42.92%). The prevalence of COPD in each study was different due to the size of the different samples. The size of the exacerbation COPD sample with comorbid heart failure varied in each study of 19-23423 cases. Statistical heterogeneity among the eleven studies is meaningful (I^2 = 99.95%, Q = 191.96, p= <0.001) because in addition to being influenced by the number of samples it is also likely to be influenced by population characteristics in the country.

As is known one of the risk factors for COPD is the deficiency of α-1 antithripsin which causes an imbalance between proteases and antiproteases, most commonly found in Europe and North America.[8] It is proved from this study that the prevalent of COPD exacerbation with comorbid heart failure of the American *subgroup region* was

32.92%(95%CI: 12.61%- 55.73%) and the European *subgroup region* 31.44%(95%CI: 17.87%-46.58%) greater than the *western pacific* subgroup 10.86% (95%CI: 10.03%-13.21%).[9]

Prolonged exposure to cigarette smoke, gases or harmful particles can cause complex changes in the pathologies of the airways and pulmonary parenchyme, resulting in worsening respiratory function due to inflammation of the lower airway, fibrosis of the airway walls, smooth muscle hypertrophy, goblet cell hyperplasia, mucus hypersecretion and damage to the pulmonary parenchyma. Peripheral lung inflammation causes spill over of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 and CRP into the systemic circulation. Inflammation itself is involved in the pathogenesis of heart failure. This condition is higher with increased levels of CRP and cytokines. The hypothesis that explains the high prevalence of left ventricular systolic dysfunction in COPD patients is that systemic inflammation will accelerate the development of coronary atherosclerosis leading to the development of ischemic heart disease. The high incidence of motor changes in the walls of the left ventricle and the dysfunction of the left ventricle that we observed in COPD patients may also explain the relationship between this chronic progressive disease.[10]

Hypoxemia in patients with COPD can lead to pulmonary vasoconstriction and vascular remodeling, resulting in diastolic dysfunction of the right ventricle. Pulmonary Hypertension in patients with severe COPD can cause right heart failure, which in turn is associated with left heart failure. In addition, altered cardiac repolarization in patients with COPD may be associated with hypoxemia and may increase the risk of ventricular arrhythmias and sudden cardiac death.[11]

Subgroup meta-analysis was carried out which was divided by subgroup of the study period, WHO *region* and research design. Subgroup analysis based on Study time period obtained from all eleven articles, the longest study by Rasmussen et al from 2003 to 2015, Kim et al from 2003 to 2015 and Rusinowicz et al from 2004 to 2016 respectively. each for 12 years Subsequently the study by janson et al for 9 years (2006-2015) then Spece et al for 6 years (2005-2011) then Genao et al for 4 years (2006-2010), then marcun et al for 2 years (2009-2011) and Westerik et al (2012-2013), Hoiseth et al (2009-2010), Santibanez et al (2011-2012), Germini et al (2014) for 1 year each. The prevalence of copd exacerbation with comorbid heart failure based on the subgroup of the study period ≤ 5 years was 24.21% (95%CI: 6.18%-46.12%) and the prevalence in the study > 5 years was 36.31% (95%CI:13.08%-61.91%). The prevalence of COPD exacerbation with comorbid heart failure in the study period > 5 years was greater than the study period ≤ 5 years because the size of the sample in the study ≤ 5 years smaller than the study > 5 year. It is also what causes heterogeneity between meaningful studies (I^2 = 99.94%, Q = 191.96, p=<0.001).[9]

The population characteristics of COPD with comorbid heart failure reported in this study were age, gender, ACEi/ARB therapy, statin therapy and comorbid cardiovascular diseases other than heart failure. The results of a systematic review of two studies that reported age in the copd population of exacerbation and heart failure were obtained over 35 years of age. The study conducted by Hoiseth et al (2016) averaged 79.6 years (mean SD±5.9) and Marcun et al 2016 also reported the average age of patients of 75 years.[9]

This is in line with research conducted by Yao et al (2021) reporting that in 146 exacerbation COPD patients were the most aged over 70 years.[12] Chen et al (2019) who reported that the highest incidence of heart failure in COPD patients aged 74 years.[13] The incidence of COPD increases with age. age is a strong risk factor for COPD, and the risk of COPD gradually increases with aging. Aging is associated with a progressive decrease in VEP1 of about 20 ml/year and a decrease in the VEP ratio of 1/KVP and an increase in residual volume with a fixed total

lung capacity.[14]

This change in lung function results in a decrease in oxygen levels and a decrease in the ability to eliminate carbon dioxide (CO2) due to a decrease in chest wall compulsion and elastic pulmonary recoil as well as respiratory muscle strength. This change in lung function with age is similar to that in COPD. Changes in pulmonary physiology with age are associated with structural changes in the alveolus involving dilatation of the alveolus, resulting in a decrease in the area available for gas exchange. However, this dilatation of the alveolus is not like what occurs in COPD, since there is a digestion on the walls of the alveolus, as occurs in emphysema in COPD. An epidemiological study reported that smokers are prone to suffer from COPD and a rapid decrease in lung function of 50-100 ml of VEP1/year. However, a recent study reported that there was a marked individual variability in the decrease in VEP1 in subjects with COPD and that the development of persistent airflow limitation characteristics in COPD was not necessarily the result of an accelerated decrease in VEP1, but could be due to factors such as suboptimal lung growth in childhood.[14]

Diastolic dysfunction, which is relatively uncommon in young adults, is acquired in 50% of cases of heart failure in the elderly and is common in women. In diastolic dysfunction, prolonged myocardial relaxation and increased stiffness (which lowers the level of filling and volume) increase the diastolic pressure of the left ventricle and reduce the contents of the sekuncup at rest and during work. As a result, heart failure occurs, even when the systolic function (which is indicated by the ejection fraction) is normal or close to normal. With age, changes in the structure of the heart and cardiovascular system lower the excitatory threshold for heart failure. Interstitial collagen in the myocardium increases, the myocardium stiffens, and the relaxation of the myocardial becomes longer. These changes lead to a significant decrease in the diastolic function of the left ventricle, even in healthy parents. A decrease in systolic function also occurs with age. In addition, there is a decrease in the myocardial and vascular response to beta adrenergic stimulation that will impair the ability of the cardiovascular system response to increased work needs. These changes significantly decrease peak working capacity (about 8% per decade after age 30) and cardiac output at peak workouts is reduced more meaningfully. Thus, elderly patients are more prone to heart failure in response to stress or systemic abnormalities.[15]

In this systematic review, a different proportion of the two studies were obtained that described the characteristics of the sex. The study conducted by Hoiseth et al (2016), reported more exacerbated COPD patients with comorbid heart failure in women than men (n=10.53% vs n=9.47%), inversely proportional to the study by Marcun et al (2016) who reported more exacerbated COPD patients with comorbid heart failure in men than women (n=17.77% vs n=5.23%). This research from Hoiseth et al is in line with a study conducted by Tine et al (2020) which reported that out of 119 COPD patients, patients who experienced exacerbation COPD with heart failure were more numerous in women. In contrast, the study from Yao et al (2021) corresponds to a study reported by Marcun et al (2016) where of the 146 exacerbated COPD patients with heart failure the most were men.[12]

Until now, the exact relationship between gender and the incidence of COPD is still unclear, previous studies have stated that the rate of pain and death due to COPD is more common in men than women, but currently the incidence of COPD is almost the same between men and women, associated with an increasing number of female smokers. Research from Torres et al. linking gender to COPD concluded that men and women smokers with COPD had differences in levels of several plasma biomarkers which had implications for emphysema (IL-6, IL 16, VEGF). The difference in plasma biomarker levels corresponds to the difference in clinical manifestations, namely in women it

is heavier.[1]

Research from Mehta et al (2006) reported the incidence and prevalence of heart failure was lower in women than in men at all ages. However, due to the sharp increase in incidence with age, and the proportionally larger number of elderly women in the population of developed countries, the total number of men and women living with heart failure is similar. Similarly, reported by Stromberg et al (2003) the incidence of heart failure is higher in men, the overall prevalence rate is similar in both sexes, since women last longer after a heart failure attack.[16,17]

Population characteristics of exacerbation COPD patients with heart failure with ACEi/ARB therapy were found in two studies. Research from Hoiseth et al (2016) of 19 total patients with exacerbated COPD with comorbid heart failure as many as 6 (32%) patients taking ACEi/ARB therapy. In contrast, from the study reported by Marcun et al (2016) more people used ACEi/ARB therapy, namely from 22 total patients with exacerbated COPD with comorbid heart failure as many as 17 (77%) patients who took ACEi/ARB therapy. In patients with heart failure and accompanying COPD, ACEi and ARB bring additional benefits by lowering the levels of angiotensin-II, which is a powerful constrictor of the pulmonary airway. Therefore, this heart failure drug reduces obstruction airway, reduces pulmonary inflammation and narrowing of pulmonary blood vessels, and improves gas exchange of the alveolar membrane.[18]

Several studies have documented a decrease in mortality rates in COPD patients in the first 90 days after hospital discharge in exacerbation COPD patients using ACEi and ARB. A 30-day and 90-day mortality decrease was noted in subjects treated with exacerbated COPD when using ACEi (OR 0.58.95% CI 0.48- 0.70, and OR 0.55.95% CI 0.45-0.66,). Mancini et al (2006) showed benefits with the use of ARB after hospitalization for exacerbation COPD and a combination of ACEi/ARB and statins (*risk ratio* [RR] 0.66, 95% *confidence interval* [CI] 0.51 to 0.85). Matamis et al hypothesized that the identification and management of heart failure in patients in intensive care due to exacerbation gave better results after exacerbation, even in the short term, suggesting that heart failure contributed to the risk of exacerbation and that early diagnosis and management of heart failure in COPD populations can reduce that risk.[19]

Pathophysiologically, there are a number of mechanisms that underlie heart failure, especially uncontrolled heart failure, can increase the risk of exacerbation. Chronic congestion can lead to a decrease in airflow and obstruction of air flow can be overcome with proper congestion management. Pulmonary edema, and impaired oxygen transport due to heart failure, can intensify dyspnea and a decrease in existing exercise capacity due to pulmonary hyperinflation in COPD. Cardiomegaly can lead to worsening of alveolus gas diffusion, resulting in restrictive pulmonary patterns and reduced alveolus volume.[19]

Two studies with characteristics of statin therapy in exacerbated COPD populations with comorbid heart failure by Hoiseth et al (2016) reported out of 19 total exacerbation COPD patients with comorbid heart failure as many as 9 (47%) patients used statins while in research conducted by marcun et al (2016) reported out of 22 total exacerbation COPD patients with comorbid heart failure as many as 6 (27%) patients taking statins. A *systematic* study *review* and *meta-analysis* by Cao et al (2015) reported that out of 238,459 COPD cases from 15 articles found a statistically beneficial and significant association between statin treatment and COPD results. The use of statins was associated with a 38% decrease in all-cause deaths (95% CI 0.52 to 0.73) and a 52% reduction in COPD deaths (95% CI 0.23-0.99). Patients receiving statins showed a 36% lower risk of COPD exacerbation with or without hospitalization (95% CI 0.55-0.75).[20]

The protective effects of statins can be

explained by their pleiotropic effects, including anti-inflammatory, antithrombotic and immunomodulatory effects. In randomized controlled trials, the researchers showed that treatment with statins caused a significant reduction in systemic inflammatory markers such as CRP and IL-6 in patients with COPD. In another report, Undas et al (2009) observed that the fibrin clot became more permeable, less dense and faster lysis after three months of statin therapy in COPD patients. In addition, it should be noted that statins can regulate the balance of Th1/Th2 cells by inhibiting the development of Th1 and increasing the development of Th2 from CD4+ T cells. Improvement of pulmonary hemodynamics may be another potential benefit of statins in COPD.[20]

Some comorbid cardiovascular disease other than heart failure in COPD exacerbations that are widely reported in articles conducted this systematic review are atrial fibrillation followed by coronary heart disease. The studies that reported atrial fibrillation as a comorbid cardiovascular disease other than heart failure were Westerik et al (2017) (7.1%,1044/14603), Rasmussen et al (2020) (22.5%, 2449/5829), Genao et al (2015) (25.8%, 13612/52741), Hoiseth et al (2016) (37%, 7/19), Marcun et al (2016) (50%, 11/22), Santibanez et al (2016) (49/148). The prevalence of comorbidities varied in each study. Research conducted by Chen et al (2021) which reported that Hypertension is the most reported cardiovascular disease 43.77% then ischemic heart disease 24.94% and angina 8.91%. Similarly, research by Gupta et al (2020) reported ischemic heart disease which was the most 21% followed by stroke 5%, arrhythmia 3% and other cardiovascular diseases. Then the study reported by Laura et al (2015) with hypertension at most 40% followed by coronary artery disease as much as 10%.[13,21,22]

Ischemic heart disease, heart failure and cardiac arrhythmias are the cardiovascular diseases most commonly observed in people with COPD. Estimates of the prevalence of ischemic heart disease in people with COPD vary from less than 20% to more than 60%, depending on the characteristics of the study's population. Estimates of the prevalence of heart failure lie in the range of 10-30%, with estimates for primary care and community-based populations falling below this range. Prevalent estimates for arrhythmias also show a degree of variability, but it is usually between 10% and 15%.[23]

The systemic inflammatory response associated with COPD has been proposed as a mechanism that may link COPD and an increased risk of cardiovascular disease. According to the hypothesis, COPD-related chronic inflammation contributes to the formation and development of atherosclerotic plaques that during periods of acute inflammatory stimulation such as respiratory tract infections or exacerbation of COPD, induce plaque rupture and acute cardiovascular events Next. Some studies have shown that patients with COPD and cardiovascular disease comorbidities have higher rates of some systemic inflammatory biomarkers compared to COPD patients without comorbidities of cardiovascular disease. Furthermore, circulatory levels of CRP inflammatory biomarkers have been linked to increased mortality among COPD patients.[23]

CONCLUSION

Based on the results, atrial fibrillation and ischemic heart disease are comorbid cardiovascular diseases in addition to heart failure in exacerbation COPD which is widely found in this study. Exacerbation COPD populations with comorbid heart failure using statin therapy had a good effect in lowering the incidence of exacerbations. This study shows that the high prevalence of COPD exacerbation with comorbid heart failure is influenced by several factors such as the size of the sample and population characteristics in a country so that future research is needed with a more complete patient profile to show the factors likely to affect exacerbated COPD with comorbid

heart failure.

Declaration by Authors

Ethical Approval: Not Applicable
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: La Ode Muhammad Nazar Ghazali Yusuf, Muhammad Ilyas, Faisal Yunus, Nirwana Fitriani Walenna, Edward Pandu Wiriansyah, Sitti Nurisyah et.al. Prevalence of chronic obstructive pulmonary disease exacerbation with heart failure comorbid: a systematic review and meta-analysis. *International Journal of Research and Review*. 2024; 11(10): 145-158. DOI: *https://doi.org/10.52403/ijrr.20241014*

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