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Meta-Analysis

Mortality and Severity of COVID-19 Patients with Chronic Obstructive Pulmonary Disease: A Meta-Analysis

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ABSTRACT

Background: COVID-19 has become a pandemic in all countries including Indonesia. The death rate from COVID-19 is concentrated in elderly patients and those with comorbidities. COPD is one of the comorbidities that can worsen and even cause death. COPD ranks in the top 3 leading causes of death in the world causing 2.3 million deaths in 2019. This study aims to analyze the effect of COPD comorbidities on mortality and severity of COVID-19 patients.
Subjects and Method: This study used a systematic review and meta-analysis by following the PRISMA flow chart. Search articles through journal databases, namely: Google scholar, PubMed, Science Direct and Link Springer. The articles search was done by considering the eligibility criteria defined in the PICO model. P= COVID-19 patient; I= COPD participant; C= without COPD; O= need for mechanical ventilation, ICU admission, and death. Inclusion criteria were cohort full paper articles, in English, multivariate analysis with adjusted Odds Ratio. Articles analyzed with RevMan 5.3.
Results: The 13 cohort study designs reviewed with a meta-analysis to estimate the risk of death showed that comorbid COPD increased the risk of death (aOR= 1.33; 95% CI= 1.08 to 1.64; p= 0.007). 9 cohort study designs were reviewed with a meta-analysis to estimate the risk of severity with indicators of mechanical ventilation need (aOR= 1.38; 95% CI= 1.05 to 1.82; p= 0.020). 7 cohort study designs were reviewed by meta-analysis to estimate the risk of severity with indicators of risk of ICU admission (aOR= 1.25; 95% CI= 1.04 to 1.50; p= 0.020).
Conclusion: COPD comorbidities increase the risk of need for mechanical ventilation, ICU admission and death among COVID-19 patients.

Keywords: COVID-19, COPD, death, severity

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BACKGROUND

In December 2019, the SARS-CoV2 or COVID-19 virus first appeared in China, precisely in Wuhan. COVID-19 is still a pandemic in Indonesia and even throughout the world. The number of positive confirmed cases of COVID-19 in September 24 2021 were 230,418,451 cases according to reported data (WHO, 2021).

Chronic Obstructive Pulmonary Disease or COPD is a non-communicable disease in which airflow obstruction occurs

in the respiratory tract caused by lung inflammation (Ministry of Health, 2008). COPD is in the top 3 diseases that cause death in the world causing 2.3 million deaths in 2019 (WHO, 2019).

Death in COVID-19 patients has a much higher prevalence if the patient has comorbidities, patients with comorbid COPD have a prevalence of 10.6% (Hu et al., 2020). Other studies have also found that COPD comorbidities can exacerbate COVID-19 disease and even increase the risk of death (Graziani et al., 2020; Hernández-Galdamez et al., 2020; Purroy and Arque, 2021).

COPD increases the risk of poor clinical outcomes due to poor lung function (Lee et al., 2021). The obstruction of air flow in the respiratory tract results in a lack of oxygen in the body, resulting in alveolar damage and changes in respiratory physiology (Asyrofy et al., 2021). Patients with COPD have a high prevalence of coronary ischemia and other risk factors that may worsen the COVID-19 prognosis (Graziani et al., 2020).

There were many primary research that have conducted studies on the association of COPD comorbidities with the risk of death and severity of COVID-19 patients, further analysis is needed to obtain more convincing conclusions. Researchers are interested in conducting a meta-analysis on "Mortality and Severity of COVID-19 Patients with Concomitant Chronic Obstructive Pulmonary Disease".

SUBJECTS AND METHOD

1. Study Design

This study used a systematic review and meta-analysis of primary articles with a cohort study design comparing comorbid COPD with no COPD on the risk of death and outcome of COVID-19 patients. This study followed the PRISMA flow diagram. Search articles through journal databases, namely: Google scholar, PubMed, Science Direct and Link Springer. Article search was done by considering the eligibility criteria defined in the PICO model. P= COVID-19 patient; I= COPD participant; C= without COPD; O = need for mechanical ventilation. ICU admission and death. The keywords used are: “COPD” OR “Comorbidity” AND “COVID-19” OR “Corona virus” AND “Mortality” OR “poor outcome”.

2. Inclusion Criteria

The articles included in the inclusion criteria are: 1) Full text articles with a cohort study design and in English; 2) Outcome articles on risk of death and severity (need for mechanical ventilation and ICU admission); 3) Analysis of multivariate adjusted Odds Ratio (aOR) data.

3. Exclusion Criteria

Articles that are not included in the criteria for analysis are: 1) Articles with bivariate odds ratio analysis; 2) the relationship measure used aHR/ARR: 3) the reported outcome is not death or COVID-19 severity.

4. Definition of Operational Variable

Mortality: is death in patients with confirmed COVID-19 who are categorized as alive or dead. The instrument is a death certificate for a COVID-19 patient.

Severity: is a worsening condition of patients with COVID-19 disease characterized by the need for mechanical ventilation and ICU admission. The instrument is the patient's medical record.

COPD: Chronic obstructive pulmonary disease is a disease in which airflow obstruction occurs in the respiratory tract, the obstruction is associated with the presence of inflammation in the lungs due to the presence of harmful and toxic particles or gases. The instrument is the medical record of patients diagnosed with COPD.

5. Data Analysis

The association of COPD comorbidity with mortality and severity of COVID-19 patients was analyzed using the Review Manager (RevMan 5.3). The severity of the COVID-19 condition with indicators of the need for mechanical ventilation and ICU admission. Relationship measure adjusted Odds Ratio 95% CI. Forest plots show the estimated effect of COPD comorbidities on mortality and severity of COVID-19 patients. Heterogeneity in studies is shown by the intuitive index (I^2). Fixed effect model is used in homogeneous research and random effects is used in heterogeneous research. Funnel plot shows publication bias.

RESULTS

An electronic database search have found 2,981 articles. After deleting duplicated articles, 2,554 articles were filtered. 370 full text articles were assessed for eligibility. A total of 22 articles that fulfilled the inclusion criteria were synthesized in a quantitative meta-analysis. 10 articles came from the North American continent, 6 from the European continent and 6 articles from the Asian continent. The process of searching for articles with a feasibility assessment is shown in Figure 1. Quality assessment using the Critical Appraisal Skill Program (CASP) for cohort research is shown in table 2.

1. **The effect of COPD on mortality in COVID-19 patients.**

The forest plot in Figure 2 showed that comorbid chronic obstructive pulmonary disease increased the risk of death in COVID-19 patients by 1.33 times and was statistically significant (aOR= 1.33; 95% CI= 1.08 to 1.64; p= 0.007). The heterogeneity of the study data showed I^2= 93% so that the estimation was carried out by using a random effects model approach. Figure 3 funnel plot showed no publication bias seen from the symmetrical distribution of the plot. 5 plots are on the right side, 7 plots are on the left side and 1 plot is in the middle of the line.

2. **The effect of COPD on the need for mechanical ventilation in COVID-19 patients**

COPD comorbidities increase the severity of COVID-19 as shown in Figures 4 and 6. Figure 4 showed that COPD comorbidities increase the need for mechanical ventilation in COVID-19 patients by 1.38 times (aOR= 1.38; 95% CI= 1.05 to 1.82; p= 0.020). The heterogeneity of the research data showed the score of I^2= 82% so that the estimation is carried out using a random effects model approach. Figure 5 funnel plot showed no publication bias seen from the symmetrical distribution of the plot. 3 plots are on the right side, 5 plots are on the left side and 1 plot is in the middle of the line.

3. **The effect of COPD on ICU admission in COVID-19 patients**

The forest plot in Figure 6 showed that COPD comorbidities increased the risk of ICU admission for COVID-19 patients by 1.25 times (aOR= 1.25; 95% CI= 1.04 to 1.50; p= 0.020). The heterogeneity of the study data showed the score of I^2 = 61% so that the estimation was carried out using a random effects model approach. The funnel plot in Figure 7 showed that there was no publication bias seen from the symmetrical distribution of the plot. 2 plots are on the right side, 2 plots are on the left side and 3 plots are close to the center line.

Table 1. Characteristics of the Meta-analysis primary article

No	Author (Year)	Country	Study Design	Sample		P (Population)	I (Intervention)	C (Comparison)	O (Outcome)
				COVID-19	COPD				
1	Cedano et al 2021	America	Cohort retrospective	132	11	Adult patient confirmed COVID-19	COPD comorbid	No COPD	Death
2	Choi et al 2020	Korea	Cohort retrospective	7341	678	COVID-19 confirmed patient	COPD comorbid	No COPD	Death, Mechanica Ventilation
3.	Gerwen et al 2020	America	Cohort retrospective	3703	145	COVID-19 confirmed patient	COPD comorbid	No COPD	Death, Mechanica Ventilation
4.	Guan et al 2020	China	Cohort retrospective	39420	636	COVID-19 confirmed patient	COPD comorbid	No COPD	Death, Mechanica Ventilation, ICU
5.	Lee et al 2021	Korea	Cohort retrospective	7590	141	COVID-19 confirmed patient	COPD comorbid	No COPD	Death
6.	Meza et al 2021	America	Cohort retrospective	387008	7449	Patients aged >35 years ol confirmed COVID-19	COPD comorbid	No COPD	Death
7.	Oh et al 2021	South Korea	Cohort retrospective	122040	4488	COVID-19 confirmed patient	COPD comorbid	No COPD	Death
8.	Lohia et al 2021	America	Cohort retrospective	1871	317	Patients aged >17 years ol confirmed COVID-19	COPD comorbid	No COPD	Death, Mechanica Ventilation, ICU
9.	Corradini et al 2021	Italia	Cohort retrospective	1505	156	Adult patient confirme COVID-19	COPD comorbid	No COPD	Death
10.	Beltramo et al 2021	France	Cohort retrospective	89530	4866	COVID-19 confirmed patient	COPD comorbid	No COPD	Death, ICU
11.	Chen et al 2020	China	Cohort retrospective	3309	42	COVID-19 confirmed patient	COPD comorbid	No COPD	Death
12.	Gude-Sampredo et al 2020	Spain	Cohort retrospective	10454	180	COVID-19 confirmed patient	COPD comorbid	No COPD	Death
13.	Carbonell et al 2021	Spain	Cohort retrospective	3795	269	COVID-19 confirmed patient	COPD comorbid	No COPD	Death
14	Angelidi et al 2021	America	Cohort retrospective	144	22	Adult patient confirmed COVID-19	COPD comorbid	No COPD	Mechanical Ventilation
15	Raad et al 2021	America	Cohort retrospective	1020	105	Patients aged >17 years old confirmed COVID-19	COPD comorbid	No COPD	Mechanical Ventilation
16.	Fried et al 2020	America	Cohort retrospective	11721	1737	COVID-19 confirmed patient	COPD comorbid	No COPD	Mechanical Ventilation
17	Hobbs et al 2021	America	Cohort retrospective	502	33	Adult patient confirmed COVID-19	COPD comorbid	No COPD	Mechanical Ventilation
18.	Wu et al 2020	China	Cohort retrospective	1048	50	COVID-19 confirmed patient	COPD comorbid	No COPD	Mechanical Ventilation

No	Author (Year)	Country	Study Design	Sample		P (Population)	I (Intervention)	C (Comparison)	O (Outcome)
				COVID-19	COPD				
29	Garcia et al 2021	Mexico	Cohort retrospective	13842	359	COVID-19 confirmed patient	COPD comorbid	No COPD	ICU
20	Santorelli et al 2021	England	Cohort retrospective	582	78	COVID-19 confirmed patient	COPD comorbid	No COPD	ICU
21	Timberlake et al 2021	America	Cohort retrospective	275	26	COVID-19 confirmed patient	COPD comorbid	No COPD	ICU
22	Doriane et al 2020	Belgium	Cohort retrospective	596	46	Adult patient confirmed COVID-19	COPD comorbid	No COPD	ICU

Table 2. CASP quality assessment for cohort studies

No	Question	Cedano et al. 2020	Choi et al. 2020	Gerwen et al. 2020	Guan et al. 2020	Lee et al. 2021	Meza et al. 2021	Oh et al. 2021	Lohia et al. 2021	Corradini et al. 2021	Beltramo et al 2021	Chen et al 2020
1.	Does this study address clearly focused issues	2	1	2	2	2	2	2	2	2	2	2
2.	Is the cohort conducted in an acceptable manner	2	2	2	2	2	2	2	2	2	2	2
3.	Is the exposure accurately measured to minimize bias	2	2	2	2	2	2	2	2	2	2	2
4.	Are the results measured accurately to minimize bias?	2	2	2	2	2	2	2	2	2	2	2
5.	Have the authors identified all the important confounding factors? Have they taken confounding factors into account in the design and/or analysis?	2	2	2	2	2	2	2	2	2	2	2
6.	Is the follow-up subject complete enough? Is the follow-up of the subject long enough?	2	2	2	2	2	2	2	2	2	2	2
7.	What is the outcome of this study on mortality or severity?	2	2	2	2	2	2	2	2	2	2	2
8.	Are the results precise?	2	2	2	2	2	2	2	2	2	2	2
9.	Do you believe in the results?	2	2	2	2	2	2	2	2	2	2	2
10.	Can the results be applied to the local population?	2	2	2	2	2	2	2	2	2	2	2
11.	Are the results of this study consistent with	2	2	2	2	2	2	2	2	2	2	2

12.	other available evidence? What are the implications of this study for practice?	2	2	2	2	2	2	2	2	2	2	2
	Total	**24**	**23**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**

Yes = 2; Cannot Tell= 1; No = 0

Table 3. Next

No	Question	Gude-Sampredo et al 2020	Carbonel et al 2021	Angelidi et al. 2021	Raad et al 2021	Fried at al 2020	Hobbs et al 2021	Wu et al 2020	Garcia et al 2021	Santoreli et al 2021	Timber-lake et al 2021	Doriane et al 2020
1.	Does this study address clearly focused issues	2	2	2	1	2	1	2	2	2	2	2
2.	Is the cohort conducted in an acceptable manner	2	2	2	2	2	2	2	2	2	2	2
3.	Is the exposure accurately measured to minimize bias	2	2	2	2	2	2	2	2	2	2	2
4.	Are the results measured accurately to minimize bias?	2	2	2	2	2	2	2	2	2	2	2
5.	Have the authors identified all the important confounding factors? Have they taken confounding factors into account in the design and/or analysis?	2	2	2	2	2	2	2	2	2	2	2
6.	Is the follow-up subject complete enough? Is the follow-up of the subject long enough?	2	2	2	2	2	2	2	2	2	2	2
7.	What is the outcome of this study on mortality or severity?	2	2	2	2	2	2	2	2	2	2	2
8.	Are the results precise?	2	2	2	2	2	2	2	2	2	2	2
9.	Do you believe in the results?	2	2	2	2	2	2	2	2	2	2	2
10.	Can the results be applied to the local population?	2	2	2	2	2	2	2	2	2	2	2
11.	Are the results of this study consistent with other available evidence?	2	2	2	2	2	2	2	2	2	2	2
12.	What are the implications of this study for practice?	2	2	2	2	2	2	2	2	2	2	2
	Total	**24**	**24**	**24**	**23**	**24**	**23**	**24**	**24**	**24**	**24**	**24**

Yes = 2; Cannot Tell= 1; No = 0

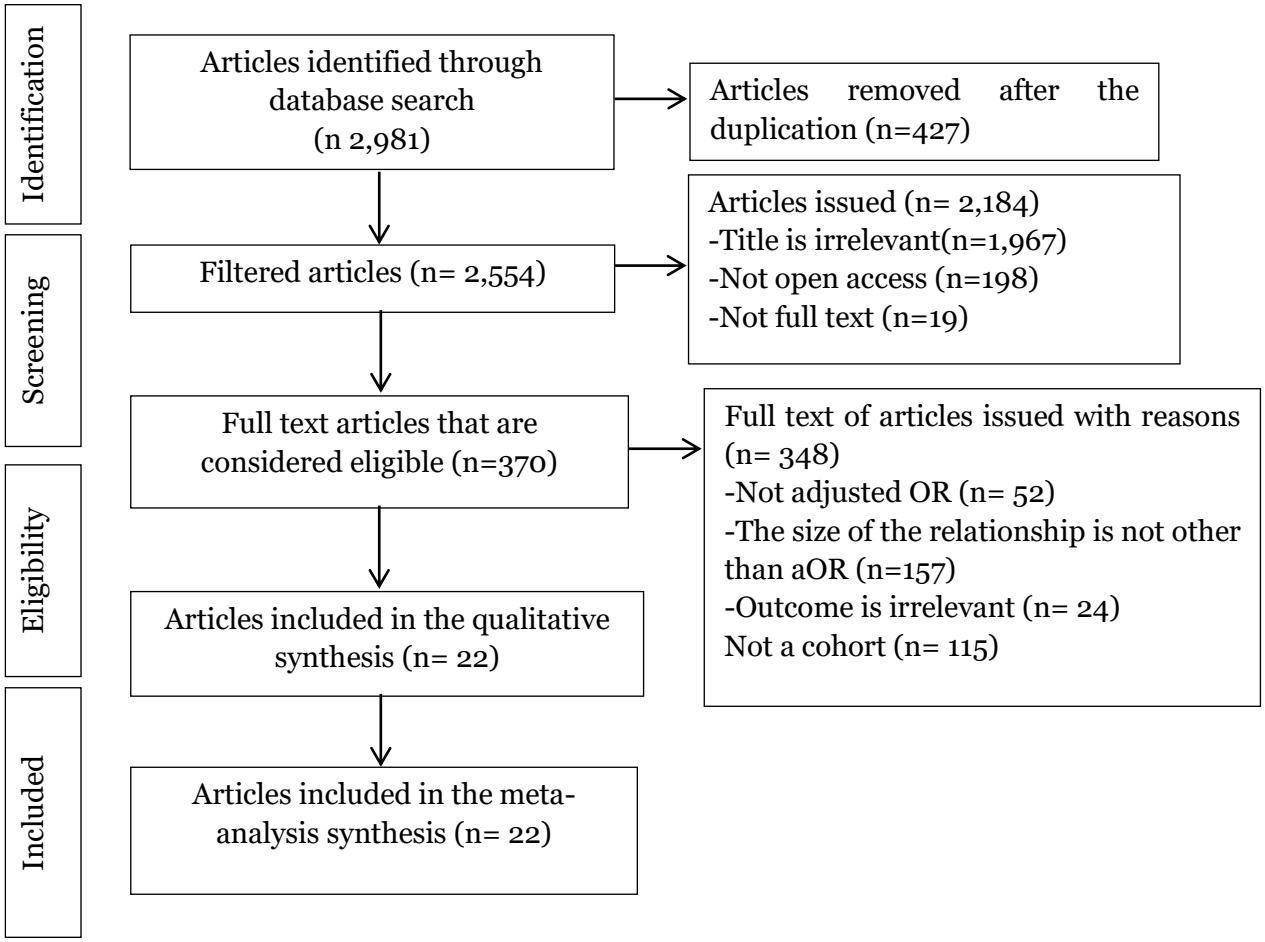

Figure 1. PRISMA Flowchart

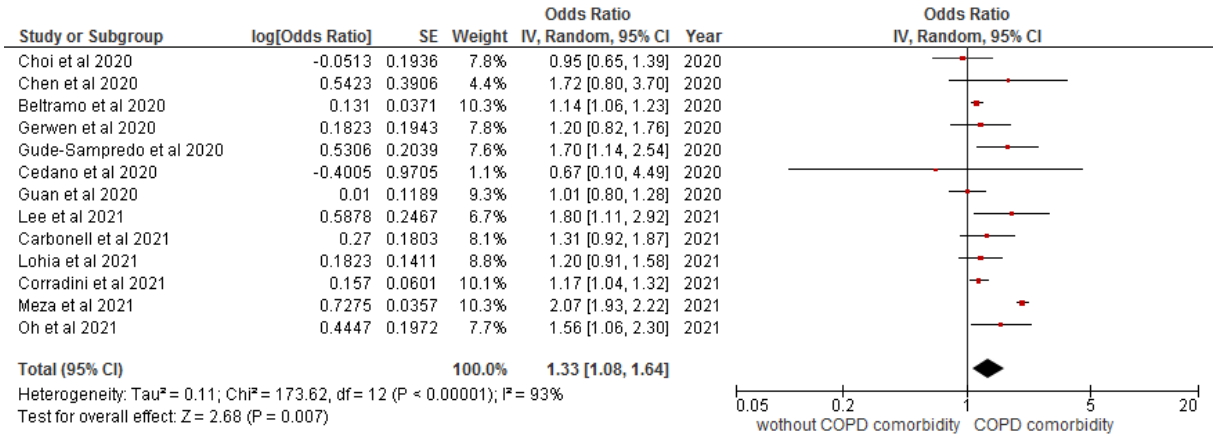

Figure 2. Forest plot of the relationship between COPD comorbidity with the death risk of COVID-19 patient

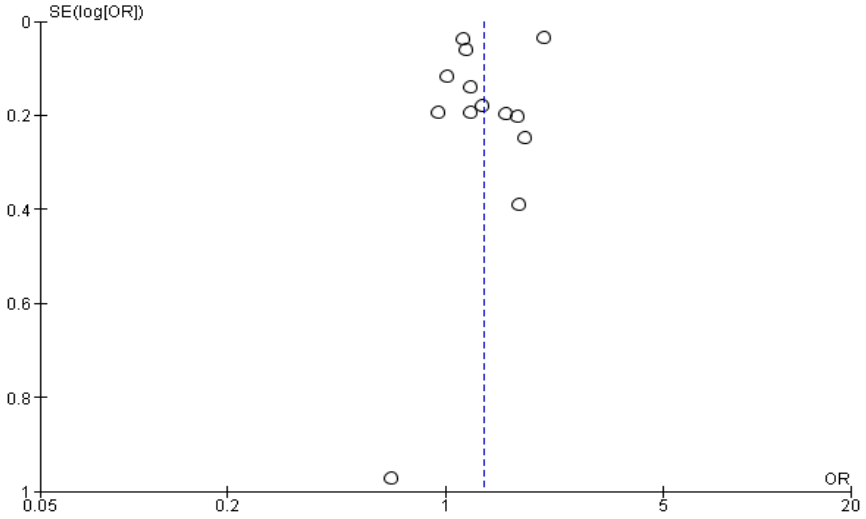

Figure 3. Funnel Plot of the relationship between COPD comorbidity with the death risk of COVID-19 patient

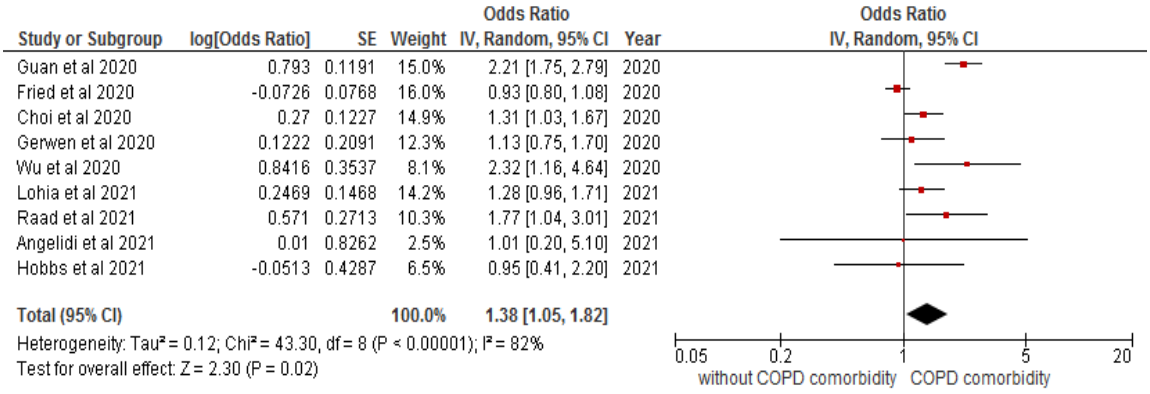

Figure 4. Forest plot of COPD comorbidity relationship with mechanical ventilation needs of COVID-19 patients

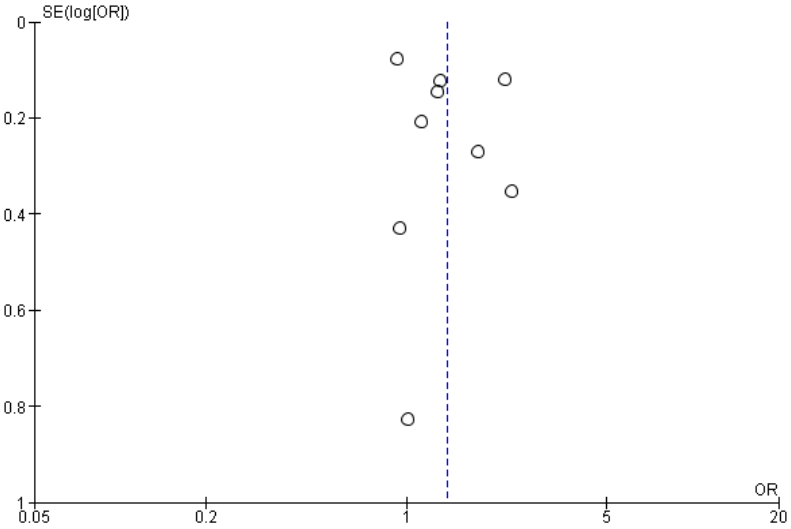

Figure 5. Funnel Plot of COPD comorbidity relationship with mechanical ventilation needs of COVID-19 patients

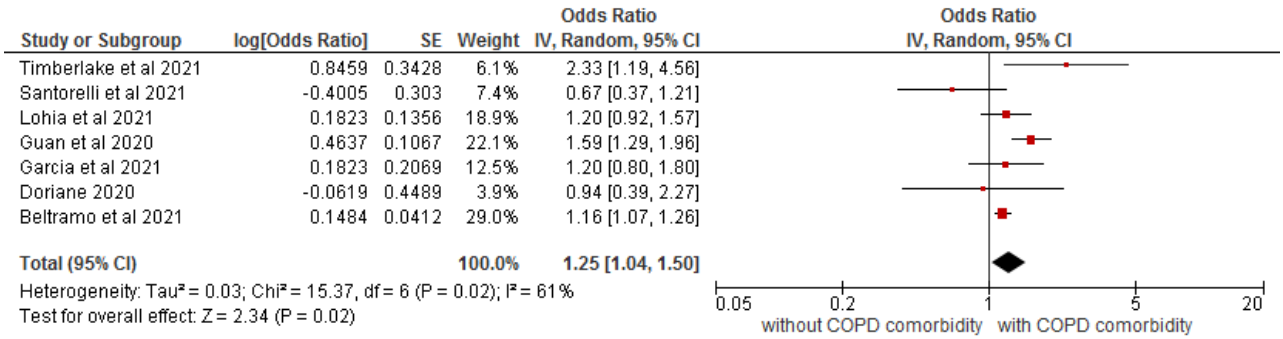

Figure 6. Forest plot of the relationship between COPD comorbidities with the risk of entering the ICU for COVID-19 patients

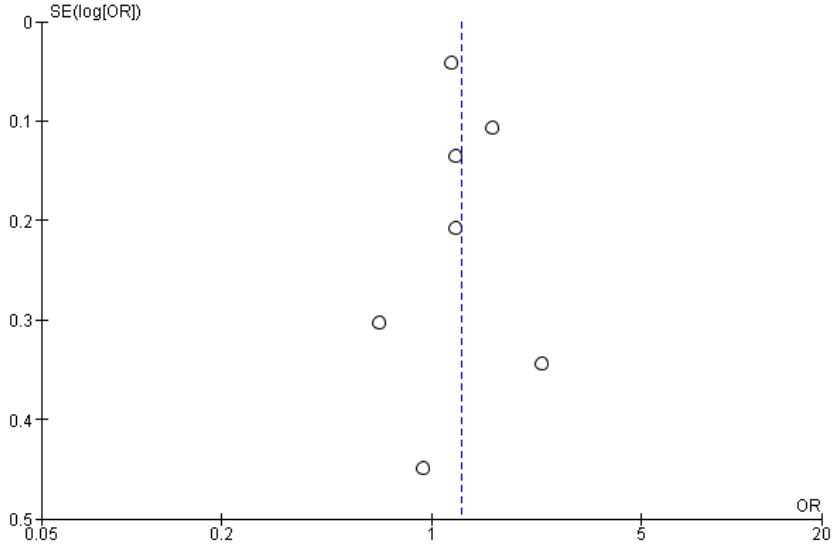

Figure 7. Funnel plot of the relationship between COPD comorbidities with the risk of ICU admission for COVID-19 patients

DISCUSSION

This systematic review study and meta-analysis estimated the association of comorbid COPD in COVID-19 patients with the risk of death and the severity of the patient's condition. The severity of the condition is seen from 2 indicators, namely the need for mechanical ventilation and ICU admission.

1. COPD increases the risk of death in COVID-19 patients

The results of the forest plot of the association of COPD comorbidity with the risk of death from COVID-19 in Figure 2 show that COPD comorbidity increased the risk of death and it was statistically significant (aOR= 1.33; 95% CI= 1.08 to 1.64; p= 0.007).

These results are similar to Meza et al (2021) who conducted a study on the risk of death in COVID-19 patients with COPD comorbidities. The study conducted by Meza showed that COPD comorbidities had a high risk of death (aOR= 2.07; 95% CI= 1.93 to 2.22; p<0.001).

COPD patients in the respiratory tract epithelium secrete inflammatory cytokines and chemokines, such as leukotriene B4 (LTB4), interleukin-6 (IL-6), IL-8 (CXCL8) and tumor necrosis factor-α (TNF-α), and other mediators in lungs (Fauzia, 2016). An excessive increase in cytokines will result in a cytokine storm, patients infected with

severe SARS-CoV-2 show a cytokine storm that continues to develop into ARDS (Rosyanti and Hadi, 2020).

2. COPD increases the risk of mechanical ventilation needs

The forest plot of the relationship between COPD comorbidities and the need for mechanical ventilation of COVID-19 patients in Figure 4 showed that COPD comorbidities increased the need for mechanical ventilation and it was statistically significant (aOR= 1.38; 95% CI= 1.05 to 1.82; p= 0.020).

Lohia et al. (2021) conducted a study on mortality, mechanical ventilation requirements and ICU admission in COVID-19 patients with COPD comorbid. COPD comorbidities increased the risk of mechanical ventilation needs (aOR = 1.28; 95% CI= 0.96 to 1.69; p= 0.090) and increased the risk of ICU admission (aOR= 1.20; 95% CI= 0.92 to 1.58; p= 0.180).

Patients with COPD have an increase in neutrophils. In the case of COVID-19, the number of neutrophils has also increased, therefore, patients with severe SARS-CoV-2 infection are often characterized by neutrophilia (Rosyanti and Hadi, 2020). Neutrophils and macrophages will release protease enzymes. Oxidative stress in COPD will affect the balance between proteolytic and anti-proteolytic by activating proteases and inactivating antiproteinases. An imbalance of protease-antiprotease enzymes caused by an increase in neutrophils causes ARDS. Proteases and oxidants will cause extensive lung tissue damage, especially in the part required for gas exchange (Amin, 2016).

3. COPD increases risk of ICU admission for COVID-19 patients

The Forest plot of the association between COPD comorbidities and the risk of ICU admission for COVID-19 patients in Figure 6 showed that COPD comorbidity increased the risk of ICU admission and was statistically significant (aOR= 1.25; 95% CI= 1.04 to 1.50; p= 0.020).

These results are similar to a study conducted by Timberlake et al (2021) who conducted a study on the risk of ICU admission in COVID-19 patients with COPD. The study showed that COPD increased the risk of ICU admission (aOR= 2.33; 95% CI= 1.19 to 4.56); p= 0.010).

COPD patients will experience an increase in the ACE-2 enzyme, the SARS CoV2 virus makes this ACE-2 enzyme as its receptor which then enters the epithelial cells. It causes infection of adjacent cells and the spread of the virus to other organ systems resulting in clinical manifestations which then exacerbates COVID-19 disease (Sin, 2020).

There are several limitations in this study, the first is language bias, because in this study the articles used in the statistical analysis used articles in English only, thus ignoring similar articles in languages other than English. Second, most of the articles in this meta-analysis study are from the North American continent, a small part from the Asian continent and the European continent. This allows for differences in the risk of comorbid COPD with mortality and COVID-19 severity in the continents of Australia, South America and Africa.

In conclusion, COPD comorbidity may be a strong risk factor for the need of mechanical ventilation, ICU admission, and mortality in COVID-19 patients. Future study is expected to use more foreign language articles to minimize language bias. Using subgroup analysis calculations to obtain more accurate evidence of the association of COPD comorbidities with COVID-19 mortality and severity. Health workers and health promoters can take this study into consideration in developing early prevention and determining treatment strategies that can reduce the severity and

mortality rate in COVID-19 patients with COPD comorbidities.

AUTHORS CONTRIBUTION

Atika Mima Amalin is the main researcher who determined the title of study, searched and collected the data. Setyo Sri Rahardjo and Hanung Prasetya analyzed the data and reviewed study articles.

CONFLICT OF INTEREST

There was no conflict of interest in this study.

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