

## Meta-Analysis Correlations between Hypertension, Smoking, and Severity Risk of COVID-19

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### ABSTRACT

**Background:** Based on the reported cases, 16.9% of COVID-19 patients were accompanied by comorbidities. Hypertension and smoking are suspected to be one of the pathological determinants that play a role in clinical predictors that are predicted to cause a worsening of the patient's condition during the treatment period. This study aimed to examine correlations between hypertension, smoking, and severity risk of COVID-19.

**Subjects and Method:** Meta-analysis was carried out using PRISMA flow diagrams. Article searches through journal databases include: PubMed, Science Direct, Google Scholar. articles used in 2020-2022. The PICOs in this study were, Population: COVID-19 patients, Intervention: hypertension and smoking Comparison: not hypertension and not smoking, Outcome: severity of COVID-19. The keywords in this study were “hypertention” OR “high blood pressure” AND “severe COVID-19” OR “severty COVID-19” OR “patient COVID-19 outcome” “cigarette” OR “smoking” OR “current smoker” OR former smoker” AND “severe COVID-19” OR “severty COVID-19” OR “patient COVID-19 outcome” Inclusion criteria were articles used in full paper articles with a cohort design, relationship size used with aOR, intervention given the association of hypertension and smoking on the severity of COVID-19. Eligible articles were analyzed using the Revman 5.3 application.

**Results:** A meta-analysis of 12 cohort articles originating from Asia, America, Africa, Europe, concluded that COVID-19 treatment patients with hypertension had higher severity 1.82 times compared to those without hypertension (aOR= 1.82; 95% CI= 1.18 to 2.79; p=0.006). Likewise, COVID-19 treatment patients with smoking habit had higher severity than those who do not smoke (aOR= 0.62; 95% CI= 0.14 to 2.65; p=0.520).

**Conclusion:** COVID-19 patients with hypertension have an increased risk of severity. COVID-19 patients with smoking lower risk of severity.

**Keywords:** Severe COVID-19, hypertention, cigarette.

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### BACKGROUND

The first case of COVID-19 was discovered in China, precisely in the city of Wuhan, Hubei province, December 31, 2019. As of March 25, 2020, the total number of confirmed cases reached 414,179 with

18,440 deaths (CFR= 4.4%), the spread of cases of confirmed COVID-19 patients reached 192 countries. or region until it is categorized as a pandemic.

Coronaviruses are a large family of viruses that cause illness ranging from mild

to severe symptoms. There are two types of coronavirus that are known to cause diseases that can cause severe symptoms, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). Coronavirus Disease 2019 (COVID-19) is a new type of disease that has never been previously identified in humans.

Some of the co-morbidities that were found to have survivors of COVID 19 were. Heart 3.7, hypertension, diabetes 8%, cerebrovascular 1.9, COPD 1.5%, and malignancy 1.1% are some of the comorbidities found in COVID-19 patients, which aggravate the condition of COVID-19 patients (Ministry of Health, 2020b).

Hypertension is one of the degenerative diseases and is the most common comorbidity in COVID-19 patients. Hypertension is a condition of increasing systolic blood pressure above 140 mmHg and diastolic blood pressure above 90 mmHg in two measurements taken at an interval of five minutes in a state of sufficient rest/quiet.

Based on the literature review that has been carried out, the proportion of hypertension has a higher number in critically ill patients until death, but these findings on the estimated effect are different. In Wang' research (2020), univariate analysis showed that the risk of hypertension was a risk factor for the occurrence of COVID 19, as well as research from Cummings (2020) showed that hypertension was significantly related to the severity and death of COVID-19 patients.

The immune system, which is a key player in the pathogenesis of COVID 19, also plays an important role in inflammation-induced adipose tissue. This inflammation of adipose tissue results in metabolic dysfunction that has the potential to cause dyslipidemia, insulin resistance,

hypertensive type diabetes mellitus, and cardiovascular disease (Kurniawati, 2021).

Smoking is one of the causes of diseases of the respiratory organs. World health organization. WHO warns more than 40 percent of smokers in the world die from lung diseases, such as cancer, chronic respiratory disease, and tuberculosis.

WHO explained that every year, tobacco use kills at least eight million people. The United Nations also reports 3.3 million users will die from lung disease. This number includes people who are exposed to secondhand smoke (passive smokers), including more than 60,000 children under the age of five who died from lower respiratory tract infections due to passive smoking (Kemenkes, 2020a).

Today's smoking habit is still a difficult problem to solve. Because smoking addiction is caused by the nicotine contained in cigarettes. In the process of cigarette smoke containing nicotine entering the airways, nicotine will release the neurotransmitters of this substance which makes you feel calm and relaxed when smoking.

Hypertension and smoking are thought to be one of the pathological determinants that play a role in clinical predictors that existed before the patient suffered from COVID-19 or would even aggravate the patient's condition during treatment. This study aims to identify the relationship between hypertension and smoking with the severity of COVID-19.

## SUBJECTS AND METHOD

### 1. Study Design

This study uses a systematic review and meta-analysis study design. Using the PRISMA flow chart guidelines. Article searches were carried out using journal databases including: PubMed, Science Direct, Google Scholar articles in the vulnerable years 2020-2022 with keywords

("hypertention" OR "high blood pressure" AND "severe COVID-19" OR "severty COVID-19" OR "patient COVID-19 outcome" "cigarette" OR "smoking" OR "current smoker" OR former smoker" AND "severe COVID-19" OR "severty COVID-19" OR "patient COVID-19 outcome").

## **2. Inclusion Criteria**

This study has inclusion criteria, including: Full paper article with a cohort study. Articles using English or Indonesian. The size of the relationship used with aOR. The intervention given is the relationship between hypertension and smoking on the severity of COVID-19, Subjects of the study were COVID patients -19.

## **3. Exclusion Criteria**

The article does not include the adjusted odds ratio (aOR). RCT research or other than observational studies, respondents are not COVID-19 patients.

## **4. Operational Definition of Variables**

The formulation of the problem in this study was carried out by considering the eligibility criteria defined using the PICO, namely, Population: Hypertension, smoking, Comparison: No hypertension. No smoking, and Outcome: Severity. Hypertension is defined as a progressive cardiovascular syndrome arising from complex and interrelated etiology. Early signs of the cardio-vascular syndrome are often present before the elevation of blood pressure is maintained. Smoking behavior is an individual activity related to smoking behavior. Severity is the condition of patients with COVID-19 patients with symptoms of COVID-19 getting more severe, characterized by high fever, respiratory rate >30 times per minute, saturation decreased <95%. Decreased consciousness, requiring treatment in an intensive room such as the ICU HCU.

## **5. Study Instruments**

The instrument in this study uses research using a critical appraisal tool from the Critical Appraisal Skills Program (CASP) Oxford Center for Triple Value Healthcare.

## **6. Data Analysis**

Data analysis in this study used the Review Manager application (RevMan 5.3). Data were analyzed based on variations between studies by determining the use of random effects analysis models. The results of the data analysis are in the form of the effect size value of the heterogeneity of the study, which later results from the data that has been analyzed and interpreted in the form of forest plots and funnel plots. Research from primary studies related to the relationship between hypertension and smoking with the severity of COVID-19 contained 12 articles with a total sample of 94,072 participants. Articles are obtained from 4 regions, namely, Asia, America, Europe, Africa. With a different number of respondents in each region.

## **RESULTS**

The search for articles was carried out using a database based on the PRISMA flow diagram, which can be seen in Figure 1. The study quality assessment was carried out qualitatively and quantitatively. Assessment of research quality with Critical Appraisal. Using the Critical Appraisal Skills Program (CASP) Oxford Center for Triple Value Healthcare can be seen in Table 1. Each of the 12 questions was answered with the answer choices: Yes, and No. After assessing the quality of the study, 12 articles included in the quantitative synthesis process of the meta-analysis were analyzed using RevMan 5.3.

**Table 1. Assessment of the quality of hypertension research on severity in COVID-19 patients**

No.	Questions	Dai et al. (2020)	Lucar et al. (2020)	Denova et al. (2020)	Yuan et al. (2020)	Lui et al. (2020)	Zang et al. (2020)	Caliskan et al. (2020)	Wang et al. (2020)
1.	Does this research clearly address the focused problem?	1	1	1	1	1	1	1	1
2.	Was the cohort recruited in an acceptable way?	1	1	1	1	0	1	1	1
3.	Is exposure accurately measured to minimize bias?	1	1	0	1	1	1	1	1
4.	Are the results accurately measured to minimize bias?	1	1	1	1	1	1	1	1
5.	Have they taken confounding factors into account in the design and/or analysis?	0	1	1	1	1	1	1	1
6.	Was the follow-up of the study complete enough?	1	1	1	1	1	1	1	1
7.	Was the follow-up of the study complete enough?	1	1	1	1	1	1	1	1
8.	What are the results of this study?	1	1	1	1	1	1	1	1
9.	How precise is the result?	1	1	1	1	1	1	1	1
10.	Do you believe in the results?	1	1	1	1	1	1	1	1
11.	Can the results be applied to the local population?	1	1	1	1	1	1	1	1
12.	Are the results of this study consistent with other available evidence?	1	1	1	1	1	1	1	1
<b>Total</b>		<b>11</b>	<b>12</b>	<b>11</b>	<b>12</b>	<b>11</b>	<b>12</b>	<b>12</b>	<b>12</b>

**Description:**

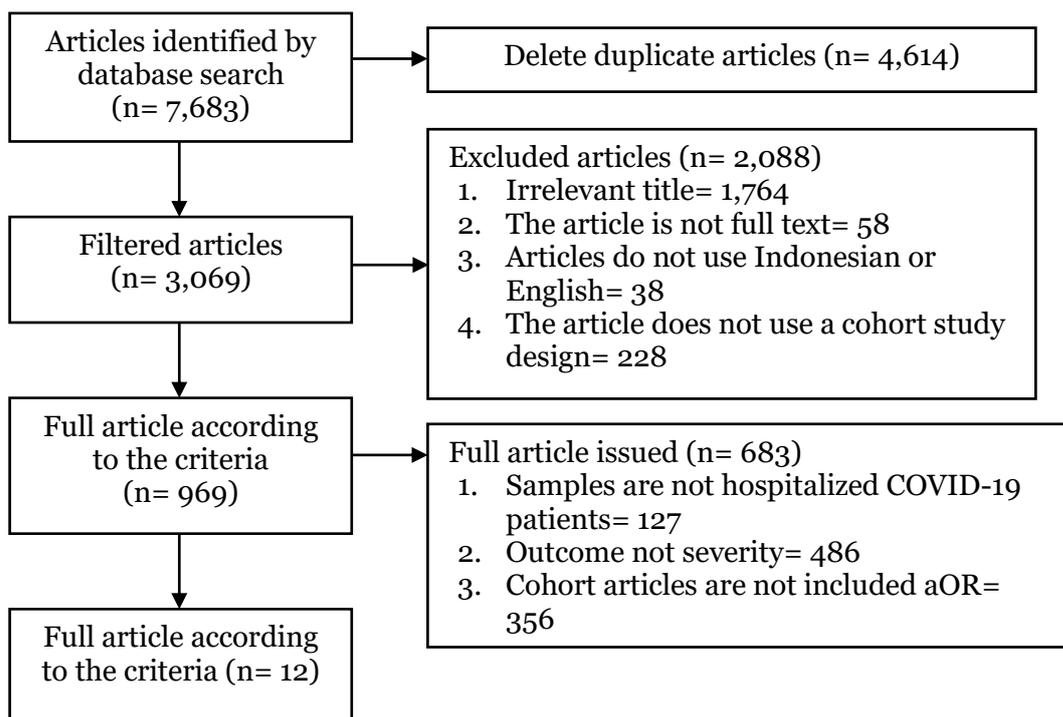
1: Yes; 0: No

**Table 2. Cont.**

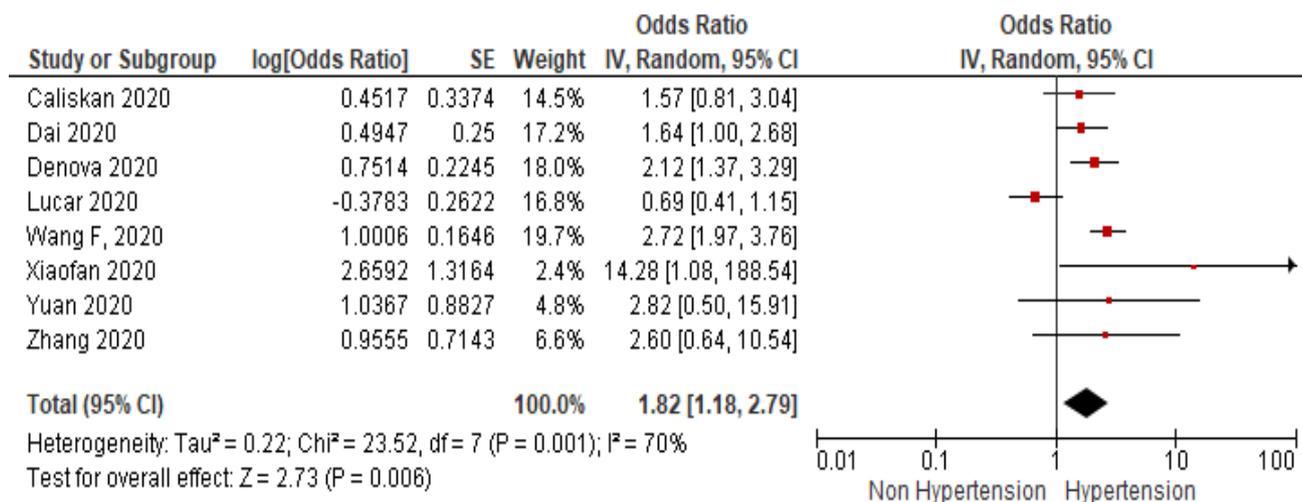
No.	Questions	Neira et al. (2020)	Lowe et al. (2020)	Mustofa et al. (2020)	Dai et al. (2020)	Lucar et al. (2020)	Caliskan et al. (2020)	Saadatian et al. (2022)
1.	Does this research clearly address the focused problem?	1	1	1	1	1	1	1
2.	Was the cohort recruited in an acceptable way?	1	1	1	1	1	1	1
3.	Is exposure accurately measured to minimize bias?	1	0	1	1	1	1	1
4.	Are the results accurate? measured to minimize bias?	1	1	1	1	1	1	1
5.	Have they taken confounding factors into account in the design and/or analysis?	1	1	1	1	1	1	1
6.	Was the follow-up of the study complete enough?	1	1	1	1	1	1	1
7.	Was the follow-up of the study complete enough?	1	1	1	1	1	1	1
8.	What are the results of this study?	1	1	1	1	1	1	1
9.	How precise is the result?	1	1	1	1	1	1	1
10.	Do you believe in the results?	1	1	1	1	1	1	1
11.	Can the results be applied to the local population?	1	1	1	1	1	1	1
12.	Are the results of this study consistent with other available evidence?	1	1	1	1	1	1	1
	<b>Total</b>	<b>12</b>	<b>11</b>	<b>11</b>	<b>12</b>	<b>12</b>	<b>12</b>	<b>12</b>

**Description:**

1: Yes; 0: No



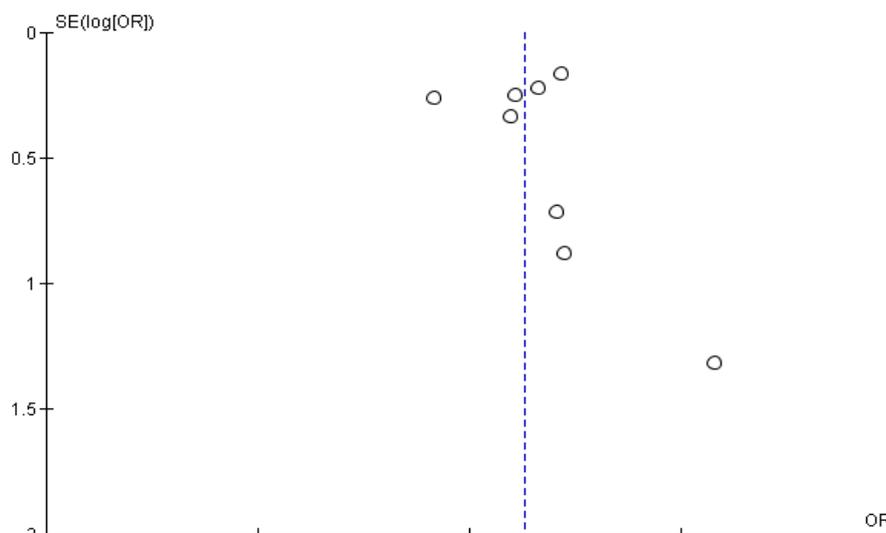
**Figure 1. PRISMA Flowchart**



**Figure 2. Forest plot of hypertension relationship with the severity of COVID-19**

Interpretation of the results of the meta-analysis process can be seen through the forest plot. Figure 2 shows that there is a relationship between hypertension which can increase the severity of COVID-19

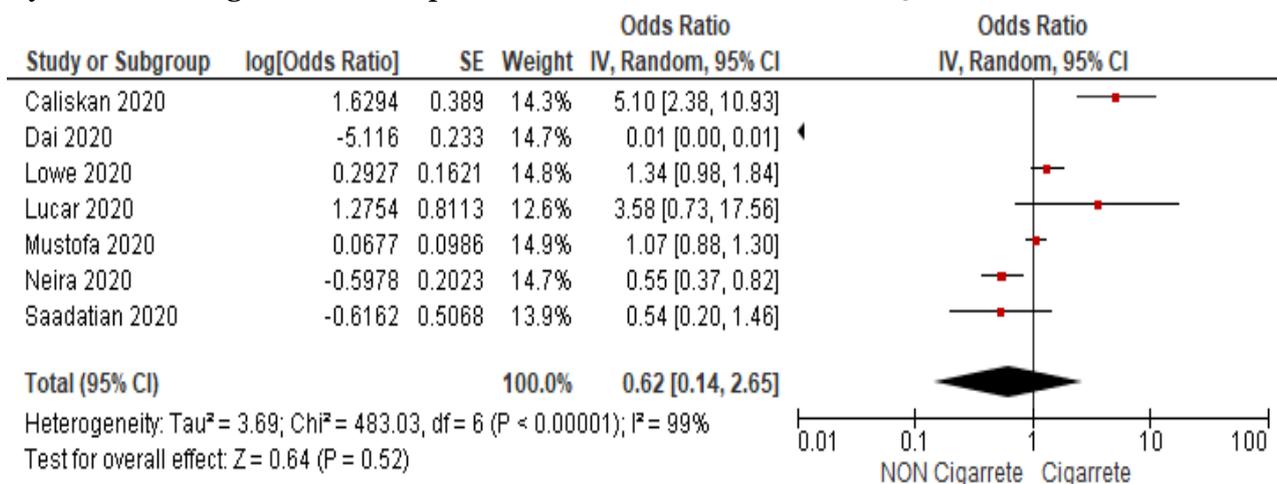
patients by 1.82 times compared to those without comorbid hypertension significantly (aOR= 1.82; 95% CI= 1.18 to 2.79; p= 0.006).



**Figure 3. Funnel plot of hypertension relationship with the severity of COVID-19**

Funnel plot is a result that can describe the distribution of research data against publication bias or standard error. Based on Figure 3. There is a publication bias with asymmetrical right and left plots where

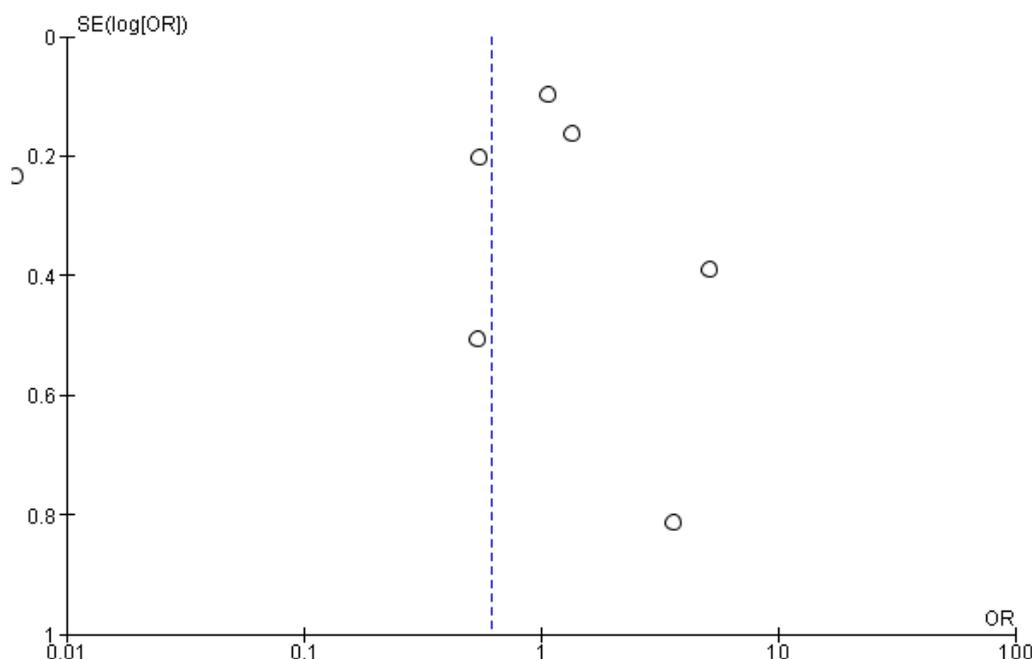
there are 3 plots on the left and 5 plots on the right. the plot on the left of the graph appears to have an SE between 0 to 0.5 while the plot on the right has an SE that is between 0 to 1.5.



**Figure 4. Forest plot smoking with the severity of COVID-19**

Interpretation of the results of the meta-analysis process can be seen through the forest plot. Figure 4 shows that COVID-19 treatment patients with smoking habits had a significantly higher risk of severity 0.62 times than those without smoking habits

(aOR= 0.62; 95% CI= 0.14 to 2.65; p= 0.520). From the forest plot, it can be concluded that the results of research on the relationship between smoking and severity in COVID-19 patients are under estimate.



**Figure 5. Smoking funnel plot with the severity of COVID-19**

Funnel plot is a result that can describe the distribution of research data against publication bias or standard error. Based on Figure 5. it shows that there is a publication bias which is indicated by the asymmetry of the right and left plots where there are 2 plots on the left and 5 plots on the right. The plot on the left of the graph appears to have a standard error between 0 to 0.5 while the plot on the right has a standard error of between 0 to 1 Bias also occurs from the imbalance in the distance between studies on both the right and left sides of the funnel plot.

## DISCUSSION

### 1. The relationship of hypertension to the severity of COVID -19

There are 10 articles with a cohort study design as a source of meta-analysis of the relationship between hypertension and the severity of COVID-19. The results of the meta-analysis on forest plots showed that COVID-19 patients with comorbid hypertension had a significantly increased severity of COVID-19 by 1.82 times compared to

COVID-19 patients without comorbid hypertension (aOR=1.82; 95%CI= 1.18 to 2.79; p= 0.006). In this study, there is a publication bias indicated by the funnel plot with the asymmetric distribution of the plot. Publication bias on the relationship of a history of hypertension suffered by COVID-19 patients to severe conditions.

Because there are studies that have a small number of samples so that the SE value is large. The primary research article identified by Lucar et al. (2021), Lui. (2020), and Wang et al. (2021) have SE values of SE= 0.26, SE= 1.31 and SE= 0.16, i.e. SE values >0.50 so that the distribution in the funnel plot is not symmetrical which causes publication bias.

These results are in accordance with the theory expressed by Murti (2018) where the variables with publication bias include sample size, type of design, sponsorship, conflict of interest and prejudice about the observed relationship. The advantage of this meta-analysis study is that it can ensure that this type of meta-analysis study can provide strong evidence about the

relationship of hypertension to the incidence of severity in COVID-19 patients who are hospitalized.

The results of this study are supported by another study by Pititto et al., (2020) stated that COVID-19 patients with hypertension had a 2.98 times risk of developing a severe condition for COVID-19 patients compared to those without hypertension (aOR= 0.89 95% CI= 2.37 to 3.75. Another study was also conducted by Zhang et al. (2020) which explained the association of hypertension with the severity and mortality of SARS-COV-2 infection with COVID-19 disease, this study was conducted through a meta-analysis method, the results of the study explained that there is a relationship between hypertension that has been had by COVID-19 survivors by 2.27 times compared to COVID-19 patients without hypertension aOR= 2.27; 95% CI= 1.80 to 2.86

A severe case (for adults) of a COVID-19 patient is characterized by breathing 30 breaths/min, oxygen saturation of 93% at rest, arterial partial pressure of oxygen (PAO<sub>2</sub>)/fraction of inspired oxygen. This condition is something that must be monitored intensively during the treatment period, usually patients with severe conditions will receive treatment in the ICU. Kuneš and Zicha (2009) explained that hypertension is a condition when blood pressure or blood circulation pressure is applied to the walls of the body's main blood vessels, namely arteries. This shows that hypertensive patients are in a condition when the circulating blood pressure is too high.

Kumar et al. (2020) stated that the severity experienced by COVID-19 patients was associated with several supporting factors, based on the results of the study it was found that age and gender and comorbid hypertension were the dominant

factors in supporting the severity of the COVID-19 treatment patients. Meanwhile, according to Bauer et al. (2021) explained that patients with comorbid hypertension had a significant effect of 3.66 compared to patients without comorbid hypertension 3.66; 95% CI= 2.79 to 4.8.

## **2. The relationship of smoking to the severity of COVID-19**

Based on the database search results, articles that were eligible to be used as meta-analysis data, there were 7 articles regarding the relationship of smoking to severe conditions in COVID-19 patients. The articles used in this analysis come from various continents in the world, namely the Asian continent, the American continent, the European continent. This shows that the incidence of severity related to the previous smoking history of these hospitalized patients occurs in almost all continents. Data analysis was carried out one by one to find the magnitude of the influence of each variable. The results of the meta-analysis on forest plots showed that COVID-19 hospitalized patients with a history of smoking had a risk of severity up to 0.62 times compared to COVID-19 patients without a previous smoking history, but this was not significant (aOR = 0.62; 95% CI 0.14 to 2.65; p=0.52). In this study, there is a publication bias indicated by the funnel plot, with the result that the plot distribution is not symmetrical. The funnel plot shows the standard error relation of effect size from several studies that have been studied, which shows that there is a publication bias which is indicated by the asymmetry of the right and left plots where there are 2 plots on the left and 5 plots on the right. The plot on the left of the graph appears to have a standard error of 0 to 0.5, while the plot on the right has a standard error of 0 to 1. Bias also occurs from the imbalance in the distance between

studies on both the right and left sides of the funnel plot.

The use of tobacco was first used in the 16th century, for ritual purposes in the Indians, in contrast to Europeans using tobacco to smoke for pleasure only. According to PP no.81/1999 article 1 paragraph (1), cigarettes are processed products of packaged tobacco including cigars or other forms produced from the *nicotiana tabacum*, *nicotiana rustica* and other species or their synthetics containing nicotine and TAR with no additional ingredients. One of the ingredients in cigarettes that can cause addiction is nicotine, nicotine is a substance or pyrrolidine compound contained in *nicotiana tabacum*, *nicotiana rustica* and other species or their synthetics which are addictive and can lead to dependence.

This is one of the factors that causes dependence on smokers and has difficulty quitting smoking. In addition, the environment affects the smoking habits of individuals. Nugraheni (2004) explains that the environment greatly affects a person's level of health. Unhealthy environmental conditions will reduce a person's level of health. this relates to the pattern of a person's smoking habit where the environment strongly supports the occurrence of this habit pattern.

Mahabee-Gittens et al. (2021) identify how the final outcome of COVID-19 treatment patients who have a smoking habit is by counting the number of packs of cigarette that have been used by each individual who has a smoking habit. The results showed that patients with smoking habits had a risk of as much as 1.3 compared to COVID-19 patients who did not smoke (aOR= 1.23; 95% CI= 1.04 to 1.44). Inpatients with smoking habits have a risk of severity experienced by male

adults, if it is associated with the environment and history of first smoking.

In this study, there are several limitations of the research experienced by the researcher, namely there is a language bias because in the research the selected articles are only published in English so that they ignore articles that use other languages. The articles analyzed in this meta-analysis are mostly from Asia and America, so the results are not representative of the rest of the world. The article on the relationship between smoking and the severity of COVID-19 patients analyzed in the meta-analysis only used 7 articles. There is a search bias because in this study the researchers only used 3 databases, namely PubMed, Google Scholar and Science Direct.

#### **AUTHORS CONTRIBUTION**

Lisa Safaah Novia L is the main researcher who chooses the topic, searches and collects research data. Didik Gunawan Tamtomo and Bhisma Murti analyzed data and reviewed research documents.

#### **FUNDINGS AND SPONSORSHIP**

This study is self-funded.

#### **CONFLICT OF INTEREST**

There is no conflict of interest.

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