Analysis of Mortality Factors in COVID-19 Patients; Systematic Review

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Abstract.
Coronavirus disease 2019 (COVID-19) is a highly contagious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. The increase in the number of COVID-19 cases is progressing quickly and has been spread between countries. As of October 14, 2020, there are 213 countries/regions around the world that have reported Covid-19 with a total of 38,002,699 confirmed cases of which 1,083,234 died. The purpose of this study was to determine the relationship between mortality factors and mortality in COVID-19 patients to predict the patient's prognosis. This research method is a systematic review through a literature review on mortality factors in COVID-19 patients Literature searches were accessed through internet searches using the Pubmed database based on the preferred reporting items for systemic review and meta-analysis (PRISMA). A systematic search was carried out on 18 October - 20 October 2020 with the keywords "COVID-19" AND "Death" OR "Decease" AND "Factor Associated". There were 8 literature selected that met the inclusion and exclusion criteria. Based on the findings of the eight journals, mortality is old age, male, has a clinical condition of hypertension, obesity, diabetes, cardiovascular disease, lung disease, neurological disease, lymphophenia laboratory test results, hyperlactate dehydrogenase, increased procalcitonin, increased neutrophils, increased C-reactive protein, and increased D-dimer. All literature reported that a p value <0.05 was obtained from the analysis of the relationship between mortality factors and cases of death in COVID-19 patients. There is a significant relationship between mortality factors and the death of COVID-19 patients, where the mortality factors are elderly, male, have a clinical condition of hypertension, obesity, diabetes, cardiovascular disease, lung disease, neurological disease, lymphophenia laboratory test results, hyperlactate dehydrogenase, increase in procalcitonin, increase in neutrophils, increase in C-reactive protein, and increase in D-dimers in which the prognosis of patients who have mortality factors tends to be worse.

Keywords: Mortality, Coronavirus, COVID-19

1. INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an international health problem that has been declared a pandemic by the World Health Organization (WHO). The COVID-19 pandemic is a major health crisis affecting almost every country.[1] WHO has identified the cause of COVID-19 as the Severe Acute Respitaratory Syndrome Coronavirus-2 (SARS-CoV-2) virus which spread rapidly at the end of 2019 in Wuhan. In a short time, several countries also reported an increase in cases of pneumonia and acute respiratory distress syndrome (ARDS) as part of COVID-19 infection which contributed to the increase in mortality in COVID-19 cases.[2]

The increase in the number of COVID-19 cases is progressing quickly and there has been a spread between countries. As of October 14, 2020, there are 213 countries/regions around the world that have reported Covid-19 with a total of 38,002,699 confirmed cases of which 1,083,234 died. Among these cases were health workers who were reported to be infected. On October 14 2020, Indonesia reported 340,622 confirmed cases of COVID-19, of which 12,027 cases died. The attack rate for COVID-19 cases in Indonesia is 0.094% and the Case Fatality Rate for COVID-19 cases in Indonesia is 3.88%.[3] Common signs and symptoms of COVID-19 infection include acute respiratory symptoms such as fever, cough, and shortness of breath. The average incubation period is 5-6 days with the longest incubation period of 14 days. Severe cases of COVID-19 can cause pneumonia, acute respiratory syndrome, kidney failure and even death. Clinical signs and symptoms reported in the majority of cases were fever, with some cases having difficulty breathing, and X-rays showing a large pneumonia infiltrate in both lungs. COVID-19 is transmitted through close contact and droplets.[4]

An observational descriptive study by Rahel Burke, et al. in the United States in 2020 reported that the symptoms of COVID-19 from 164 patients were cough, dry cough, productive cough, bloody cough, fever, myalgia, chills, fatigue, headache, shortness of breath, sore throat, rhinorrhea, diarrhea, appetite decreased eating, nausea, chest pain, decreased sense of smell and taste, abdominal pain, wheezing, vomiting, nasal congestion, conjunctivitis, night sweats, rash, dizziness, atralgia, and seizures.[5] Research related to COVID-19 infection is ongoing, and research data shows that not all infected people become sick or, in other words, do not have clinical symptoms (asymptomatic). COVID-19 patients experience clinical symptoms that vary from mild to severe. This shows that the morbidity rate between one patient and another patient is different. The variation in symptoms is influenced by the ability of the patient's immune system.[6] An observational descriptive study by Guan WJ in Wuhan in 2020 reported that clinical symptoms of COVID-19 patients include cough, fever, runny nose, sore throat, headache, spasms, myalgia, headache, and diarrhea.[7]

In addition, an observational descriptive study by Huang CL, et al. in China also reported clinical symptoms of COVID-19 patients including fever, cough, shortness of breath, bloody cough, myalgia, diarrhea, and headache.[8.] Observational descriptive research by Zhiliang Hu, et al. in Nanjing in 2020 reported that 24 cases were found asymptomatic (asymptomatic). All cases were subjected to CT scans, as many as 12 people found ground-glass images, 5 people had pneumonia, and 7 people had normal CT-scan images. A few days later after undergoing treatment at the hospital, five cases experienced one of the symptoms of COVID-19 infection such as fever, cough, and shortness of breath.[9] COVID-19 patients are classified into mild to moderate and severe symptoms based on the need for treatment. Patients with mild to moderate symptoms should rest at home with supportive care.[10]

Patients experiencing severe symptoms require supportive hospital care because the patient develops acute respiratory distress syndrome (ARDS) one week after symptoms.[11] Hilda Razzaghi, et al. reported the estimated prevalence of individuals ≥18 years of age with certain medical conditions experiencing severe symptoms in the United States, namely patients who are obese (0.3), diabetes mellitus (0.11), chronic obstructive pulmonary disease (0.069), heart disease (0.068), and chronic kidney disease (0.031).[12] Studies have also shown that the mortality rates for confirmed case patients differ from one another, determining whether the patient is healing or dying. This is caused by several factors such as the presence of comorbidities and age.[13] An observational descriptive study by Jeremy Gold, et al. in the United States in 2020 reported that the characteristics of COVID-19 patients (n = 114,411) who died were mostly patients aged ≥85 years (30.4%), 75-84 years (26%), 65-74 years (21.7%), and 50-64 years (16.4%). The place where patients died mostly were in the hospital when the patients were receiving supportive care, as much as 64.3%. This shows that patients who die experience severe symptoms that require supportive care in the hospital and are mostly the elderly group.[14]

A retrospective cohort study by Xiaochen Li, et al. in Wuhan in 2020 reported that elderly patients (≥ 65 years), obesity, hypertension, diabetes, heart disease, and chronic kidney disease had high morbidity rates with severe symptoms.[15] n addition, a retrospective cohort study by Lee Lennard in the United Kingdom in 2020 reported that in COVID-19 patients who have cancer, cancer or cancer treatment is not the main cause of death, but the comorbidities of hypertension and diabetes.[16] A retrospective cohort study by Jiang Xie in China in 2020 reported the results of an analysis that the mortality of COVID-19 patients was significantly associated with hypoxemic conditions. Patients with hypoxemia have comorbid hypertension, whereas patients who do not have hypertension do not experience hypoxemia and only have dyspnea.[17]

Based on the data, the number of confirmed COVID-19 cases is very large, with the increase in the number of cases that are taking place quite rapidly and the number of deaths can also continue to increase, so the aim of this study is to conduct a systematic review of the factors that influence the mortality of COVID-19 patients to predict patient prognosis. After knowing the factors that affect the mortality of COVID-19 patients, intervention steps can be taken to reduce the mortality and morbidity rates of COVID-19 patients so that the mortality rate can be reduced.

II. METHODS

The main data source in this study using the Pubmed database. The data inclusion criteria for this research are analytic studies or research related to the mortality factor of COVID-19 patients by adjusting the required variables, the study can be accessed freely and for free, full text, using English, and able to answer. the purpose of this research. Exclusion criteria included systematic reviews, letters,

comments, and editorial studies. A systematic search was carried out on 20 November - 4 December 2020 with the keywords “COVID-19” AND “Death” OR “Decease” AND “Factor Associated”. To identify relevant studies in this study, title and abstract screening were carried out. Data from each study were extracted in standard form including author name, year, title, research design, number of samples, and research findings. Assessment of the study quality of each data used the Joanna Briggs Institute (JBI) Critical Appraisal guidelines. Based on literature search results from data based pubmed and using customized keywords, the researcher found 641 articles that matched these keywords. The search results that have been obtained are then checked by screening titles and abstracts based on inclusion criteria, 22 articles are obtained, then from the 22 articles a number of 14 articles that do not meet the requirements are issued, leaving 8 articles.

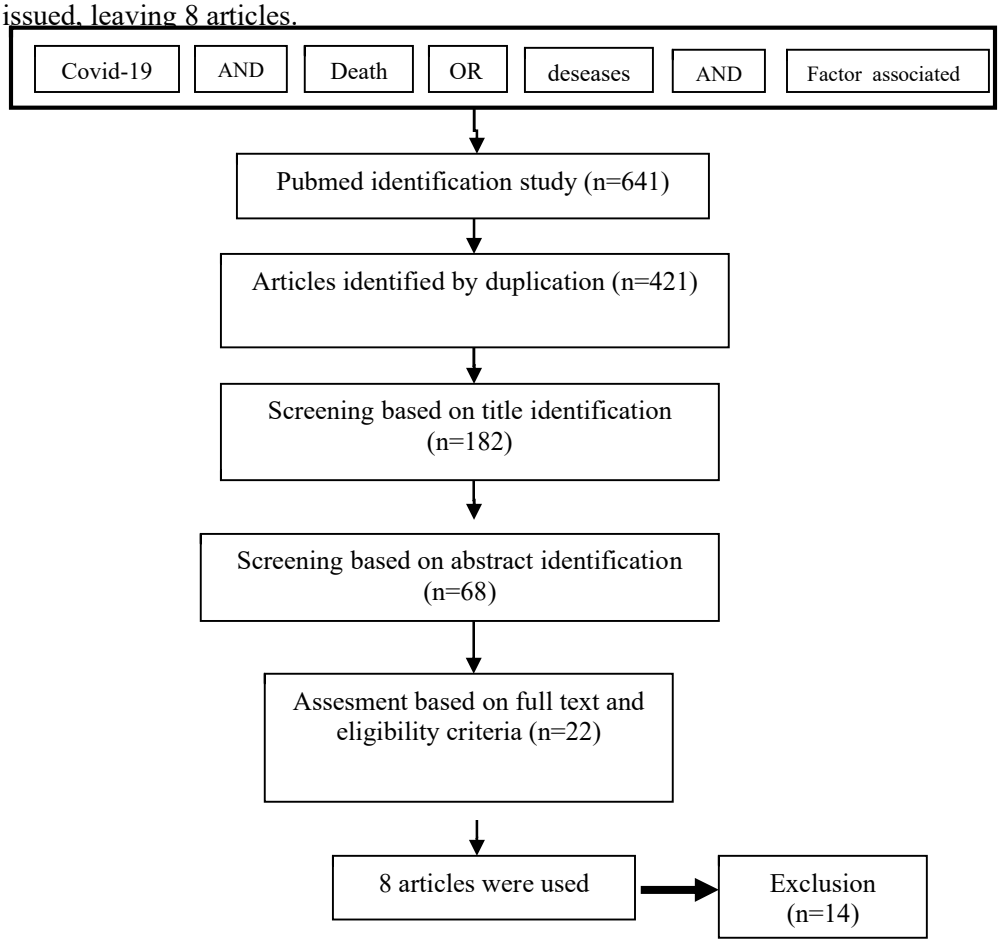

Diagram 1. PRISMA *Flowchart*

III. RESULT AND DISCUSSION

Table 1. Search Results Summary

Author, Year, Place of Research	Research Design	Number of Samples and Characteristics	Data Retrieval Tools	Findings
Turcotte JJ, et al.18 (2020) United States	Retrospective Cohort	The sample of this study was 117, who were confirmed COVID-19 patients through PCR with age >18 years who were hospitalized at least one night in the hospital in the period 1 March - 1 April 2020. Characteristics of COVID-19 patients who have a mortality factor were identified, then carried out observation until April 1 to see the outcome of whether the patient died or was alive.	Medical Records	The mortality rate for COVID-19 patients was 24.8% and the average length of stay in the hospital was 11.82 days (95% CI: 10.01-13.63). As many as 30.8% of patients were admitted to the Intensive Care Unit (ICU) and 29.1% needed a ventilator. The results of multivariate regression analysis showed that the risk factors that had a significant relationship with the mortality of COVID-19 patients were hypoxia (OR: 1.208, 95% CI: 1.011-1.443, p = 0.037), diabetes mellitus (OR: 11.873, 95% CI: 2.218-63.555, p = 0.004) and chronic kidney disease (OR: 4.793, 95% CI: 1.528-15.037, p = 0.007).
Caizheng Yu, et al.19 (2020) Wuhan, China	Retrospective Cohort	The study sample was 1663 who were COVID-19 patients diagnosed in the period January 14 -February 28, 2020. Characteristics of COVID-19 patients who have a mortality factor were identified, then observation was carried out until March 26, 2020 to see the outcome of whether the patient died or was alive.	Medical Records	The results of the multivariate regression analysis showed that there was an increase in the odds ratio of mortality in patients who were >65 years old (OR: 2.15, 95% CI: 1.35-3.43, p = 0.000), male gender (OR: 1.97, 95% CI: 1.29 - 2.99, p = 0.000), diabetes mellitus (OR: 2.34, 95% CI: 1.45 - 3.76, p = 0.000), and lymphophenia (OR: 1.59, 95% CI: 1.03-2.46, p = 0.002).
Sousa G, et al.20 (2020) Brazil	Cross-sectional	The sample of this study was 2070 confirmed patients with COVID-19. Identification of the characteristics of COVID-19 patients and analysis of the relationship between characteristics and outcome was carried out.	Medical Records	Obtained from 2070 patients confirmed COVID-19, as many as 131 patients (6.3%) died and 1939 (93.7%) lived. Mortality increased in patients aged > 60 years (OR: 3.6, 95% CI: 2.3-5.8, p <0.001), neurological disease (OR: 3.9, 95% CI: 1.9- 7.8, p <0.001), lung disease (OR: 2.6, 95% CI: 1.4-4.7, p <0.001), and cardiovascular disease (OR: 8.9, 95% CI: 5 , 4-14.5, p <0.001).
Feng Pan, et al.21 (2020)	Case-control	The sample of this study was 35 patients categorized as the control group and as many as 89 patients were categorized as cases (deaths). An analysis of the relationship between	Medical Records	The analysis showed a significant relationship between male gender (p = 0.01), hypoxia (p = 0.001), diastolic blood pressure (0.037), neutrophils> 0.64 × 109 / L (p = 0.037), lymphophenia. (p <0.0001), C-reactive protein> 77.35 mg / L (p = 0.001), procalcitonin> 0.20µg

China		mortality factors and the death of COVID-19 patients was carried out.		/ L (p = 0.001), lactate dehydrogenase> 481 U / L (p = 0.001) , and D-dimer> 3.06 mg / L (p = 0.013) with mortality cases.
Qiao Shi, et al.22 (2020) China	Retrospective Cohort	There are 1561 patients confirmed COVID-19. A total of 153 patients were sampled because they had a history of diabetes, the rest were matched to serve as a control group (n = 153) during the period 1 Janurai - 8 March 2020. Identification of patient characteristics and observations to see the outcome of whether the patient died or was alive were carried out dead or alive until March 24, 2020.	Medical Records	The obtained mean age of the sample is 64 years. Diabetic patients who entered the intensive care unit had a proportion of 17.6%, higher than the control group which was only 7.8%. The proportion of cases of death in the COVID-19 patient group was 20.3%, greater than the control group at 10.5% (p = 0.017). The results of multivariate regression showed that the factors of age ≥70 years (OR: 2.39, 95% CI: 1.03-5.56) and hypertension (OR: 3.10, 95% CI: 1.14-8.44) was an independent factor of case death in diabetic patients infected with COVID-19 (p <0.05).
Haiying Sun, et al.23 (2020) Wuhan	Case-control	The sample of this study was 244 confirmed COVID-19 patients aged ≥60 years who were treated at Tongji Hospital, of which 123 were alive (controls) and 121 died in hospital (cases). Characteristics of COVID-19 patients were identified and analysis of the relationship between mortality factors and mortality of COVID-19 patients.	Medical Records	The results of the analysis showed that there were significant differences in clinical characteristics and laboratory results (p <0.05) between patients who died and patients who were alive. Multivariate analysis found that lymphophenia (OR: 0.009, 95% CI: 0.001-0.138, p = 0.001) and older age (OR: 1.122, 95% CI: 1.007-1.249, p = 0.037) were independent mortality factors for COVID -19. patients. There were no significant differences between women and men.
Zhang J, et al.24 (2020) Wuhan	Retrospective Cohort	The sample of this study were 663 patients with confirmed COVID-19 from 11 January-6 February 2020 at Remnin Hospital. Identification of the characteristics of COVID-19 patients was carried out and the outcome was observed for patients who died or lived until March 5, 2020.	Medical Records	The analysis showed that the mortality rate for COVID-19 was 3.77%. Patients over 60 years of age, male, had one or more chronic diseases had a significant association with severe symptomatic cases. The results of multivariate regression analysis showed that severe symptom cases were significantly associated with case death (p = 0.001).

Leonidas Palaiodimos, et al.25 (2020) New York	Retrospective Cohort	The sample of this study consisted of 200 patients who were confirmed COVID-19 and had been treated for at least one week during the period 9 March-22 March 2020. Identification of patient characteristics and observation of patient outcomes were carried out until 12 April 2020.	Medical Records	The average age of the sample was 64 years, with the most common comorbid factors being hypertension (76%), hyperlipidemia (46.2%), and diabetes (39.5%). The analysis showed that there was a significant relationship between old age (p = 0.001), male gender (p = 0.027), body mass index> 35kg / m2 (p <0.0001), cardiovascular disease (p = 0.026), and chronic renal failure disease (p = 0.024) with mortality in COVID-19 patients. The results of multivariate analysis of body mass index> 35kg / m2 (OR: 3.78, 95% CI: 1.45-9.83, p = 0.03), male (OR: 2.74, 95% CI: 1.25-5.98, p = 0.011), and old age (OR: 1.73, 95% CI: 1.13-2.63, p = 0.11) were independent factors for the high mortality rate of COVID-19 patients.

Based on the results of the literature search process which can be seen in Diagram 1, it was found that 641 literatures were available in the database. These results were re-selected, and most were excluded after screening. A total of 22 studies matched the inclusion criteria, then 14 were excluded and 8 were selected. A summary of the study data selected in this study is presented in Table 1. There were 5 retrospective cohort studies, 2 case control studies, and 1 cross-sectional study. The methodological quality assessment using the JBI Critical Appraisal shows that the studies are generally of good quality.[26-28]

Based on the findings of the eight journals, it was found that the mortality factors were old age, male, had a clinical condition of hypertension, obesity, diabetes, cardiovascular disease, lung disease, neurological disease, hypoxia, lymphophenia laboratory test results, hyperlactate dehydrogenase, increased procalcitonin, increased neutrophils, increased C-reactive protein, and increased D-dimers. As many as 6 of the 8 literature found a significant relationship between elderly> 60 years old and cases of death in COVID-19 patients. As many as 3 of the 8 literature found a significant relationship between male sex and laboratory results in the form of lymphophenia, hyperlactate dehydrogenase, increased procalcitonin, increased neutrophils, increased C-reactive protein, and increased D-dimers with cases of death in COVID-19 patients. The entire literature reports the results of the analysis that there is a significant relationship between comorbid diseases and cases of death in COVID-19 patients.

These findings are consistent with systematic review research and meta-analysis by Zhaohai Zheng, et al. in 2020 which reports the findings that there is a statistically increased odds ratio of severity and mortality in male patients, over 65 years of age, smoking, hypertension, diabetes, pulmonary disease, cardiovascular

disease, lymphophenia laboratory results, hyperlactic dehydrogenase, increased procalcitonin, increased neutrophils, increased C-reactive protein, and increased D-dimers.[26] A meta-analysis study by Farha Musharrat Noor and Momin Islam in 2020 reported the findings of the highest mortality rate, namely in the European region and the factor of age> 60 years, being admitted to the Intensive Care Unit, and patients with comorbid diseases had a significant association with death cases.[29]

Based on existing data, comorbid hypertension and diabetes mellitus, male gender, and active smoking are risk factors for mortality and morbidity for COVID-19 patients. Patients with primary underlying disease, especially those with a history of chronic diseases such as hypertension, diabetes, coronary heart disease and cancer, are more prone to have a poor prognosis risk than patients without comorbid diseases. Patients who have comorbid diseases have low systemic immunity due to the primary underlying disease itself and due to its treatment.[30]

The higher distribution in males is thought to be associated with a higher prevalence of active smoking. In smokers, hypertension, and diabetes mellitus, it is suspected that there is an increased expression of angiotensin converting enzyme-2 (ACE2) receptors so that they are at risk of experiencing more severe clinical symptoms of COVID-19. Cancer and chronic liver disease patients are more susceptible to SARS-CoV-2 infection. Patients with cirrhosis or chronic liver disease experience a decreased immune response, so they are more prone to catching COVID-19 and can experience a worse outcome.[31]

The increased risk of disease severity will gradually increase starting from around the age of 40. It is important for individuals in this age group to maintain their own health, and that of those around them who are more susceptible to this disease. Children are not included in the group at risk of experiencing severe symptoms of COVID-19 because children have a much better immune response than adults in responding to COVID-19. This can be influenced by several factors, such as children still receive food that supports the growth and development of the immune system, children are not as exposed to irritants such as cigarette smoke, and children rarely have a history of hypertension. Adults must continue to teach children to maintain hygiene as an effort to prevent infection.[20]

Age affects the body's immunity in responding to SARS-CoV-2 infection. In the population of those aged 40 years, it is found that there is a decrease in immunity and as age increases, there is a decrease in immunity. In addition, immunity is also influenced by mental health. The COVID-19 pandemic has an impact on decreasing people's income, and there is sadness and loneliness felt by families who experience grief because a loved one has died due to COVID-19, worry and stress. The hormones produced at this time can reduce the protective properties of antibodies and lymphocyte cells.[20] One theory regarding the pathogenesis of SARS-CoV states that severe clinical symptoms occur because the host's immune response ability is inadequate. Thus, increasing the ability of the body's immunity has the potential to reduce the risk of

morbidity and mortality of COVID-19 patients. In addition, the mortality rate must start with adequate preventive and management measures.[32]

IV. CONCLUSION

There is a significant relationship between the mortality factor and the death of COVID-19 patients, where the mortality factors are old age, male, have a clinical condition of hypertension, obesity, diabetes, cardiovascular disease, lung disease, neurological disease, lymphophenia laboratory test results, hyperlactate dehydrogenase, increase in procalcitonin, increase in neutrophils, increase in C-reactive protein, and increase in D-dimers so that the prognosis of patients who have mortality factors tends to be worse.

V. ACKNOWLEDGMENTS

Thank you to all those who have contributed and been involved in this research so that the research can be carried out well.

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