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Analysis of Comorbidity Disease as A Risk Factor COVID-19 Death

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ABSTRACT

The COVID-19 disease which became a pandemic in early 2020 was caused by SARS-CoV-2 which attacks the human respiratory system. The transmission of COVID-19 that occurs through human-to-human transmission causes a high risk of infection worldwide. A high-risk factor for death from COVID-19 occurs in people who have comorbidities that aggravate symptoms in COVID-19 patients. Although the incidence of this disease is not influenced by age and gender, the fact that most deaths from COVID-19 occur in elderly men. Comorbidities play an important role in the infection process that occurs, presumably due to an increase in the expression of the ACE2 enzyme, and a decrease in the cellular immune system. This literature review aims to determine the role of comorbid disease as a risk factor for COVID-19 death. This paper was prepared using the Literature Review method with a Narrative Review approach. By referring to research results from reputable national and international journals from 2020 to 2021 through the Pubmed, Clinical Key, and Google Scholar databases. Based on the analysis of the Literature Review, it was found that the presence of comorbid diseases increases the risk of infection, exacerbates symptoms, and death in COVID-19 patients. The comorbid disease with the highest mortality rate was found in hypertension, followed by diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease (COPD), and cancer. Patients who have more than one co-morbidity have a higher risk of death if they are infected with COVID-19. Comorbid diseases will increase the risk of death in COVID-19 patients.

Keywords: COVID-19, comorbidity, SARS-CoV-2

Introduction

In early 2020, the world was shocked by the incidence of severe infections with unknown causes, which began with a report from China to the World Health Organization (WHO) that there were 44 severe pneumonia patients in an area in Wuhan City, Hubei Province, China. The initial assumption was that this was related to a market selling fish, marine animals, and various other animals. On January 10, 2020, the cause was identified and the genetic code was obtained, namely the new coronavirus (Handayani et al., 2020).

On January 30, 2020, WHO declared the incident a Public Health Emergency of International Concern (PHEIC). On February 11, 2020, WHO named it COVID-19. On March 11, 2020, WHO has declared COVID-19 as a pandemic (Handayani et al., 2020; Kemenkes RI, 2020).

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a new type of coronavirus that has never been previously identified in humans. Common signs and symptoms of COVID-19 infection include symptoms of acute respiratory distress such as fever, cough, and shortness of breath. In severe cases of COVID-19, it can cause pneumonia, acute respiratory syndrome, kidney failure, and even death (Kemenkes RI, 2020).

Globally, as of January 21, 2022, the number of confirmed cases of COVID-19 infection reached 340,543,962 cases spread across 227 countries, with a total death toll of 5,570,163. Countries with the most cases are the United States of America, India, Brazil, The United Kingdom, and France. (World Health Organization, 2021) Indonesia ranks 16th in the world with the number of confirmed cases, namely 4,280,248 cases, with a death rate of 144,201 people (Satgas Penanganan COVID-19, 2021).

Previous studies have shown that elderly patients or patients with comorbidity diseases such as cardiovascular disease, diabetes mellitus, cancer, hypertension, or lung disease are at higher risk of death. (Majeed et al., 2020) Based on the research of Chen et al. Shows that out of 799 people treated in hospital wards in Wuhan, there were 113 patients (14.4%) who died. Of the 113 people who died, the average was male, aged over 60 years, and had comorbidity diseases such as hypertension, diabetes, cardiovascular disease, or chronic obstructive pulmonary disease (Chen et al., 2020).

Material and Methods

This research is a Literature Review with a Narrative Review approach. The study was conducted by reviewing narratively articles related to comorbidity and COVID-19. The articles used are secondary data obtained using databases such as Clinical Key, Google Scholar, and NCBI. The articles used in this study amounted to 10 articles that had been filtered according to the reference criteria of this study.
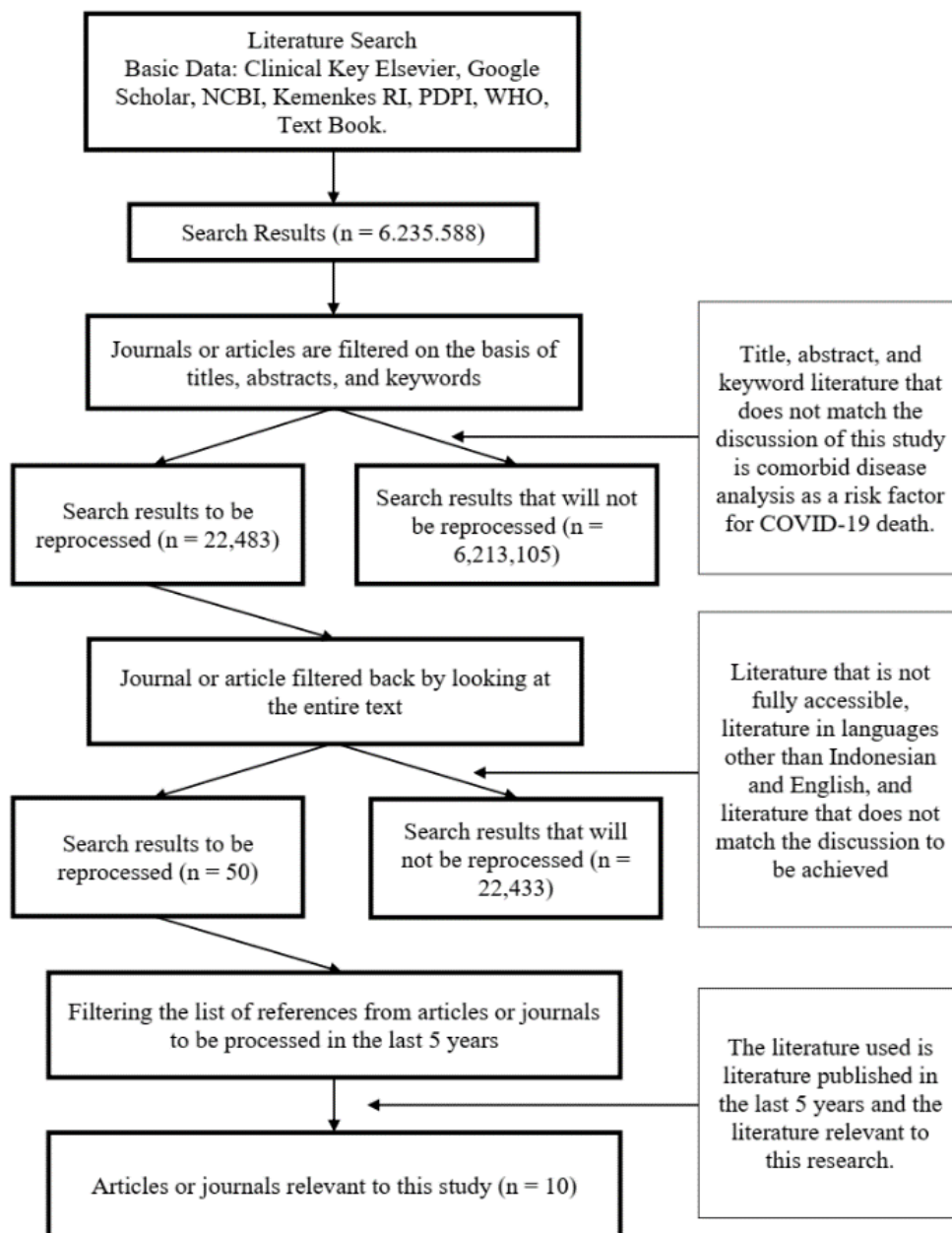
Figure 1. Literature search flow

Results and Discussion

Based on the search results as many as 6,235,588 articles from the keyword search "COVID-19, Comorbid, Hypertension, Diabetes, Tuberculosis, COPD, Heart Disease, CKD, Cancer, and Autoimmunity". All articles included in the search and music were then filtered based on titles, abstracts, and keywords that matched the research discussed. The search results after being filtered were 22,483 which were then filtered by looking at the suitability of the article content and the accessibility of the article. The results after being filtered again obtained 50 which were then filtered again by looking at the year of publication of the desired article, namely the last 5 years. The final results of the search and search for articles are 10 relevant articles for use in this study.

Table 1. Resesarch Results

No	Year of Issue	Title	Study Type	Authors	Result	Conclusion
1	2020	Delineating clinical characteristics and comorbidities among 206 COVID-19 deceased patients in India: Emerging significance of renin angiotensin system derangement	Retrospective with descriptive research design	Majeed, J. Ajmera, P. Goyal, R. K.	Death is more common in patients over 60 years of age and male. And 50.5% of the patients who died had pre-existing comorbidities. Diabetes and hypertension are the main comorbidities.	Patients with cardiovascular disease, diabetes mellitus, and hypertension have a greater risk of developing COVID-19 infection.
2	2020	Analisis Faktor Risiko Kematian Dengan Penyakit Komorbid COVID-19	Observational analytics with retrospective study design	Satria, Raden M. Ali. Tutupoho, Resty V. Chalidyanto, Djazuly.	Patients with comorbid diabetes and heart disease are risk factors for death in Bhakti Dharma Husada Hospital, Surabaya. Meanwhile, comorbidities, TB, COPD, CKD, CVA, Asthma, and HIV/AIDS are not risk factors for COVID-19 death.	Male, advanced age, diabetes, and hypertension are risk factors for death in COVID-19.
3	2021	Gejala dan Komorbid yang Memengaruhi Mortalitas Pasien Positif COVID-19 di Jakarta Timur, Maret-September 2020	Analytical study with retrospective cohort design	Drew, C. Adisasmita, Asri C.	Male sex increased mortality RR by 2.15, age ≥60 years by 4.49, respiratory symptoms by 2.17, external respiratory symptoms by 2.47, history of hypertension by 2.45, and history of chronic kidney failure by 3.33.	Gender, age, respiratory symptoms, external respiratory symptoms, history of hypertension, and history of chronic renal failure significantly increase the mortality risk of COVID-19 patients.
4	2021	Prevalence of comorbidities among individuals with COVID-19: A rapid review of current literature	Systematic Review	Bajgain, Kalpana T. Badal, Sujan. Bajgain, Bhisnu B. Santana, Maria J.	Major comorbidity-specific data showed a significant mortality in the CVD, HTN, and Diabetes groups, with relatively low mortality in COPD, CKD, Cancer, and other groups.	The higher prevalence of comorbid conditions in COVID-19 patients is accompanied by higher mortality in this cohort. The prevalence of hypertension, CVD, and diabetes is higher than COPD.

No	Year of Issue	Title	Study Type	Authors	Result	Conclusion
5	2021	Association of Sex, Age, and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis	Systematic Review and Meta-Analysis	Biswas, Mohitosh. Rahaman, Shawonur. Biswas, Tapas K. et al	Male patients, age ≥50 years, or having comorbid conditions (such as kidney disease, cerebrovascular disease, cardiovascular disease, respiratory disease, diabetes, hypertension, and cancer) were significantly associated with an increased risk of death in COVID-19.	Adequate protection and intervention for COVID-19 patients in general and male patients ≥50 years of age who have comorbidities can significantly reduce the risk of death related to COVID-19.
6	2021	Impact of comorbidity burden on mortality in patients with COVID-19 using the Korean health insurance database	Retrospective Cohort Study	Cho, Soo Ick. Yoon, Susie. Lee, Ho-Jin.	Hypertension, diabetes, CHF, dementia, chronic lung disease, liver disease, kidney disease, and cancer are significant risk factors for death in patients with COVID-19.	ACCI, combined with age and various comorbidities, is associated with mortality of patients with COVID-19 in South Korea.
7	2020	The potential association between common comorbidities and severity and mortality of coronavirus disease 2019: A pooled analysis	Systematic Review	Luo, Liman. Fu, Menglu. Li, Yuanyuan et al	A higher risk of severity was observed in COVID-19 patients with comorbidities. Comorbidities such as hypertension, diabetes, cardiovascular disease, COPD, CKD, and cancer. All comorbidities indicated a higher risk of death. In addition, the prevalence of acute cardiac injury was higher in the group with severe symptoms, and acute cardiac injury was associated with an increased risk	Comorbidity and acute cardiac injury are closely related to poor prognosis in COVID-19 patients.
8	2020	Comorbid Chronic Diseases and Acute Organ Injuries Are Strongly Correlated with Disease Severity and Mortality among COVID-19 Patients: A Systemic Review and Meta-Analysis	Systematic Review and Meta-Analysis	Wang, Xinhui. Fang, Xuexian. Cai, Zhaoxian et al	Pre-existing hypertension, CVD, CKD, and Diabetes are strongly associated with increased disease severity and poor prognosis in COVID-19 patients.	There is a strong correlation between the severity of COVID-19 and Hypertension, CVD, CKD, and Diabetes, four chronic diseases that are relatively common in the community.

No	Year of Issue	Title	Study Type	Authors	Result	Conclusion
9	2020	COVID-19 and comorbidities: Deleterious impact on infected patients	Systematic Review	Ejaz, Hasan. Alsrhani, Abdullah. Zafar, Aizza et al	COVID-19 patients with diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), hypertension, malignancy, HIV, and other commodities are at risk for severe symptoms and life-threatening situations.	A critical situation develops in patients with hypertension, diabetes, COPD, CVD, malignancy, and HIV. COPD patients tend to have more severe symptoms and a relatively high mortality rate.
10	2020	Prevalence of comorbidities in patients and mortality cases affected by SARS-CoV2: a systematic review and meta-analysis	Systematic Review and Meta-Analysis	Espinosa, Omar Ariel. Zanetti, Andernice. Antunes, Ednardo F. et al	The most common comorbidities in patients who died were hypertension, diabetes, heart disease, and COPD. In addition, cerebrovascular disease, cancer, kidney disease, liver disease, and others are also evaluated. 2.4-fold increased risk of death in patients with comorbid disease.	The increased risk of death by 2.4 times in COVID-19 patients who have comorbidities. The most common comorbidities are hypertension, heart disease, and diabetes.

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a new type of coronavirus that has never been previously identified in humans. (Kemenkes RI, 2020) Previous studies have shown that elderly patients or patients with comorbid diseases such as cardiovascular disease, diabetes mellitus, cancer, hypertension, or lung disease are at a higher risk of death (Majeed et al., 2020).

A study conducted by Majeed et al. showed that the death of COVID-19 patients was more common in patients aged over 60 years (53.4%) and men (69.3%) were more susceptible than women (30.68%). Of the 50.5% of patients who died had pre-existing comorbidities. Diabetes and hypertension were the main comorbidities (27.8% and 22.1%), and 13% had diabetes with hypertension. This is interesting because only 13.6% had respiratory problems, and 6.2% had previous heart disease (Majeed et al., 2020). The mortality rate of patients aged over 60 years (53.4%) is the same as that reported from most countries, indicating that the elderly are at higher risk of COVID-19 infection. This is because, in the elderly, there is: a decrease in the immune system, weak lung capacity, and a possible decreased ability to cope with physiological changes that occur in the body with age. They are also more prone to have conditions such as heart and lung disease, diabetes, or kidney problems that weaken the body's ability to fight infection (Majeed et al., 2020).

Weak immune mechanisms coupled with the occurrence of cytokine surges are one of the main causes that result in decreased cellular oxygenation at the alveoli level, as the main cause of death. ACE2 is expressed by epithelial cells of the lung, intestine, kidney, and blood. In patients with type 1 or 2 diabetes, hypertension, and possibly in patients with cardiomyopathy, increased ACE2 expression has been reported (Majeed et al., 2020). ACE2 gene expression is also expressed in the cardiovascular system, therefore patients with cardiovascular disease are likely to experience a greater risk of COVID-19 infection and also affect the prognosis of pneumonia. Pneumonia causes substantial obstruction of air exchange, leading to hypoxemia, which reduces energy supply by cellular metabolism and increases anaerobic fermentation. This causes damage to the phospholipid layer of cell membranes by intracellular acidosis and oxygen free radicals that cause respiratory disorders. Severe respiratory distress is considered the leading cause of death from COVID-19 (Majeed et al., 2020).

Majeed et al. concluded that patients with cardiovascular disease, diabetes mellitus, and hypertension had a greater risk of developing COVID-19 infection. As well as the possibility of damage to the entire RAS after the COVID-19 attack. Because of this, patients with pre-existing comorbidities and those on ACE inhibitors or angiotensin receptor blocker therapy should be monitored carefully (Majeed et al., 2020).

Research Satria et al. stated that from data from the Bhakti Dharma Husada Hospital in Surabaya, it was found that from 358 patients infected with COVID-19, 66 patients (18%) died. Of the 66 patients who died, 60.6% were male (OR 1.87, P 0.041), 22.7% were >64 years old (OR 2.097, P 0.041), and 83.3% had comorbidities. Diabetes mellitus (30.3%) (OR 4,348, P 0.000) and cardiovascular disease (10.6%) (OR 4,319, P 0.016) were the highest risk factors for death in COVID-19 (Satria et al., 2020). The age factor is a crucial factor for the outcome of COVID-19. The median age of patients who died was 68 years. Furthermore, 80% of deaths in COVID-19 are aged 65 years, so old age can be said to be a risk factor for COVID-19 mortality. The percentage of COVID-19 deaths is increasing due to increasing age. Patients with comorbid diabetes mellitus have a 2-fold greater risk of a more severe prognosis or critical illness requiring treatment in an intensive care unit (Satria et al., 2020).

COVID-19 patients with a history of cardiovascular disease or chronic obstructive pulmonary disease (COPD) have a higher tendency to die. Chronic heart and metabolic disease, acute inflammation, and decreased organ function (heart, kidney, liver, and hematology) experienced by patients at the beginning of treatment can increase the risk of death due to COVID-19 infection (Satria et al., 2020).

Few Covid-19 patients with risk factors for pregnancy, asthma, HIV/AIDS were observed and did not die, so they could not be risk factors for death. Other risk factors for death, such as hypertension, TB, COPD, CKD, and CVA have not risked factors for death because the number of reported cases was small with a P-value > 0.05. Satria et al. concluded that men, advanced age, diabetes, and hypertension were risk factors for death in COVID-19 (Satria et al., 2020).

Research conducted by Drew and Adisasmita stated that male sex increased mortality RR by 2.15 (95% CI: 1.47-3.14), age ≥60 years by 4.49 (95% CI: 3.05-6.63), respiratory symptoms by 2.17 (95% CI: 1.26-3.72, external respiratory symptoms 2.47 (95% CI: 1.43-4.29), history of hypertension 2.45 (95% CI: 1.46-4.10), and history of chronic kidney failure 3.33 (95% CI: 1.27-8.68) times higher. The history of DM and COPD was not found to have a significant effect (p-values 0. 269 and 0.141)(Drew & Adisasmita, 2021). The proportion of deaths of COVID-19 patients is increasing with age. The increased risk of death was 4.49 (95% CI: 3.05-6.63) times higher in patients ≥60 years of age. This is because the reserves of homeostatic functions will decrease with age, which positions the elderly in conditions that are not conducive to fighting aggressive infections, such as COVID-19. The results of studies related to a history of hypertension found an increased risk of death by 2.45 times higher. Populations with hypertension tend to have a higher number of ACE2 receptors, causing the coronavirus to be more easily disseminated in the body (Drew & Adisasmita, 2021).

A history of CKD was also found to increase the risk of mortality by 3.33 (1.27-8.68) times. This is because the course of the COVID-19 disease generally involves the release of inflammatory cytokines and the formation of antigen-antibody complexes that will affect cell membrane permeability. However, in patients with chronic kidney failure, the glomerular filtration process has worsened, so systemic inflammation due to COVID-19 can worsen kidney function. In addition, due to the presence of ACE2 receptors in the urogenital system, the COVID-19 virus can also easily stimulate the inflammatory process in the kidneys which will worsen the patient's condition (Drew & Adisasmita, 2021).

Meanwhile, the history of DM and COPD is different from the results obtained by Majeed et al. and Satria et al., in this study the effect of history of DM and COPD did not significantly affect mortality. This is presumably due to the results of missing data analysis performed after univariate analysis, which allows selection bias to occur that affects the accuracy of the analysis carried out (Drew & Adisasmita, 2021). Drew and Adisasmita concluded that male sex, aged over 60 years, having respiratory symptoms, having external respiratory symptoms, a history of comorbid hypertension and CKD significantly increased the risk of mortality in COVID-19 cases (Drew & Adisasmita, 2021). A study conducted by Bajgain et al. stated that the main comorbidity-specific data showed significant mortality in the CVD (34.9%), hypertension (35.2%), Diabetes (33.2%), and relatively low mortality in COPD (13%), cancer groups. (9.6%), CKD (8.3%), and others (11.6%) (Bajgain et al., 2021).

Cardiovascular diseases, including hypertension, coronary heart disease, cerebrovascular disease, cause about 17.9 million deaths per year worldwide. Viral infections can cause a variety of cardiovascular diseases, including myocarditis, pericarditis causing arrhythmias, and heart failure. In COVID-19, a possible association with ACE2 expression in cardiac tissue leads to myocardial injury. This study showed that acute cardiac injury occurs in about 7%-28% of all cases of COVID-19, with mortality around 10.5%. Of all cardiovascular diseases, hypertension was the most common comorbid (~30%) with death in 6% of cases (Bajgain et al., 2021).

Diabetes is one of the most common comorbidities. The long-term effects of increasing blood sugar lead to a decrease in the immune system and an increased risk of developing infections such as COVID-19. In addition, severity in COVID-19 patients is associated with possible overexpression of ACE2 in diabetic patients. Diabetes (17.4%) was the most common comorbidity after hypertension with a mortality of about 9.2% (Bajgain et al., 2021).

For COPD research shows that COPD (1.5%-3%) is uncommon in COVID-19 cases, with a mortality rate of around 6.3%. However, the severity of the risk appears to be comparable to that

of cardiovascular disease and diabetes (3-4-fold). Meanwhile, for cancer in COVID-19 patients, the prevalence is around 2.6% with a mortality rate of around 5%-7%. Complications of malignancy will disrupt the immune system, thereby increasing the risk of exposure and the possibility of severe symptoms in COVID-19. However, overall there is no clear correlation between COVID-19 mortality and cancer. This is due to the lack of data available in this study (Bajgain et al., 2021).

Complications of CKD include metabolic, electrolyte, and cardiovascular disturbances can cause severe symptoms and are often exacerbated by AKI. Although the impact of COVID-19 on the kidney is unclear, it is believed that the pathogenesis likely involves the expression of ACE2 in renal tissue, as the primary COVID-19 receptor. The prevalence of CKD in COVID-19 patients is 3.5% with mortality data varying from 16% to 53%. Thus, no clear association was found between COVID-19 mortality and CKD (Bajgain et al., 2021).

Bajgain et al. concluded a higher prevalence of comorbid conditions in COVID-19 patients along with higher mortality in this cohort. The prevalence of hypertension, CVD, and diabetes was higher in this group compared to COPD (Bajgain et al., 2021).

In a study conducted by Biswas et al. stated that male patients were associated with a significantly increased risk of death compared to female patients (RR 1.86: 95% confidence interval {CI} 1.67-2.07; p < 0.00001). Patients ≥50 years of age were associated with a 15.4-fold significantly increased risk of death compared to patients <50 years of age (RR 15.44: 95% CI 13.02-18.31; p < 0.00001). Comorbidities were also associated with a significantly increased risk of death, such as kidney disease (RR 4.90: 95% CI 3.04–7.88; p < 0.00001), cerebrovascular disease (RR 4.78; 95% CI 3.39–6.76; p < 0.00001), cardiovascular disease (RR 3.05: 95% CI 2.20–4.25; p < 0.00001), respiratory disease (RR 2.74: 95% CI 2.04–3.67; p < 0.00001), diabetes (RR 1.97: 95% CI 1.48–2.64; p < 0.00001), hypertension (RR 1.95: 95% CI 1.58–2.40; p < 0.00001), and cancer (RR 1.89; 95% CI 1.25–2.84; p = 0.002) (Biswas et al., 2021).

Comorbidities may be associated with decreased immune function. For example, in diabetic patients, the natural immune function is substantially reduced, which can limit the body from producing antibodies against infection. Comorbidity and polypharmacy are also interrelated and influence each other. Due to decreased natural immunity due to comorbid conditions and at the same time patients taking multiple drugs often experience adverse drug reactions (ADRs) this can increase the risk of death (Biswas et al., 2021).

After the transmission of SARS-CoV-2 into the human body, the ACE-2 receptor accelerates the binding of this pathogenic virus to its target cells. ACE-2 is widely expressed in the epithelium of the lung, intestine, kidney, and blood vessels and is largely upregulated in patients with diabetes or hypertension treated with ACE inhibitors (ACEIs) and angiotensin II type-1 receptor blockers (ARBs) (Biswas et al., 2021).

Each comorbidity has its pathophysiology and the mechanistic relationship between SARS-CoV-2 infection and death, some have been established while others have not been revealed. Chronic kidney disease (CKD) is associated with inflammation and dysregulation of immune function that may result in an increased risk of death in COVID-19 patients with kidney disease. It has been reported that the ACE2 receptor is overexpressed in tubular cells of COVID-19 patients with renal disease characterized by elevated serum creatinine and urea nitrogen (Biswas et al., 2021).

Increased expression of ACE2 at the mRNA and protein levels was found in patients with heart failure, suggesting that if infected by SARS-CoV-2 patients may have a higher risk of heart attack and poorer clinical outcomes. Biswas et al. concluded that male patients were associated with a significantly increased risk of death compared to female patients. Patients aged 50 years had a significantly higher risk of death than patients aged 50 years. Mortality was significantly higher in patients with kidney disease, cerebrovascular disease, cardiovascular disease, respiratory disease, diabetes, hypertension, and cancer (Biswas et al., 2021).

Research conducted by Cho et al. stated that hypertension (OR 1.89; 95% CI 1.38-2.60), diabetes (OR 2.22; 95% CI 1.63-2.95), congestive heart failure (OR 2.14; 95% CI 1.42-3.23),

dementia (OR 1.91; 95% CI 1.35-2.70), chronic lung disease (OR 1.88; 95% CI 1.38-2.58), liver disease (OR 1.50; 95% CI 1.02-2.20), kidney disease (OR 4.95; 95% CI 2.37-10.31), and cancer (OR 1.88; 95 % CI 1.17-3.02) was a significant risk factor for death in patients with COVID-19 (Cho et al., 2021).

SARS-CoV-2 binds to target cells via the ACE-2 receptor which is expressed in epithelial cells of several organs. Because the ACE-2 expression is elevated in patients with hypertension, diabetes, and chronic obstructive pulmonary disease (COPD), this comorbidity may increase the risk and severity of COVID-19 infection. In addition, evidence of myocardial or hepatic damage has been observed in patients with COVID-19, and pre-existing cardiovascular and liver disease may be associated with the severity of COVID-19 (Cho et al., 2021).

Recent meta-analyses have identified that cardiovascular disease and COPD can greatly influence the severity of COVID-19. Kidney disease, dementia, and cancer can also be important risk factors for severe COVID-19. Cho et al. concluded that this study identified that ACCI, combined with age and various comorbidities, was associated with mortality in patients with COVID-19 in South Korea (Cho et al., 2021).

Research conducted by Luo et al. stated that a higher risk of severity was observed in COVID-19 patients with comorbidities. Comorbidities such as hypertension (OR 2.57, 95% CI: 2.12-3.11), diabetes (OR 2.54, 95% CI: 1.89-3.41), cardiovascular disease (OR 3.86, 95% CI: 2, 70-5.52), COPD (OR 2.71, 95% CI: 1.98-3.70), CKD (OR 2.20, 95% CI: 1.27-3.80), and cancer (OR 2.42, 95% CI: 1.81-3.22). All comorbidities indicated a higher risk of death. In addition, the prevalence of acute cardiac injury was higher in the group with severe symptoms, and acute cardiac injury was associated with an increased risk of in-hospital death (Luo et al., 2020).

Comorbidities such as hypertension and diabetes are recognized as poor prognostic factors for ARDS and SIRS. However, the relationship between these comorbidities and the severity of COVID-19 remains unclear. Another important finding is that acute cardiac injury increases the risk of severity and in-hospital death for patients with COVID-19. However, the pathogenesis of acute cardiac injury associated with COVID-19 still requires further investigation. The affinity of SARS-CoV-2 for the ACE2 receptor increases the likelihood of infection of the vascular endothelium and myocardium. Hypoxemia and cytokine storm may also be important causes of acute cardiac injury (Luo et al., 2020).

Previous studies in patients with MERS-CoV found that comorbidity was significantly associated with poor prognosis. Recently, meta-analyses have evaluated the impact of comorbidities in the COVID-19 population, and the results are consistent with studies in MERS-CoV patients. Luo et al. concluded that comorbidities and acute cardiac injury are closely related to poor prognosis in COVID-19 patients (Luo et al., 2020).

Research conducted by Wang et al. stated that hypertension, CVD, CKD, and pre-existing diabetes were strongly associated with increased disease severity and poor prognosis in COVID-19 patients. However, no correlation was found between Chronic Liver Disease and the severity of COVID-19. The study also found that impaired organ function, including acute heart injury, and acute kidney injury, was strongly correlated with increased mortality in COVID-19 patients (Wang et al., 2020).

Currently, the mechanism underlying the development of acute cardiac injury in patients infected with SARS-CoV-2 remains unclear. However, it is thought to be related to ACE2 in the renin-angiotensin system. ACE2 is expressed throughout the lung, but is also expressed in the cardiovascular system, and has a direct effect on cardiac function. In one study, experimentally induced ACE2 loss in rats led to severe cardiac contractility impairment and an increased risk of heart failure (Wang et al., 2020).

Immunohistochemistry showed that the SARS-CoV-2 NP antigen accumulated in the renal tubules, with severe acute tubular necrosis. So, it is thought that there is a role between SARS-CoV-2 and the ACE2 enzyme in the kidney. In various clinical studies, it was found that there was

an increase in various cytokines and chemokines in COVID-19 patients with severe symptoms, which may have kidney injury mediated by the immune system (Wang et al., 2020).

In patients with diabetes, ACE2 can be expressed strongly in pancreatic islet cells, suggesting that these cells can be targets of SARS-CoV-2. Wang et al. concluded that there is a strong correlation between the severity of COVID-19 and hypertension, CVD, CKD, and diabetes, four chronic diseases that are relatively common in the community (Wang et al., 2020).

Research conducted by Ejaz et al. stated that COVID-19 patients with diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), hypertension, malignancy, HIV, and other comorbidities are at increased risk of severe symptoms and life-threatening situations. Certain comorbidities are associated with increased expression of the ACE-2 receptor and a higher release of proprotein convertase that enhances viral entry into host cells (Ejaz et al., 2020).

Diabetics tend to get infections because their phagocytic ability is impaired. Elevated levels of ACE-2 receptors found in diabetic patients are also thought to be a factor that increases the risk of COVID-19 infection. In addition, impaired T cell function and increased levels of interleukin-6 (IL-6) also affect the prognosis of COVID-19 in diabetic patients. In COPD patients, there is a transitional inflammatory response, microbiome imbalance, weakened immunity, excessive mucus production, use of inhaled corticosteroids, and structural lung damage. It was also found that an increase in ACE-2 receptor expression contributed to the severe symptoms of COVID-19 patients (Ejaz et al., 2020).

Uncontrolled blood pressure is associated with COVID-19 infection and also with a high mortality rate. In patients suffering from hypertension, ACE inhibitors and ARBs are often used for medicinal purposes. If this drug is used in high amounts, it will increase the expression of the ACE2 receptor, thereby increasing susceptibility to SARS-CoV-2 infection. High expression in lung cells makes infection more susceptible and the possibility of severe lung injury and increased risk of respiratory failure.

The high risk of COVID-19 in pre-existing CVD patients is thought to be due to an increase in ACE-2 receptors on cardiac muscle cells. Patients with CVD are at high risk for developing acute coronary syndromes. This syndrome increases the risk of injury or myocardial infarction. In addition, increased inflammatory cytokines in COVID-19 mediate atherosclerosis, procoagulant activation, and hemodynamic instability leading to ischemia and thrombosis (Ejaz et al., 2020).

Patients suffering from malignancy have a higher risk of contracting COVID-19 infection because of a weak immune response. SARS-CoV-2 provides an efficient replication environment for initiating infection in patients with malignancies. People with HIV have a high risk of developing the COVID-19 disease because of a compromised immune system. Ejaz et al. concluded that a critical situation develops in patients with hypertension, diabetes, COPD, CVD, malignancy, and HIV. COPD patients tend to have more severe symptoms and a relatively high mortality rate (Ejaz et al., 2020).

Research conducted by Espinosa et al. stated that the most common comorbidity in COVID-19 patients who died were hypertension 35% (95% CI: 25-29; weight 8.10%), diabetes 19% (95% CI: 16-22; weight 8.53%), heart disease 17% (95% CI: 14-20; weight 8.61%), and COPD 9% (95% CI: 7-11; weight 9.22%). In addition, patients with cerebrovascular disease (6%), cancer (5%), kidney disease (4%), liver disease (3%), and others (2%) were also evaluated (Espinosa et al., 2020).

The odds ratio for each comorbidity was 2.4 to 95% CI 1. 7–3. 3 with statistical significance P < 0.0001. In other words, patients with co-morbidities have a 2.4 times chance of dying from COVID-19 compared to patients without co-morbidities. This may explain the high prevalence of comorbidity among fatal cases. Espinosa et al. concluded that the presence of comorbidities increased the risk of death in COVID-19 patients by 2.4 times compared to patients without comorbid diseases. The most common comorbidities were hypertension, heart disease, and diabetes (Espinosa et al., 2020).

The results of the analysis of the COVID-19 Task Force Expert Team regarding COVID-19 deaths based on age and history of comorbid or comorbid diseases. Based on the age aspect, patients aged 31-45 years have a 2.4-fold risk, those aged 46-59 years have an 8.5-fold risk, and over 60 years the risk is 19.5-fold (Satgas Penanganan COVID-19, 2020).

For comorbid types, kidney disease has a 13.7 times greater risk of death, 9 times greater heart disease, 8.3 times greater diabetes disease, hypertension, and 6 times greater immune disease, respectively. For the number of comorbid diseases, patients who have one comorbid disease have a 6.5-fold risk, those who have 2 comorbid diseases have a 15-fold risk, and those who have more or equal to 3 comorbid diseases have a 29-fold higher risk of dying when infected with COVID-19 (Satgas Penanganan COVID-19, 2020).

Conclusion

Based on the literature study that has been carried out, it can be concluded that:

1. The presence of comorbid diseases increases the risk of infection, worsens symptoms, and death in COVID-19 patients. The comorbidity disease with the highest mortality rate was found in hypertension, followed by diabetes mellitus, cardiovascular disease, kidney disease, and chronic obstructive pulmonary disease (COPD).
2. Patients who have more than one comorbidity disease will further increase the risk of death if infected with COVID-19.

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