



Clinical Characteristics and Comorbidities Associated With COVID-19 Deaths in Brebes Regency (Retrospective Cohort Study)

Diah Hasanah[✉], Lukman Fauzi
Universitas Negeri Semarang, Indonesia

Article Info

Article History:
Submitted 13 February 2023
Accepted 07 October 2023
Published 30 October 2023

Keywords:
COVID-19, Comorbid, Brebes Regency

DOI
<https://doi.org/10.15294/jhe.v8i1.64107>

Abstract

Background: Until now, COVID-19 is still a major global health problem. Even though Brebes Regency is not the regency with the highest number of COVID-19 cases in Central Java, Brebes Regency has not been spared from a spike in COVID-19 cases. The active case of COVID-19 in Brebes Regency in 2021 is 0.43% with a CFR of 10.98%. It is proven that active cases of COVID-19 have increased from the previous year which was only 0.05%. This research aimed to determine the factors associated with COVID-19 deaths in Brebes Regency.

Method: The study design was a retrospective cohort using secondary data from Brebes Regency Health Office 2021. This research was conducted in September-November 2022. The number of samples studied was 10,374 samples. Data were analyzed using univariate, bivariate (chi-square and fisher), and multivariate (logistic regression) analysis.

Results: The results showed that age ≥ 50 years (OR: 3.74; 95% CI: 3.28-4.26), symptoms of shortness of breath (OR: 2.84; 95% CI: 2.42-3, 34), heart disease (OR: 3.21; 95% CI: 1.29-7.99) and type of work as a health worker (OR: 0.30; 95% CI: 0.09-0.97) have significant relationship to the death of COVID-19 patients in Brebes Regency.

Conclusion: Age ≥ 50 , symptoms of shortness of breath, heart disease and type of work as a health worker increase the risk of death in COVID-19 patients in Brebes Regency.

[✉] Correspondence Address:
Email : hasanahdiah13@students.unnes.ac.id

INTRODUCTION

Coronavirus disease (COVID-19) is a respiratory tract infection that is still a major global health problem (Gupta et al., 2021). The clinical manifestations of COVID-19 are very heterogeneous, it can cause death, mild symptoms, severe symptoms, and no symptoms (Chen et al., 2020). WHO states that transmission of COVID-19 from someone who does not show symptoms (asymptomatic) has a very small risk of transmission. However, previous research suggests that asymptomatic people still have the possibility of transmitting the infection to others. Someone who does not show symptoms still has a chance of transmitting the infection around 0–2.2%, while for symptomatic people, it is around 0.8–15.4%. (WHO, 2020). Other research proves that asymptomatic people still have a risk of transmitting the COVID-19 virus around 59%. (J. Michael et al., 2021).

The prevalence of COVID-19 cases in the world in 2021 was 8.76% active cases and 1.93% case fatality rate. Active cases of COVID-19 in Indonesia in 2021 were 0.11%, this figure is below the world average of 8.76%, while the case fatality rate is 3.38% and this figure is above the world average, namely 1.93%. Active cases in Central Java in 2021 were 0.21% with a case fatality rate of 6.22% (COVID-19 Task Force, 2021). Even though Brebes Regency is not in the 10 regencies/cities with the highest COVID-19 cases in Central Java, Brebes Regency will not escape the threat of a spike in COVID-19 cases. The prevalence of COVID-19 cases in Brebes Regency in 2021 with active cases of 0.43% and a case fatality rate of 10.98% (Dinkes Brebes, 2021). The prevalence of COVID-19 active cases in Brebes Regency has increased from the previous year which was only 0.05%. This coincided with the spread of the delta and omicron variants of COVID-19 at that time. The delta variant causes a higher infection rate, while the omicron has a stronger transmission power. However, further research is needed to determine the impact of morbidity and mortality in COVID-19 patients (Susilo et al., 2022; T. May, 2021).

Knowing the risk factors associated with COVID-19 mortality is essential to guide policy making, targeting public health, and appropriate

clinical interventions. The variables analyzed in this research including age, sex, occupation, shortness of breath symptoms, fatigue symptoms, fever symptoms, comorbidities of diabetes mellitus, hypertension, heart disease, kidney disease, COPD, and asthma status. According to previous studies, these variables are believed to have a strong association with COVID-19 mortality. At the individual level, older age and pre-existing chronic comorbidities are consistently reported as major risk factors for COVID-19 mortality (Surendra, Salama, et al., 2022). The age of COVID-19 patients >50 years old is believed to have a risk of death from COVID-19 of 15.4 times compared to patients <50 years old. (Biswas et al., 2021).

Another study explained that male patients contributed to the risk of death from COVID-19 by 2.4 times compared to female patients (Jin et al., 2020). Another study explained that male patients contributed to the risk of death from COVID-19 by 2.4 times compared to female patients (Angulo-Zamudio et al., 2021). Health workers who work in COVID-19 wards have a much higher seroprevalence than health workers in other wards. (Ramanathan et al., 2020). In previous studies, several clinical manifestations have been shown a relationship with the death of COVID-19 patients. Supported by other studies which suggest that shortness of breath symptoms is the most common symptom in the death of COVID-19 patients. (Hentsch et al., 2021). Furthermore, fatigue symptoms are also shown to increase the risk of death in COVID-19 patients, while fever symptoms are not shown to increase the risk of death in COVID-19 patients, despite fever symptoms are the most common symptoms in COVID-19 patients (Rezaei et al., 2021; Yang et al., 2020).

COVID-19 patients have a higher risk of death, especially in patients with comorbidities and elderly patients (Djoharuddin et al., 2020). COVID-19 patients have a higher risk of death, especially in patients with comorbidities and elderly patients (Ge et al., 2021). The most common comorbidities found in deaths of COVID-19 patients are hypertension, diabetes, and coronary heart disease (Zhou, 2020). This is supported by previous studies which suggest that hypertension, cardiovascular disease, and

diabetes are comorbidities that have a higher risk of death in COVID-19 patients (Parohan et al., 2021).

Another study states that COVID-19 patients with kidney disease have a risk of death from COVID-19 of 5.82 times (Surendra et al., 2021). Previous studies have shown that comorbidities such as COPD and coronary heart disease contribute to the highest mortality rate in COVID-19 patients (Fang et al., 2020). COPD has been shown to increase poor clinical outcomes and even mortality, hence COVID-19 patients with COPD are considered high-risk patients and require aggressive prevention and treatment efforts (Gerayeli et al., 2021). In another study, asthma was not a risk factor for COVID-19 death, but asthma patients who had experienced an exacerbation had a risk of death from COVID-19 (Lee et al., 2020).

This research has differences from previous research on the same topic, one of which is in research of (Nugrahani & Fauzi, 2022) conducted at the COVID-19 Referral Hospital, Karanganyar Regency, Central Java. In that research, researchers did not consider and analyze some of the most common symptoms of COVID-19. Meanwhile, in this research, researchers considered and analyzed the most common symptoms of COVID-19, including symptoms of shortness of breath, symptoms of fatigue, and symptoms of fever. In addition, this research is the first study on the topic of COVID-19 death conducted in Brebes Regency. So, this research is expected to be a novel idea so that it has a positive contribution to science and further research references. This research aimed to determine the factors associated with COVID-19 deaths in Brebes Regency.

METHODS

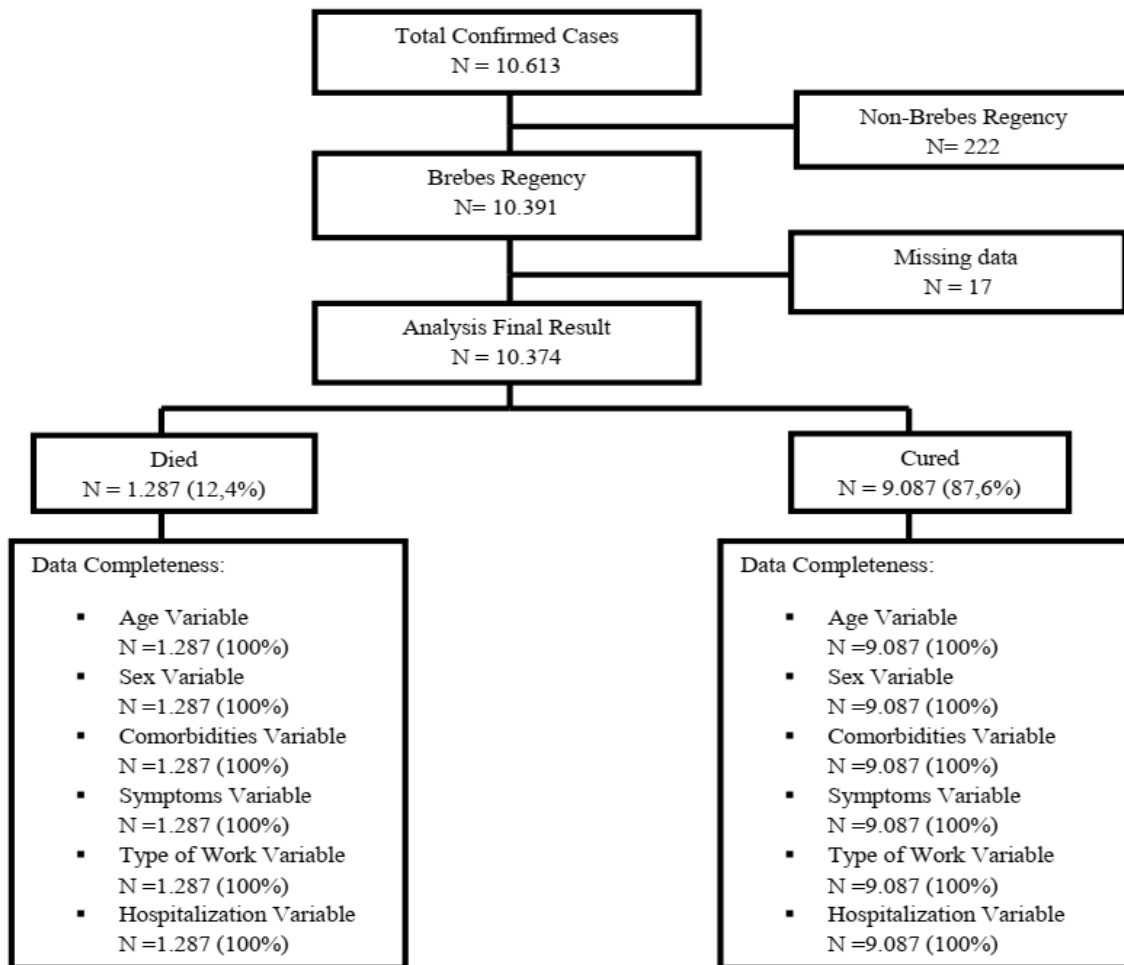


Figure 1: Flow Chart and Data Completeness

This research type was observational analytic with a cohort-retrospective study design. The data used secondary data from the Brebes Regency Health Office. The samples in this research were all patients diagnosed with COVID-19 during 2021 that were recorded at Brebes Regency Health Office. The number of samples studied was 10,374 samples. Independent variables include age, sex, type of work, shortness of breath symptoms, fatigue symptoms, fever symptoms, diabetes mellitus, hypertension, heart disease, kidney disease, COPD, and asthma status. The dependent variable in this study is the death of COVID-19 patients.

The study of flow chart and data completeness is presented in (Figure 1), between January-December 2021, the total of confirmed COVID-19 cases in Brebes Regency was 10,613 cases. A total of 222 non-Brebes District respondents were excluded from the research sample. The total number of respondents residing in Brebes Regency was 10,391 respondents. Missing data of 17 respondents were excluded from the research sample. The final results included in the analysis were 1,287 (12.4%) patients who died and 9,087 (87.6%) patients who were declared cured.

The inclusion criteria in this research were all COVID-19 patients recorded at the Brebes Regency Health Office during 2021, while the exclusion criteria were incomplete patient data and illegible by researchers. Data analysis was carried out by univariate, bivariate, and multivariate analysis. Bivariate analysis was in the form of a chi-square test and fisher test, while multivariate analysis was performed using a logistic regression test. This study was approved by the Health Research Ethics Committee of Universitas Negeri Semarang with number: 431/KEPK/EC/2022.

RESULTS AND DISCUSSIONS

The results of the univariate analysis in table 1, show that of the 10,374 cases included in the analysis, with COVID-19 patient age ≥ 50 years (43.5%) and < 50 years (56.5%), male (42.5%) and female (57.5%), job type subjects as a health worker (1.1%) and non-health worker (98.8%), patients with shortness of

breath symptoms (10.0%) and patients without shortness of breath symptoms (90.0%), patients with fatigue symptoms (4.3%) and patients without fatigue symptoms (95.7%), patients with fever symptoms (8.5%) and patients without fever symptoms (91.5%), patients with diabetes mellitus (2.6%) and patients without diabetes mellitus (97.4%), patients with heart disease (0.2%) and patients without heart disease (99.8%), patients with hypertension (1, 4%) and patients without hypertension (98.6%), patients with kidney disease (0.3%) and patients without kidney disease (99.7%), patients with COPD (0.1%) and patients without COPD (99.9%), patients with asthma status (0.1%) and patients without asthma status (99.9%).

The results of the bivariate analysis can be seen in Table 2, of the 10,374 cases included in the analysis, the variables of age, type of work, shortness of breath symptoms, fatigue symptoms, diabetes mellitus, heart disease, and hypertension are significantly related to COVID-19 deaths in Brebes Regency with ($p < 0.05$). Whereas sex, symptoms of fever, kidney disease, COPD, and asthma status are not significantly associated with COVID-19 deaths in Brebes Regency. The age of COVID-19 patients has a Risk Ratio (RR) of 3.48 (95% CI: 3.09-3.91), meaning that COVID-19 patients aged ≥ 50 years have a risk of death from COVID-19 of 3.48 times compared to COVID-19 patients aged < 50 years. Furthermore, for the type of work in COVID-19 patients has an RR of 0.20 (95% CI: 0.07-0.62), meaning that COVID-19 patients with the type of work as health workers are associated with a lower risk of death from COVID-19 by 0.20 times less than COVID-19 patients with types of work other than health workers.

Patients who have symptoms of shortness of breath and fatigue with an RR of 2.76 (95% CI: 2.47-3.09) and 1.42 (95% CI: 1.15-1.75) respectively, meaning that patients with symptoms of shortness of breath have a risk of death from COVID-19 of 2.76 times compared to patients without symptoms of shortness of breath, also patients with symptoms of fatigue have a risk of death from COVID-19 of 1.42 times compared to patients without symptoms

of fatigue. Moreover, diabetes mellitus and heart disease are significantly associated with an RR of 2.14 (95% CI: 1.74-2.64) and 3.86 (95% CI: 2.46-6.06) respectively, meaning that COVID-19 patients with diabetes mellitus have a risk of death from COVID-19 of 2.14 compared to patients without diabetes mellitus, while COVID-19 patients with heart disease

have a risk of death from COVID-19 of 3.86 times compared to patients without heart disease. While hypertension has an RR of 2.13 (95% CI: 1.62-2.80), meaning that patients with hypertension have a risk of death of 2.13 times compared to COVID-19 patients without hypertension.

Table 1. Respondent Distribution

Variable	N	%
Age		
≥50 years old	4.511	43,5
<50 years old	5.863	56,5
Sex		
Male	4.405	42,5
Female	5.969	57,5
Type of Work		
Health worker	119	1,1
Non-health worker	10.255	98,9
Shortness of Breath Symptoms		
Yes	1.041	10,0
No	9.333	90,0
Fatigue Symptoms		
Yes	450	4,3
No	9.924	95,7
Fever Symptoms		
Yes	882	8,5
No	9.492	91,5
Diabetes Mellitus		
Yes	267	2,6
No	10.107	97,4
Heart Disease		
Yes	21	0,2
No	10.353	99,8
Hypertension		
Yes	150	1,4
No	10.224	98,6
Kidney Disease		
Yes	26	0,3
No	10.348	99,7
COPD		
Yes	8	0,1
No	10.366	99,9
Asthma Status		
Yes	13	0,1
No	10.361	99,9

Table 2. Bivariate Analysis Results

Variable	Died		Cured		RR (95% CI)	p-value
	N	%	N	%		
Age						
≥50 years old	937	20,8	3.574	79,2	3,48 (3,09-3,91)	<0,001
<50 years old	350	6,0	5.513	94,0		
Sex						
Male	556	12,6	3.849	87,4	1,03 (0,93-1,14)	0,587
Female	731	12,2	5.238	87,8		
Type of Work						
Health worker	3	2,5	116	97,5	0,20 (0,07-0,62)	0,002
Non-health worker	1.284	12,5	8.971	87,5		
Shortness of Breath Symptoms						
Yes	303	29,1	738	70,9	2,76 (2,47-3,09)	<0,001
No	984	10,5	8.349	89,5		
Fatigue Symptoms						
Yes	78	17,3	372	82,7	1,42 (1,15-1,75)	0,002
No	1.209	12,2	8.715	87,8		
Fever Symptoms						
Yes	117	13,3	765	86,7	1,08 (0,90-1,28)	0,450
No	1.170	12,3	8.322	87,7		
Diabetes Mellitus						
Yes	69	25,8	198	74,2	2,14 (1,74-2,64)	<0,001
No	1.218	12,1	8.889	87,9		
Heart Disease						
Yes	10	47,6	11	52,4	3,86 (2,46-6,06)	<0,001
No	1.277	12,3	9.076	87,8		
Hypertension						
Yes	39	26,0	111	74,0	2,13 (1,62-2,80)	<0,001
No	1.248	12,2	8.976	87,8		
Kidney Disease						
Yes	7	26,9	19	73,1	2,18 (1,15-4,11)	0,051
No	1.280	12,4	9.068	87,6		
COPD						
Yes	3	37,5	5	62,5	3,03 (1,24-7,42)	0,106
No	1.284	12,4	9.082	87,6		
Asthma Status						
Yes	3	23,1	10	76,9	1,86 (0,69-5,03)	0,455
No	1.284	12,4	9.077	87,6		

Table 3. Multivariate Analysis Results

Variable	B	Wald	Nilai p	OR (95% CI)
Age	1,32	384,28	<0,001	3,74 (3,28-4,26)
Shortness of Breath Symptoms	1,04	164,18	<0,001	2,84 (2,42-3,34)
Heart Disease	1,16	6,26	0,012	3,21 (1,29-7,99)
Type of Work	0,25	4,05	0,044	0,30 (0,09-0,97)

After controlling for other variables, there are four variables that continue to significantly affect the risk of death in COVID-19 patients, namely age ≥ 50 ($p < 0.001$; AdjOR=3.74; 95% CI: 3.28-4.26), symptoms of shortness of breath ($p < 0.001$; AdjOR=2.84; 95% CI: 2.42-3.34),

heart disease ($p = 0.012$; AdjOR=3.21; 95% CI: 1.29-7.99) and type of work as a health worker ($p = 0.044$; AdjOR=0.30; 95% CI: 0.09-0.97).

The age ≥ 50 years of COVID-19 patients increases the risk of death by 3.74 times compared to COVID-19 patients aged < 50

years. This is in line with previous research which explained that COVID-19 patients aged ≥ 50 years have a risk of death from COVID-19 of 15.4 times (Biswas et al., 2021). COVID-19 patients aged ≥ 50 years are indeed more easily infected with COVID-19 due to higher ACE2 expression, resulting in easier transmission of SARS-CoV-2. In addition, patients aged ≥ 50 years usually have other factors such as reduced immunity, low organ function, or comorbidities that can increase the risk of death (Biswas et al., 2021). COVID-19 patients aged ≥ 50 are also more susceptible to infection and severe clinical manifestations, affected by physiological factors, the aging process, and comorbidities that can contribute to functional reserves and thus inhibit the intrinsic capacity to fight infection (Bonanad & García-blas, 2020). In another study, it was explained that aging affects CD4+ T cells, CD8 + T cells, B cell function, decreased T cell function, and B cell clonal diversity which is associated with impaired responses to viral infections such as influenza and overproduction of type 2 cytokines which may result in prolonged pro-inflammatory immune responses, that can cause severity and even death in COVID-19 patients (Dessie & Zewotir, 2021).

Shortness of breath symptoms increase the risk of death in COVID-19 patients by 2.84 times compared to COVID-19 patients without shortness of breath symptoms. This is in line with previous research which states that symptoms of shortness of breath in COVID-19 patients have a risk of death of 1.46 times (Santos et al., 2020). Shortness of breath in COVID-19 patients occurs because SARSCoV-2 has receptors located in the lungs that can trigger the respiratory system infection process. The respiratory system infection can cause inflammation and oxygen exchange is closed by latent cells. Hypoxia or lack of oxygen in COVID-19 patients with shortness of breath if it occurs in brain cells can cause oxygen deprivation in brain cells which eventually leads to decreased consciousness, even death. According to other studies, COVID-19 patients who have shortness of breath symptoms have a higher risk of severity, even death. Symptoms of shortness of breath or dyspnea indicate poor lung function and lack of oxygen which worsens

the patient's condition (Zheng et al., 2020). Previous studies have found that shortness of breath symptoms are more at risk of COVID-19 death, especially in elderly patients. Shortness of breath symptoms associated with the risk of death in COVID-19 patients is acute hypoxia stemming from ventilation deficits. Therefore, respiratory distress and oxygen saturation in COVID-19 patients should be monitored continuously, especially in elderly patients (Souza et al., 2020).

Heart disease is the comorbidity that most influences the death of COVID-19 patients in Brebes Regency. COVID-19 patients with heart disease increase the risk of death by 3.21 times compared to COVID-19 patients without heart disease. This is in line with previous research which states that heart disease increases the risk of death in COVID-19 patients by 4.00 times. Prolonged fever and pro-inflammation in COVID-19 patients with heart disease cause acute respiratory distress syndrome, respiratory failure, sepsis, acute heart injury, heart failure, and complications during exacerbations are increased in COVID-19 patients with heart disease (Cordero et al., 2021). SARS CoV-2 infection and pre-existing heart disease become overlapping which may eventually exacerbate the infection in the cardiovascular system of the patient (Suri & Arora, 2020). The direct mechanism occurs when COVID-19 infects the heart resulting in inflammation and death of the heart muscle, the indirect mechanism when the virus infects the respiratory tract resulting in disruption of the respiratory system leaving the body deprived of oxygen and the heart working harder to pump blood and distribute oxygen throughout the body. This condition causes a heavier heart workload leading to narrowing of blood vessels and heart rhythm disturbances (Akhmerov & Marbán, 2020). Previous research has also explained that COVID-19 infection can cause an increase in cardiomyocytes and cause sympathetic hyperactivity or ischemia which can increase the risk of arrhythmia and heart failure in COVID-19 patients with pre-existing heart disease (Gu et al., 2020).

Patients with occupations as health workers are associated with a 0.30 times reduced risk of dying from COVID-19 compared to COVID-19 patients with occupations other

than health workers. This is in line with previous research which states that health workers do have a risk of exposure to COVID-19, but not with death from COVID-19. This is due to health workers tend to acquire better health information and receive treatment earlier when confirmed infected with COVID-19. Health workers have easier access to health facilities, receive early treatment, are able to self-medicate, and are able to identify symptoms that cause severity and death from COVID-19 (Ferland et al., 2022). This is supported by other studies which found that health workers only experienced mild symptoms and only a few experienced severity from COVID-19 infection. This is likely due to health workers who are more knowledgeable about health information including how to deal with severe symptoms of COVID-19 infection and know how to self-medicate. (Díez-Manglano et al., 2021).

Comorbidities of diabetes mellitus, hypertension, and fatigue symptoms were shown to inconsistently affect the risk of death in COVID-19 patients in Brebes Regency. This is not in line with several previous studies which state that diabetes and hypertension are comorbid diseases that affect the death of COVID-19 patients (Surendra, Praptiningsih, et al., 2022). Diabetes with hyperglycemia is one of the factors leading to increased expression of angiotensin-converting enzyme 2 (ACE2) in the lungs and other tissues. In this case, ACE2 is the cellular receptor where the virus enters. Pre-existing chronic inflammation with increased inflammatory response to infection and increased viral load leads to an extreme systemic immune response (cytokine storm) which can increase the severity and mortality in COVID-19 patients (Rajpal et al., 2020). While previous research explained that high blood glucose levels are an important predictor of mortality in COVID-19 patients, this is due to insulin resistance encouraging the synthesis of glycosylated final products and stimulating the production of pro-inflammatory cytokines, oxidative stress, and molecular adhesion resulting in a higher likelihood of infection (Wu et al., 2021).

The results of multivariate analysis on hypertension inconsistently affect mortality

in COVID-19 patients in Brebes Regency. This is in contrast to previous studies which state that hypertension consistently emerges as the most common comorbid in the death of COVID-19 patients. Several investigations have speculated on the association between the renin-angiotensin-aldosterone system (RAAS) and susceptibility to COVID-19, as well as the relationship between RAAS inhibitors and increased mortality in COVID-19 patients (Tadic et al., 2020). Activation of the renin-angiotensin system (RAAS) in the pathophysiology of hypertension plays a role in increasing the severity and even death of COVID-19. In fact, ACE2 (angiotensin-converting-enzyme 2) acts as a receptor for SARS-CoV-2 to enter host cells, thus COVID-19 and RAAS are interrelated (Savoia et al., 2021). Previous research explained that COVID-19 patients with hypertension experience immune function, abnormal coagulation function balance, have impaired liver and kidney function which can eventually aggravate and even cause the death of COVID-19 patients with hypertension (Tadic et al., 2020).

The results of this study are also in contrast to previous research which stated that fatigue symptoms is one of the most experienced symptoms during COVID-19 infection, not only that fatigue symptoms are the most dangerous symptoms and are often felt by patients after COVID-19. Therefore, it is common for patients who are unable to survive after experiencing symptoms of fatigue, both during COVID-19 infection and post-COVID-19 fatigue symptoms. According to previous research, post-COVID-19 fatigue may be due to respiratory complications such as dyspnea, pneumonia, and acute respiratory distress syndrome. The weakening of mitochondrial dysfunction can result in decreased stamina and increased fatigue. COVID-19 infection is also characterized by losing the sense of taste, smell, and causing anorexia, which is an important contributor to a person experiencing malnutrition. In addition, a high catabolic response to COVID-19 infection leads to weight loss and decreased muscle performance which can eventually lead to fatigue (Azzolino & Cesari, 2022). According to another study, fatigue symptoms last up to

10 weeks from the first COVID-19 infection (Townsend et al., 2020).

The secondary data obtained by researchers has limitations on the time person variable. Therefore, researchers were unable to conduct survival analysis or time-to-event analysis which aims to analyze the relationship between survival time and variables that are thought to affect survival time. In addition, this study also did not consider and analyze the wave of COVID-19 variants (delta and omicron) in the year when the data was obtained (2021), which may have caused the incidence of death due to COVID-19 in that year.

CONCLUSION

After controlling other variables, it can be concluded that age ≥ 50 years, shortness of breath symptoms, heart disease, and type of work as a health worker increases the risk of death in COVID-19 patients in Brebes Regency. The suggestion for the community is to consume a maximum of 4 tablespoons of sugar per day, consume a maximum of 5 tablespoons of fatty foods per day, and do physical activity at least 5 times a week as an effort to prevent non-communicable diseases. Local health centers are expected to conduct early detection and monitoring of risk factors for non-communicable diseases on a regular basis, as well as launch and increase the frequency of GERMAS activities. In addition, the Brebes Regency Health Office is expected to continue to improve health service facilities as a preparation effort to tackle the threat of the COVID-19 pandemic in the future, so that these various prevention efforts can minimize the COVID-19 mortality rate in Brebes Regency.

REFERENCES

- Akhmerov, A., & Marbán, E. (2020). COVID-19 and the Heart. *Circulation Research*, 1443–1455. <https://doi.org/10.1161/CIRCRESAHA.120.317055>
- Angulo-Zamudio, U. A., Martínez-Villa, F. M., Leon-Sicairos, N., Flores-Villaseñor, H., Velazquez-Roman, J., Campos-Romero, A., Alcántar-Fernández, J., Urrea, F., Muro-Amador, S., Medina-Serrano, J., Martinez-Garcia, J. J., Sanchez-Cuen, J., Angulo-Rocha, J., & Canizalez-Roman, A. (2021). Analysis of Epidemiological and Clinical Characteristics of COVID-19 in Northwest Mexico and the Relationship Between the Influenza Vaccine and the Survival of Infected Patients. *Frontiers in Public Health*, 9(March), 1–10. <https://doi.org/10.3389/fpubh.2021.570098>
- Azzolino, D., & Cesari, M. (2022). Fatigue in the COVID-19 pandemic. *The Lancet Healthy Longevity*, 3(3), e128–e129. [https://doi.org/10.1016/S2666-7568\(22\)00029-0](https://doi.org/10.1016/S2666-7568(22)00029-0)
- Biswas, M., Rahaman, S., Biswas, T. K., Haque, Z., & Ibrahim, B. (2021). Association of Sex, Age, and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis. *Intervirolgy*, 64(1), 36–47. <https://doi.org/10.1159/000512592>
- Bonanad, C., & García-blas, S. (2020). Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information. *Jamda*, January, 915–918.
- Chen, Y., Klein, S. L., Garibaldi, B. T., Li, H., Wu, C., Osevala, N. M., Li, T., Margolick, J. B., Pawelec, G., & Leng, S. X. (2020). Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information. January.
- Cordero, A., Santos García-Gallego, C., Bertomeu-González, V., Fácila, L., Rodríguez-Mañero, M., Escribano, D., Castellano, J. M., Zuazola, P., Núñez, J., Badimón, J. J., & González-Juanatey, J. R. (2021). Mortality associated with cardiovascular disease in patients with COVID-19. *REC: CardioClinics*, 56(1), 30–38. <https://doi.org/10.1016/j.rcc.2020.10.005>
- COVID-19 Task Force. (2021). Analisis data COVID-19 di Indonesia. 30 Desember 2021.
- Dessie, Z. G., & Zewotir, T. (2021). Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. *BMC Infectious Diseases*, 21(1). <https://doi.org/10.1186/s12879-021-06536-3>
- Díez-Manglano, J., Solís-Marquínez, M. N., García, A. Á., Alcalá-Rivera, N., Riesco, I. M., Aseguinolaza, M. G., Pérez, J. L. B., Bailón, M. M., Ruiz, A. E. L. I., Gómez, M. G., Cilleros, C. M., Fontan, P. M. P., Vázquez, L. A., Encinar, J. C. B., Boixeda, R., Sánchez, R. G., de la Peña Fernández, A., Amigo, J. L., Sevilla, J. E., ... Feijoo, M. B. V. (2021).

- Healthcare workers hospitalized due to COVID-19 have no higher risk of death than general population. Data from the Spanish SEMI-COVID-19 Registry. *PLoS ONE*, 16(2 February), 1–18. <https://doi.org/10.1371/journal.pone.0247422>
- Dinas Kesehatan Kabupaten Brebes. (2021). *Kabupaten Brebes Tanggap Corona (COVID-19)*.
- Djagaruddin, I., Munawwarah, S., Nurulita, A., Ilyas, M., & Ahmad, N. (2020). Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. *The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information*. January.
- Fang, X., Li, S., Yu, H., Wang, P., Zhang, Y., Chen, Z., Li, Y., Cheng, L., Li, W., Jia, H., & Ma, X. (2020). Epidemiological, comorbidity factors with severity and prognosis. *Aging*, 12(13), 12493–12503.
- Ferland, L., Carvalho, C., Gomes Dias, J., Lamb, F., Adlhoch, C., Suetens, C., Beauté, J., Kinross, P., Plachouras, D., Hannila-Handelberg, T., Fabiani, M., Riccardo, F., van Gageldonk-Lafeber, A. B., Teirlinck, A. C., Mossong, J., Vergison, A., Melillo, J., Melillo, T., Mook, P., ... Monnet, D. L. (2022). Risk of hospitalization and death for healthcare workers with COVID-19 in nine European countries, January 2020–January 2021. *Journal of Hospital Infection*, 119, 170–174. <https://doi.org/10.1016/j.jhin.2021.10.015>
- Ge, E., Li, Y., Wu, S., Candido, E., & Wei, X. (2021). Association of pre-existing comorbidities with mortality and disease severity among 167,500 individuals with COVID-19 in Canada: A population-based cohort study. *PLoS ONE*, 16(10 October), 1–18. <https://doi.org/10.1371/journal.pone.0258154>
- Gerayeli, F. V., Milne, S., Cheung, C., Li, X., Yang, C. W. T., Tam, A., Choi, L. H., Bae, A., & Sin, D. D. (2021). COPD and the risk of poor outcomes in COVID-19: A systematic review and meta-analysis. *EClinicalMedicine*, 33, 100789. <https://doi.org/10.1016/j.eclinm.2021.100789>
- Gu, T., Chu, Q., Yu, Z., Fa, B., Li, A., Xu, L., Wu, R., & He, Y. (2020). History of coronary heart disease increased the mortality rate of patients with COVID-19: A nested case-control study. *BMJ Open*, 10(9). <https://doi.org/10.1136/bmjopen-2020-038976>
- Gupta, A., Nayan, N., Nair, R., Kumar, K., Joshi, A., Sharma, S., Singh, J., & Kapoor, R. (2021). Diabetes Mellitus and Hypertension Increase Risk of Death in Novel Corona Virus Patients Irrespective of Age: a Prospective Observational Study of Co-morbidities and COVID-19 from India. *SN Comprehensive Clinical Medicine*, 3(4), 937–944. <https://doi.org/10.1007/s42399-021-00851-1>
- Hentsch, L., Cocetta, S., Allali, G., Santana, I., Eason, R., Adam, E., & Janssens, J. P. (2021). Breathlessness and COVID-19: A call for research. *Respiration*, 100(10), 1016–1026. <https://doi.org/10.1159/000517400>
- Jin, J. M., Bai, P., He, W., Wu, F., Liu, X. F., Han, D. M., Liu, S., & Yang, J. K. (2020). Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Frontiers in Public Health*, 8(April), 1–6. <https://doi.org/10.3389/fpubh.2020.00152>
- Lee, S. C., Son, K. J., Han, C. H., Jung, J. Y., & Park, S. C. (2020). Impact of comorbid asthma on severity of coronavirus disease (COVID-19). *Scientific Reports*, 10(1), 1–9. <https://doi.org/10.1038/s41598-020-77791-8>
- Michael A Johansson, Talia M Quandelacy, Sarah Kada, Pragati Venkata Prasad, Molly Steele, John T Brooks, Rachel B Slayton 1 2, Matthew Biggerstaff 1 2, J. C. B. 2. (2021). SARS-CoV-2 Transmission From People Without COVID-19 Symptoms. *Jama Network Open*.
- Nugrahani, A., & Fauzi, L. (2022). Risiko Mortalitas Pasien Covid-19 (Studi Kohort Retrospektif Di Rumah Sakit Rujukan COVID-19). *Higeia Journal of Public Health Research and Development*, 6(2), 260–267.
- Parohan, M., Yaghoubi, S., Seraji, A., Javanbakht, M. H., Sarraf, P., & Djalali, M. (2021). Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. *Aging Male*, 23(5), 1416–1424. <https://doi.org/10.1080/13685538.2020.1774748>
- Rajpal, A., Rahimi, L., & Ismail-Beigi, F. (2020). Factors leading to high morbidity and mortality of COVID-19 in patients with type 2 diabetes. *Journal of Diabetes*, 12(12), 895–908. <https://doi.org/10.1111/1753-0407.13085>
- Ramanathan, K., Antognini, D., Combes, A., Paden, M., Zakhary, B., Ogino, M., Maclaren, G., & Brodie, D. (2020). Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- research that is available on the COVID-19 resource centre - including this for unrestricted research re-

- use a. January, 19–21.
- Rezaei, F., Ghelichi-Ghojogh, M., Hemmati, A., Ghaem, H., & Mirahmadizadeh, A. (2021). Risk factors for COVID-19 severity and mortality among inpatients in Southern Iran. *Journal of Preventive Medicine and Hygiene*, 62(4), E808–E813. <https://doi.org/10.15167/2421-4248/jpmh2021.62.4.2130>
- Santos, M. M., Lucena, E. E. S., Lima, K. C., Brito, A. A. C., Bay, M. B., & Bonfada, D. (2020). Survival and predictors of deaths of patients hospitalized due to COVID-19 from a retrospective and multicenter cohort study in Brazil. *Epidemiology and Infection*. <https://doi.org/10.1017/S0950268820002034>
- Savoia, C., Volpe, M., & Kreutz, R. (2021). Hypertension, a moving target in COVID-19: Current views and perspectives. *Circulation Research*, 128(7), 1062–1079. <https://doi.org/10.1161/CIRCRESAHA.121.318054>
- Souza, C. D. F. De, Magalh, A. J. D. A., Lima, A. J. P. D., Nunes, D. N., Fátima, É. De, Soares, M., Silva, L. D. C., Santos, L. G., Vitória, I., Cardoso, S., Nobre, Y. V. S., & Carmo, R. F. (2020). EPIDEMIOLOGY , CLINICAL PRACTICE AND HEALTH Clinical manifestations and factors associated with mortality from COVID-19 in older adults : Retrospective population- based study with 9807 older Brazilian COVID-19 patients. 1177–1181. <https://doi.org/10.1111/ggi.14061>
- Surendra, H., Elyazar, I. R., Djaafara, B. A., Ekawati, L. L., Saraswati, K., Adrian, V., Widyastuti, Oktavia, D., Salama, N., Lina, R. N., Andrianto, A., Lestari, K. D., Burhan, E., Shankar, A. H., Thwaites, G., Baird, J. K., & Hamers, R. L. (2021). Clinical characteristics and mortality associated with COVID-19 in Jakarta, Indonesia: A hospital-based retrospective cohort study. *The Lancet Regional Health - Western Pacific*, 9, 100108. <https://doi.org/10.1016/j.lanwpc.2021.100108>
- Surendra, H., Praptiningsih, C. Y., Ersanti, A. M., Rahmat, M., Noviyanti, W., Harmani, J. A. D., Mansur, E. N. A., Suleman, Y. Y., Sudrani, S., Rosalina, R., Mukhtar, I., Rosadi, D., Fauzi, L., Elyazar, I. R. F., Hawley, W. A., & Wibisono, H. (2022). Clinical characteristics and factors associated with COVID-19-related mortality and hospital admission in 5 rural provinces in Indonesia: a retrospective cohort study. *MedRxiv*, 021, 1–20.
- Surendra, H., Salama, N., Lestari, K. D., Adrian, V., Widyastuti, W., Oktavia, D., Lina, R. N., Djaafara, B. A., Fadilah, I., Sagara, R., Ekawati, L. L., Nurhasim, A., Ahmad, R. A., Kekalih, A., Syam, A. F., Shankar, A. H., Thwaites, G., Baird, J. K., Hamers, R. L., & Elyazar, I. R. F. (2022). Pandemic inequity in a megacity: a multilevel analysis of individual, community and healthcare vulnerability risks for COVID-19 mortality in Jakarta, Indonesia. *BMJ Global Health*, 7(6), e008329. <https://doi.org/10.1136/bmjgh-2021-008329>
- Suri, P., & Arora, V. (2020). COVID 19 and cardiovascular disease. *JK Science*, 22(4), 153–154.
- Susilo, A., Jasirwan, C. O. M., Wafa, S., Maria, S., Rajabto, W., Muradi, A., Fachriza, I., Putri, M. Z., & Gabriella, S. (2022). Mutasi dan Varian Coronavirus Disease 2019 (COVID-19): Tinjauan Literatur Terkini. *Jurnal Penyakit Dalam Indonesia*, 9(1), 59. <https://doi.org/10.7454/jpdi.v9i1.648>
- Tadic, M., Cuspidi, C., Grassi, G., & Mancia, G. (2020). COVID-19 and arterial hypertension: Hypothesis or evidence? *Journal of Clinical Hypertension*, 2(May), 1120–1126. <https://doi.org/10.1111/jch.13925>
- Tim May, Malcolm Williams, Richard Wiggins, and P. A. B. (2021). *The Lambda variant of SARS-CoV-2 has a better chance than the Delta variant to escape vaccines*. 1996, 6.
- Townsend, L., Dyer, A. H., Jones, K., Dunne, J., Mooney, A., Gaffney, F., O'Connor, L., Leavy, D., O'Brien, K., Dowds, J., Sugrue, J. A., Hopkins, D., Martin-Loeches, I., Ni Cheallaigh, C., Nadarajan, P., McLaughlin, A. M., Bourke, N. M., Bergin, C., O'Farrelly, C., ... Conlon, N. (2020). Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS ONE*, 15(11 November), 1–12. <https://doi.org/10.1371/journal.pone.0240784>
- WHO. (2020). *Transmisi SARS-CoV-2: implikasi terhadap kewaspadaan pencegahan infeksi*. 1–10.
- Wu, Z. hong, Tang, Y., & Cheng, Q. (2021). Diabetes increases the mortality of patients with COVID-19: a meta-analysis. *Acta Diabetologica*, 58(2), 139–144. <https://doi.org/10.1007/s00592-020-01546-0>
- Yang, L., Jin, J., Luo, W., Gan, Y., Chen, B., & Li, W. (2020). Risk factors for predicting mortality of COVID-19 patients: A systematic review and meta-analysis. *PLoS ONE*, 15(11 November 2020), 1–11. <https://doi.org/10.1371/journal.pone.0243124>
- Zheng, Z., Peng, F., Xu, B., Zhao, J., Liu, H., & Peng,

- J. (2020). Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information. *Journal of Infection*, January.
- Zhou, F. (2020). Clinical Course And Risk Factors For Mortality Of Adult In Patients With COVID-19 In Wuhan, China: A Retrospective Cohort Study. *Journal of Medicine Study & Research*, 3(1), 01-02. <https://doi.org/10.24966/msr-5657/100015>