The Association between Comorbidity and Severity of SARS-CoV-2 Omicron Variant (B.1.1.529) Infection in Bengkulu: A Cross-Sectional Study

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KEYWORDS

Comorbid, COVID-19, Omicron, SARS-CoV-2, Severity

ABSTRACT

Introduction: The Omicron variant is a strain of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) with higher infectivity and transmissibility (2.8 and 3.2 times) than Delta, but the pathogenicity of Omicron is weaker. Some studies indicate that a history of comorbidities can enhance the pathogenicity.
Objectives: This research investigates the correlation between comorbidity and disease severity in COVID-19 patients with the Omicron variant in Bengkulu.
Methods: This observational type with cross-sectional design consisted of 191 COVID-19 patients from January to December 2022. COVID-19 positive confirmation was collected through RT-PCR and medical records from Dr. M. Yunus, Harapan dan Doa, and Rafflesia Hospital with total sampling method. The medical record encompassed demographic characteristics, clinical manifestation features, and comorbid types. Subsequently, an analysis was conducted to examine the correlation between comorbidity and disease severity using the Spearman Rank test.
Results: The majority of subjects were 18-60 years (60.7%) and 53.9% were male. Most of the subjects experienced cough (72,7%) and were at a moderate level (47.6%). The most common comorbid were hypertension (21.3%), and cardiovascular diseases (20.6%), and the third common comorbid were diabetes and chronic kidney disease (15.4%). Overall, the disease severity was observed in 58 patients with mild, 91 moderate, and 42 severe. Spearman Rank test showed a significant correlation (p = 0,000) between comorbidities and disease severity of COVID-19 patients with the Omicron variant in Bengkulu City with moderate correlation strength (rs = 0,572).
Conclusions: The comorbidity history significantly influences the severity of illness among COVID-19 Omicron variant patients, whereby an increased number of comorbidities aggravated the severity of the disease.

1. Introduction

The variant of SARS-CoV-2 known as Omicron (B.1.1.529) was identified in November 2021 in South Africa.1 There were 753 million confirmed cases with 6.8 million reported deaths.2 The Indonesian Ministry of Health reported 4,262,720 COVID-19 cases in Indonesia in December 2021, with Jakarta having the highest number of positive cases (865,297). Meanwhile, Badan Pusat Statistik Bengkulu (2022) reported an outbreak in the past year, with COVID-19 being the leading cause.

According to genomic analysis, the Omicron variant has more than 30 genetic mutations, including in the receptor-binding domain (RBD) of spike protein, which has high affinity with the angiotensin-converting enzyme 2 (ACE2) receptor, as the main protein for viral entry.3 World Health Organization (WHO) classifies the clinical spectrum of SARS-CoV-2 infection into 5 categories, such as asymptomatic, mild, moderate, severe, and critical. Omicron has been reported to cause milder symptoms compared to previous variants.1 However, comorbid factors such as hypertension, diabetes, cardiovascular diseases (CVD), chronic obstructive pulmonary disease (COPD), tuberculosis, chronic kidney disease (CKD), and malignancy are associated with disease severity and increased risk of severe outcomes.4–6

From the issues above, there is no data regarding the prevalence of comorbidities related to the Omicron variant of SARS-CoV-2 in Bengkulu City. Therefore, this study aimed to analyze the severity of the SARS-CoV-2 Omicron variant in patients with comorbidities such as hypertension, cardiovascular

diseases, diabetes, COPD, tuberculosis, CKD, and malignancies in Bengkulu City.

2. Methodology

The method used is observational with a cross-sectional design. The study population is medical records of COVID-19 patients from RSUD Dr. M. Yunus Bengkulu, RSUD Harapan dan Doa, and RS Rafflesia recorded in the PCR laboratory of RSUD Dr. M. Yunus Bengkulu during the period from January to December 2022. The research was conducted after obtaining ethical approval from the Research Ethics Committee of the Faculty of Medicine and Health Sciences, University of Bengkulu No. 238/UN30.14.9/LT/2023.

Data collection was carried out through three stages: sampling of confirmed Omicron-positive cases, identification of severity levels in patients, and assessment of comorbidity status. Samples were taken using the total sampling technique. The inclusion criteria for the study included confirmed COVID-19 patients with or without comorbidities, along with complete medical record data for age and gender. Exclusion criteria for the study were COVID-19-positive patients with primary reasons recorded in hospitals other than COVID-19, and comorbid patient groups other than hypertension, diabetes, CVD, COPD, tuberculosis, CKD, and malignancy. Univariate data were presented for distribution (n) and percentage (%). Bivariate data were analyzed using the Spearman Rank test for the relationship between comorbidity status and severity level, and Chi-square for the relationship between demographic characteristics and severity level. The data were collected and processed using the statistical analysis software IBM SPSS Statistics 25. A p-value <0.005 was considered statistically significant.

3. Results and Discussion

A total subject of this study is 191, 148 patients from RSUD Dr. M. Yunus, 25 patients from RSUD Harapan dan Doa, and 18 patients from RS Rafflesia. Demographic characteristics assessed included age and gender. Table 1 shows a significant difference between age groups and disease severity levels ($p < 0.05$). In both gender groups, the majority had moderate severity (27.2% and 20.4%). The chi-square test results indicate a significant difference between these two groups ($p < 0.05$).

Table 1. The Demographic and Severity Level of Study Participants

Patient's Characteristic	**Severity Level (N (%))**			**Total**	***p-value***
	Mild (n = 58)	Moderate (n = 91)	Severe (n = 42)		
Age					
0-17	15 (7,9)	13 (6,8)	2 (1)	30 (15,7)	0,000
18-60	36 (18,8)	59 (30,9)	21 (11)	116 (60,7)	
>60	7 (3,7)	19 (9,9)	19 (9,9)	45 (23,6)	
Gender					
Male	21 (11)	52 (27,2)	30 (15,7)	103 (53,9)	0,002
Female	37 (19,4)	39 (20,4)	12 (6,3)	88 (46,1)	
Source: Author					

The severity level is determined through medical record diagnosis, considering clinical manifestations. 18 clinical manifestations appear. Table 2 shows the most common clinical manifestation in patients, which is cough (dry or productive), occurring in 139 patients (72.7%).

Table 3 presents the results of subvariant identification. There were 38 individuals confirmed positive for SGTF (BA-1 and BA.2). The comparison between known Omicron variants shows the dominance of BA.2 (16.8%) over BA.1 (3.1%). Among BA.1 cases, patients tend to exhibit mild severity (1.6%), while BA.2 cases show moderate symptoms (8.4%). Other unknown variants are grouped under the 'unknown' category (80.1%).

Table 2. Clinical Manifestation of Symptomatic Patients

Clinical Manifestation	**Frequency (n)**	**Percentage (%)**

Cough	139	72,7
Fever	122	63,8
Malaise	101	52,8
Shortness of breath	100	52,3
Nauseous	65	34
Vomit	60	31,4
Decreased appetite	38	19,8
Sore throat	35	18,3
Cold	32	16,7
Headache	24	12,5
Stomach discomfort	18	9,4
Heartburn	16	8,3
Dizzy	11	5,7
Muscle/joint pain	10	5,2
Chest pain	9	4,7
Diarrhea	8	4,1
Loss of consciousness	5	2,6
Chills	2	1
Source: Author		

Source: Author

Table 3. Omicron Subvariant Identification

Characteristic	**Severity Level (N (%))**			**Total**
	Mild (n = 58)	**Moderate (n = 91)**	**Severe (n = 42)**	
Omicron Subvariant				
BA.1	**3 (1,6)**	**1 (0,5)**	**2 (1)**	**6 (3,1)**
BA.2	**11 (5,8)**	**16 (8,4)**	**5 (2,6)**	**32 (16,8)**
Unknown	**44 (23)**	**74 (38,7)**	**35 (18,3)**	**153 (80, 1)**

Source: Author

Correlation Comorbid Types and Severity Level

Figure 1 shows the dominant comorbid is hypertension. Furthermore, Table 4 presents the results between each type of comorbid and severity with chi-square test obtained significant values ($p < 0.05$) in the group of hypertension, cardiovascular disease, COPD, tuberculosis, and chronic kidney disease. Meanwhile, in those who were not eligible with chi-square followed by the Mann-Whitney test, $p < 0.05$ was found in patients with DM and malignancy.

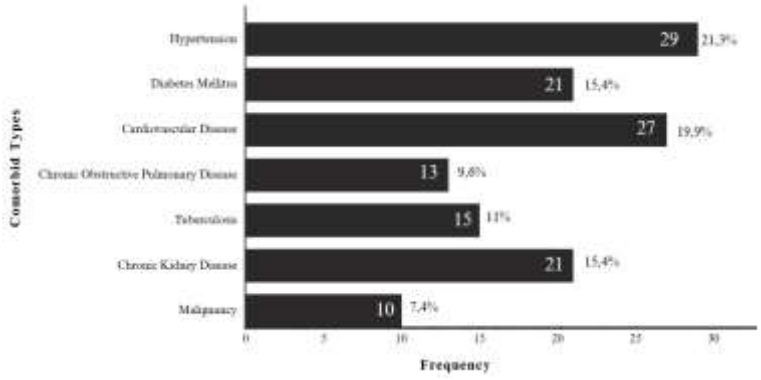

Figure 1. Distribution of Comorbid Types of Omicron Variant COVID-19 Patien

Table 4. Analysis of Comorbid Type and Severity

Comorbid types	Severity Level (N (%))			Total	
	Mild (n = 58)	Moderate (n = 91)	Severe (n = 42)		*p-value*
Hypertension (n = 126)					
Yes	3 (10,3)	17 (58,6)	9 (31)	29	0,000
No	50 (51,5)	46 (47,4)	1 (1)	97	
Diabetes Mellitus (n = 118)					
Yes	5 (23,8)	12 (57,1)	4 (19)	21	0,003*
No	50 (51,5)	46 (47,4)	1 (1)	97	
Cardiovascular Disease (n = 124)					
Yes	2 (7,4)	12 (44,4)	13 (48,1)	27	0,000
No	50 (51,5)	46 (47,4)	1 (1)	97	
Chronic Obstructive Pulmonary Disease (n = 110)					
Yes	0 (0)	3 (23,1)	10 (76,9)	13	0,000
No	50 (51,5)	46 (47,4)	1 (1)	97	
Tuberculosis (n = 112)					
Yes	0 (0)	8 (53,3)	7 (46,7)	15	0,000
No	50 (51,5)	46 (47,4)	1 (1)	97	
Chronic Kidney Disease (n = 118)					
Yes	0 (0)	7 (33,3)	14 (66,7)	21	0,000
No	50 (51,5)	46 (47,4)	1 (1)	97	
Malignancy (n = 107)					
Yes	1 (10)	6 (60)	3 (30)	10	0,001*
No	50 (51,5)	46 (47,4)	1 (1)	97	
Description: cross-tabulation with Chi-Square and (*)Mann-Whitney **Source: Author**					

Table 5 shows the analysis of the correlation between comorbid status and disease severity in Omicron patients obtained a significant value ($p < 0.05$) and a moderate correlation coefficient.

Table 5. Analysis The Number of Comorbid and Severity

Comorbid	Severity Level (N (%))			Total	*p- value*	r_s
	Mild (n = 58)	Moderate (n = 91)	Severe (n = 42)			
Without comorbid	50 (51,5)	46 (47,4)	1 (1)	97	0,000	0,572
1 comorbid	5 (8,2)	31 (50,8)	25 (41)	61		
>1 comorbid	3 (9,1)	14 (42,2)	16 (48,5)	33		
Description: cross-tabulation (% comorbid) and Rank Spearman correlation **Source: Author**						

Description: cross-tabulation (% comorbid) and Rank Spearman correlation

Source: Author

The age group of 18-60 was the most common, resembling previous studies (76.34%).[7] Active social activities lead to high infection rates. Meanwhile, the low number of infections in childhood is thought to be due to Indonesian government programs that contribute to strict restrictions on children, for example, PP No. 21/2020 on PSBB through school holidays supported by parental protective measures.[8] Males (53.9%) were found to outnumber females (46.1%). The low incidence and severity in women may be a protective effect of the X chromosome (which contains the ACE2 gene).[9] Single nucleotide peptide in transmembrane protease serine-type II (TMPRSS2) which plays a role in viral membrane fusion, was also found to be responsive to androgen than estrogen.[10]

The most common complaints in Omicron patients are fever, cough, and fatigue to several previous studies.[11] Omicron's ability to express TMPRSS2 and ACE2 is slower in type II pneumocytes, resulting in poorer replication in the lung. This leads to Omicron infection of the upper respiratory tract (such as cough and sore throat).[12] Omicron variants produce variants with multiple offspring, given that Omicron variants are not single strains. However, BA.3 transmission is very limited and cases are few.[1] This study only included two subvariants of the Omicron variant detected by the SGTF method, BA.1 and BA.2. Other subvariant types that were not detected were included in the unknown category. The large number of BA.2 discoveries in this period was due to a unique mutation that allows higher transmissibility with 1.5 times faster transmission than BA.1, while other variants such as BA.4 and BA.5 are thought to cause a new wave of infections after BA.2.[13]

Hypertension is influenced by lifestyle, education, and environmental factors.[14] Bengkulu is located on the west coast of Sumatra Island (Indonesia) with ±525 km of coastline, coastal areas, and a high contribution of the fisheries sector.[15] This high hypertension is likely influenced by a high salt diet, for example in dried salted fish and staple foods that are high in sodium and cholesterol.[16] While the association of hypertension and infection (p = 0.000), because the immune system is strongly influenced by hypertension, hypertensive patients have higher neutrophil counts and a low proportion of lymphocytes. This fact is supported by the NLR (neutrophil-lymphocyte ratio) which is positively correlated with the blood pressure of hypertensive patients and higher in patients without blood pressure control. The result of the NLR inflammation indicator is also a marker of COVID-19 severity through a worse prognosis.[17]

Diabetes mellitus and disease severity had a significant association (p = 0.003). Potential mechanisms of susceptibility and severity of infection stem from the direct effect of elevated glucose levels on the replicative function of SARS-CoV-2, dysregulation of immune and inflammatory responses, hypercoagulability, and activation of the renin-angiotensin-aldosterone system (RAAS) which increases the risk of insulin resistance and in turn increases mortality and morbidity.[18]

The association of cardiovascular disease (CVD) and severity risk was found to be significant (p = 0.000). These results are supported by a meta-analysis of the prevalence of hypertension and CVD associated with increased need for care management of severe critical conditions. CVD through RAAS imbalance leads to increased ACE2 expression, slowing viral clearance. High expression of ACE2 receptors on cardiomyocytes favors amplification of inflammatory signals and ACE2 expression, thus promoting viral replication into the host and contributing to the development of COVID-19 severity.[19]

Chronic obstructive pulmonary disease (COPD) based on the percentage of severity showed a higher value of severe (76.9%), although only 13 patients with COPD were recorded. Statistical analysis of COPD patients showed a significant association (p = 0.000), indicating an association between the presence of COPD and disease severity. COPD patients are at higher risk of intensive critical care and ventilation than patients without COPD, which is attributed to the increased expression of ACE-2 receptors in the small airways and alveoli of COPD patients and patients who smoke.[20] The systematic review added that impaired innate and adaptive immune responses in COPD patients impair viral clearance action (impaired interferon response to SARS-CoV-2) in the respiratory tract, which tends to result in delayed clearance.[21]

Tuberculosis in this study is an infectious disease associated with the severity of COVID-19 (p = 0.000). Research states that tuberculosis infection and COVID-19 are a "cursed duet" and require immediate attention, as 85 (11.08%) of 767 patients died from European studies. In addition,

tuberculosis is a global health priority.[22] The unfavourable immune response in COVID-19 and tuberculosis patients promotes the recruitment of neutrophils containing harmful substances linked to tissue damage, thereby worsening inflammation. The IL-10 response and Treg differentiation are lower than the harmful immune response, resulting in immune dysregulation against SARS-CoV-2 infection.[23]

Epidemiologic data on chronic kidney disease (CKD) suggests nearly 10% of the global population has CKD. Research shows a significant association (p = 0.000) between chronic kidney disease and disease severity in COVID-19 patients, CKD also displays a high severity in other groups. The condition of kidney damage in CKD patients with SARS-CoV-2 infection through the characteristic overproduction of proinflammatory cytokines (IL-6, TNF-alpha) supports systemic inflammatory conditions, hypercoagulation, and multi-organ dysfunction.[24] CKD patients are also prone to an increase in inflammatory biomarkers (e.g. CRP, ferritin, and D-dimer) during hospitalization after experiencing a decline in renal function through the systemic effects of COVID-19 on the kidneys.[25]

Cancer patients or malignancies in the study had a significant association with increased severity (p = 0.001). Genetic and epigenetic changes in cancer patients have the potential to increase COVID-19 susceptibility. Cancer patients infected with SARS-CoV-2 show complications and a high risk of worsening.[26] A systematic review found that chemotherapy 30 days before COVID-19 diagnosis can increase the risk of death, based on immunosuppression in patients with chemotherapy. Therefore, hematologic malignancies have the highest risk of mortality due to greater immunosuppression in patient treatment, the mechanism promoting immune system dysfunction in the microenvironment.[27]

The presence of multimorbidity referring to >1 comorbidity predisposes to higher severity characterized by an increased risk of severity in this study (48.5%), these co-occurring comorbidities in turn exacerbate the concomitant pathologic mechanisms of each comorbid patient's mechanism of destruction by reducing the patient's tolerance to organ injury.[28] For example, some comorbidities can exacerbate immune-mediated lung injury by reducing the viral clearance response, whereas other comorbidities contribute to an early decline in lung function, thus predisposing an individual to respiratory failure and lung injury is better tolerated in patients who display only one comorbidity than those with multimorbidity.[18,28] Comorbidity as a risk factor is certainly not the only one considered for disease severity, other factors such as vaccination status, age (especially for the elderly), gender, and race need to be considered to further look at clinical risk considerations present in the Omicron wave period.[29]

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