Clinical Characteristics of Patients with Different SARS-CoV-2 Variants in South Kalimantan, Indonesia

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Abstract

Background: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has undergone various mutations of Corona Virus Disease 2019 (COVID-19). The World Health Organization (WHO) has designated B.1.617.2 (Delta) and B.1.1.529 (Omicron) as variants of concern (VOC). Since clinical features and epidemiological characteristics of patients infected with SARS-CoV-2 variants remain largely unknown, especially in Indonesia, this study aimed to identify the clinical characteristics of COVID-19 patients from South Kalimantan, Indonesia.

Methods: Data from medical records of COVID-19 patients at Ulin General Hospital Banjarmasin from June 2021 to February 2022 were randomly extracted, containing demographic data, comorbidities, and laboratory data, as well as the type of virus.

Results: In total, 32 patients were included, 9 were infected with delta, 14 with probable omicrons, and 9 with non-VOC. Patients in the probable Omicron group were significantly older than other groups (median age 64 years old, range 54–73 years; p=0.049), had hypertension as the dominant comorbidity (85.7%; p=0.039), the onset appeared slightly earlier (median 3 days; range 2-3 days, p=0.062), with no anosmia symptom (p=0.006). Critical illness predominated and mostly survived in all variants but was not statistically significant (p=0.590 and 0.726, respectively). The three variants showed similarities in laboratory findings; hence, statistical analysis suggested that the leucocytes differed significantly (p=0.020).

Conclusions: Patients with the likely Omicron variant are much older, have hypertension as their main comorbidity, do not have any symptoms of anosmia, and have higher leukocyte counts compared to other variants.

Keywords: Clinical characteristics, COVID-19, Delta, non-VOC, probable Omicron .

Introduction

Corona Virus Disease 2019 (COVID-19) pandemic has spread rapidly to over 200 nations since its appearance in December 2019, including Indonesia. Globally, more than 400 million people have been infected, resulting in over 5 million deaths.[1] The first wave of COVID-19 reported cases in Indonesia was identified on March 2, 2020, and the number gradually dropped in April 2021. The second wave began in June 2021, and the number had steadily decreased by October 2021. The third wave started in late January 2021. As of February 2021, the total number of confirmed cases was 4,708,043, contributing to 144,958 deaths.[2]

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the etiologic agent of COVID-19, belongs to the Betacoronavirus genus. It is a virus with positive-sense single-stranded RNA with approximately 30,000 bases and replicates utilizing the viral RNA-dependent RNA polymerase, lacking the proofreading function.[3] As a consequence, the virus has a high capability for generating genetic variants by selecting a genetically varied population based on fitness and or environmental adaption. With such a massive pool of infected people worldwide,

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a rapid generation of variants with increased infectivity and or resistance to the host's immunological response is predicted.[4]

Multiple viral strains have evolved and grown in numerous nations. The World Health Organization (WHO) has designated several variants as a variant of concern (VOC), including B.1.617.2 (Delta) and B.1.1.529 (Omicron) variants.[5] The Delta variant is more transmissible, has a higher viral load, has a high reinfection rate, and evades natural immunity.[6] Although the Delta has become the dominant variant in Indonesia since its first appearance in April 2021,[7] the Omicron variant, which was recently discovered, is quickly surpassing the delta as the most prevalent SARS-CoV-2 variant. While there is still much to learn about Omicron's epidemiology, available evidence suggests that it might have a higher transmission rate than the previous Delta variant. It has the ability to avoid the immune protection provided by antibodies from either the vaccine or previous SARS-CoV-2 infection.[8]

Ulin Regional Hospital Banjarmasin, as a main COVID-19 referral hospital in South Kalimantan, has treated many COVID-19 patients, including Delta and Omicron variants, during the second and third waves. This study aimed to identify the clinical characteristics of COVID-19 patients infected with different SARS-CoV-2 variants at Ulin General Hospital, South Kalimantan. To our knowledge, this is the first study in Indonesia.

Methods

The design of the study was a descriptive study. This research has been approved by the Research Ethics Committee of Ulin Hospital Banjarmasin with registration number 17/III-Reg Riset/RSUD/22.

All cases were from Ulin Regional Hospital Banjarmasin and met the clinical diagnostic criteria of COVID-19. Cases had positive results on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays of specimens taken from nasopharyngeal swabs. During the second and third waves, from June 2021 to February 2022, 32 cases of COVID-19 patients were randomly selected and tested to differentiate the variant. The Delta variants and the non-VOCs were identified based on whole-genome sequencing (WGS) performed by the Indonesian Center for Biomedical Research and Development and Basic Health Technology. Probable Omicron infection was suggested by Spike-gene target failure (SGTF) on the COVID-19 RT-PCR test. The data observed included demographic variables and laboratory investigation. The demographic variables were age, gender, comorbidities, history of smoking, history of vaccine, the onset of disease (the first day of any symptom until the day of admission), symptoms, disease severity (asymptomatic, mild, moderate, severe, or critically illness based on Indonesia COVID-19 management guidelines for the severity of clinical presentation) and outcome patient survived or died. Laboratory data include complete blood count (CBC) and inflammatory markers such as absolute lymphocyte count (ALC), neutrophil to lymphocyte ratio (NLR), C-reactive protein (CRP), lactate dehydrogenase (LDH) at the beginning of hospital admission.

Statistical analysis was performed with IBM SPSS 25.0. Categorical variables were summarized as counts and percentages, then proceeded with Fisher's exact test. Numerical variables were reported in median and interquartile ranges. Test for normality and homogeneity with Kolmogorov-Smirnov and Levene's tests. The ANOVA test was performed on normally distributed, homogeneous variables, and the Kruskal-Wallis test was performed on variables that did not meet one of the criteria. Statistical significance was indicated by a p-value less than 0.05.

Results

Infection with the probable Omicron variant of COVID-19 tended to affect older patients (median 64 years; range 54-73). Based on gender, both Delta and Omicron variants were dominated by males (66.7% and 71.4%), while non-VOC variants were dominated by females (77.8%). Hypertension was the most common comorbidity in Delta (55.6%), probable omicron (85.7%), and VOC (33.3%) variants. Meanwhile, diabetes was the second most common comorbidity in patients with Delta (44.4%) and probable Omicron (50.0%) variants (Table 1).

Interestingly, smoking history was only found in one patient with probable Omicron variant infection. In this study, 44.4% of Delta patients and 35.7% of Omicron patients had a history of the COVID-19 vaccine, but in non-VOC patients, only 11.1% were found. The day of onset of clinical symptoms was uniform in all three variants, but the Omicron variant appeared slightly earlier (median 3 days). Cough, shortness of breath, and fever were the most common symptoms in all three variants. There were no patients with anosmia in the

Table 1 Demographics and Clinical Characteristics at Admission based on COVID-19 Variants

Characteristics	Delta n=9	Probable Omicron n =14	Non-VOC n =9	p-value
Age in yr, median (IQR)	51 (49–62)	64 (54–73)	43 (39–58)	0.049
Gender				0.073
Male	6 (66.7%)	10 (71.4%)	2 (22.2%)	
Female	3 (33.3%)	4 (28.6%)	7 (77.8%)	
Comorbidities				
Hypertension	5 (55.6%)	12 (85.7%)	3 (33.3%)	0.039*
Diabetes mellitus	4 (44.4%)	7 (50.0%)	1 (11.1%)	0.210
Obesity	3 (33.3%)	1 (7.1%)	2 (22.2%)	0.372
Coronary heart disease	1 (11.1%)	0 (0.0%)	2 (22.2%)	0.165
Heart failure	1 (11.1)	5 (35.7%)	0 (0.0%)	0.128
Malignancy	0 (0.0%)	2 (14.3%)	0 (0.0%)	0.492
Chronic kidney disease	1 (11.1%)	2 (14.3%)	0 (0.0%)	0.771
History of smoking	0 (0.0%)	1 (7.1%)	0 (0.0%)	1.000
History of COVID-19 vaccine	4 (44.4%)	5 (35.7%)	1 (11.1%)	0.382
Onset in days, median (IQR)	4 (2–5)	3 (2–3)	5 (4–7)	0.062
Symptom				
Cough	7 (77.8%)	8 (57.1%)	9 (100%)	0.075
Fever	8 (88.9%)	10 (71.4%)	8 (88.9%)	0.610
Shortness of breath	4 (44.4%)	7 (50.0%)	7 (77.8%)	0.396
Anosmia	3 (33.3%)	0 (0.0%)	5 (55.6%)	0.006*
Nausea and/ or vomitus	4 (44.4%)	4 (28.6%)	2 (22.2%)	0.703
Diarrhea	1 (11.1%)	1 (7.1%)	4 (44.4%)	0.088
Fatigue	3 (33.3%)	5 (35.7%)	1 (11.1%)	0.482
Myalgia	1 (11.1%)	0 (0.0%)	2 (22.2%)	0.165
Sore throat	1 (11.1%)	3 (21.4%)	1 (11.1%)	1.000
Headache	0 (0.0%)	0 (0.0%)	1 (11.1%)	0.563
Runny nose	1 (11.1%)	0 (0.0%)	0 (0.0%)	0.563
Disease severity				0.590
Asymptomatic	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Mild	2 (22.2%)	5 (35.7 %)	1 (11.1%)	
Moderate	3 (33.3%)	2 (14.3%)	2 (22.2%)	
Severe	1 (11.1%)	0 (0.0%)	1 (11.1%)	
Critical	3 (33.3%)	7 (50.0%)	5 (55.6%)	
Outcome				0.726
Survived	7 (77.8%)	10 (71.4%)	5 (55.6%)	
Deceased	2 (22.2%)	4 (28.6%)	4 (44.4%)	

probable Omicron variant, while 33.3% were found in the Delta variant and 55.6% in the Non-VOC.

Based on the severity of the disease, patients with moderate or critical degree dominated the Delta variant, both 33.3%. Probable Omicron variant and non-VOC were dominated by critical illness by 50.0% and 55.6%, respectively. The survival rate of the Delta and probable Omicron variant appears to be high at 77.8% and 71.4%, respectively.

Statistical analysis of the demographic and clinical characteristics of the patients in this study revealed that only age (p=0.049), comorbid hypertension (p=0.039), and the presence of anosmia (p=0.006) had significant differences in the three COVID-19 variants.

The patient's laboratory findings showed that hemoglobin, leukocyte, and platelet count between groups were normal. Neutrophilia had been seen in all three variants, and lymphopenia was more observed in the non-

Table 2 Laboratory Findings at Admission based on COVID-19 Variants

Laboratory Findings at Admission	Normal range	Delta n =9	Probable Omicron n =14	Non-VOC n =9	p-value
Hemoglobin in g/dL, median (IQR)	12.0–16.0	13.9 (13.0–14.6)	12.0 (9.5–13.8)	12.6 (11.7–14.6)	0.272
Leukocytes × 109/L, median (IQR)	4.5–11.0	5.9 (5.6–6.7)	7.9 (6.0–10.8)	5.9 (5.4–7.3)	0.020*
Platelet count × 109/L, median (IQR)	150–400	186 (162–274)	179 (167–242)	228 (163–267)	0.572
Neutrophil %, median IQR)	40–60	66.2 (62.2–72.0)	68.2 (56.9–76.2)	72.0 (67.0–75.7)	0.596
Lymphocyte %, median (IQR)	20–40	21.5 (20.2–23.4)	20.8 (11.8–31.1)	18.6 (15.7–24.6)	0.810
Eosinophils %, median (IQR)	1.0–3.0	1.0 (1.6–0.6)	0.3 (0.2–1.9)	0.0 (0.0–0.6)	0.260
NLR, median (IQR)		3.1 (2.8–3.2)	3.4 (1.9–6.4)	3.7 (2.7–4.8)	0.593
ALC × 109/L, median (IQR)		1.3 (1.1–1.6)	1.5 (0.8–2.8)	1.2 (0.8–1.3)	0.423
LDH in U/L, median (IQR)	< 400	618.0 (342.0–940.0)	418.0* (378.0–577.0)	668.5 (424.5–729.8)	0.468
CRP in mg/dL, median (IQR)	< 6.00	12.0 (5.2–29.8)	40.6** (18.8–142.9)	22.5 (6.0–33.1)	0.259

Note: *n=9, due to limited data on admission, ** n=8, due to limited data on admission, IQR= interquartile range, NLR= neutrophil to lymphocyte ratio, ALC= absolute lymphocyte count, LDH= lactate dehydrogenase, CRP= C-reactive protein, VOC= variant of concern

VOC. The NLR and ALC had similar values between the three variants; hence LDH and CRP were increased in all three variants.

There was no statistically significant difference in the laboratory findings at admission for the three variants of COVID-19, except for the leukocyte count (p=0.020).

Discussion

More than two years have passed since the COVID-19 pandemic, and cases in Indonesia continue to rise, as well as hospitalization and death. However, SARS-CoV-2 has been undergoing several mutations, prompting concern that these mutations could result in a more severe and lethal COVID-19. Variant B.1.617.2 (Delta) and B.1.1.529 (Omicron) are both variants of concern, which are variants that contain one or more mutations that allow the virus to be more transmissibble and lessen the virus' receptivity to treatment or affect effectiveness of vaccinations.

The Delta variant has spread rapidly across a mostly unvaccinated country since first identified in India in December 2020, resulting in many cases, hospitalizations, and deaths. Two months after India's first case, the Delta variant spread rapidly in Indonesia. It caused a massive surge in daily new confirmed COVID-19 cases, leading to an increase in the hospital bed occupancy rate (BOR).[9] On December 15, 2021, the identification of the first Omicron variant of SARS-CoV-2 in Indonesia sparked interest. Given the experience from other countries, the Delta variant will most likely be displaced by Omicron as the dominant variant in Indonesia.[10] The S gene target failure (or S gene dropout) is one of the Omicron variant's mutations, as the PCR testing fails to detect one of the multiple sections of the targeted gene, allowing a marker for focused genome sequencing.[11]

In this study, infection of probable Omicron variant COVID-19 tends to affect older patients (median age 64 years old), compared to the Delta variant (median age 51 years old) and non-VOC (median age 43 years old), indicating that three variants of COVID-19 have significant age differences (p=0.049). Similarly, another study has shown that older age has a higher risk of COVID-19 than the younger population.[12] Older people are more susceptible to severe SARS-CoV-2 infection due to the aging

process that produces a variety of physiologic modifications in the immune system. These modifications impair the immune system's capacity to combat latent and new infections, and mount appropriate vaccination responses. Increased proinflammatory phenotypes may affect an individual's vulnerability to coronavirus infections, the illness course, and clinical consequences.[13]

Previous research on SARS-CoV-2 showed that people with comorbidities were at higher risk of poor clinical outcomes,[12] and the most critical components are cardiovascular disorders and diabetes.[14] Elderly patients with comorbidities are among the highest risk groups for SARS-CoV-2 and fatal outcomes.[15] In this study, hypertension was the most common comorbidity in patients with Delta, probable Omicron, and Non-VOC infection. In addition, diabetes is the second most common comorbidity in patients with delta and probable Omicron variants. In a meta-analysis study, hypertension was an independent risk factor for critical COVID-19. COVID-19 patients with hypertension were associated with a significantly increased risk of developing a critical illness and mortality,[16] and diabetes was the best predictor of COVID-19-related death.[17] Several diabetes-related aspects have been taken into account.

Individuals with diabetes ares prone to infection due to increased activation of the renin-angiotensin system (RAS) in various organs associated with a worsened inflammatory response.[18] Furthermore, the diabetic population has pulmonary dysfunction due to reduced lung volume, pulmonary diffusing capacity, bronchomotor tone, ventilation control, and noradrenergic innervation impairment.[19] Furthermore, the increased CV risk associated with diabetes and hypertension can exacerbate a poor COVID-19 prognosis.[17]

Interestingly, in this study, infected Delta (44.4%) and Omicron patients (35.7%) had a history of the COVID-19 vaccine, but lower in infected non-VOC patients (11.1%). The history of the COVID-19 vaccine was thought to have a dominant role in the progression of the disease. Even though the prevalence of Delta variant infection was not different between the vaccinated and unvaccinated population, the proportion of COVID-19 hospitalization, disease progression, and deaths was significantly lower in the partially vaccinated and fully vaccinated than in the unvaccinated.[20] There is currently no accurate data on how vaccination can protect against infection with Omicron variants. UK Health Security Agency (UKHSA) stated that two vaccinations are less effective against the Omicron variant than they were against prior variants, and their effectiveness declines with time. However, the vaccine is effective at about 59% against Omicron mortality in those over 50.[21] The Omicron variant had many mutations in the Spike protein, resulting in more significant evasion of immunological protection produced by past SARS-CoV-2 infection and possibly even existing COVID-19 vaccines.[22]

The day of onset or the interval between onset of symptoms and hospital admission on the Omicron variant appeared to be slightly earlier (median 3 days), compared to the Delta variant (median 4 days) and non-VOC (median 5 days). In addition, the median time from the onset of symptoms to the first admission to the hospital was seven days.[23] However, another study showed that the median duration from the first sign of symptoms to hospital admission was five days in the first wave of COVID-19.[24]

The most common clinical symptoms reported in all three variants were cough in delta (77.8%), probable Omicron (57.1%), and non-VOC (100%). Furthermore, fever and shortness of breath are also prevalent. Interestingly, there were no patients with anosmia in the probable Omicron variant, whereas anosmia was found in the Delta variant (33.3%) and in the Non-VOC (55.6%). Thus, there were significant differences in the presence of anosmia between the three variants of COVID-19 ($p=0.006$). Preliminary data suggest that anosmia appears less common in Omicron infection than reported for other strains and variants.[25] An experimental study on the golden hamster showed that Omicron infection caused less damage to the olfactory mucosa and most likely lowered the risk of developing anosmia.[26]

At first evaluation, patients with a moderate or critical degree dominated the Delta variant (33.3%), probable Omicron variant (50%), and non-VOC (55.6%). Although half of the patients with possible Omicron infections were critical, the survival rate was relatively high (71.4%), suggesting that infection by the Omicron variant may fall into a bad state, but improvement can still be expected.

The median value of hemoglobin, leukocyte, and platelet count between groups was normal. These results is in line with previous study which showed no difference in CBC values at diagnosis.[27] However, other studies revealed low hemoglobin, high leukocytes,

and low platelet count that correlated with mortality.[28] However, leukocyte value is higher in the probable omicron group compared to other groups (p=0.020). Neutrophilia was detected in all three variants, and lymphopenia was observed in the non-VOC. A meta-analysis shows that lymphopenia and neutrophilia in admission are linked to poor outcomes in COVID-19 patients.[29]

Our study also shows that the NLR and ALC had similar values between the three variants, and LDH and CRP are increased in all three variants. Previous study suggests that ANC, NLR, LDH, and CRP values are significantly increased in patients with severe and critical diseases compared to mild and moderate diseases.[30]

This study has a limitation that this is only a single-center research study with minimal samples. More extensive studies are needed to better describe the clinical characteristics of the COVID-19 population with different variants to construct data and provide insights into this ongoing pandemic, especially in Indonesia.

In conclusion, most patients in all variants have predominant comorbidities such as hypertension and DM. The probable Omicron variant infected in older patients, with onset slightly earlier, has no anosmia symptom, and a relatively higher survival rate. Laboratory findings for the three variants showed similar results, namely normal values for hemoglobin, leukocyte, platelet, neutrophilia, NLR, and ALC, as well as elevated LDH and CRP. The SARS-CoV-2 variants are constantly evolving and changing. which can lead to change in the characteristics of the virus. Information about infection characteristics with new variants is crucial for decision-making about control approaches and strategies.

Conflicts of Interest

The author reports no conflicts of interest in this work.

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