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ORIGINAL RESEARCH

Insights into Omicron: Genomic Characterization and Inpatient Risk Assessment at Single Tertiary Hospital in Indonesia

Dewi Kartika Turbawaty, Dewi Ratna Komala, Basti Andriyoko

Department of Clinical Pathology, Faculty of Medicine Universitas Padjadjaran/Hasan Sadikin General Hospital, Bandung, West Java, Indonesia

Correspondence: Dewi Kartika Turbawaty, Hasan Sadikin General Hospital, Jl. Pasteur No. 38, Bandung, West Java, Indonesia, Tel +628122150145, Email dewi.kartika@unpad.ac.id

Purpose: Omicron is a variant with the highest number of mutations among all Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) viruses, making whole genome sequencing (WGS) an essential tool for public health surveillance and molecular epidemiology. It is important to note that surveillance data can provide insights into the virus evolution and disease control. This study aims to provide an overview of WGS results for the SARS-CoV-2 Omicron Variant at Hasan Sadikin General Hospital Bandung.

Patients and Methods: This study was conducted using an analytical observational method. Data was collected retrospectively from medical records, SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) results, and WGS results of patients at Hasan Sadikin General Hospital Bandung from July to December 2022, who met the inclusion criteria. The lineage trends, mutation profiles, characteristics differences, and factors influencing hospitalization were also described.

Results: Among 239 subjects, 50 Omicron lineages were identified, with BA.5.2 (28%) and XBB.1 (19.2%) dominating since July and October 2022, respectively. The spike gene had the highest frequency, accounting for 28.8% out of the 532 types of mutations identified. In BA.5.2 lineage, 97.01, 92.53, and 100% had L452R mutation, F486V mutation, and H69/V70 deletion, respectively. In the XBB.1 lineage, 100% had R346T and N460K mutations, with no H69/V70 deletion observed. XBB.1 lineage was associated with a 5.49 times greater risk of inpatient treatment (95% CI: 1.73–17.38) compared to BA.5.2, while the adjusted odds ratio (aOR) for the number of vaccinations was 0.45 (95% CI: 0.29–0.7).

Conclusion: BA.5.2 and XBB.1 lineage dominated Omicron variant infections from July to December 2022, with the most mutations occurring in the spike gene. Inpatient risk was influenced by the type of lineage, with XBB.1 showing a higher risk. A greater number of vaccinations significantly reduced this risk, emphasizing the protective role of vaccination.

Keywords: SARS-CoV-2, Omicron variant, whole genome sequencing

Introduction

Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), is being rapidly spread globally since the emergence in China.[1] In Indonesia, the first cases were reported in early March 2020.[2] The causative virus continues to mutate to adapt to the environment, leading to the origination of new variants. Omicron variant of SARS-CoV-2, also known as B.1.1.529, was first identified in South Africa in November 2021 and officially declared a Variant of Concern (VOC) by the World Health Organization (WHO) on November 26, 2021.[3] This variant has become the dominant strain globally, representing over 98% of viral sequencing data shared in Global Initiative on Sharing All Influenza Data (GISAID).[4,5]

Compared to previous variants, Omicron variant has at least 50 mutations in the genome, with 32 occurring in the spike protein. In SARS-CoV-2, the spike protein is a component of the virus responsible for recognizing and binding to ACE-2 receptors in humans. Mutations can alter the structure and function, making the recognition of the virus by antibodies more challenging.[6] Over 60 insertions, substitutions, and deletions have been detected in Omicron. As a result, the variant has the highest number of mutations among all existing SARS-CoV-2 variants. Each mutation that occurs may

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present distinct public health risks, requiring further investigation to assess the differences in characteristics with those of previous variants.[7]

Several nomenclature systems currently in use were established by WHO, GISAID, NextStrain, and the Phylogenetic Assignment of Named Global Outbreak Lineages (Pango lineages). These systems facilitate the tracking of genetic lineages of SARS-CoV-2 at both local and global levels.[8] Pango nomenclature is dynamic and integrates genetic and geographic information to generate genetic lineages with epidemiological relevance. Pango lineage names consist of alphabetical prefixes and numeric suffixes, such as B.1.1.529 for the Omicron variant.[9]

The method for detecting and identifying Omicron variants includes the application of whole genome sequencing (WGS). Reverse transcriptase polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 with specific reagents targeting lineages BA.1, BA.4, and BA.5 indicates failure in detecting the S gene. Consequently, the S gene target failure (SGTF) method can be adopted as a screening tool for these lineages.[10,11] The emergence of Omicron sublineages, like BA.4 and BA.5, has raised concerns about mutations in the spike protein affecting diagnostic accuracy. These mutations can cause mismatches between assay primers/probes and the virus, leading to false negatives and reducing the effectiveness of RT-PCR tests.[12] WGS is the process of determining the complete DNA sequence of an organism's genome in a single undertaking. Furthermore, its examination is crucial for recognizing and monitoring changes over time, leading to the emergence of new variants.[13]

The genetic characteristics of SARS-CoV-2 are crucial for monitoring the virus evolution and epidemiology. Information about circulating variants can aid in determining transmission potential, changes in antigenicity, or the severity of the disease. The importance of sequencing data will continue to grow with the availability of SARS-CoV-2 vaccination and antiviral therapy. This data provides details into variants susceptible to vaccination and the potential emergence of antiviral resistance. WGS examinations serve as essential tools for public health surveillance and molecular epidemiology.[14]

Genomic surveillance for SARS-CoV-2 primarily aims to provide information for national and global decision-making concerning public health policies, diagnostics, therapies, and COVID-19 vaccination. Variant surveillance can be conducted through the detection of epidemiological signals and unexpected trends. This information should be rapidly integrated to provide a comprehensive understanding of the virus evolution and the potential impact on disease control, thereby guiding public health responses.[15] As a result, it is crucial to have surveillance data regarding SARS-CoV-2 variants. This study aims to elucidate the results of WGS examinations for Omicron variant of SARS-CoV-2 at Hasan Sadikin General Hospital Bandung.

Materials and Methods

Study Design and Population

This study adopted an analytical observational method. Data was collected retrospectively from medical records, comprising gender, age, treatment status, vaccination numbers, and vaccination timing. RT-PCR examinations for SARS-CoV-2 were performed at the Clinical Laboratory of Hasan Sadikin General Hospital located in Bandung City, West Java Province, Indonesia. WGS examinations were conducted using the Next Generation Sequencing (NGS) method with the Illumina Nextseq 550 instrument at the Health Laboratory of West Java Province.

The study population consisted of outpatients and inpatients at Dr. Hasan Sadikin Hospital Bandung who were subjected to RT-PCR testing for SARS-CoV-2 from July to December 2022. The inclusion criteria for the subjects were patients with CT values in the RT-PCR examination for SARS-CoV-2 <30 and a minimum specimen volume of 600 μL.[16] The exclusion criteria included incomplete or unanalyzable WGS results and incomplete medical record data throughout the study period. A total sampling method was adopted, where the entire population meeting the inclusion criteria becomes the subjects during the specified period.

Statistical Analysis

Data was recorded using Microsoft Excel software and trends in COVID-19 lineage and mutation profiles were descriptively presented in tables and graphs. Statistical analysis was performed using Stata MP15 software.

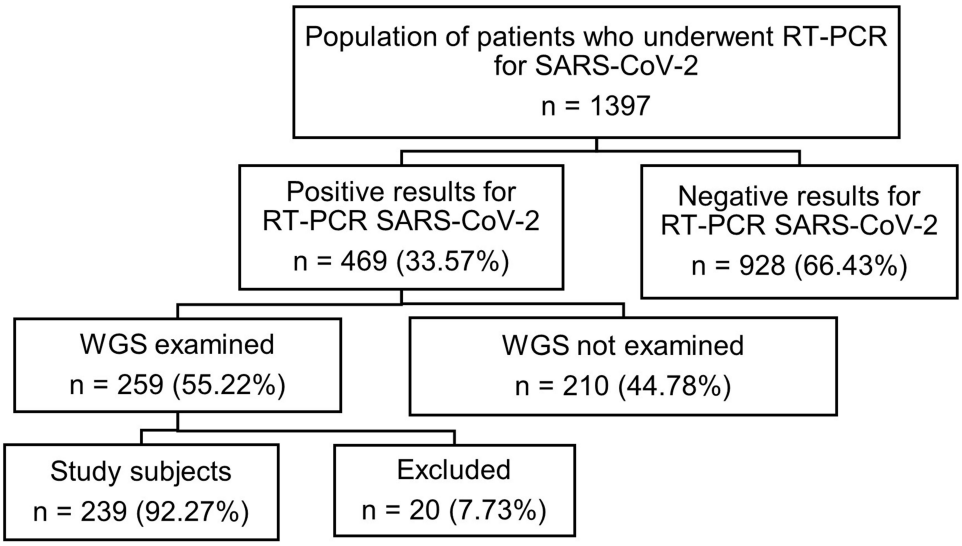

Figure 1 Flowchart of Study Subject Determination.
Abbreviations: RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; WGS, whole genome sequencing; n, number of patients.

Differences in characteristics based on the most prevalent lineage were assessed using the Chi-square and the Mann–Whitney tests for normally and non-normally distributed data, respectively. Logistic regression was applied to analyze factors influencing treatment status in a multivariate context. This study obtained ethical approval from the Research Ethics Committee of Hasan Sadikin General Hospital in Bandung.

Results

Figure 1 shows that 1397 patients were subjected to RT-PCR testing for SARS-CoV-2 from July to December 2022, with 469 (33.57%) tested positive. Out of this number, 259 who met the inclusion criteria were subjected to WGS. A total of 20 patients were excluded due to incomplete or unanalyzable WGS outcomes, resulting in 239 subjects for the study.

Based on Table 1, the majority of subjects were female (50.6%). The average age of subjects was 43.83 years with a standard deviation of 23.04. The majority were subjected to inpatient treatment, accounting for 80.3%. Regarding comorbidities, the most common were hypertension (10.0%), diabetes mellitus (7.9%), and cancer (6.7%). In terms of COVID-19 severity, most subjects were classified as having a moderate condition (74.5%). Regarding vaccination status, 64.9% of participants had received at least one dose of vaccination, and 35.1% received booster vaccinations.

Table 1 Characteristics of Study Subjects

Variable	n=239
Gender, n (%)	
Female	121 (50.6)
Male	118 (49.4)
Age, mean ± SD	43.83 ± 23.04
Comorbidities, n (%)	
Hypertension	24 (10.0)
Cardiovascular Disease	10 (4.2)
Diabetes Mellitus	19 (7.9)
Chronic Kidney Disease	9 (3.8)
Cancer	16 (6.7)
Human Immunodeficiency Virus Infection	8 (3.3)

(*Continued*)

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Table 1 (Continued).

Variable	n=239
COVID-19 Severity, n (%)	
Mild	22 (9.2)
Moderate	178 (74.5)
Severe	22 (9.2)
Critical	17 (7.1)
Treatment status, n (%)	
Self-isolation	47 (19.7)
Inpatient	192 (80.3)
Vaccination Status, n (%)	
No	74 (31.0)
Yes	165 (69.0)
Booster Vaccination, n (%)	
No	155 (64.9)
Yes	84 (35.1)
Number of vaccinations, mean ± SD	1.68 ± 1.29
The difference in days between vaccination and positive swab, mean ± SD	287.82 ± 128.15

Abbreviations: n, number of patients; SD, standard deviation.

Furthermore, the average number of vaccinations received was 1.68 times with a standard deviation of 1.29. The average difference in days between the last vaccination and the positive swab result was 287.82 days with a standard deviation of 128.15.

In this study, 50 lineage types were identified from July to December 2022, with the most detected being BA.5.2 (28%) and XBB.1 (19.2%). In the initial observation in July 2022, BA.5.2 and the other lineages dominated the detected lineages. Over the course of the study, the counts of these two lineages decreased, and the dominance was replaced by the emergence of others. In October 2022, the detection of XBB.1 and the other lineages began, and the dominance rapidly increased in the following month, surpassing BA lineages as shown in Figure 2.

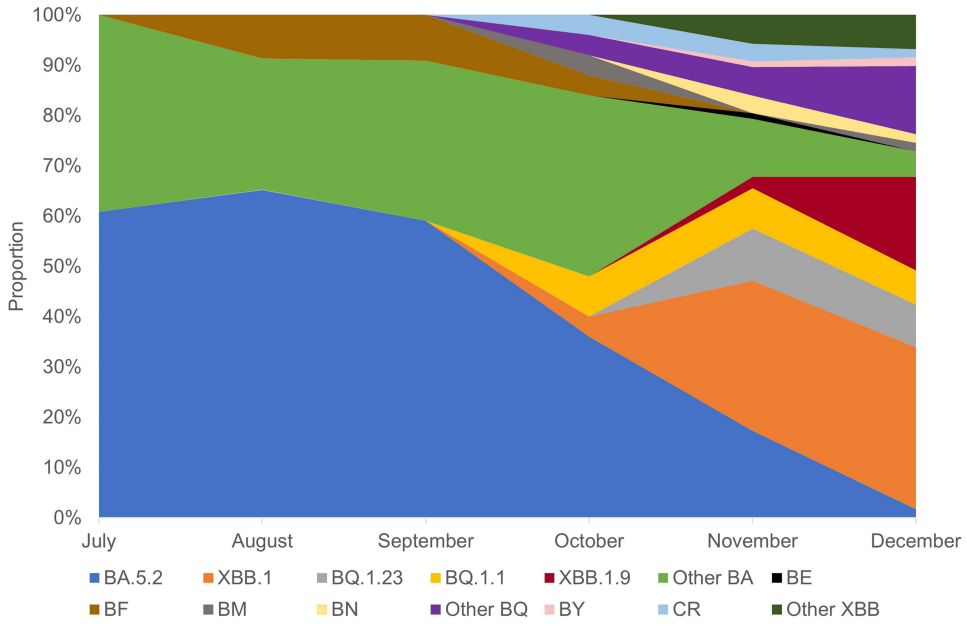

Figure 2 Trend and Proportion of SARS-CoV-2 Lineages from July to December 2022.

Based on WGS results, a total of 532 types of mutations were identified among the study subjects. Figure 3 shows that the spike gene (28.8%) was the most affected by mutations, followed by NSP3 (12.8%) and NSP2 genes (7.3%). Mutations such as E_T9I, M_A63T, N_E31del, N_P13L, N_R32del, NSP12_P323L, NSP14_I42V, NSP4_T492I, NSP6_G107del, NSP6_S106del, Spike_N679K, Spike_N764K, Spike_N969K, and Spike_P681H were observed in all subjects. A total of 8 were exclusively identified in the BA.5.2 lineage, including H69del (100%) and V70del (100%), while 18 mutations were specific to the XBB.1 lineage, as shown in Figure 4. In BA.5.2, L452R and F486V mutations were identified in 65 (97.01%) and 62 subjects (92.53%), respectively. In XBB.1, R346T and N460K mutations were observed in 46 subjects (100%).

In the bivariate analysis in Table 2, a significant difference in lineage proportions (P = 0.01) was observed in the treatment status variable. This showed that the proportion of inpatients in BA.5.2 and XBB.1 lineages was more

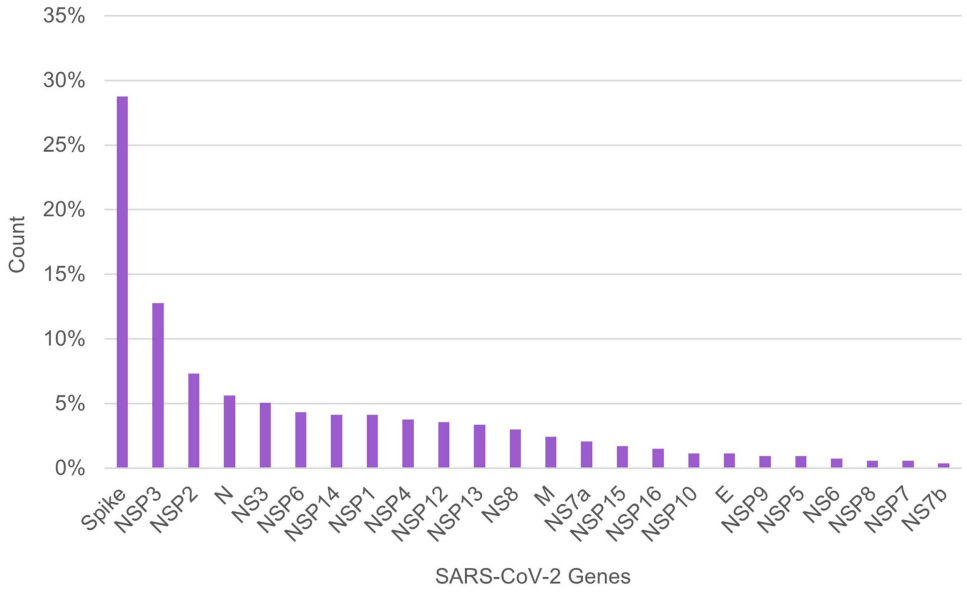

Figure 3 Total Number of Mutations in SARS-CoV-2 Genes.
Abbreviation: SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2.

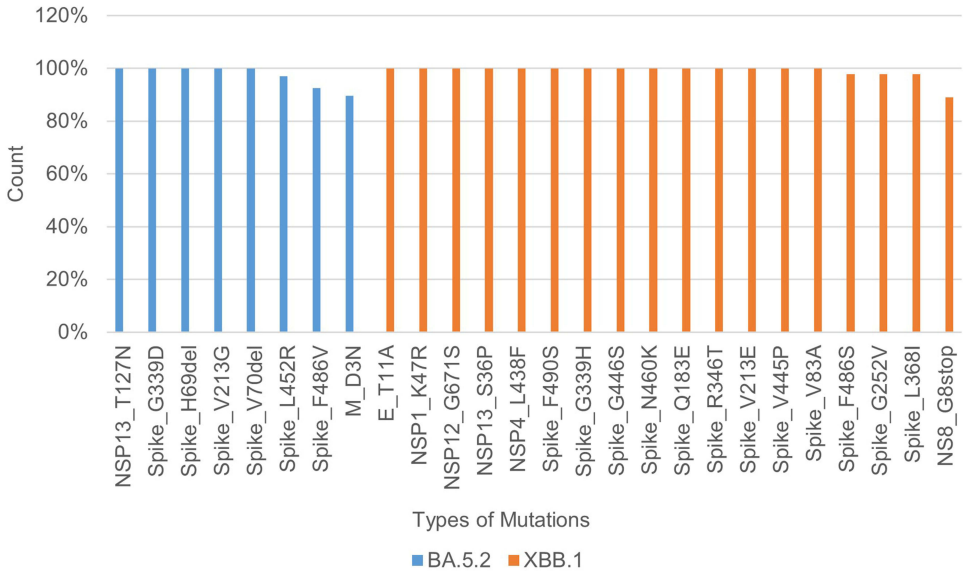

Figure 4 Differences in Mutations between BA.5.2 and XBB.1 Lineages.

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Table 2 Differences in Proportions of Characteristics Between BA.5.2 and XBB Lineage

Variable	Lineage		P
	BA 5.2 (n=67)	XBB 1 (n=46)	
Gender, n (%)			
Female	35 (52.2)	20 (43.5)	0.36[a]
Male	32 (47.8)	26 (56.5)	
Age, mean ± SD	44.8 ± 24.74	45.76 ± 22.79	0.61[b]
Treatment Status, n (%)			
Self-isolation	21 (31.3)	5 (10.9)	0.01[a]
Inpatient	46 (68.7)	41 (89.1)	
COVID-19 Severity, n (%)			
Mild	11 (16.4)	2 (4.3)	0.04[a]
Moderate	43 (64.2)	39 (84.8)	
Severe	10 (14.9)	2 (4.3)	
Critical	3 (4.5)	3 (6.5)	

Notes: [a]Analysis using the Chi-Square test. [b]Analysis using the Mann–Whitney test.
Abbreviations: n, number of patients; SD, standard deviation; P, p-value.

dominant compared to self-isolation. The proportion of inpatients in XBB.1 lineage is also larger than in BA.5.2. Additionally, a significant difference in COVID-19 severity (P = 0.04) was observed, with moderate cases being most dominant in both lineages, particularly in XBB.1 compared to BA.5.2. Mild cases were less frequent in XBB.1 than in BA.5.2, suggesting differences in the clinical presentations between the lineages.

Table 3 presents a bivariate analysis of the significant relationship between inpatient status and lineage, vaccination status, booster vaccination, and the number of vaccinations. The group that has never been vaccinated and has not

Table 3 Proportional Distribution of Inpatients by Lineage, Vaccination Status, Booster Vaccination, and Number of Vaccinations

Variable	Inpatient				Total		P
	No		Yes				
	n	%	n	%	n	%	
Lineage							
BA.5.2	21	31.34	46	68.66	67	100	0.01[a]
XBB.1	5	10.87	41	89.13	46	100	
Total	26	23.01	87	76.99	113	100	
Vaccination Status							
No	4	10.81	33	89.19	37	100	0.03[b]
Yes	22	28.95	54	71.05	76	100	
Total	26	23.01	87	76.99	113	100	
Booster Vaccination							
No	10	13.33	65	86.67	75	100	0.001[a]
Yes	16	42.11	22	57.89	38	100	
Total	26	23.01	87	76.99	113	100	
Number of vaccinations							
Never	4	10.81	33	89.19	37	100	0.002[a]
1–2 times	6	15.79	32	84.21	38	100	
3–4 times	16	42.11	22	57.89	38	100	
Total	26	23.01	87	76.99	113	100	

Notes: [a]Analysis using the Chi-Square test. [b]Analysis using the Fisher's Exact test.
Abbreviations: n, number of patients; P, p-value.

received a booster dose shows a higher percentage of inpatient treatment compared to the group that has been vaccinated and boosted. As the number of vaccinations increases, the percentage of subjects requiring inpatient treatment decreases. There were no statistically significant differences in the number of days between vaccination and a positive swab result, as shown in Table 4. The median difference in days between vaccination and positive swab was slightly longer in the inpatient group compared to the group that was not admitted as inpatient.

In the multivariate analysis, the variables identified as predictors of inpatient treatment were lineage and the number of vaccinations. XBB.1 lineage was associated with a 5.49 times greater risk of inpatient treatment (95% CI: 1.73–17.38) compared to BA.5.2, while the adjusted odds ratio (aOR) for the number of vaccinations was 0.45 (95% CI: 0.29–0.7). This indicates that lineage XBB.1 is a risk factor for inpatient treatment, whereas a higher number of vaccinations acts as a protective factor against inpatient care (Table 5). The probability of inpatient treatment due to XBB.1 decreases as the number of vaccinations increases (Table 6). Figure 5 illustrates this trend, demonstrating that receiving three vaccinations significantly reduces the probability of inpatient treatment compared to receiving only one vaccination.

Table 4 Frequency Distribution of Difference in Days Between Vaccination and Positive Swab

Variable	Median	Mean	SD	P
Inpatient				
No	260	243.76	154.03	0.33
Yes	279.5	293.2	154.82	

Note: Analysis using the Mann–Whitney test.
Abbreviations: SD, standard deviation; P, p-value.

Table 5 Factors Influencing Inpatient Status with Adjusted Odds Ratios

Variable	Influencing Factors	aOR	P	95% CI
Inpatient	XBB.1 lineage	5.49	0.004	1.75–17.23
	Number of vaccinations	0.45	0.000	0.45–0.29
	Constant	9.16	0.000	3.13–26.85

Notes: Analysis using logistic regression. The "Constant" represents the baseline odds (intercept) in the logistic regression model, where all predictor variables are set to zero.
Abbreviations: aOR, adjusted odd ratio; P, p-value; CI, confidence interval.

Table 6 Inpatient Probability by Number of Vaccinations for XBB.1 Lineage

Vaccination Count	Probability (%)	95% CI
1 time	86.7	78.9–94.51
2 times	75.6	67.2–83.99
3 times	60.4	47.84–72.95
4 times	43.61	24.33–62.89

Abbreviation: CI, confidence interval.

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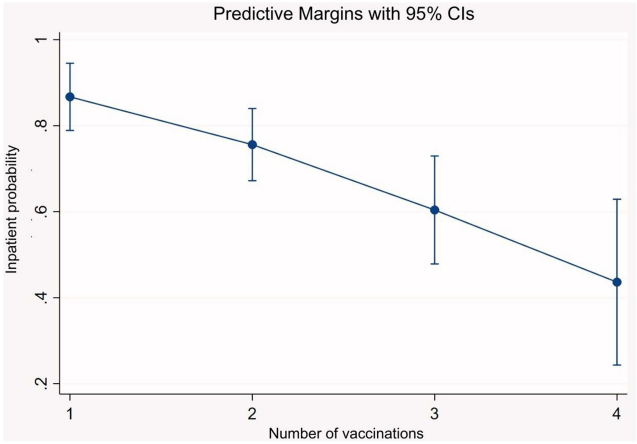

Figure 5 Probability of Inpatient Treatment.

Discussion

This study integrates genomic information on lineages from Omicron variant circulating along with various subject characteristics to understand the dynamics of SARS-CoV-2 evolution. The emergence of various SARS-CoV-2 lineages presented the importance of continuous surveillance for early detection of lineages that may be more pathogenic.

The study subjects were predominantly female with an average age of 43.83±23.04 years. This was in line with the study by Wang et al on Omicron variant, where more females were included with an average age of 39.1±23.4 years.[17] The most common comorbidity in this study was hypertension (10%), which is also commonly observed in COVID-19 patients. The relationship between hypertension and COVID-19 may stem from shared inflammatory pathways, as hypertension is associated with immune activation, oxidative stress, and endothelial dysfunction.[18] The majority of subjects were inpatients, and various studies showed that the risk of hospitalization and visits to the emergency unit in cases of Omicron variant infection was lower. However, hospitalization can still occur due to increased transmission, the ability of the virus to evade the immune system, and a decrease in vaccine effectiveness.[17,19]

In this study, a total of 50 Omicron lineages were dynamically identified in the observation period. Between July and October 2022, the number of COVID-19 cases was dominated by BA lineages. Since its emergence in October 2022, XBB.1, XBB.1.9, and other XBB lineages began to replace the dominance of BA, as presented in Figure 2. GISAID data showed that infections with BA.5.2 lineage were first detected in Indonesia by January 2022 and started to increase in July 2022. Meanwhile, XBB.1 lineage was initially detected in January 2022 but began to rise in October 2022.[20]

A total of 28.8% of mutations occurred in the spike gene, and all subjects had the same experience (T19I, N679K, N764K, N969K, and P681H), as shown in Figure 3. Gautam et al's study similarly identified the spike gene (21%) as the focal point of mutations.[21] In the other study, Dhawan et al explained that there were 30 mutations in the S protein of Omicron variant, including N679K, N764K, N969K, and P681H.[22] H69del and V70del mutations occurred in 100% of the BA 5.2 lineage but were not identified in the XBB.1 lineage, as shown in Figure 4. Mutations comprising the deletion of amino acids 69–70 in the spike protein of SARS-CoV-2, result in the failure to detect the S gene in RT-PCR tests using specific reagents. Consequently, SGTF serves as a useful screening tool for BA 5.2 lineage.[11]

In this study, L452R and F486V mutations were observed in BA.5.2 at rates of 97.01% and 92.53%, respectively, as presented in Figure 4. GISAID data showed that L452R and F486V mutations account for 95.7% and 97.3% of all WGS results in Indonesia.[20] Furthermore, the specific mutations in BA.5 lineage can enhance transmission and the ability of the virus to evade the immune system.[22,23] Approximately 100% of R346T and N460K mutations were identified in XBB.1 lineage, as shown in Figure 4. According to GISAID data, R346T and N460K mutations account for 93.3% and 88.2%, respectively, of all WGS results in Indonesia. These mutations result in the inability of antibody neutralization mechanisms.[24–26]

The proportion of inpatients in the XBB.1 lineage was larger than in BA.5.2, as shown in Table 2. XBB.1 lineage also had a 5.49 times greater risk of hospitalization compared to BA.5.2, as presented in Table 5. Wang et al's study showed

that XBB.1 lineage had 49 times higher resistance to neutralizing antibodies compared to BA.4/5.[27] In addition to the lineage type, other factors such as the number of vaccinations received can influence the treatment status of the patient. Primary vaccination has been proven to provide protection against hospitalization, severity, and Omicron-related deaths, even months after the last dose. However, booster doses offer stronger and longer-lasting protection against hospitalization incidents.[28]

In addition to the insights provided by genomic sequencing in identifying and monitoring SARS-CoV-2 variants, wastewater-based genome monitoring has emerged as a valuable supplement to clinical surveillance efforts. This method enables the early detection of viral presence at the population level, providing crucial information on the spread of variants and their transmission routes. Wastewater monitoring offers an efficient, real-time approach for identifying changes in variant prevalence that may not yet be captured through clinical testing. This surveillance tool is particularly useful for detecting emerging mutations and monitoring the evolutionary dynamics of the virus, complementing clinical efforts and enhancing public health responses to the ongoing pandemic.[29]

A limitation of this study is the absence of patient domicile data and incomplete pre-COVID-19 travel history, which could have helped determine the geographical distribution of each SARS-CoV-2 lineage. While travel history can be valuable for understanding regional variations in the spread of the virus, the study's findings remain robust, as they are based on comprehensive clinical data and focus on key factors influencing disease outcomes. Smoking status, a known risk factor for respiratory diseases, was not fully assessed, and its potential impact on disease outcomes in some patients remains unclear. Although smoking status could have influenced disease progression or severity, the overall findings are not affected, as the study emphasizes other significant clinical variables. Additionally, the retrospective nature of this study, which relies on existing patient records, may have limitations such as incomplete or missing data. Despite these factors, the findings provide important insights into the impact of Omicron variants in the Indonesian context, contributing valuable knowledge to public health efforts.

This study combines genomic analysis of SARS-CoV-2 Omicron sublineages with vaccination data and clinical outcomes within a single tertiary hospital in Indonesia. While broader surveillance systems have documented Omicron's spread, this research examines specific lineage-associated risks, such as higher inpatient care rates with the XBB.1 sublineage, and the role of increased vaccine doses in reducing inpatient rates. This approach offers a deeper understanding of variant evolution and its impact on patient outcomes, providing valuable insights for regional public health strategies and emphasizing the importance of genomic surveillance at the hospital level.

Conclusion

In conclusion, BA.5.2 and XBB.1 were the dominant lineages in Omicron variant infections from July to December 2022, with mutations primarily in the spike gene. XBB.1 was associated with a 5.49 times higher risk of hospitalization compared to BA.5.2. However, a higher number of vaccinations significantly reduced this risk, emphasizing the protective role of vaccination. Continuous genomic surveillance was essential to identify new SARS-CoV-2 variants and their impact on public health.

Ethical Considerations

This study was conducted under the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Hasan Sadikin General Hospital (LB.02.01/X.6.5/265/2023). The Ethics Committee waived the requirement for informed consent due to the retrospective nature of the study and the use of data obtained from hospital and laboratory information systems. All data were anonymized to ensure the privacy and confidentiality of the patients.

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Disclosure

The authors declare no relevant conflicts of interest in this work.

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