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BA.5 sub-lineages associated with higher severity of COVID-19 infection: A cross-sectional study in Indonesia

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ABSTRACT

Objectives: We aimed to compare the clinical severity and outcome among laboratory-confirmed Omicron variant cases admitted between January and December 2022.
Methods: This is a cross-sectional study conducted in Hasan Sadikin General Hospital between January and December 2022. We enrolled patients aged ≥18 years with laboratory-confirmed Omicron infection. Data were collected from clinical records and a whole genome sequencing database. We compared the risk of severe symptoms and mortality using a logistic regression analysis adjusted for sex, age, comorbidities, and vaccination status.
Results: We enrolled 255 patients and the main sub-lineages were BA.1 (16.1%), BA.2 (11.4%), BA.5 (35.7%), XBB (22.7%), and BQ.1 (14.1%). Compared with BA.1/BA.2, BA.5 sub-lineages were associated with severe symptoms (adjusted odds ratio of 2.9, 95% confidence interval 1.1-8.2, P <0.05). The highest risk of severe symptoms and mortality was linked with a high number of comorbidities (adjusted odds ratio of 7.8, 95% confidence interval 1.7-22.4, P <0.05). Booster vaccination was protective of severity and mortality.
Conclusions: Disease severity was associated with BA.5 sub-lineages and multiple comorbidities. Good management is particularly important for people with comorbidities. Furthermore, booster vaccination is also required to reduce severity and mortality.

Introduction

After Delta, Omicron is one of the SARS-CoV-2 variants, first identified in South Africa in November 2021 and quickly classified as a "variant of concern" by the World Health Organization (WHO) [1]. Compared with the previous variants of concern such as Alpha (B.1.1.7), Beta (B.1.351), and Delta (B.1.617.2), the Omicron (B.1.1.529) variant has unique mutations in the spike protein that could potentially affect the virus' transmissibility, severity, and ability to evade immunity [2,3]. There are several sub-lineages of the Omicron variant, each with unique mutations in the virus' spike protein. These sub-lineages include BA.1(B.1.1.529.1), BA.2 (B.1.1.529.2), BA.3 (B.1.1.529.3), BA.5 (B.1.1.529.5), BQ.1(B.1.1.529.5.3.1.1.1.1.1), and XBB, among others [2,4,5].

To date, the Omicron variant has been reported as the predominant lineage in the world, including Indonesia. Until April 2023, the Global Initiative on Sharing All Influenza Data registered 8 million Omicron cases of infections worldwide. The initial lineages were BA.1 and BA.2 detected in January 2022, followed by BA.4 and BA.5 that were detected in January and February 2022 in South Africa [6]. Later, BQ.1 and BQ.1.1 were identified in Nigeria in early July and expanded to Europe, North America, and Asia, followed by XBB and XBB.1, which were first distinguished in India in mid-August [5]. BQ.1 and BQ.1.1 evolved from BA.5, whereas XBB and XBB.1 were recombinants between two

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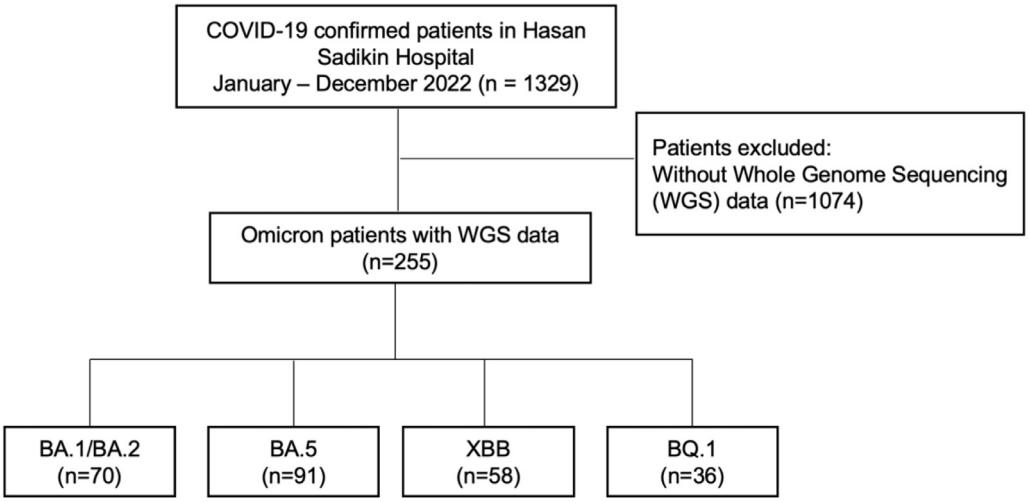


Figure 1. Study flow chart of patient recruitment.

BA.2 lineages (BJ.1 and BA.2.75) [5]. In early January 2023, XBB.1.16 first appeared in India causing a surge of hospitalizations and it was named Arcturus on March 13, 2023 [7].

Omicron has been reported as more contagious than previous variants, with the transmissibility of the Omicron variant being ~3.2 times that of Delta [2]. Although more contagious, Omicron was found to be less severe than the previous Delta variants [8–10]. The virus is less pathogenic due to Omicron spikes mainly rely on the endocytic pathway to enter the cells, which leads to a decrease in replication in the lung parenchyma and an enhanced ability to infect the upper respiratory tract [2]. The severity of illness due to BA.1 and BA.2 was more or less the same, with overall odds ratio (OR) ranging between 0.2 and 0.65 [9]. In addition, greater immune escape has been observed in BA.5 than its parent BA.2. These data have been largely based on genomic and laboratory data [11,12].

Studies assessing Omicron's clinical characteristics and outcomes are still limited. We, therefore, aimed to compare the clinical severity and outcome among laboratory-confirmed Omicron variants admitted to the Hasan Sadikin General Hospital between January and December 2022.

Methods

Study design and population

This is a cross-sectional study of admitted COVID-19 cases admitted to Hasan Sadikin General Hospital between January and December 2022. The cases included in the analysis were (i) adult patients aged 18 years or older and (ii) had polymerase chain reaction results of confirmed Omicron (B.1.1.529) infection, including its respective sub-lineages: BA.1, BA.2, BA.4, BA.5, BQ.1, and XBB. The sub-lineages of the Omicron variants were analyzed using whole genome sequencing (WGS) with next-generation sequencing Illumina. The sequencing was carried out according to the manufacturer's guide [13]. Furthermore, exclusion criteria are patients without WGS data. The study flow chart is presented in Figure 1.

Data collection

Clinical records of patients with confirmed COVID-19 admitted in 2022 were screened, collected, and managed using RedCap (Research Electronic Data Capture) hosted at Hasan Sadikin General Hospital. The baseline clinical characteristics, including age, sex, the presence of comorbidities, vaccination status, symptom severity, hospitalization status (outpatients or hospitalized), and outcomes (died or discharged alive), were extracted from medical records.

Study variable definition

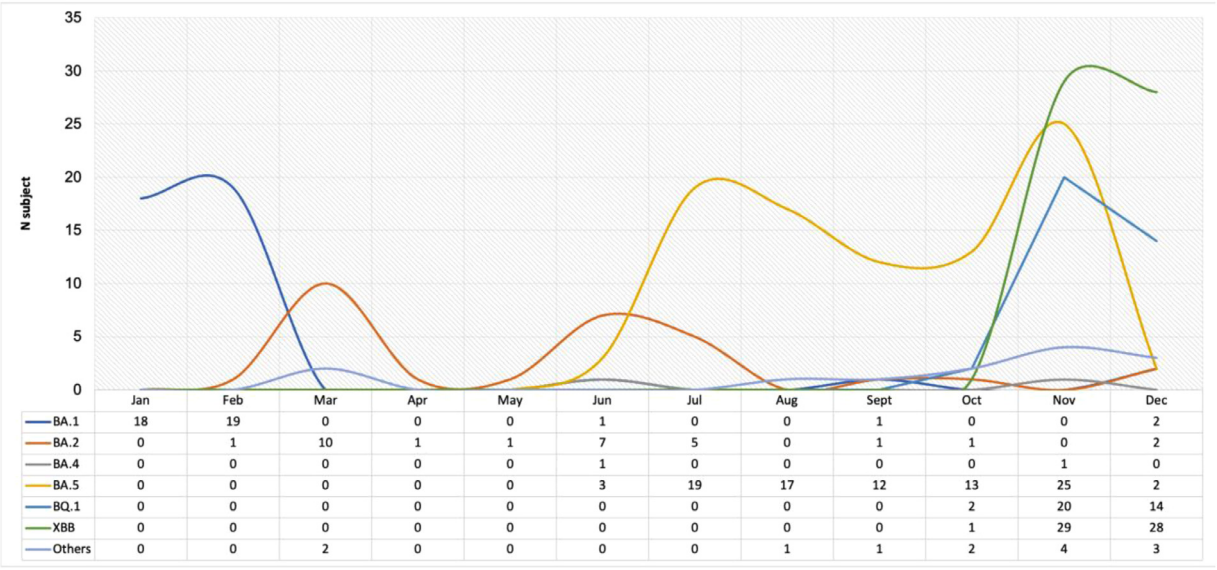
Comorbidities present in this study were hypertension, diabetes, cardiovascular diseases, neurological diseases, pulmonary diseases, chronic kidney diseases (CKDs), malignancies, and infection of HIV/AIDS. Hypertension was defined as a blood pressure of ≥140/90 mm Hg [14]. Diabetes was defined as an increase in plasma glucose level of more than 126 mg/dL (7.0 mm/L) or HbA1C ≥6.5 [15]. Cardiovascular diseases were all cardiac diseases, including coronary artery disease, heart failure, and arrhythmia. Pulmonary diseases include tuberculosis, asthma, and chronic obstructive pulmonary disease. CKD was defined as either kidney damage or a decreased glomerular filtration rate of <60 ml/min/1.73 m^2 for at least 3 months [16]. The severity of COVID-19 was defined according to the WHO guidelines; patients with severe disease were those with oxygen saturation below 90% (room air) or respiratory rate exceeding 30 breaths/min or signs of severe respiratory distress [17].

Statistical analysis

The basic clinical characteristics are presented as descriptive statistics. The comparison of categorical variables was analyzed using chi-square or Fisher exact test, as appropriate. OR and 95% confidence intervals (CIs) were analyzed using bivariate and multi-variate logistic regression analysis to estimate the association between the variants' sub-lineages and outcomes (severity and mortality) adjusted for age, sex, comorbidities, and vaccination status. All statistical tests were two-sided, and P <0.05 were considered statistically significant. In the sensitivity analysis, we examined the difference in baseline characteristics (age, sex, and severity) between the analyzed patients with Omicron compared with the total patients (Supplementary Table 1). All data were analyzed using the Statistical Product and Service Solution Windows version 25.0 (IBM, USA) and GraphPad PRISM version 9.

Ethical considerations

This study was approved by the ethics committee with ethics number LB.02.01/X.6.5/100/2020, May 6, 2020. Secondary data from medical records of patients with COVID-19 were used in this study, thus waiving informed consent by the ethics committee. The study was conducted in accordance with the Declaration of Helsinki, and all data were kept anonymous.



	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
BA.1	18	19	0	0	0	1	0	0	1	0	0	2
BA.2	0	1	10	1	1	7	5	0	1	1	0	2
BA.4	0	0	0	0	0	1	0	0	0	0	1	0
BA.5	0	0	0	0	0	3	19	17	12	13	25	2
BQ.1	0	0	0	0	0	0	0	0	0	2	20	14
XBB	0	0	0	0	0	0	0	0	0	1	29	28
Others	0	0	2	0	0	0	0	1	1	2	4	3

Figure 2. Omicron subtypes prevalence based on periods.

Results

We enrolled a total of 255 patients with COVID-19 with laboratory-confirmed Omicron variants. The main sub-lineages of Omicron observed were BA.1, BA.2, BA.5, XBB, and BQ.1, with percentages of 16.1%, 11.4%, 35.7%, 22.7%, and 14.1%, respectively. As seen in Figure 2, the BA.1 sub-lineage was largely found in January and February, the BA.2 sub-lineage between March and June, and the BA.5 sub-lineage from July until November, whereas the BQ.1 and XBB sub-lineages appeared in November and December of 2022.

The baseline characteristics of the patients are presented in Table 1. A similar number of male and female patients were observed (51% vs 49%), with a median age of 48 years (interquartile range [IQR] 31-63). Patients with BA.5 infections were older than those with BA.1/BA.2, with a median age of 52 (IQR 33-68) years versus 39 (IQR 28-48) years. Most of the patients (183 of 255 [81.3%]) have received a full-dose vaccination and 77 of 255 patients or 30.9% already had boosters. Because there was a time difference in the appearance of the sub-variants, a higher number of patients already had booster vaccine for BA.5, XBB, and BQ.1 infection than the BA.1/BA.2, with percentages of 40.0%, 36.8%, 38.9% vs 9.1%, respectively.

A higher number of comorbidities were observed in BA.5, XBB, and BQ.1 sub-lineages infection than the BA.1/BA.2 sub-lineage. The main comorbidities reported were hypertension (51 of 255 or 24.5%), diabetes (31 of 255 or 14.9%), and cardiovascular diseases (31 of 255 or 14.9%). Significant differences between each sub-lineage in were observed in diabetes, neurological disease, and HIV/AIDS comorbidities. The highest number of diabetes and neurologic diseases comorbidities were reported in BQ.1 compared with BA.1/BA.2. In addition, a high number of HIV/AIDS comorbidities was reported in BA.1/BA.2 (15.7%) than in XBB (1.9%) or BQ.1 (0.0%).

Overall, patients with Omicron reported asymptomatic to mild symptoms (143 of 255, 56.1%), followed by moderate (61 of 255, 23.9%) and severe symptoms (51 of 255, 20.0%). A significant difference in disease severity was reported in the BA.5 sub-lineage compared with the BA.1/BA.2 sub-lineage ($P = 0.001$). Patients with BA.1/BA.2 infection mostly reported asymptomatic to mild symptoms, with only 11.4% reporting severe symptoms. Compared with BA.1/BA.2, a higher number of patients with the BA.5 infection reported severe symptoms, 30.8% vs 11.4%, respectively.

Because most patients had mild symptoms, 42.9% of patients with BA.1/BA.2 were discharged and 57.1% were hospitalized. Furthermore, in other sub-lineages, a higher number of patients were hospitalized.

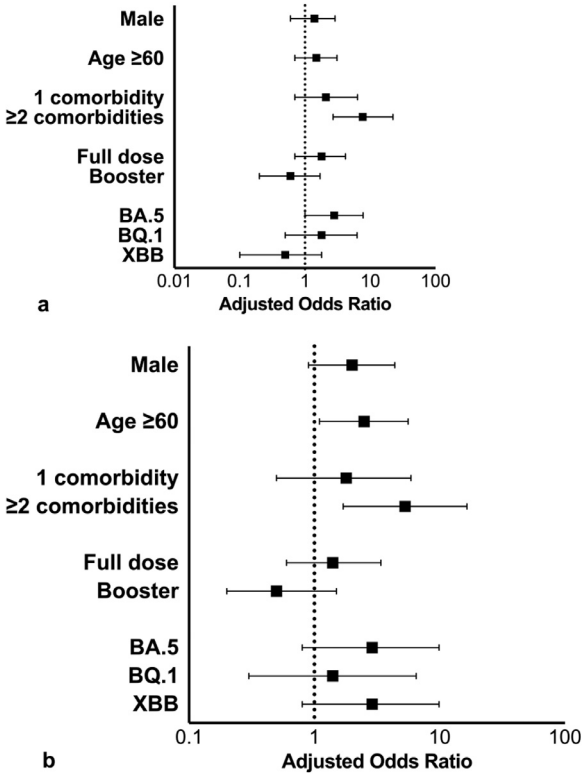


Figure 3. Adjusted odds ratios of Omicron variants and other factors associated with (a) severity and (b) mortality.

The mortality rate of all Omicron variant cases reported in this study was 18.4%. Higher mortality rates were observed in BA.5, XBB, and BQ.1 than the BA.1/BA.2 sub-lineages, with a mortality rate of 23.1%, 24.1%, and 16.7% vs 8.6%, respectively.

A logistic regression analysis was performed to evaluate the variables associated with severity (Table 2a and Figure 3a). The bivariate analysis showed that BA.5 was associated with more severe symptoms, with an OR of 3.4 (95% CI 1.4-8.1). Other associated factors were age and multiple comorbidities, with ORs of 3.6 (95% CI 1.9-6.7) and 7.2 (2.9-18.1), respectively. Vaccination was protective of severe symptoms; a

Table 1
Baseline characteristics of patients with Omicron by sub-variants/lineages (n = 255).

Characteristics	Total, n (%)	BA.1/BA.2 (n = 70)	BA.5 (n = 91)	XBB (n = 58)	BQ.1 (n = 36)	*P*-value
Sex (n = 255)			0.945	0.846	0.416	0.735
Male	130 (51.0)	35 (50.0)	47 (51.6)	27 (46.6)	21 (58.3)	
Female	125 (49.0)	35 (50.0)	44 (48.4)	31 (53.4)	15 (41.7)	
Age category (n = 255)			0.000[b]	0.000[b]	0.013[a]	0.000[b]
18-29	50 (19.6)	18 (25.7)	15 (16.5)	13 (22.4)	4 (11.1)	
30-49	85 (33.3)	36 (51.4)	25 (27.5)	9 (15.5)	15 (41.7)	
50-69	83 (32.5)	13 (18.6)	32 (35.2)	29 (50.0)	9 (25.0)	
70-	37 (14.5)	3 (4.3)	19 (20.9)	7 (12.1)	8 (22.2)	
Vaccination status (n = 249)			0.000[b]	0.001[b]	0.000[b]	0.000[b]
None	66 (26.5)	18 (27.3)	22 (24.4)	13 (22.8)	13 (36.1)	
Full dose	106 (42.6)	42 (63.6)	32 (35.6)	23 (40.4)	9 (25.0)	
Booster	77 (30.9)	6 (9.1)	36 (40.0)	21 (36.8)	14 (38.9)	
Number of comorbidities (n = 211)			0.057	0.025[a]	0.005[a]	0.027[a]
0	73 (34.6)	22 (43.1)	30 (38.0)	12 (22.6)	9 (32.1)	
1	69 (32.7)	20 (39.2)	22 (27.8)	22 (41.5)	5 (17.9)	
≥2	69 (32.7)	9 (17.6)	27 (34.2)	19 (35.8)	14 (50.0)	
Comorbidities						
Hypertension	51 (24.5)	8 (16.0)	21 (26.9)	13 (25.0)	9 (32.1)	0.208
Diabetes	31 (14.9)	1 (2.0)	14 (17.9)[a]	8 (15.4)[a]	8 (15.4)[a]	0.014[a]
Cardiovascular	31 (14.9)	5 (10.0)	12 (15.4)	10 (19.2)	4 (14.3)	0.407
Neurologic diseases	27 (13.0)	2 (4.0)	11 (14.1)	5 (9.6)	9 (32.1)[a]	0.004[a]
Pulmonary diseases	26 (12.4)	7 (13.7)	9 (11.5)	9 (17.3)	1 (3.6)	0.205
Chronic kidney diseases	16 (7.7)	2 (4.0)	8 (10.3)	3 (5.8)	3 (10.7)	0.223
Malignancies	15 (7.2)	2 (4.0)	3 (3.8)	7 (13.5)[a]	3 (10.7)	0.152
HIV/AIDS	12 (5.7)	8 (15.7)	3 (3.8)	1 (1.9)[a]	0 (0.0)[a]	0.002[a]
Severity (n = 255)			0.001[b]	0.200	0.100	0.002[a]
Asymptomatic-mild	143 (56.1)	51 (72.9)	38 (41.8)	35 (60.3)	19 (52.8)	
Moderate	61 (23.9)	11 (15.7)	25 (27.5)	17 (29.3)	8 (22.2)	
Severe-critical	51 (20.0)	8 (11.4)	28 (30.8)	6 (10.3)	9 (25.0)	
Hospital admission (n = 255)			0.001[b]	0.000[b]	0.047[a]	0.000[b]
Hospitalized	193 (75.7)	40 (57.1)	74 (81.3)	51 (87.9)	28 (77.8)	
Outpatients	62 (24.3)	30 (42.9)	17 (18.7)	7 (12.1)	8 (22.2)	
Outcomes (n = 255)			0.051	0.044[a]	0.569	0.067
Discharged alive	208 (81.6)	64 (91.4)	70 (76.9)	44 (75.9)	30 (83.3)	
Died	47 (18.4)	6 (8.6)	21 (23.1)	14 (24.1)	6 (16.7)	

[a] $P < 0.05$
[b] $P \leq 0.01$

Table 2a
Multivariable logistic regression analysis evaluating the association between Omicron sub-lineages and severity.

Variables	OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Sex (Male)	1.5 (0.8-2.8)	0.212	1.4 (0.6-2.9)	0.411
Age (≥60 years)	3.6 (1.9-6.7)	0.000[a]	1.5 (0.7-3.1)	0.378
Comorbidities				
0	Ref		Ref	
1	2.0 (0.7-5.4)	0.178	2.1 (0.7-6.4)	0.173
≥2	7.2 (2.9-18.1)	0.000[a]	7.7 (2.7-22.3)	0.000[a]
Vaccination status				
Unvaccinated	Ref		Ref	
Full dose	0.9 (0.4-1.8)	0.747	1.8 (0.7-4.2)	0.199
Booster	0.3 (0.1-0.8)	0.019[a]	0.6 (0.2-1.7)	0.344
Variants' strains				
BA.1/BA.2	Ref		Ref	
BA.5	3.4 (1.4-8.1)	0.005[a]	2.8 (1.0-7.8)	0.047[a]
BQ.1	2.6 (0.9-7.4)	0.078	1.8 (0.5-6.3)	0.401
XBB	0.9 (0.3-2.7)	0.845	0.5 (0.1-1.8)	0.304

CI: confidence interval; OR: odds ratio; Ref: reference.
[a] Statistically significant.

Table 2b
Multivariable logistic regression analysis evaluating the association between the Omicron sub-lineages and mortality.

Variables	OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Sex (Male)	2.1 (1.1-4.1)	0.025[a]	2.0 (0.9-4.4)	0.080
Age (≥60 years)	4.9 (2.5-9.7)	0.000[a]	2.5 (1.1-5.6)	0.021[a]
Comorbidities				
0	Ref		Ref	
1	2.9 (0.9-8.6)	0.061	1.8 (0.5-5.9)	0.357
≥2	9.3 (3.3-25.9)	0.000[a]	5.3 (1.7-16.5)	0.004[a]
Vaccination status				
Unvaccinated	Ref		Ref	
Full dose	0.8 (0.4-1.7)	0.592	1.4 (0.6-3.4)	0.437
Booster	0.3 (0.1-0.8)	0.017[a]	0.5 (0.2-1.5)	0.213
Variants' strains				
BA.1/BA.2	Ref		Ref	
BA.5	3.2 (1.2-8.4)	0.019[a]	2.9 (0.8-9.9)	0.090
BQ.1	2.1 (0.6-7.2)	0.220	1.4 (0.3-6.5)	0.661
XBB	3.4 (1.2-9.5)	0.020[a]	3.2 (0.9-11.6)	0.070

CI: confidence interval; OR: odds ratio; Ref: reference.
[a] Statistically significant.

booster dose reduced the risk of severe symptoms by 70% ($P = 0.019$). Even after adjusting for sex, age, vaccination status, and comorbidities, BA.5 remained significantly associated with having severe symptoms.

Similar results were also observed in the analysis of factors associated with mortality (Table 2b, Figure 3b). Sex, age, and a high number of comorbidities increased the mortality risk; however, boosters reduced it. Higher mortality rates were observed in XBB and BA.5 infections, with OR of 3.4 (95% CI 1.2-9.5) and 3.2 (95% CI 1.2-8.4), respectively. However, after adjusting for other factors, none of the sub-variants showed a significant association with mortality.

Discussion

The appearance of Omicron variant sub-lineages observed in this study was in line with previous reports where BA.1 and BA.2 were the initial lineages, followed by BA.5 in mid-2022 and BQ.1 and XBB

sub-lineages in the last months of 2022. Because the BA.5, XBB, and BQ.1 sub-lineages occurred later, a higher proportion of patients had already received a booster vaccine than the BA.1/BA.2 sub-lineages. This demonstrated that these sub-lineages could evade protection provided by immunization. Previous research in the United States from April to July 2022 found that BA.4/BA.5 infections occurred among subjects with higher levels of immunity against SARS-CoV-2 than time-matched BA.2 infections [12]. This supports previous findings that BA.4 and BA.5 showed a more robust immune evasion ability than the BA.1 and BA.2 sub-lineages [4]. Data showed that the BA.5 subvariant could substantially escape neutralizing antibodies induced by vaccination, previous infection, or both because neutralizing antibody titers against BA.5 are lower than those against BA.1 and BA.2 [18]. Overall, patients reported asymptomatic to mild symptoms, followed by moderate and severe symptoms. Patients with BA.1/BA.2 infection mainly reported asymptomatic to mild symptoms. In addition, more patients with BA.5 infection had severe symptoms than those with BA.1/BA.2. The regression analysis after adjusting for sex, age, vaccination status, and comorbidities showed that BA.5 and a high number of comorbidities (≥2) was significantly associated with severe disease, with adjusted ORs of 2.9 (95% CI 1.1-8.2) and 7.8 (95% CI 2.7-22.4), respectively. As previously reported, the presence of comorbidities, mainly, CKD, diabetes mellitus, hypertension, and coronary heart disease, contributed to severe COVID-19 and subsequently to higher mortality [19].

Previous study in hamsters also showed that BA.4/BA.5 was more pathogenic than BA.2 [6]. Other than a more robust immune evasion ability, the BA.4/BA.5 sub-lineages can even invalidate the neutralization efficiency of antibodies produced by BA.1 infections because of the presence of F486V and D405N mutations [4]. All Omicron variants were found to considerably evade the neutralizing antibodies from vaccination or infection/convalescence. However, BA.5 has shifted back to using the angiotensin-converting enzyme 2–transmembrane serine protease 2 pathway seen in pre-Omicron lineages, which has been associated with lung infection and increased disease severity in animal models [11]. BA.1 and BA.2 diverged from the angiotensin-converting enzyme 2–transmembrane serine protease 2 pathway to another serine/cysteine protease, targeting the upper airway; thus, the viral load is higher in the upper airway, especially in the nose, windpipe, and throat but not in the lower respiratory system [4,11].

Although studies *in vitro* showed the higher antibody evasion properties in BA.5, most clinical studies found no significant difference in severity between BA.5 and BA.1/BA.2 [6,20]. In a study in Japan, BA.5 infections were associated with more systemic symptoms than BA.2 in vaccinated and unvaccinated persons. However, the two subvariant groups showed comparable risks for progression to severe disease [21]. A previous study in South Africa also reported no significant difference in severity found between the sub-variants, with severe disease reported in BA.1, BA.2, and BA.4/BA.5, with 33.7%, 26.2%, and 27.5%, respectively [6]. Another study in South Africa in May 2022 also found a similar adjusted hazard ratio of severity and mortality in BA.4/BA.5 compared with BA.1. Both showed lower severity and mortality than Delta infection; however, this study used the time of infection as a proxy for the variant causing infection rather than actual genomic sequencing [22]. Although our findings showed that BA.5 is associated with higher severity, no Omicron sub-lineages were significantly associated with higher mortality. Factors associated with mortality in Omicron variants are similar to previous variants, which were age and high number of comorbidities.

Although breakthrough infections still occurred in vaccinated subjects, we discovered that vaccination was associated with less severe symptoms. A booster dose is strongly protective of severe symptoms and death, with an OR of 0.3 (95% CI 0.1-0.8, P <0.05). Therefore, high-risk individuals should be also encouraged to receive at least three doses of the vaccination to reduce case fatality rates. A study by Zhou *et al.*, confirmed that booster vaccination reduced the risk of death in patients with Omicron. Patients during the Omicron period also benefited from the strong protection against severe disease by the COVID-19 vaccine [23]. The WHO has also recommended a third dose of vaccination (extended primary series), as well as a booster dose (fourth dose) for immunocompromised patients [24].

However, recent *in vitro* data show that the geometric mean 50% inhibitory dose titers against BA.2 and BA.4/5 are lower than those against the D614G variant. Compared with the D614G, the neutralization titers against BQ.1, BQ.1.1, XBB, and XBB.1 were also found to be significantly lower [5]. This highlights the need for other preventive measures to aid in infection control, particularly, in people with multiple comorbidities.

There were several limitations of this study, including a small sample size and the lack of patient data during the Delta wave outbreak, which prevented us from comparing the Omicron variant to the Delta variant. Furthermore, we did not have complete data on the types of vaccination received and history of COVID-19 infections, which may act as a protection against severe disease due to additional immunity provided by previous COVID-19 infections. However, based on the time, the majority of the subjects received inactivated vaccines (Sinovac or CoronaVac); however, some patients may have received mRNA vaccines (Moderna, Pfizer, and AstraZeneca). Based on the sensitivity analysis (Supplementary Table 1), there is a difference in baseline characteristics between the included patients and excluded patients with COVID-19. There were significantly more females and patients with severe disease in the excluded group. There is a higher number of patients with severe disease in the excluded group because patients might have died before being sampled for WGS. Due to the reagents' limitations, between January to April 2022, we only include a small proportion of patients because of the limitation of the WGS test capacity. During that time, we tested in patients with cycle threshold values below 30.

Conclusion

In conclusion, BA.5 infections were associated with more severe symptoms than BA.1/BA.2 infections. BA.5 might become a greater challenge than its predecessor variant. As in previous waves, individuals with multiple comorbidities had worse outcomes, whereas booster vaccinations provided protection against severe symptoms and mortality. High-risk individuals should be encouraged to receive at least three doses of the vaccination to reduce the fatality rates of Omicron infections.

Declarations of competing interest

The authors have no competing interests to declare.

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Ethical approval

This study was approved by the ethics committee or institutional review board of Hasan Sadikin General Hospital with ethics number LB.02.01/X.6.5/100/2020, May 6, 2020.

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Author contributions

YH and BA designed the study, while BA, AYS, DKT, and ARG supervised the study. YH, BA, JD, FF, FRR, ARG, and ES collected and verified the accuracy of the data. YH, BA, JD, FRR and ES had full

access to all the data and did the analysis. All authors drafterd and revised the manuscript content, and gave their final approval for the version to be published.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2024.100379.

References

[1] World Health Organization *Enhancing response to Omicron SARS-CoV-2 variant: Technical brief and priority actions for Member States*. Geneva: World Health Organization; 2022.

[2] Fan Y, Li X, Zhang L, Wan S, Zhang L, Zhou F. SARS-CoV-2 Omicron variant: recent progress and future perspectives. *Signal Transduct Target Ther* 2022;**7**:141. doi:10.1038/s41392-022-00997-x.

[3] Dhawan M, Saied AA, Mitra S, Alhumaydhi FA, Emran TB, Wilairatana P. Omicron variant (B.1.1.529) and its sublineages: what do we know so far amid the emergence of recombinant variants of SARS-CoV-2? *Biomed Pharmacother* 2022;**154**:113522. doi:10.1016/j.biopha.2022.113522.

[4] Chatterjee S, Bhattacharya M, Nag S, Dhama K, Chakraborty C. A detailed overview of SARS-CoV-2 omicron: its sub-variants, mutations and pathophysiology, clinical characteristics, immunological landscape, immune escape, and therapies. *Viruses* 2023;**15**:167. doi:10.3390/v15010167.

[5] Wang Q, Iketani S, Li Z, Liu L, Guo Y, Huang Y, et al. Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants. *Cell* 2023;**186** 279–286.e8. doi:10.1016/j.cell.2022.12.018.

[6] Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, Groome MJ, et al. Clinical severity of SARS-CoV-2 Omicron BA.4 and BA.5 lineages compared to BA.1 and Delta in South Africa. *Nat Commun* 2022;**13**:5860. doi:10.1038/s41467-022-33614-0.

[7] Looi M-K. What do we know about the Arcturus XBB.1.16 subvariant? *BMJ* 2023;**381**:1074. doi:10.1136/bmj.p1074.

[8] Strasser ZH, Greifer N, Hadavand A, Murphy SN, Estiri H. Estimates of SARS-CoV-2 omicron BA.2 subvariant severity in new England. *JAMA Netw Open* 2022;**5**:e2238354. doi:10.1001/jamanetworkopen.2022.38354.

[9] Sievers C, Zacher B, Ullrich A, Huska M, Fuchs S, Buda S, et al. SARS-CoV-2 Omicron variants BA. 1 and BA. 2 both show similarly reduced disease severity of COVID-19 compared to Delta, Germany, 2021 to 2022. *Eurosurveillance* 2022;**27**:2200396.

[10] Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet* 2022;**399**:1303–12. doi:10.1016/S0140-6736(22)00462-7.

[11] Aggarwal A, Akerman A, Milogiannakis V, Silva MR, Walker G, et al. SARS-CoV-2 Omicron BA.5: evolving tropism and evasion of potent humoral responses and resistance to clinical immunotherapeutics relative to viral variants of concern. *EBiomedicine* 2022;**84**:104270. doi:10.1016/j.ebiom.2022.104270.

[12] Lewnard J, Hong V, Kim JS, Shaw SF, Lewin B, Takhar H, et al. Association of SARS-CoV-2 BA.4/BA. 5 Omicron lineages with immune escape and clinical outcome. *Nat Commun* 2023;**14**:1407. doi:10.1038/s41467-023-37051-5.

[13] Illumina *Illumina DNA prep reference guide*. San Diego: Illumina, Inc; 2020.

[14] Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension global hypertension practice guidelines. *Hypertension* 2020;**75**:1334–57. doi:10.1161/HYPERTENSIONAHA.120.15026.

[15] American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2018. *Diabetes Care* 2018;**41**:S13–27. doi:10.2337/dc18-S002.

[16] Levey AS, Eckardt K-U, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: improving Global Outcomes (KDIGO). *Kidney Int* 2005;**67**:2089–100. doi:10.1111/j.1523-1755.2005.00365.x.

[17] World Health Organization *Living guidance for clinical management of COVID-19: living guidance, 23 November 2021*. Geneva: World Health Organization; 2021.

[18] Tan C-W, Lim B-L, BE Young, Yeoh AY-Y, Yung C-F, Yap W-C, et al. Comparative neutralisation profile of SARS-CoV-2 omicron subvariants BA.2.75 and BA.5. *Lancet Microbe* 2022;**3**:e898. doi:10.1016/S2666-5247(22)00220-8.

[19] Hartantri Y, Debora J, Widyatmoko L, Giwangkancana G, Suryadinata H, Susandi E, et al. Clinical and treatment factors associated with the mortality of COVID-19 patients admitted to a referral hospital in Indonesia. *Lancet Reg Health Southeast Asia* 2023;**11**:100167. doi:10.1016/j.lansea.2023.100167.

[20] Goller KV, Moritz J, Ziemann J, Kohler C, Becker K, Hübner N-O, et al. Differences in clinical presentations of Omicron infections with the lineages BA.2 and BA.5 in Mecklenburg-Western Pomerania, Germany, between april and July 2022. *Viruses* 2022;**14**:2033. doi:10.3390/v14092033.

[21] Nakakubo S, Kishida N, Okuda K, Kamada K, Iwama M, Suzuki M, et al. Associations of COVID-19 symptoms with Omicron subvariants BA.2 and BA.5, host status, and clinical outcomes: a registry-based observational study. *Lancet Infect Dis* 2023;**23**:1244–56. doi:10.1016/S1473-3099(23)00271-2.

[22] Davies M-A, Morden E, Rousseau P, Arendse J, Bam J-L, Boloko L, et al. Outcomes of laboratory-confirmed SARS-CoV-2 infection during resurgence driven by Omicron lineages BA.4 and BA.5 compared with previous waves in the Western Cape Province, South Africa. *Int J Infect Dis* 2023;**127**:63–8. doi:10.1016/j.ijid.2022.11.024.

[23] Zhou C, Wheelock ÅM, Zhang C, Ma J, Dong K, Pan J, et al. The role of booster vaccination in decreasing COVID-19 age-adjusted case fatality rate: evidence from 32 countries. *Front Public Health* 2023;**11**:1150095. doi:10.3389/fpubh.2023.1150095.

[24] World Health Organization *Good practice statement on the use of second booster doses for COVID 19 vaccines, 18 August 2022*. Geneva: World Health Organization,; 2022.