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Research article

Clinical outcomes and risk factors for SARS-CoV-2 breakthrough cases following vaccination with BNT162b2, CoronaVac, or ChAdOx1-S: A retrospective cohort study in Malaysia

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ABSTRACT

Background: The SARS-CoV-2 pandemic drove global vaccination. However, breakthrough infections raised concerns about vaccine performance, leading the World Health Organization (WHO) to recommend investigations thereof. This study aimed to evaluate the clinical outcomes (time to breakthrough infection, intensive care unit [ICU] admission, and in-hospital mortality) of hospitalised patients with SARS-CoV-2 breakthrough infection. This was the primary outcome and the risk factors associated with its severity were the secondary outcomes.

Methods: This retrospective cohort study at a multispecialty tertiary hospital in Selangor, Malaysia included 200 fully adult vaccinated patients, with confirmed SARS-CoV-2 infection, admitted from September 2021 to February 2022. Participants were selected by simple random sampling. Infection severity was categorised as CAT 2–3 (mild–moderate) and 4–5 (severe–critical).

Results: The time to breakthrough infection was significantly longer for BNT162B2 recipients (128.47 ± 46.21 days) compared to CoronaVac (94.09 ± 48.71 days; P = 0.001) and ChAdOx1-S recipients (90.80 ± 37.59 days; P = 0.019). No significant associations were found between SARS-CoV-2-related ICU admission, mortality, and the vaccines. Multivariable analysis identified vaccine type, variant of concern, ethnicity, and hypertension as significant predictors of severity. BNT162b2 and ChAdOx1-S recipients had significantly (81 % and 74 %, respectively) lower odds of CAT 4–5 infection compared to CoronaVac recipients. Indian patients had a significantly (83 %) lower chance of CAT 4–5 infection compared to Malay patients. Patients with breakthrough infections during the Omicron period had a significantly (58 %) lower risk of CAT 4–5 compared to those in the Delta period. The CAT 4–5 risk was significantly (nearly threefold) higher in hypertensive patients.

Conclusion: The results support the Malaysian Ministry of Health's recommended booster three months after primary vaccination and the WHO's recommended heterologous booster following CoronaVac. Certain ethnic groups, hypertensive patients, and viral variants may require attention in future pandemics.

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Clinical trial registry

Not applicable.

1. Introduction

The emergence of the novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2])[1] triggered the global coronavirus disease (COVID-19) pandemic, with over 60.5 million confirmed cases and more than 800,000 deaths in Southeast Asia [1]. Malaysia launched its National COVID-19 Immunization Program (Program Imunisasi COVID19 Kebangsaan; PICK) on February 24, 2021 with three main vaccines: the mRNA vaccine BNT162B2 (Pfizer-BioNTech: Comirnaty), the inactivated viral vaccine CoronaVac (Sinovac), and the non-replicative viral vector vaccine AZD1222/ChAdOx1-SnCoV-19 (Oxford-AstraZeneca: Vaxzevria) [2]. While vaccines are one of the most effective preventive measures against infectious disease, breakthrough infection (BI) can occur, particularly where herd immunity has not been achieved [3,4]. Concerns about breakthrough infections and new virus variants have led to recommendations for booster doses after the initial vaccination [4]. However, recommendations on the interval and type of booster have been revised several times by various health authorities based on new scientific evidence and real-world clinical data. For example, in Malaysia, the recommended interval for booster doses was initially six months after the primary doses of BNT162b2 or ChAdOx1-S, and 3–6 months after the primary series of CoronaVac but was later revised to a uniform interval of three months after the primary series for all vaccines [5] (Fig. S1).

Since SARS-CoV-2 vaccines were developed on multiple platforms at an unprecedented pace, questions on the duration of immunity and protection against emerging viral variants remained [3,4]. This led the World Health Organisation (WHO) [4] to recommend further research to fill these information gaps, particularly in low- and middle-income countries utilising the inactivated viral vaccines.

This study aimed to evaluate the clinical outcomes (time to BI, intensive care unit [ICU] admission, and in-hospital mortality) of hospitalised patients with SARS-CoV-2 BI as the primary outcome, and the risk factors associated with its severity as the secondary outcome, in Malaysia.

2. Material and methods

2.1. Study design and population

This retrospective, single-centre, observational cohort study utilised secondary data from the electronic healthcare information system of a 620-bed multispecialty hospital in Selangor, Malaysia, that provides both specialist secondary and tertiary levels of care. The hospital was designated, by the Malaysian Ministry of Health (MOH), one of four full COVID-19 hospitals for the Klang Valley area from August 1, 2021 to September 30, 2021 and as a hybrid COVID-19 hospital thereafter.

Fully vaccinated patients, ≥18 years, with confirmed SARS-CoV-2 infections, who belonged to the Malay, Chinese, or Indian ethnic groups were included. These patients were fully vaccinated (two doses) with either BNT162b2, CoronaVac, or ChAdOx1-S, and were hospitalised during the period from September 2021 to February 2022. This period was chosen because BIs started to increase in Malaysia in late July 2021 [6]. The study commenced in September 2021 because significant data for July and August 2021 were missing. The following patients were excluded: those with missing data, unvaccinated or partially vaccinated and boosted patients, and pregnant women. The last was due to an increased risk of severe outcomes during pregnancy [4]. Additionally, hospitalised patients who tested positive for SARS-CoV-2 less than 14 days after their second vaccine dose were excluded to allow time for a sufficient immune response [3]. To avoid interfering with the primary outcome, we also excluded fully vaccinated patients admitted for a concomitant medical emergency (e.g. ST-elevation myocardial infarction) and those admitted for reasons other than SARS-CoV-2 infection who had a BI during hospitalisation (Fig. 1).

Patients with confirmed SARS-CoV-2 were classified into five categories in accordance with the established national COVID-19 Management Guidelines [7]. Clinical SARS-CoV-2 disease severity was classified according to the WHO [8] guidelines as follows.

Category 1 asymptomatic (mild disease);
Category 2 symptomatic without evidence of pneumonia (mild disease);
Category 3 symptomatic with evidence of pneumonia (moderate disease);
Category 4 symptomatic, pneumonic, and requiring supplemental oxygen (severe disease);
Category 5 critically ill, with or without other organ failure (critical disease).

The highest progression stage of the disease was documented in this study.

[1] aIRR, adjusted incidence rate ratio; BI, breakthrough infection; EA, east Asians; hg, haplogroup; MOH, Malaysian Ministry of Health; SA, south Asians; VE, vaccine effectiveness.

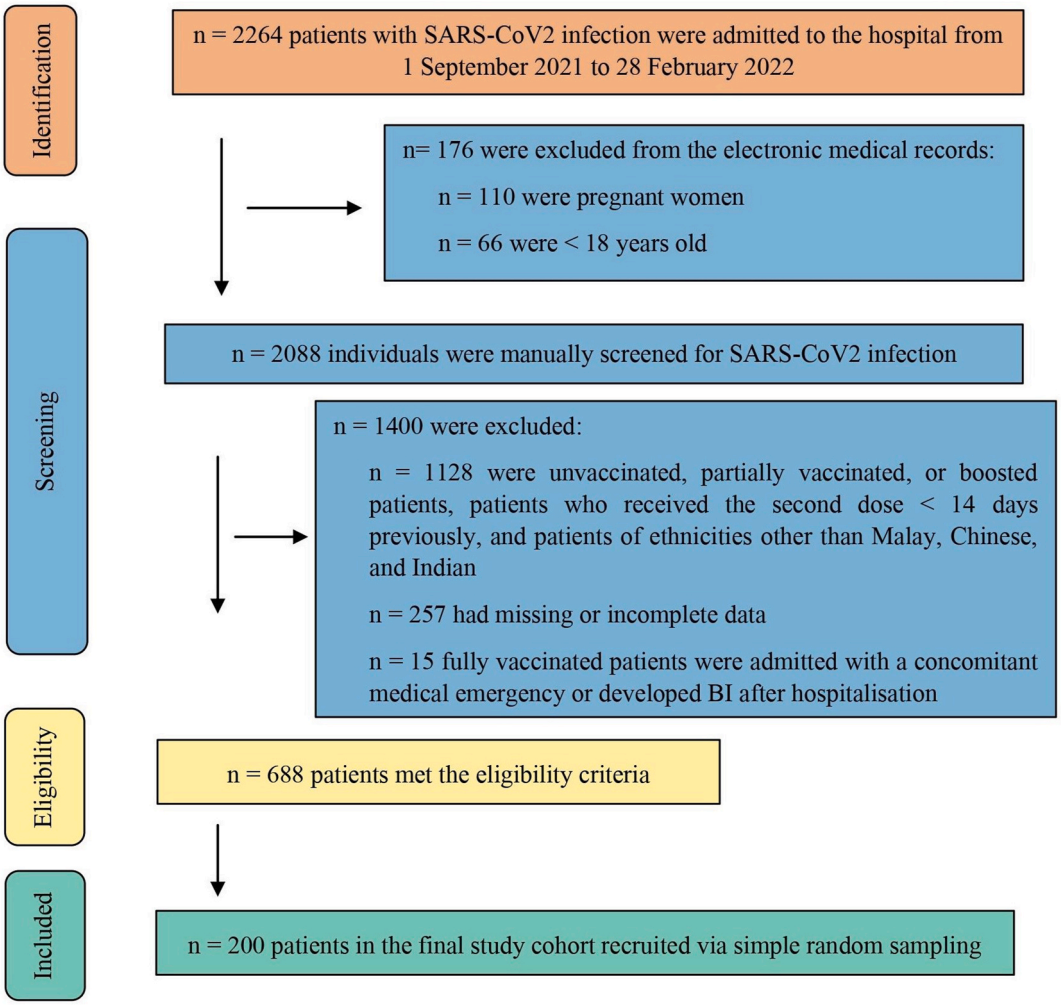

Fig. 1. Flowchart of participant selection.

2.2. Sample size and sampling method

A power analysis, conducted with G*Power version 3.1.9.4, indicated that our chosen sample size of 200 achieved a power of 89.1 %. Participants were selected through simple random sampling. Additional details are available in S1 in the supplementary materials.

2.3. Study variables definitions

See S2 in the supplementary materials for detailed definitions.

2.4. Statistical analysis

The data were analysed using IBM SPSS software version 28 (IBM Corp., Armonk, NY, USA). A two-tailed significance level of 5 % ($P < 0.05$) and a 95 % confidence interval (CI) were established for all tests. Continuous data with a normal distribution are reported as means ± standard deviations (SDs), while medians and interquartile ranges (IQRs) are used for non-normally distributed data. Categorical data are presented as frequencies and percentages. To address the primary outcome, a one-way analysis of variance test was used to compare the continuous dependent variable (time to BI) among the three vaccine cohorts. The normality assumption of the numerical data was checked using the Kolmogorov–Smirnov test, and the homogeneity of variance assumption was assessed using Levene's test. The assumptions of both tests were met when P was >0.05. Chi-square or Fisher–Freeman–Halton exact tests (for expected cell counts <5) were performed to evaluate the association between binary categorical outcomes and the three vaccines. To evaluate the secondary outcomes, univariable and multivariable binary logistic regression analyses were conducted to calculate the odds ratios (ORs) and 95 % CIs to predict the independent risk factors associated with the dependent SARS-CoV-2 severity variables.

This was consistent with the MOH guidelines [7,9]. SARS-CoV-2 severity was dichotomised into CAT 2–CAT 3 (mild–moderate) and CAT 4–CAT 5 (severe–critical). The risk factors in the univariable analysis with $P < 0.05$ were selected for inclusion in the final multivariable-adjusted regression model. The regression model's goodness of fit was confirmed using the Hosmer–Lemeshow test ($P > 0.05$). The absence of multicollinearity was assessed using the variance inflation factor, with a threshold >5 and tolerance values < 0.20 indicating multicollinearity.

3. Results

3.1. Baseline demographic and clinical characteristics and vaccine status

Of the 200 study participants, 52.5 % were male (n = 105), with a mean age of 47.3 years (SD ± 17.0) on the index date. Most participants (73.0 %, n = 146) were Malay, followed by Chinese (20.5 %, n = 41), and Indian (6.5 %, n = 13). At least one comorbidity was present in 75.5 %, (n = 151) of patients: hypertension was the most prevalent (43.5 %, n = 87), followed by diabetes mellitus (32.0 %, n = 64). Body mass index (BMI) was reported for 43.5 % (n = 87) of the total cohort. One-quarter were obese (n = 50), with a median BMI of 31.74 (IQR ± 12.89) kg/m^2. Smoking status was reported for only 23 % (n = 46): 6 % (n = 12) were current and 3.5 %

Table 1
Baseline demographic and clinical characteristics of the participants (n = 200).

Variables	Values
Sex	**Frequency (%)**
Male	105 (52.5)
Female	95 (47.5)
Ethnicity	**Frequency (%)**
Malay	146 (73.0)
Chinese	41 (20.5)
Indian	13 (6.5)
Age (years)	**Mean (SD)**
Cohort	47.3 (17.03)
	Frequency (%)
Young adults (18–39)	76 (38.0)
Middle-aged adults (40–59)	72 (36.0)
Older adults (≥ 60)	52 (26.0)
BMI, kg/m^2	**Median (IQR)**
Cohort	31.74 (12.89)
	Frequency (%)
Underweight (< 18.5)	1 (0.5)
Normal (18.5–24.9)	17 (8.5)
Overweight (25.0–29.9)	19 (9.5)
Obese (> 30)	50 (25.0)
Smoking status	**Frequency (%)**
Non-smoker	27 (13.5)
Former smoker	7 (3.5)
Current smoker	12 (6.0)
Comorbidities	**Frequency (%)**
No comorbidities	49 (24.5)
Comorbidities	151 (75.5)
Pre-existing comorbidities	**Frequency (%)**
Hypertension	87 (43.5)
Diabetes mellitus	64 (32.0)
Chronic respiratory disease	27 (13.5)
Chronic cardiac disease	24 (12.0)
Chronic kidney disease	10 (5)
Chronic liver disease	2 (1.0)
Immunosuppression	7 (3.5)
Co-infection	4 (2.0)
Type of vaccination	**Frequency (%)**
CoronaVac	150 (75.0)
BNT162b2	30 (15.0)
ChAdOx1-S	20 (10.0)
Severity	**Frequency (%)**
CAT 2–3	97 (48.5)
CAT 4–5	103 (51.5)
Variant of Concern	**Frequency (%)**
Delta	158 (79)
Omicron	42 (21)
History of COVID-19 infection prior to vaccination	**Frequency (%)**
	2 (1)

BMI: Body mass index, COVID-19: Coronavirus disease, IQR: interquartile range.

(n = 7) were former smokers (Table 1). Most participants were fully vaccinated with CoronaVac (75 %, n = 150), followed by BNT162b2 (15 %, n = 30), and ChAdOx1-S (10 %, n = 20).

The distribution of SARS-CoV-2 infection severity was nearly equal: 48.5 % were CAT 2–3 (n = 97) and 51.5 % were CAT 4–5 (n = 103). Of the BIs, 79 % occurred during the Delta period (n = 158). Only two patients (1 %) had histories of SARS-CoV-2 infection prior to vaccination (Table 1). Most participants had received their second doses of CoronaVac (63.3%) and BNT162b2 (88%) in July and August, while 80% of the second doses of ChAdOx1-S were received in August and September (Fig. 2).

A sub-analysis of the participants' baseline demographic and clinical characteristics in relation to vaccine type revealed no statistically significant differences (all P-values >0.05; Table S1).

3.2. Time to BI

There were significant differences between the three vaccine groups in the time to BI (F [2, 197] = 6.90, P = 0.001); this was significantly longer among BNT162b2 recipients (128.47 ± 46.21 days) than among CoronaVac (94.09 ± 48.71 days; P = 0.001; post hoc Bonferroni) and ChAdOx1-S recipients (90.80 ± 37.59 days; P = 0.019; post hoc Bonferroni). However, the time to BI did not differ significantly between CoronaVac and ChAdOx1-S recipients (P = 1.00; post hoc Bonferroni).

3.3. SARS-CoV-2–related ICU admission

Of all the patients, 8.5 % (n = 17) required SARS-CoV-2-related ICU admission. CoronaVac was associated with 7.5 % (n = 15) of these cases, while BNT162b2 was associated with 1 % (n = 2). However, these associations were not statistically significant (P = 0.389). ChAdOx1-S was not associated with any ICU admissions.

3.4. SARS-CoV-2–related in-hospital mortality

SARS-CoV-2-related in-hospital mortality occurred in 1.5 % of all patients (n = 3). There were no significant differences among the three vaccine groups (P = 0.325). CoronaVac was associated with 1 % (n = 2) and ChAdOx1-S vaccine with 0.5 % (n = 1) while no in-hospital deaths were associated with BNT162b2.

3.5. Risk factors associated with SARS-CoV-2 severity

Fourteen potential predictors of severity were investigated using univariable binary logistic regression. Of the seven significant predictors in the univariable analysis, four (vaccine type, variant of concern, ethnicity, and hypertension) retained statistical significance (P < 0.05) in the final multivariable model and were identified as independent determinants of SARS-CoV-2 severity (Table 2). The variables representing smoking and BMI were excluded as > 70 % and >50 % of the data were missing, respectively (Table 1).

A multivariable analysis by vaccine group revealed that BNT162b2 recipients had significantly (81 %) lower odds of Cat 4–5 BIs compared to CoronaVac recipients (adjusted odds ratio [aOR]: 0.19; 95 % CI: 0.07–0.47; P < 0.001]). Similarly, ChAdOx1-S recipients had significantly (74 %) lower odds of Cat 4–5 BIs compared to CoronaVac recipients (aOR: 0.26; 95 % CI: 0.08–0.75; P = 0.014). Analysis by ethnicity showed that Indians had a significantly (83 %) lower chance of experiencing Cat 4–5 BIs compared with Malays (aOR: 0.17; 95 % CI: 0.06–0.45; P < 0.001). The risk of more severe BIs was significantly (nearly threefold) higher in patients with hypertension (aOR: 2.92; 95 % CI: 1.49–5.73; P = 0.002). Patients who had BIs during the Omicron period had a 58 % lower chance of severe–critical BIs than those infected during the Delta period (aOR: 0.42; 95 % CI: 0.19–0.95; P = 0.038). The overall model was statistically significant ($\chi 2$ = 86.13, DF = 10, P < 0.001). All seven predictors explained 36.8 % of the variability in SARS-CoV-2 severity (Nagelkerke R2). The model correctly predicted severity in 73.4 % of cases.

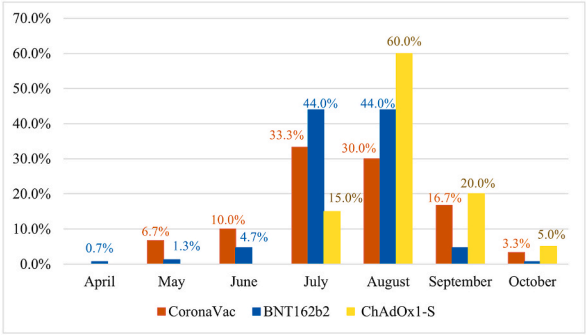

Fig. 2. Monthly distribution of each vaccine type administered to the participants during the study period in 2021.

Table 2
Risk factors and their association with SARS-CoV-2 severity as determined by univariable and multivariable binary logistic regression analysis.

Variable	Univariable Analysis		Multivariable Analysis	
	OR[a] (95 % CI)	P-value[b]	aOR[a] (95 % CI)	P-value[b]
Age, years				
Young (18–39)	Ref		Ref	
Middle-aged (40–59)	1.85 (1.03–3.32)	**0.038**	1.27 (0.62–2.63)	0.506
Elderly (≥ 60)	2.27 (1.22–4.22)	**0.009**	1.69 (0.72–3.94)	0.223
Sex				
Male	Ref		Ref	
Female	0.49 (0.30–0.80)	**0.005**	0.67 (0.32–1.04)	0.070
Race				
Malay	Ref		Ref	
Chinese	2.96 (1.64–5.32)	**< 0.001**	1.94 (0.89–3.70)	0.098
Indian	0.32 (0.14–0.73)	**0.007**	0.17 (0.06–0.45)	**< 0.001**
Vaccine				
CoronaVac	Ref		Ref	
BNT162b2	0.21 (0.10–0.46)	**< 0.001**	0.19 (0.07–0.47)	**< 0.001**
ChAdOx1-S	0.31 (0.12–0.80)	**0.016**	0.26 (0.08–0.75)	**0.014**
Variant of Concern				
Delta	Ref		Ref	
Omicron	0.27 (0.14–0.53)	**< 0.001**	0.42 (0.19–0.95)	**0.038**
Comorbidities				
Hypertension	3.48 (2.09–5.78)	**< 0.001**	2.92 (1.49–5.73)	**0.002**
Diabetes mellitus	2.02 (1.19–3.41)	**0.008**	1.38 (0.68–2.81)	0.363
Chronic cardiac disease	0.663 (0.32–1.33)	0.250	_	
Chronic respiratory disease	0.75 (0.37–1.51)	0.424	_	
Chronic liver disease	1.45 (0.22–9.56)	0.699	_	
Chronic kidney disease	0.56 (0.17–1.75)	0.320	_	
Immunosuppression	0.29 (0.07–1.10)	0.069	_	
Co-infection	2.48 (0.65–9.44)	0.183	_	
Previous COVID-19 infection	Not estimable		_	

COVID-19: Coronavirus disease.
[a] Odds ratio with 95 % confidence intervals (CI) calculated using logistic regression.
[b] A P-value <0.05 indicates statistical significance.

4. Discussion

4.1. Baseline demographic and clinical characteristics and vaccine status of the study participants

The middle-aged mean age of 47.3 years (SD ± 17.0) observed in our study can be partly explained by behavioural and cultural differences across age groups. For example, early in the pandemic in Malaysia, Sim et al. [10] observed a lower median age (34 years; IQR: 24–51) among ill individuals, attributing this to a three-day religious mass gathering attended predominantly by younger individuals. Most participants were of Malay ethnicity, followed by Chinese and Indian, reflecting the general ethnic distribution in Malaysia [11], while BMI was under reported in our study with a median of 31.74 kg/m^2. Nevertheless, evidence links obesity to a higher risk of hospitalisation for SARS-CoV-2, likely due to impaired immune function and respiratory complications [12]. Only 23 % of participants had their smoking status documented, yet global trends suggest underreporting, potentially due to clinicians prioritizing patient stabilization rather than documenting smoking history [13]. Most study participants had at least one comorbidity, consistent with growing data that show an overrepresentation of comorbidities in fully vaccinated inpatients [14–16]. CoronaVac recipients were overrepresented (75 %, n = 150) compared to BNT162b2 (15 %, n = 30) and ChAdOx1-S (10 %, n = 20) recipients. This can be partly explained by the national vaccination timeline. Most CoronaVac recipients received their second dose in July and August (Fig. 2), and in July, CoronaVac was more frequently utilised in Malaysia (Figs. S2 and S3). However, this timeline may not fully explain the vaccine trend observed from August onwards, in which BNT162b2 was more frequently utilised than CoronaVac. Therefore, the disparities observed between vaccines may also be attributable to differences in vaccine effectiveness (VE) against hospitalisation. Only two patients (1 %) had histories of SARS-CoV-2 infection before vaccination, which supports growing evidence [17] that hybrid immunity may offer greater protection against SARS-CoV-2 and its variants compared to naturally acquired immunity or vaccination alone.

4.2. Comparison of time to BI in different vaccine groups

We found that BNT162b2 recipients displayed protection against SARS-CoV-2 BI for the longest period (128.47 ± 46.21 days), compared to CoronaVac (94.09 ± 48.71 days) and ChAdOx1-S (90.80 ± 37.59 days) recipients. While direct comparisons between the three vaccines are limited, these findings are consistent with those of Li et al. [18], who found that mRNA vaccines provided a significantly longer postvaccination interval, with a median of 30.5 days, than CoronaVac (with median times to BI of 111.5 and 81

days, respectively). Suleyman et al. [16] revealed that among patients with BIs (n = 982), BNT162b2 offered significantly longer protection, with a mean time of 138 ± 62 days, compared to the viral vector vaccine JNJ78436735 (99 ± 47 days). In a non-comparative study, Brosh-Nissimov et al. [19] reported a shorter median duration of 39.5 days (IQR, 25.5–52) from full vaccination to hospitalisation among BNT162b2 recipients during the Alpha period. However, a later study by Brosh-Nissimov et al. [15] revealed that compared to the Alpha variant group, the Delta variant group had a significantly longer median time to BI of 179 days (IQR, 166–187). These results appear to contradict the growing body of evidence that the Delta variant was associated with greater transmissibility and lower VE than the Alpha variant [20]. This discrepancy may be attributed to the Alpha group having a higher prevalence of comorbidities (96 %) especially immunosuppression (40 %), in contrast to the Delta group's lower rates of comorbidities (88.9 %) and immunosuppression (13.7 %). Although the present study was not designed to investigate VE, the findings are nevertheless in line with those of Suah et al. [14] who compared the effectiveness of BNT162b2 and CoronaVac and revealed a decline in effectiveness over 3–5 months, with BNT162b2 exhibiting superior VE retention: BNT162b2 effectiveness waned from 90.8 % to 79.3 %, while CoronaVac declined from 74.5 % to 30.4 %. The differences in the durability of the vaccine-induced immune responses could explain the differences in time to BI between vaccines. In Malaysia, Tan et al. [21] observed a higher level of anti-spike immunoglobulin G with BNT162b2 compared to CoronaVac 13 weeks after the second dose. Another study found that the levels of memory T and B cells induced by mRNA vaccines remained relatively stable for 3–6 months after receiving the vaccine [22]. Altogether, BNT162b2 appears to provide the longest-lasting protection among the three vaccines. Thus, our findings support the recommendation of the Malaysian guidelines that a booster dose be administered three months after primary vaccination [5].

4.3. Associations between SARS-CoV-2–related ICU admission, in-hospital mortality, and the three vaccine groups

We found that, among ICU-hospitalised patients with BIs, CoronaVac recipients more commonly received ICU care, at 7.5 % (n = 15), than BNT162b2 recipients, at 1 % (n = 2). However, this association was not statistically significant. Additionally, three participants died; two had received CoronaVac and one ChAdOx1-S, and there were no statistically significant differences among the three vaccine groups. In a retrospective population study in Malaysia, the relationship between ICU admission and full vaccination with either BNT162b2 or CoronaVac was assessed over time. It was observed that the effectiveness of CoronaVac against ICU admissions declined significantly (28.7 %) after 3–5 months. However, it still offered substantial protection against mortality, at above 75 %. In contrast, BNT162b2 remained stable and effective against both ICU admission and mortality, at 77.5 % and around 90 %, respectively [12]. A similar pattern was observed in the Bahraini population; individuals aged <50 years vaccinated with the inactivated virus vaccine BBIBP-CorV had a higher risk of all postvaccination outcomes except mortality, including SARS-CoV-2 infection, hospitalisation, and ICU admission, than those who received the BNT162b2 vaccine and the two viral vector vaccines, ChAdOx1-S and Gam-COVID-Vac [23]. While our findings are consistent with previous research, the lack of statistical significance, likely due to the small sample size, suggests the need for further research with larger samples to confirm these results and investigate potential differences between the three vaccines.

4.4. Factors associated with progression to severe–critical SARS-CoV-2 BI

4.4.1. Vaccine type

We found that BNT162b2 and ChAdOx1-S recipients had significantly lower odds (81 % and 74 %, respectively) of developing severe–critical SARS-CoV-2 BI compared to CoronaVac recipients. Premikha et al. [24] conducted a retrospective cohort study in Singapore during the Delta period on more than 2.5 million fully vaccinated individuals; 74 % had received BNT162b2 and 2 % CoronaVac. They found that CoronaVac recipients were more likely to develop severe disease (adjusted incidence rate ratio (aIRR): 4.59; 95 % CI: 3.25–6.48) than BNT162b2 recipients. They also showed that individuals vaccinated with the inactivated virus vaccine BBIBP-CorV (1 %) were at greater risk (aIRR: 1.62; 95 % CI: 1.43–1.85). However, Kang et al. [25] reported 100 % (95 % CI: 98.4%–100.0 %) effectiveness for CoronaVac against severe–critical disease during the Delta period. This high effectiveness could be attributed to several limitations of that study. First, only six fully vaccinated individuals aged ≥60 years were included (n = 1403), limiting the generalizability of the findings to older adults, who are known to be at higher risk of severe SARS-CoV-2 infection [8]. Second, emerging evidence has suggested that CoronaVac may be less effective among older adults than other vaccines [26]. Finally, the study appeared to have calculated the VE on unadjusted relative risk and did not account for important confounding factors that may have influenced the observed VE. The observed differences between the three vaccines may be attributed to the distinct technologies used, which yield different degrees of immunogenicity. Evidence has shown that mRNA and adenovirus vector vaccines are efficiently immunogenic in different populations with high specificity [27]. However, the superiority of BNT162b2 or ChAdOx1-S in terms of immunogenicity is still controversial [27]. Contrarily, data from clinical trials and studies on inactivated virus-based vaccines have shown lower neutralizing antibody responses against the SARS-CoV-2 S protein, with weaker T cell responses compared to mRNA and viral vector vaccines [28,29]. This may be partly explained by proteins and nucleic acids in the whole-viral antigen that might have caused the body to produce non-specific and broader-range antibodies that could have reduced specificity in targeting the key proteins necessary to neutralise the virus, as proposed by Zhang et al. [30]. Taken together, the findings from this study reinforce the WHO's recommendation [4] to use heterologous booster mRNA or viral vector vaccines following a primary series of CoronaVac to achieve better immunogenicity and effectiveness.

4.4.2. Variants of concern

We found that patients with BIs during the Omicron period had a significantly lower risk (58 %) of CAT 4–5 compared to those

infected during the Delta period. This is consistent with mounting evidence indicating a milder course of illness in most Omicron-infected patients compared to Delta-infected patients. For instance, a study conducted by the WHO [31] in South Africa showed that patients infected during the Omicron period were 57 % less likely to develop severe–critical disease (aOR: 0.43; 95 % CI: 0.41–0.46). Two plausible explanations for this difference were proposed. First, there were likely rising levels of herd immunity by the time Omicron emerged in Malaysia, possibly via both vaccinations and previous infections. As of January 10, 2022, 78.6 % of Malaysians had been fully vaccinated (97.8 % of adults and 87.9 % of adolescents) [32]. Second, Omicron is potentially less virulent than Delta. The SARS-CoV-2 wild type, and previous variants, primarily infected lung epithelial cells, which express high levels of TMPRSS2 and utilise the cell-surface fusion route for host cell entry. Contrarily, clinical data suggest that Omicron, which is highly mutated, mainly infects upper airway epithelial cells, which express low levels of TMPRSS2, and utilises endosomal fusion for host cell entry. This fundamental biological shift from the lower to the upper respiratory tract likely explains the higher transmissibility and lower relative severity of Omicron [33]. This is supported by clinical indications that the most common symptoms during the Omicron period were throat and nasal [34].

4.4.3. Ethnic group

We found that, compared to Malays, Indians had a significantly (83 %) lower chance of developing severe–critical BI. Conversely, the odds of developing severe–critical disease were nearly twice as high among Chinese participants. However, this finding did not reach statistical significance. In a multi-centre Malaysian study, Chinese patients demonstrated a statistically significant higher mortality risk compared to Malays (aOR: 2.58; 95 % CI, 1.06–6.26). Conversely, Indians showed a reduced risk, despite being older with more comorbidities; however, this observation was not statistically significant (aOR: 0.25; 95 % CI: 0.03–2.10) [35]. Contrarily, a meta-analysis from the United Kingdom and Canada found that south Asians (SAs) had a 67 % higher risk of ICU admission than the general population, while Chinese individuals had a 28 % higher risk. However, there was substantial heterogeneity in the results for SA individuals ($I^2 = 74.9$ %) but not in those for Chinese individuals ($I^2 = 0$ %) [36]. Although the exact reason for the disparities between ethnic groups remains unclear, both non-genetic factors, including socioeconomic differences, and predisposing host genetic factors may contribute to these observations [36–38]. The potential impact of socioeconomic factors in the present study could not be investigated as such information is not routinely recorded in medical records. Population data in Malaysia show that Malaysian Chinese and Indians typically have higher incomes and live in urban areas compared with Malaysian Bumiputra [39,40]. Hence, population data may not offer a clear explanation for inferring sociodemographic differences. Genetic factors also play a role, although the evidence is still controversial and several genes and their alleles might contribute to this severity. Given the role of ACE2 as the host receptor for SARS-CoV-2, ACE2 gene polymorphisms have been extensively studied as a potential genetic cause of predisposition to disease severity. For instance, Cao et al. [37] found that east Asians (EAs) tended to have a higher frequency of upregulated ACE2 expression than other populations. Pan et al. [38] reported that individuals with severe symptoms were more likely to carry the haplogroup (hg) ACE2-hg1, while mild cases were more likely to be ACE2-hg2 carriers. They showed that EAs had a high 43 % prevalence of ACE2-hg1, suggesting greater severity risk, whereas SAs had a 24 % frequency, indicating fewer severe cases. While the association between ethnicity and SARS-CoV-2 infection severity needs to be confirmed with larger sample sizes, and consider both genetic and non-genetic factors, our findings suggest varying degrees of SARS-CoV-2 infection severity in different ethnic groups.

4.4.4. Hypertension

The Centers for Disease Control [41] reported that, to date, there is inconclusive evidence regarding the association between hypertension and SARS-CoV-2 infection severity. Numerous studies have shown that hypertension is significantly associated with disease progression in unadjusted models. However, this association disappeared in multivariable analysis, leading to the conclusion that hypertension is dependent on other major confounders [10,42]. This conclusion was justified by the fact that hypertension has a high global prevalence, affecting more than 30 % of adults [43]. It is thus expected that a high incidence of SARS-CoV-2 infection would be observed in this population [44]. Although this argument is valid and cannot be disregarded, especially considering the high prevalence of hypertension in Malaysia (30.3 %) [45], an emerging body of evidence, supported by multivariable analyses and clinical data, suggests that hypertension is a significant predictor of severity, and hypertensive patients exhibit a distinctive immune system, in comparison to their normotensive counterparts, when infected with SARS-CoV-2. For instance, a meta-analysis including 15,302 patients, mostly Chinese individuals, showed that hypertensive COVID-19 patients have a worse prognosis than patients without hypertension (OR: 1.44; 95 % CI: 1.24–1.66; $I^2 = 41.4$ %) [46]. Bauer et al. [47] identified similar patterns in younger patients ($\leq$65 years), finding that hypertension remained an independent risk predictor associated with severity (aOR: 1.72; 95 % CI: 1.03–2.87). It has been postulated that the association between hypertension and poor prognosis in patients with COVID-19 is due to their interplay through endothelial dysfunction and a renin-angiotensin system imbalance [48]. This hypothesis is supported by clinical data showing that COVID-19 patients with hypertension had different clinical laboratory results than normotensive patients [44].

4.5. Study limitations

First, as with other single-centre retrospective studies, this study was limited to a specific geographic area and relied on electronic medical record data, which may have introduced residual confounding effects that could not be fully controlled. Second, we were unable to document the intervals of the primary vaccinations, which may have influenced the findings on the durability of vaccine protection. Third, while we assumed that the patients received homologous primary vaccinations as per the local guidelines [49], some people might have received varied schedules, which may have affected the results. Finally, we could not access individual genomic sequencing data to determine specific variants of concern in our study population. However, we considered the period of variant

predominance in our analysis, which aligns with the WHO [50] guidelines for evaluating VE. Although individual sequencing would have been ideal to establish a precise association between variants and severity, our approach is sufficient. Despite these limitations, our findings demonstrate uniform consistency with many peer-reviewed national and large-cohort studies.

5. Conclusions

This study revealed a mean time to BI of 3–4 months. Therefore, the study findings reinforce the Malaysian guideline recommendation that a booster dose should be administered three months after primary vaccination. Both BNT162b2 and ChAdOx1-S recipients appear less likely to progress to severe SARS-CoV-2 BI compared to CoronaVac recipients. Hence, our findings support the WHO's recommendation to use heterologous booster mRNA vaccines or viral vector vaccines following a primary series of CoronaVac to achieve better immunogenicity. Nonetheless, our findings emphasise the value of CoronaVac in containing the pandemic, as it retains a substantial protective effect against mortality. In future pandemics, it will be crucial to monitor the emergence of different viral variants. Additionally, special attention should be paid to various ethnic groups and individuals with hypertension.

We recommend conducting multi-centre studies with more extensive data pools to increase the generalizability of the results. Comprehensive studies should investigate the smoking status, BMI, and other potential non-genetic and genetic factors among different ethnic groups in Malaysia and their association with severe SARS-CoV-2 infection, which could provide preliminary data for future pandemics. It is also recommended that research on mRNA vaccines be expanded to consider their potential use in the prevention of infectious diseases beyond SARS-CoV-2, such as dengue fever, and their potential as therapeutic vaccines for immuno-oncological and autoimmune diseases.

6. Declarations

6.1. Ethics statement

This study was registered in the National Medical Research Register (Reference number ID-22-02143-HCM) and approved by the Medical Research and Ethics Committee. Prior to the commencement of the study and accessing of patient medical records, permission was sought and granted by the hospital. All datasets were anonymised by assigning a study number to each de-identified patient to ensure privacy. The requirement for informed consent was waived owing to the retrospective study design and the use of pre-existing data from the database.

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Data availability statement

The datasets generated and/or analysed during the current study contain sensitive personal information related to SARS-CoV-2 infection and vaccination and are deemed confidential for upload as mandated by the Medical Research and Ethics Committee and the hospital policy. Access to the data will be granted upon a reasonable request to the corresponding author, subject to approval by the aforementioned authorities.

CRediT authorship contribution statement

Hessa Tamim: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rosnani Hashim:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **Nurdiana Jamil:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Li Yin Chong:** Supervision, Resources, Data curation. **Zainol Johari:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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