Characteristics and clinical outcomes of patients with pre-delta, delta and omicron SARS-CoV-2 infection in Indonesia (2020–2023): a multicentre prospective cohort study

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Summary

Background Limited data exist from southeast Asia on the impact of SARS-CoV-2 variants and inactivated vaccines on disease severity and death among patients hospitalised with COVID-19.

Methods A multicentre hospital-based prospective cohort was enrolled from September 2020 through January 2023, spanning pre-delta, delta, and omicron periods. The participant hospitals were conveniently sampled based on existing collaborations, site willingness and available study resources, and included six urban and two rural general hospitals from East Nusa Tenggara, Jakarta, and North Sumatra provinces. Factors associated with severe disease and day-28 mortality were examined using logistic and Cox regression.

Findings Among 822 participants, the age-adjusted percentage of severe disease was 26.8% (95% CI 22.7–30.9) for pre-delta, 50.1% (44.0–56.2) for delta, and 15.2% (9.7–20.7) for omicron. The odds of severe disease were 64% (18–84%) lower for omicron than delta ($p < 0.001$). One or more vaccine doses reduced the odds of severe disease by 89% (65–97%) for delta and 98% (91–100%) for omicron. Age-adjusted mortality was 11.9% (8.8–15.0) for pre-delta, 24.4% (18.8–29.9) for delta and 9.6% (5.2–14.0) for omicron. The day-28 cumulative incidence of death was lower for omicron (9.2% [5.6–13.9%]) than delta (28.6% [22.0–35.5%]) ($p < 0.001$). Severe disease on admission

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was the predominant prognostic factor for death (aHR34.0 [16.6–69.9] vs mild-or-moderate; p < 0.001). After controlling for disease severity on admission as an intermediate, the risk of death was 48% (32–60%) lower for omicron than delta (p < 0.001); and 51% (38–61%; p < 0.001) lower for vaccinated participants than unvaccinated participants overall, and 56% (37–69%; p < 0.001) for omicron, 46% (−5 to 73%; p = 0.070) for pre-delta (not estimable for delta).

Interpretation Infections by omicron variant resulted in less severe and fatal outcomes than delta in hospitalised patients in Indonesia. However, older, and unvaccinated individuals remained at greater risk of adverse outcomes.

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Keywords: COVID-19; SARS-CoV-2 variants of concern; Disease severity; Mortality; Indonesia; Inactivated vaccine; Prospective study

Research in context

Evidence before this study

We searched PubMed on June 8, 2023, for articles in English that assessed clinical outcomes in patients hospitalised with COVID-19 during successive SARS-CoV-2 variant waves, using the search terms ("SARS-CoV-2" OR "COVID-19") AND ("death" OR "mortality" OR "disease severity" OR "ICU admission") AND ("waves" OR "variants of concern" OR "Omicron" OR "Delta"). Studies mostly from high-income countries in North America and Europe have suggested a substantially reduced risk of progression to severe clinical outcomes and COVID-19-related in-hospital mortality for infections by omicron variant (relative to pre-delta and delta variants). This has been variably attributed to differences in pathogenicity between delta (B.1.617.2) and non-delta viral strains, mounting vaccine and virus exposure elicited immunity, as well as improved clinical management and treatments. Initially, Indonesia's COVID-19 vaccination programme was largely based on inactivated whole-virus vaccines such as CoronaVac (Sinovac Biotech, Beijing, China). However, there has been limited evaluation of the impact of the vaccination programme on severe and fatal disease outcomes of delta and omicron infections.

Added value of this study

This study, conducted in eight rural and urban hospitals in three provinces spanning the pre-delta, delta and omicron predominance periods from September 2020 through January 2023, is among the few prospective studies in southeast Asia to describe the changed clinical profile, treatments received, and severe and fatal outcomes of patients hospitalised with COVID-19. Patients admitted with omicron had a lower risk of severe disease and death, compared to delta-infected patients. Severe COVID-19 at hospital admission remained the predominant prognostic factor of death across the successive SARS-CoV-2 variants. COVID-19 vaccination was associated with a substantial reduction of severe disease from delta and omicron, and death from pre-delta and omicron (and could not be estimated for delta). The data also corroborated existing evidence that, a third heterologous vaccine dose, after primary vaccination with CoronaVac, was associated with protection against severe and fatal COVID-19 outcomes.

Implications of all the available evidence

Despite lower severity than delta, the omicron variant still caused substantial public health and patient burdens, with older and unvaccinated individuals remaining at higher risk of adverse outcomes. Given the dynamic nature of the pandemic, continuous context-specific evaluations of emerging variants of concern, and their impact on vaccine effectiveness, are warranted. Such evaluations would further optimise treatment and vaccine booster strategies, especially for older and otherwise vulnerable populations in low-income and middle-income countries.

Introduction

As of October 4, 2023, COVID-19 caused by SARS-CoV-2 has resulted in nearly 7 million reported deaths worldwide. Reported case-fatality ratios in patients hospitalised with COVID-19 have varied substantially between settings, mostly explained by differences in disease severity, age distribution and pre-existing comorbidities.[1,2] In addition, successive SARS-CoV-2 variants of concern (VOCs) have driven epidemic waves throughout the world, with differences in transmissibility and disease severity.[3,4] Initially detected in South Africa in November 2021, the omicron VOC and subsequent sublineages replaced the delta variant as the predominant variant worldwide due to higher transmissibility yet lower disease severity. However, the evidence to date, for lower disease severity and mortality from omicron compared with delta is mostly from high-income countries in North America and Europe,[5,6] and

has been variably attributed to differences in pathogenicity,[3,4] immune evasion,[7,8] and improved treatments. There is also limited data on the impact on clinical outcomes of the different VOCs in hospitalised populations in Asia, especially in low-resource settings.

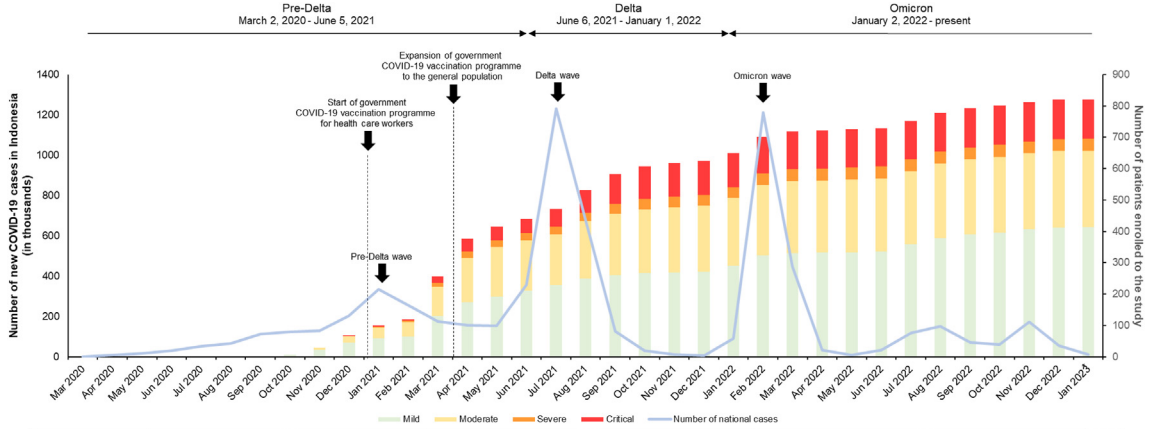
Indonesia has the world's fourth largest population (275 million) and reported the highest numbers of COVID-19 cases (6.8 million) and deaths (161,811) in southeast Asia (as per June 8, 2023) through three major waves, driven mainly by B.1.466.2 (pre-delta), delta (B.1.617.2, AY.23, and AY.24) and omicron (B.1.1.529), and two minor waves, driven by omicron subvariants BA.4/BA.5 and XBB (Fig. 1). Indonesia's COVID-19 vaccination programme commenced in January 2021, mostly based on inactivated whole-virus SARS-CoV-2 vaccines such as CoronaVac (Sinovac Biotech, Beijing, China), and by January 2023, 87% of the population had received at least one vaccine dose.[9] Inactivated vaccines have been shown to effectively prevent COVID-19-related death and severe illness,[10] but previous data have suggested decreasing immunity within months, particularly in older people.[11,12] There has been limited evaluation of the impact of Indonesia's COVID-19 vaccination programme on clinical disease outcomes during the delta and omicron waves.

We report findings from a multicentre hospital-based longitudinal cohort study in Indonesia, spanning the pre-delta, delta and omicron waves, from September 2020 through January 2023. The main aim of this temporal analysis was to discern if the clinical profile and severe and fatal disease outcomes of patients hospitalised with COVID-19 differed between SARS-CoV-2 variants, and to examine the effects of vaccination with inactivated vaccines thereof.

Methods

Study design and participants

This study is a multicentre hospital-based longitudinal cohort, based on the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) clinical characterisation protocol[13] The participant hospitals were conveniently sampled based on existing collaborations, site willingness and available study resources, and included six urban and two rural general hospitals in three provinces (East Nusa Tenggara 3, Jakarta 3, North Sumatra 2). The study population included children and adults (with no age limits) who were hospitalised with SARS-CoV-2 PCR-confirmed COVID-19 between Sept 21, 2020 and Jan 5, 2023. All participants or their proxy provided written informed consent. The participant hospitals used criteria for hospitalisation from the COVID-19 National Task Force (i.e., clinical signs of pneumonia, respiratory distress, oxygen desaturation, and/or sepsis).[14] In accordance with national COVID-19 guidelines, confirmatory SARS-CoV-2 PCR testing was conducted on nasopharyngeal and/or oropharyngeal swab specimens in reference laboratories. All participant hospitals had an intensive care unit (ICU) with capacity for non-invasive



Enrollment date		2020										2021												2022												2023
		Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan
N		0	0	0	0	0	0	2	5	24	38	32	19	138	120	38	25	31	60	52	24	11	7	25	50	18	4	3	4	23	27	14	8	11	8	1
Mortality	n	0	0	0	0	0	0	0	0	1	1	6	1	21	18	2	3	7	13	18	6	2	0	0	9	3	1	0	0	0	3	0	0	0	1	0
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.2	2.6	18.8	5.3	15.2	15.0	5.3	12.0	22.6	21.7	34.6	25.0	18.2	0.0	0.0	18.0	16.7	25.0	0.0	0.0	0.0	11.1	0.0	0.0	0.0	12.5	0.0
Severe clinical disease	n	0	0	0	0	0	0	0	0	0	1	7	1	25	28	3	3	12	19	29	9	5	1	0	10	5	2	0	0	0	3	0	0	0	1	0
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.6	21.9	5.3	18.1	23.3	7.9	12.0	38.7	31.7	55.8	37.5	45.5	14.3	0.0	20.0	27.8	50.0	0.0	0.0	0.0	11.1	0.0	0.0	0.0	12.5	0.0

Fig. 1: Timeline of the cumulative cohort enrolment in the context of the epidemic waves caused by the successive SARS-CoV-2 variants in Indonesia. *Participants were enrolled up to Jan 5, 2023. SARS-CoV-2 epidemic waves were defined as the week in which ≥50% of new nationwide infections were attributed to each VOC based on the government's genomic surveillance programme: pre-delta (before June 6, 2021), delta (June 6, 2021–Jan 1, 2022), and omicron (Jan 2, 2022–present). Line chart shows the number of nationwide monthly new of COVID-19 cases in Indonesia (left y-axis, in thousands), and bar graph shows the cumulative number of patients enrolled in the cohort, stratified by disease severity at admission (right y-axis).

and invasive ventilation. This study was approved by the research ethics committees of the Faculty of Medicine Universitas Indonesia-Cipto Mangunkusumo Hospital, Universitas Sumatera Utara, Eijkman Institute for Molecular Biology, Universitas Nusa Cendana, and Oxford Tropical Research Ethics Committee. In addition, this study was reported as per Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Data collection

The study teams extracted routinely collected demographic, clinical and laboratory data from the patient medical records into an online study database, with verification by central data managers. Age, sex, symptoms, disease severity, comorbidities, COVID-19 vaccination status, SARS-CoV-2 PCR test were recorded at admission, and disease severity, treatment received, hospital and ICU admission, discharge, and death were recorded daily. Viral pneumonia was diagnosed by the treating physician, based on clinical and radiological evaluation. Disease severity was categorised according to the WHO Clinical Progression Scale, as follows: (i) mild, not receiving oxygen therapy; (ii) moderate, receiving simple oxygen by mask or nasal prongs; (iii) severe, receiving oxygen by non-invasive ventilation or high flow oxygen therapy; and (iv) critical, receiving invasive ventilation, renal replacement therapy, vasopressors, and/or extracorporeal membrane oxygenation.[15] If after hospital discharge, day-28 outcomes were ascertained by phone call. The main study outcome measures were: (i) 28-day mortality for any reason and (ii) severe clinical disease (defined as severe or critical disease or ICU admission). The nasopharyngeal and/or oropharyngeal swab taken from each participant at admission was forwarded to the Genomik Solidaritas Indonesia Laboratory in Jakarta for SARS-CoV-2 whole genome sequencing (see Supplementary Fig. S1 for details).

Statistical analysis

No formal sample size estimation or power calculation was performed before the study. Descriptive statistics included proportions for categorical variables and medians and IQRs for continuous variables. We used χ^2 or Fisher's exact test, and independent *t*-test or ANOVA to compare characteristics between patient outcomes and epidemic waves. SARS-CoV-2 epidemic waves were defined as the week in which ≥50% of new nationwide infections were attributed to each VOC based on the government's genomic surveillance programme: pre-delta (before June 6, 2021), delta (June 6, 2021–Jan 1, 2022), and omicron (Jan 2, 2022-present), the latter subdivided into early subvariants BA.1/BA.2/BA.3 (Jan 2, 2022–June 11, 2022) and recent subvariants BA.4/BA.5/XBB (June 12, 2022–present). Time-period thresholds were based on last date of the corresponding week. Age-standardised mortality and severe clinical disease were calculated by multiplying age-specific percentages with age-specific weights, weighted by the proportion of patients in the corresponding age group in our cohort.

Data completeness was high overall (Supplementary Fig. S2 and Table S1). Investigation of missing data using Little's MCAR (missing completely at random) tests and missing-indicator analysis by regression analysis did not identify bias of missing data with respect to both outcome measures and identified one independent variable (chronic cardiac disease for severe clinical disease) to be not missing at random, which was therefore excluded from the main regression models. As data were deemed missing at random for both outcomes, we used multiple imputation analysis for missing data in the main regression models by means of chained equations using fully conditional specification with 100 imputation sets. The observed and imputed data showed similar distributions for all imputed variables (data not shown).

Supplementary Table S2 summarises the participant hospital profiles. Inclusion of hospital as a random-effect variable in null-model regressions showed that hospital accounted for 37% of the variance (intraclass correlation [ICC] 0.85 [95% CI 0.56–0.96]) for symptoms, 47% (0.42 [0.19–0.68]) for severe disease, and 14% (0.44 [0.05–0.83]) for mortality. Likelihood-ratio tests showed better fitness of the mixed-effect models for both severe clinical disease ($p < 0.001$) and mortality ($p = 0.006$). Therefore, all models included hospital as a random-effect variable to adjust for clustering of observations within hospitals.

We used mixed-effects logistic regression to examine the association between the variant wave (independent variable) and individual or groups of presenting symptoms (dependent variable), adjusting for age, sex, presence of comorbidity, vaccination, and time from symptom onset to admission. We used mixed-effects logistic regression to examine factors associated with severe clinical disease, and Cox proportional hazards with shared frailty regression to examine factors associated with death. Independent variables were SARS-CoV-2 epidemic wave, age, sex, comorbidities (presence and type), vaccination status, pneumonia (for severe clinical disease) and disease severity on admission (for mortality), time since last vaccination, and time of symptom onset to admission. We also performed a subgroup analysis comparing patients infected with recent (BA.4/BA.5/XBB) and earlier omicron subvariants (BA.1/BA.2/BA.3). The proportional hazards assumption was met, tested by including an interaction term with log-transformed time for each independent variable. Independent variables associated with the outcome at $p \leq 0.20$ were included in multivariable analyses, and final model selection was informed by likelihood ratio tests. Interaction terms were used to examine potential effect modification by variant wave.

We additionally examined disease severity on admission as a potential intermediate on the pathway of the association between vaccination, SARS-CoV-2 variants, and death, using four-way decomposition mediation analysis on the main Cox regression model, adjusting for age, sex, presence of one or more comorbidities, and time from symptom onset to admission (Supplementary Fig. S3). We estimated (a) the total effect, to determine if the exposure (variant or vaccination) was associated with the outcome (death) when controlling for disease severity on admission as an intermediate; and (b) the pure indirect effect, to determine if the effect of the exposure on the outcome was significantly mediated by disease severity on admission. Collinearity diagnostics showed no violation of independence assumption between vaccination status and SARS-CoV-2 variants (correlation coefficients <0.700, tolerance 0.863) and thus these variables were included simultaneously in the model.

To assess the robustness of the main regression analyses, we conducted four additional analyses: (i) included only the available (non-imputed) values for the independent variables; (ii) included individually detected SARS-CoV-2 variants (N = 372) (Supplementary Fig. S1) instead of ecologically imputed variant waves; (iii) included adjustment for corticosteroid treatment, and (iv) assessed the effect of the most dominant hospitals on the distribution of the random-effects and risk estimates for severe clinical disease and mortality. The p-values less than 0.05 were considered as statistically significant. All statistical analyses were done in Stata/IC 15.1 (StataCorp, College Station, TX, USA).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The first and corresponding authors had full access to all the data and share the final responsibility to submit for publication.

Results

From September 2020 to January 2023, a total of 822 patients hospitalised for COVID-19 were enrolled, from Medan (Sumatra) (n = 378, 46.0%), Jakarta (Java) (n = 281, 34.2%), West Sumba (n = 133, 16.2%) and Kupang (both East Nusa Tenggara) (n = 30, 3.6%) (Supplementary Fig. S4). Fig. 1 presents a timeline of cohort enrolment, in the context of the variant waves in Indonesia. Supplementary Fig. S2 presents the study flow chart and completeness of key data.

Participant characteristics at admission

Of the 822 participants, 425 (51.7%) were admitted during pre-delta, 201 (24.5%) during delta, and 196 (23.8%) during omicron periods (Table 1 and Supplementary Table S3). Among the SARS-CoV-2 sequences obtained from the participants (372, 45.3%), the predominant strain was B.1 (B.1.466.2, B.1.1.398, and B.1.470) in the pre-delta period through June 6, 2021, followed by delta (B1.617.2, AY.23 and AY.24) through Jan 1, 2022, and omicron with subvariants (BA.1, BA.2, BA.4, BA.5 and XBB) from Jan 2, 2022 onwards (Supplementary Fig. S1). Women comprised 421 (51.2%) of the participants. The median age was 48 years (IQR 32–59; range 1–104) overall, 49 (34–58) for pre-delta, 48 (33–60) for delta, and 43.5 (28–61.5) for omicron; children comprised 4.9% (40), including 2.6% (11) for pre-delta, 4.5% (9) for delta, and 10.2% (20) for omicron. Of the total participants, 20% (164/821) were admitted with severe or critical disease 20%, including 15.6% (66/424) for pre-delta, 38.3% (77/201) for delta and 10.7% (21/196) for omicron. Furthermore, 57.2% (470/822) of the total participants had a record of one or more comorbidities, including 48.9% (208/425) for pre-delta, 63.7% (128/201) for delta and 68.4% (134/196) for omicron (each $p < 0.001$).

At the time of admission, 259 (36.1%) of participants had received one or more COVID-19 vaccine doses overall, including 7.1% (24/339) for pre-delta, 47.6% (88/185) for delta and 76.2% (147/193) for omicron ($p < 0.001$). For the age groups <50, 50–59 and ≥ 60 years, the proportions of participants who had received one or more vaccine doses were 6.4% (11/173), 7.8% (7/90), 8.2% (6/73) during pre-delta; 63.0% (63/100), 25.0% (10/40) and 34.9% (15/43) during delta; and 87.0% (100/115), 66.7% (16/24) and 57.4% (31/54) during omicron, respectively. Vaccines (primary regimen) comprised CoronaVac (93.1% [241/259]), followed by ChAdOx1 (AstraZeneca; 3.1% [8/259]), BNT162b2 (Pfizer-BioNTech; 1.9% [5/259]), mRNA-1273 (Moderna; 0.4% [1/259]), and unspecified (1.5% [4/259]). Among those vaccinated, 44 had received one dose, 153 two doses, and 62 three doses (including 60 heterologous boosters with mRNA or ChAdOx1).

Presenting symptoms at admission

The median number of days from symptom onset to hospital admission was 3 days (IQR2-6) overall, including 4 (2–7) for pre-delta, 4 (2–6) for delta, and 2 (2–4) for omicron ($p = 0.003$). The median number of symptoms was 6 (IQR 4–8, range 0–16) overall, 6 (4–8; 0–16) for pre-delta, 6 (4–9; 0–15) for delta and 5 (4–7; 0–15) for omicron ($p = 0.002$); and cough and fever were consistently the most common presenting symptoms across the variant waves (Fig. 2a and Supplementary Table S3).

After adjusting for confounders, compared with pre–delta and delta, omicron was associated with a lower probability of anorexia (adjusted odds ratio [aOR] 0.45 [95% CI 0.25–0.80]; $p = 0.007$; and 0.39 [0.24–0.63]; $p < 0.001$), anosmia (0.06 [0.03–0.15]; and 0.05 [0.02–0.10]; each $p < 0.001$), ageusia (0.03 [0.01–0.11];

Variables	Total N = 822		Pre-delta N = 425 (51.7%)		Delta N = 201 (24.5%)		Omicron N = 196 (23.8%)		p-value
	N	%	N	%	N	%	N	%	
Age (years)–median (IQR)		48.0 (32.0–59.0)		49.0 (34.0–58.0)		48.0 (33.0–60.0)		43.5 (28.0–61.5)	<0.001
0–17	40	4.9	11	2.6	9	4.5	20	10.2	
18–29	123	15.0	57	13.5	29	14.6	37	18.9	
30–39	150	18.3	76	18.0	36	18.1	38	19.4	
40–49	123	15.0	68	16.1	33	16.6	22	11.2	
50–59	181	22.1	114	27.0	42	21.1	25	12.8	
60–69	120	14.7	66	15.6	27	13.6	27	13.8	
≥70	81	9.9	31	7.3	23	11.6	27	13.8	
Sex									0.217
Male	401	48.8	219	51.5	89	44.3	93	47.4	
Female	421	51.2	206	48.5	112	55.7	103	52.6	
Disease severity at admission									<0.001
Mild	410	49.9	198	46.7	71	35.3	141	71.9	
Moderate	247	30.1	160	37.7	53	26.4	34	17.3	
Severe	38	4.6	22	5.2	12	6.0	4	2.0	
Critical	126	15.3	44	10.4	65	32.3	17	8.7	
Pneumonia	718	88.1	397	94.8	184	92.0	137	69.9	<0.001
Number of vaccine doses[a]									<0.001
0	458	63.9	315	92.9	97	52.4	46	23.8	
1	44	6.1	13	3.8	18	9.7	13	6.7	
2	153	21.4	11	3.3	68	36.8	74	38.3	
3	62	8.7	0	0.0	2	1.1	60	31.1	
Time since last vaccine dose (days)–median (IQR)		121.5 (50.0–196.0)		16.0 (9.5–51.5)		92.5 (42.0–144.0)		173.5 (82.0–287.0)	<0.001[b]
Number of symptoms–median (IQR)		6.0 (4.0–8.0)		6.0 (4.0–8.0)		6.0 (4.0–9.0)		5.0 (4.0–7.0)	0.002[b]
Presence of comorbidity	470	57.2	208	48.9	128	63.7	134	68.4	<0.001
SARS-CoV-2 PCR Ct value—median (IQR)		24.9 (19.7–29.7)		26.3 (21.4–30.6)		25.2 (19.5–30.0)		22.5 (18.9–27.4)	<0.001[b]
Length of hospital stay (days)–median (IQR)		7.0 (5.0–10.0)		8.0 (5.0–10.0)		6.0 (5.0–10.0)		7.0 (4.0–9.0)	<0.001[b]
Outcomes									
28-day mortality	115	14.1	49	11.6	49	24.4	17	8.7	<0.001
Severe clinical disease	235	28.6	109	25.7	102	50.8	24	12.2	<0.001
Intensive care unit (ICU) admission	189	23.0	77	18.1	95	47.3	17	8.7	<0.001

Unless otherwise specified, values are presented in frequencies and percentages, and p-values are derived from chi-squared tests. SARS-CoV-2 epidemic waves were defined as the week in which ≥50% of new nationwide infections were attributed to each VOC based on the government's genomic surveillance program: Pre-delta (before June 6, 2021), delta (June 6, 2021–Jan 1, 2022), and omicron (Jan 2, 2022–present). [a]Primary vaccination was predominantly CoronaVac (93.1% [241/259]), followed by ChADOx1 (AstraZeneca; 3.1% [8/259]), BNT162b2 (Pfizer-BioNTech; 1.9% [5/259]), mRNA-1273 (Moderna; 0.4% [1/259]), and unspecified (1.5% [4/259]). [b]P-value derived from ANOVA.

Table 1: **Participant characteristics, by epidemic wave.**

and 0.03 [0.01–0.09]; each p < 0.001), diarrhoea (0.37 [0.18–0.78]; p = 0.008; and 0.43 [0.22–0.87]; p = 0.018), and myalgia (0.56 [0.31–0.98]; p = 0.043; and 0.38 [0.23–0.64]; p < 0.001) (Fig. 2b). Omicron was associated with a lower probability of fatigue (0.39 [0.24–0.63]; p < 0.001), shortness of breath (0.51 [0.31–0.84]; p = 0.009), runny nose (0.54 [0.34–0.87]; p = 0.011), and nausea or vomiting (0.58 [0.37–0.91]; p = 0.019) than delta, and a lower probability of sore throat (0.54 [0.32–0.94]; p = 0.029) than pre–delta. The additional analyses based on the non–imputed data or the individually detected SARS–CoV–2 variants found largely similar associations as the main models (Supplementary Tables S5 and S6).

Clinical course and treatments received during admission

The median length of hospital stay was 8 days (IQR 5–10) overall, including 8 (5–10) for pre–delta, 6 (5–10) for delta, and 7 (4–9) for omicron (p < 0.001) (Table 1). By day 28 the incidence proportion of participants discharged was 90.0% (95% CI 84.7–93.6%) for omicron, 85.7% (81.8–88.8%) for pre–delta and 69.8% (62.3–76.1%) for delta (both p < 0.001) (Supplementary Fig. S5). The most common pharmacological treatments across the variants were antibiotics, followed by antiviral agents (mostly favipiravir or remdesivir) and corticosteroids (mostly dexamethasone or methylprednisolone). Overall, 49.9% of participants received any oxygen

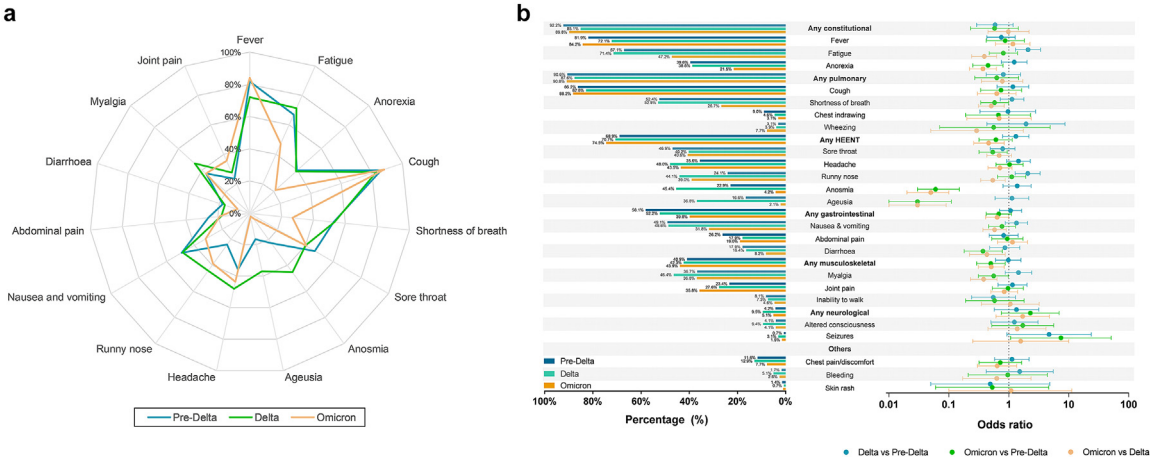


Fig. 2: Presenting symptoms for each the different SARS-CoV-2 variants. (A) Radar chart showing percentage of participants with the top-15 presenting symptoms by the different SARS-CoV-2 variants. (B) Bar chart (left panel) showing the percentage of participants reporting each presenting symptom by the different SARS-CoV-2 variants. Forest plot (right panel) showing the association between the different SARS-CoV-2 variants and each presenting symptom, expressed as adjusted odds ratio (on a logarithmic scale). Logistic regression model of SARS-CoV-2 variant (independent variable) and presenting symptoms (dependent variable), adjusted for age, sex, vaccination status, presence of comorbidity, and time from symptom onset to admission. Chills, lymphadenopathy, and conjunctivitis are not included in the models due to rarity of cases. Data points of the crude and adjusted odds ratios are shown in Supplementary Table S5. HEENT–head/ears/eyes/nose/throat.

therapy, including 53.1% for pre–delta, 64.2% for delta and 28.6% for omicron ($p < 0.001$), including invasive ventilation in 11.6%, 8.0%, 23.4% and 7.1%, respectively (Table 2).

Severe clinical disease

Of 822 participants, 235 (28.6%) developed severe clinical disease overall, comprising 25.7% (109/424) for pre–delta, 50.8% (102/201) for delta and 12.2% (24/196)

Variables	Total (N = 822)		Pre-delta (N = 425, 51.7%)		Delta (N = 201, 24.5%)		Omicron (N = 196, 23.8%)		p-value
	N	%	N	%	N	%	N	%	
Oxygen therapy	410	49.9	225	53.1	129	64.2	56	28.6	<0.001
Low-flow nasal oxygen	261	38.8	163	45.0	61	45.9	37	20.9	<0.001
High-flow oxygen	95	14.0	42	14.9	45	22.4	8	4.1	<0.001
Non-invasive ventilation	35	4.3	16	3.8	15	7.5	4	2.0	0.022
Invasive ventilation	95	11.6	34	8.0	47	23.4	14	7.1	<0.001
Pharmacological treatment									
Antibiotics	775	94.7	413	97.9	187	93.0	175	89.7	<0.001
Antivirals	645	78.7	289	68.3	176	87.6	180	91.8	<0.001
Favipiravir	331	40.3	145	34.1	99	49.3	87	44.4	0.001
Remdesivir	296	36.0	102	24.0	104	51.7	90	45.9	<0.001
Neuraminidase inhibitor	50	6.2	43	10.4	2	1.0	10	2.6	<0.001
Lopinavir/ritonavir	22	2.7	21	4.9	1	0.5	0	0.0	<0.001
Convalescent plasma therapy	20	2.5	13	3.1	6	3.0	1	0.5	0.127
Chloroquine/hydroxychloroquine	9	1.1	9	2.1	0	0.0	0	0.0	0.014
Interleukin-6 inhibitor	4	0.5	3	0.7	1	0.5	0	0.0	0.607
Ivermectin	1	0.1	0	0.0	1	0.5	0	0.0	0.213
Other	49	6.0	21	4.9	4	2.0	24	12.2	<0.001
Corticosteroids	508	62.2	238	56.5	151	75.1	119	61.0	<0.001
Anticoagulant	342	51.0	159	57.8	123	61.2	60	30.8	<0.001
Antifungal	82	10.0	30	7.1	42	20.9	10	5.1	<0.001
Other	59	7.2	25	6.0	13	6.4	21	10.7	0.095

Unless otherwise specified, values are presented in frequencies and percentages or medians and interquartile ranges, and p-values are derived from chi-squared tests.

Table 2: **Treatments received, by epidemic wave.**

for omicron (p < 0.001); and 189 (23.0%) were admitted to ICU overall, comprising 18.1% (77/425) for pre–delta, 47.3% (95/201) for delta, and 8.7% (17/196) for omicron (p < 0.001) (Supplementary Table S7). The age-adjusted severe clinical disease was 28.4% (95% CI 25.4–31.3) overall, 26.8% (22.7–30.9) for pre–delta, 50.1% (44.0–56.2) for delta, 15.2% (9.7–20.7) for omicron (20.7% [13.2–28.1] for early and 7.2% [0.2–14.1] for recent subvariants) (Fig. 3a).

In unadjusted analysis, the probability of severe clinical disease in vaccinated vs unvaccinated participants was 13.1% (34/259) vs 33.2% (152/458) overall (p < 0.001); and 25.0% (6/24) vs 21.0% (66/315) for pre–delta (p = 0.218); 25.0% (22/88) vs 72.2% (70/97) for delta (p < 0.001); and 4.1% (6/16) vs 34.8% (16/46) for omicron (p < 0.001) (Supplementary Table S8); and 7.3% (5/69) vs 44.8% (13/29) for early subvariants (p < 0.001); and 1.3% (1/78) and 17.7% (3/17) for recent subvariants (p = 0.018). The proportion of participants with severe clinical disease decreased with each additional vaccine dose: 33.2% (152/458) for 0 doses, 27.3% (12/44) for 1 dose, 14.4% (22/153) for 2 doses and 0.0% (0/62) for 3 doses.

After adjusting for confounders, omicron was independently associated with a lower odds of severe clinical disease than delta (aOR 0.36 [95% CI 0.16–0.82], p = 0.015), but not with pre–delta (0.93 [0.38–2.3], p = 0.883); and the difference in the odds of severe clinical disease between early and recent omicron subvariants was not statistically significant (0.40 [0.08–2.0], p = 0.261). Compared with unvaccinated participants, among vaccinated participants, the odds of severe clinical disease were 89% lower (0.11 [0.03–0.35]; p < 0.001) for delta, 98% lower (0.02 [0.003–0.09]; p < 0.001) for omicron, 99.6% lower (0.004 [0.001–0.04]; p < 0.001) for early subvariants, and 90% lower (0.10 [0.01–1.0]; p = 0.054) for recent subvariants, but not lower for pre–delta (1.7 [0.56–5.2]; p = 0.341). Among vaccinated participants, the odds of severe clinical disease for omicron were 97% lower (0.03 [0.01–0.16]; p < 0.001) than pre–delta, and 87% lower (0.13 [0.03–0.57]; p = 0.008) than delta; and 77% lower (0.23 [0.05–0.94]; p = 0.041) for delta than pre–delta. Compared with age <50 years, among those aged ≥60 years the increase in the odds of severe clinical disease was statistically significant for pre–delta (2.4 [1.2–4.8], p = 0.014), delta (3.9 [1.2–13.2], p = 0.026) and omicron (4.7 [1.1–20.6], p = 0.041). The odds of severe clinical disease were increased for presence of pneumonia (9.2 [2.5–33.3], p = 0.001), chronic kidney disease (8.6 [1.9–38.1], p = 0.005), and obesity (2.3 [1.3–4.2], p = 0.007) across all variants; and for presence of one or more comorbidities for delta (6.0 [1.7–21.2], p = 0.005) only (Table 3).

Mortality

Of 818 patients with a known 28–day outcome (4 unknown), 115 (14.1%) had died, 703 (85.9%) were alive at censoring (Supplementary Table S7). The age–adjusted mortality was 14.1% (95% CI 11.8–16.4) overall, 11.9% (8.8–15.0) for pre–delta, 24.4% (18.8–29.9) for delta, and 9.6% (5.2–14.0) for omicron (12.0% [6.2–17.8] for early and 7.2% [0.2–14.1] for recent subvariants) (Fig. 3b). Fig. 4 shows the time–dependent probability of survival across the epidemic waves. The crude probability of death was 11.6% (49/421) for pre–delta, 24.4% (49/201) for delta and 8.7% (17/196) for omicron (both p < 0.001), and 12.9% [13/101] for early and 4.2% [4/95] for recent subvariants (p = 0.031). The cumulative incidence of death at day 28 was lower for omicron (9.2% [5.6–13.9%]) than delta (28.6% [22.0–35.5%]; which was statistically significant (p < 0.001). However, although the cumulative incidence of death at day 28

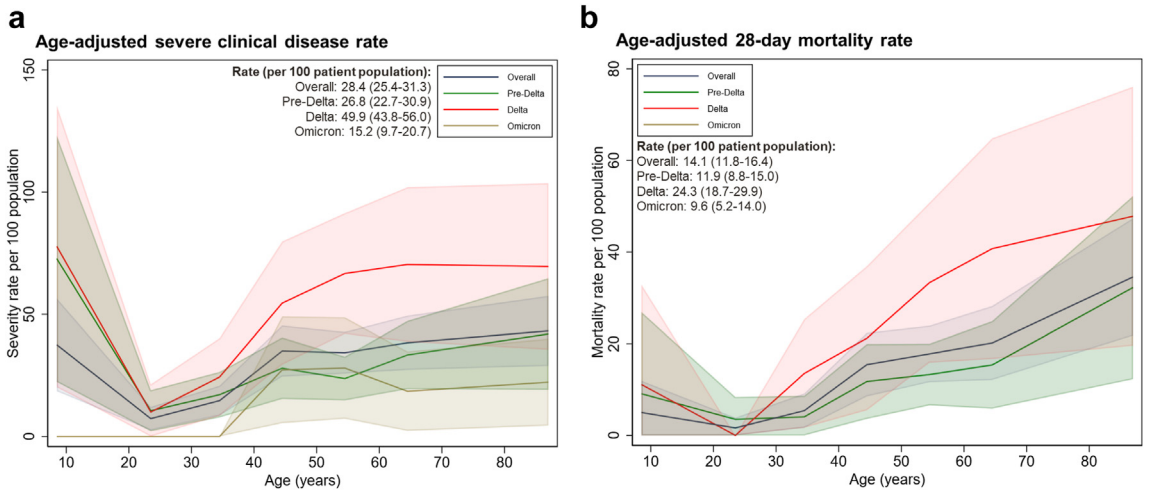


Fig. 3: Age-adjusted severe clinical disease and mortality rates for the different SARS-CoV-2 variants.

Variables	Severe clinical disease (Odds ratio)					Death for any reason (Hazard ratio)				
	Exposed (%)	Unexposed (%)	OR	95% CI	p	Exposed (%)	Unexposed (%)	HR	95% CI	p
Delta vs pre-delta wave	102/201 (50.7)	109/425 (25.6)	**2.60**	**1.30–5.21**	**0.007**	49/201 (24.4)	49/421 (11.6)	0.95	0.60–1.53	0.846[h]
Omicron vs pre-delta wave	24/196 (12.2)	109/425 (25.6)	0.93	0.38–2.29	0.883	17/196 (8.7)	49/421 (11.6)	0.92	0.47–1.80	0.808[h]
Omicron vs delta wave	24/196 (12.2)	102/201 (50.7)	**0.36**	**0.16–0.82**	**0.015**	17/196 (8.7)	49/201 (24.4)	0.96	0.51–1.82	0.911[h]
Omicron recent (BA.4/BA.5/XBB) vs early (BA.1/BA.2/BA.3) subvariants[a]	4/95 (4.2)	20/101 (19.8)	0.40	0.08–2.0	0.261	3/69 (4.2)	3/44 (6.4)	2.34	0.64–8.46	0.196
Age group: 50–59 years (vs 0–49 years)	62/181 (34.3)	89/436 (20.4)	1.51	0.84–2.70	0.166	32/180 (17.8)	31/434 (7.1)	1.15	0.68–1.96	0.596
Age group: ≥60 years (vs 0–49 years)	69/174 (31.4)	89/436 (20.4)	**2.80**	**1.60–4.92**	**<0.001**	52/200 (45.2)	31/434 (7.1)	1.59	1.00–2.52	0.051
Male (vs Female)	132/401 (32.9)	103/421 (24.5)	1.25	0.79–1.99	0.343	62/400 (15.5)	53/418 (12.7)	0.76	0.51–1.12	0.170
Severe or critical disease at admission						101/164 (61.6)	14/653 (2.1)	**34.03**	**16.56–69.94**	**<0.001**
Pneumonia	213/718 (29.7)	20/96 (20.8)	**9.19**	**2.54–33.25**	**0.001**					
COVID-19 vaccination (≥1 dose)	34/259 (13.1)	152/458 (33.2)	**0.16**	**0.08–0.34**	**<0.001**	17/259 (6.6)	74/456 (16.2)	1.09	0.61–1.94	0.768[i]
One or more (≥1) comorbidities	82/297 (27.6)	65/352 (18.5)	**2.15**	**1.30–3.58**	**0.003**	87/469 (18.6)	28/349 (8.0)	1.22	0.76–1.93	0.410
Chronic cardiac disease[b]						18/59 (30.5)	80/689 (11.6)	1.57	0.88–2.79	0.129
Hypertension[b]	82/189 (43.4)	123/579 (21.2)	1.34	0.76–2.34	0.311	45/188 (23.9)	60/577 (10.4)	1.35	0.87–2.10	0.183
Chronic kidney disease[b]	23/26 (88.5)	174/728 (23.9)	**8.56**	**1.93–38.08**	**0.005**	10/26 (38.5)	91/725 (12.6)	0.62	0.30–1.28	0.192
Obesity[b]	64/220 (29.1)	171/595 (28.7)	**2.28**	**1.25–4.15**	**0.007**					
Diabetes mellitus[b]	52/118 (44.1)	156/651 (24.0)	0.98	0.51–1.88	0.961	28/116 (24.1)	76/649 (11.7)	0.86	0.53–1.40	0.553
Time from symptom onset to admission in days—median (IQR)						4.0 (2.0–7.0)	3.0 (2.0–6.0)	1.02	0.99–1.05	0.251
Pre-delta wave[c]										
Age group: 50–59 years (vs 0–49 years)	27/114 (23.7)	46/211 (21.8)	0.98	0.47–2.03	0.957[d]	15/113 (13.3)	14/210 (6.7)	1.54	0.71–3.31	0.272
Age group: ≥60 years (vs 0–49 years)	35/97 (36.1)	46/211 (21.8)	**2.39**	**1.20–4.76**	**0.014**	20/96 (20.8)	14/210 (6.7)	**2.11**	**1.04–4.28**	**0.038**
Male sex (vs Female)	68/219 (31.1)	41/205 (20.0)	1.31	0.73–2.35	0.362[e]	33/218 (15.1)	16/203 (7.9)	1.01	0.53–1.92	0.967
COVID-19 vaccination (≥1 dose)	6/24 (25.0)	66/315 (21.2)	1.72	0.56–5.24	0.341[f]	2/24 (8.3)	30/313 (9.6)	0.72	0.16–3.19	0.664[i]
One or more (≥1) comorbidities	73/208 (35.1)	36/216 (16.7)	1.64	0.91–2.98	0.101[g]	33/207 (15.9)	16/214 (7.5)	0.66	0.34–1.27	0.214
Delta wave[c]										
Age group: 50–59 years (vs 0–49 years)	28/42 (66.7)	37/107 (34.6)	**3.51**	**1.05–11.77**	**0.042**[d]	14/42 (33.3)	13/107 (12.1)	1.01	0.46–2.23	0.980
Age group: ≥60 years (vs 0–49 years)	35/50 (70.0)	37/107 (34.6)	**3.94**	**1.17–13.22**	**0.026**	22/50 (44.0)	13/107 (12.1)	1.25	0.62–2.54	0.533
Male sex (vs Female)	49/89 (55.1)	53/112 (47.3)	1.32	0.50–3.51	0.578[e]	20/89 (22.5)	29/112 (25.9)	0.66	0.37–1.20	0.172
COVID-19 vaccination (≥1 dose)	22/88 (25.0)	70/97 (72.2)	**0.11**	**0.03–0.35**	**<0.001**[f]	11/88 (12.5)	32/97 (33.0)	1.64	0.82–3.29	0.161[i]
One or more (≥1) comorbidities	76/128 (59.4)	26/73 (35.6)	**6.00**	**1.70–21.18**	**0.005**[g]	39/128 (30.5)	10/73 (13.7)	**2.26**	**1.09–4.68**	**0.029**
Omicron wave[c]										
Age group: 50–59 years (vs 0–49 years)	7/25 (28.0)	6/117 (5.2)	3.79	0.67–21.43	0.132	3/25 (12.0)	4/117 (3.4)	0.48	0.09–2.54	0.387
Age group: ≥60 years (vs 0–49 years)	11/54 (20.4)	6/117 (5.2)	**4.69**	**1.07–20.61**	**0.041**	10/54 (18.5)	4/117 (3.4)	1.17	0.32–4.21	0.813
Male sex (vs Female)	15/93 (16.1)	9/103 (8.7)	0.91	0.27–3.07	0.878[e]	9/93 (9.7)	8/103 (7.8)	0.51	0.17–1.51	0.224
COVID-19 vaccination (≥1 dose)	6/147 (4.1)	16/46 (34.8)	**0.02**	**0.003–0.09**	**<0.001**[f]	4/147 (2.7)	12/46 (26.1)	0.72	0.20–2.60	0.611[i]
One or more (≥1) comorbidities	21/134 (15.7)	3/62 (4.8)	2.54	0.52–12.33	0.248[g]	15/134 (11.2)	2/62 (3.2)	1.01	0.21–4.72	0.995

Table shows results of the multivariable regression models of factors associated with severe clinical disease and death, using logistic and Cox proportional hazard regression respectively. The independent variables time since last vaccination (for both death and severe clinical disease) and time from symptom onset to admission (for severe clinical disease) were not associated in univariable analysis and were therefore not included in the multivariable models. All models are adjusted for clustering of observations within hospitals. Bold indicates the p-values less than 0.05 were considered as statistically significant. [a]Risk estimates were derived from a model that only included the subset of participants admitted during omicron (N = 196). [b]Independent variables were fitted in separate regression models to prevent multicollinearity with the comorbidity variable included in the main regression model. [c]Risk estimates for each SARS-CoV-2 epidemic wave were derived from regression models with interaction terms between the epidemic waves and each of the independent variables. [d]Risk of severe clinical disease was higher for patients aged 50–59 years during delta than pre-delta (aOR5.3 [95% CI 1.7–16.8], p = 0.004). [e]Risk of severe clinical disease was higher for male patients during delta than pre-delta (aOR2.5 [95%CI 1.1–5.8], p = 0.036), and during delta than omicron (3.4 [1.1–10.3], p = 0.028). [f]Risk of severe clinical disease was lower for vaccinated patients during delta than pre-delta (aOR0.23 [95% CI 0.05–0.94], p = 0.041), during omicron than pre-delta (0.03 [0.01–0.16], p < 0.001), and during omicron than delta (0.13 [0.03–0.57], p = 0.008). [g]Risk of severe clinical disease was higher for patients with one or more comorbidities during delta than pre-delta (aOR3.3 [95% CI 1.6–7.2]; p = 0.002) and omicron (3.6 [1.4–9.1], p = 0.007). [h]Mediation analysis, adjusted for age, sex, presence of one or more comorbidities, time from symptom onset on admission, revealed that there was evidence of a mediating effect of disease severity on admission on the pathway between variants and death for the comparison between delta and pre-delta (pure indirect effect: 4.44 [2.12–9.33], p < 0.001) and omicron and delta (0.49 [0.42–0.57], p < 0.001). When controlling for disease severity on admission as an intermediate, omicron was associated with a 48% lower risk of death compared to delta (0.52 [0.40–0.68], p < 0.001). Refer to Supplementary Table S9 for further details. [i]Mediation analysis, adjusted for age, sex, presence of one or more comorbidities, time from symptom onset on admission, and SARS-CoV-2 variants, revealed that there was evidence of a mediating effect of disease severity on admission on the pathway between vaccination and death overall (pure indirect effect: 0.58 [0.50–0.68], p < 0.001) and for omicron (0.49 [0.36–0.68], p < 0.001), but not for pre-delta (0.94 [0.50–1.8], p = 0.850) or delta (not estimable). When controlling for disease severity on admission as an intermediate, vaccination reduced the risk of death by 51% overall (aHR0.49 [95% CI 0.39–0.62], p < 0.001), and by 56% (0.44 [0.31–0.63], p < 0.001) for omicron, 46% (0.54 [0.27–1.1], p = 0.070) for pre-delta, and was not estimable for delta. Refer to Supplementary Table S9 for further details.

Table 3: **Regression models of the factors associated with the risk of severe clinical disease and 28-day mortality.**

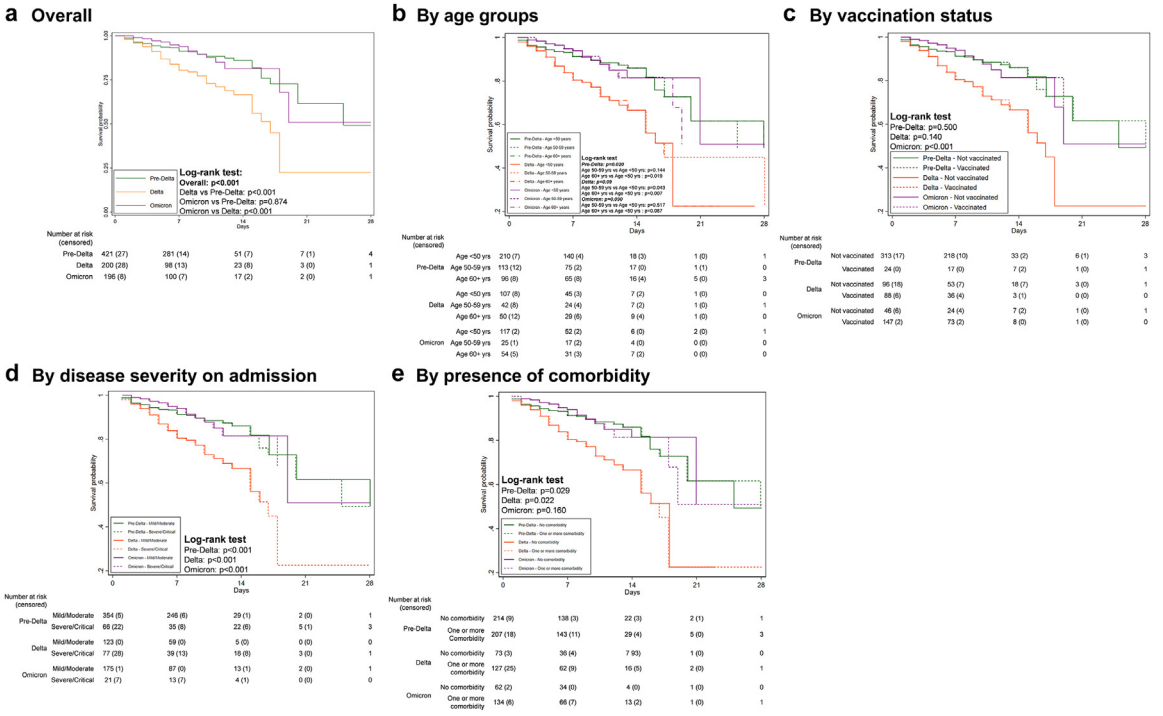


Fig. 4: Kaplan–Meier curves showing time-dependent survival probability by the different epidemic waves. SARS-CoV-2 epidemic waves were defined as the week in which ≥50% of new nationwide infections were attributed to each VOC based on the government genomic surveillance program: pre-Delta (before June 6, 2021), delta (June 6, 2021–Jan 1, 2022), and omicron (Jan 2, 2022–present).

was lower for pre–delta (12.5% [9.4–16.0]) than delta, it did not reach statistical significance (p = 0.338) (Supplementary Fig. S5). Fig. 5 shows survival based on disease severity at admission.

In unadjusted analysis, the probability of death was higher for delta than pre–delta and omicron overall, and for age group ≥60 years and for severe or critical COVID–19 at admission across all variants (Fig. 5). The probability of death in vaccinated vs unvaccinated participants was 6.6% (17/259) vs 16.2% (74/456) overall (p = 0.001); 8.3% (2/24) vs 9.6% (30/313) for pre–delta (p = 0.491); 12.5% (11/88) vs 33.0% (32/97) for delta (p = 0.141); 2.7% (4/147) vs 26.1% (12/46) for omicron (p < 0.001); 4.4% (3/69) vs 31.0% (9/29)

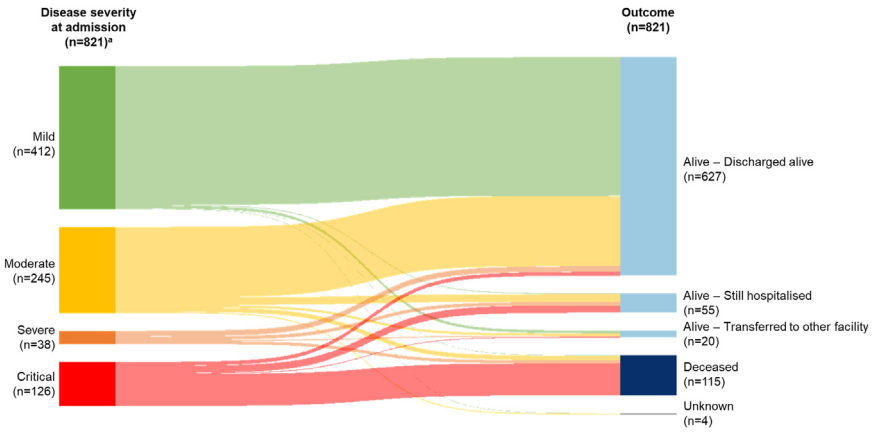


Fig. 5: Patient survival by COVID-19 disease severity at admission. Sankey diagram showing the clinical course from hospital admission to survival on day 28 after admission. Disease severity at admission was based on the WHO Clinical Progression Scale. [a]Disease severity at admission was not known for one participant, who was therefore not included in the Sankey diagram.

for early subvariants (p = 0.004), and 1.3% (1/78) vs 17.7% (3/17) for recent subvariants (p = 0.029) (Fig. 4). The proportion of deaths decreased with each additional vaccine dose: 16.2% (74/456) for 0 doses, 9.1% (4/44) for 1 dose, 8.5% (13/153) for 2 doses and 0.0% (0/62) for 3 doses.

After adjusting for confounders, the increase in risk of death was statistically significant for participants aged ≥60 years for pre–delta (adjusted hazard ratio [aHR] 2.1 [1.0–4.3]; p = 0.038), but not for delta (1.3 [0.62–2.6], p = 0.533) or omicron (1.2 [0.32–4.2], p = 0.813), compared to age <50 years; and for the presence of one or more comorbidities for delta (2.3 [1.1–4.7], p = 0.029), but not for pre–delta (0.66 [0.34–1.3], p = 0.214) or omicron (1.01 [0.21–4.7], p = 0.995). Severe disease on admission was the predominant risk factor of death across all variants (aHR 34.0 [95% CI 16.6–69.9] vs mild–to–moderate disease, p < 0.001; 61.6% vs 2.1%) (Table 3). Mediation analysis revealed that there was evidence of a mediating effect of disease severity on admission on the pathway between variants and death for the comparison between delta and pre–delta (pure indirect effect: 4.44 [2.12–9.33], p < 0.001) and omicron and delta (0.49 [0.42–0.57], p < 0.001). Hence, when controlling for disease severity on admission as an intermediate, omicron was associated with a 48% lower risk of death compared to delta (0.52 [0.40–0.68], p < 0.001) (Supplementary Table S9). Mediation analysis further revealed that there was evidence of a mediating effect of disease severity on admission on the pathway between vaccination and death overall (pure indirect effect: 0.58 [0.50–0.68], p < 0.001) and for omicron (0.49 [0.36–0.68], p < 0.001), but not for pre–delta (0.94 [0.50–1.8], p = 0.850) or delta (not estimable). Hence, when controlling for disease severity on admission as an intermediate, vaccination reduced the risk of death by 51% overall (aHR 0.49 [95% CI 0.39–0.62], p < 0.001), and by 56% (0.44 [0.31–0.63], p < 0.001) for omicron, 46% (0.54 [0.27–1.1], p = 0.070) for pre–delta, and was not estimable for delta (Supplementary Table S9).

Compared with the main models, the additional analyses of non-imputed data (Supplementary Table S10) and individually detected variants (Supplementary Table S11) found similar associations, including high agreement (96.5%) between ecologically imputed and individually detected variants (Cohen's kappa = 0.949). Adding corticosteroid use did not improve the models, nor did it substantially affect the observed associations (Supplementary Table S12). Removing the two dominant hospitals from the main models resulted in similar effect directions for the main associations, supporting the robustness of the main findings (Supplementary Table S13).

Discussion

This longitudinal study in eight hospitals across three provinces in Indonesia extends available evidence from mostly North America and Europe that patients with COVID-19 were hospitalised with less severe and fatal clinical disease over time. Furthermore, infections by omicron variant were independently associated with substantially reduced risk of progression to severe clinical outcomes relative to delta variant.[2,4,6]

We observed a changed case-mix in the patients hospitalised with COVID-19 across the successive VOCs, i.e., more frequent mild-to-moderate disease and vaccination, and a younger age distribution. In the Indonesian context, we surmised that these changes resulted from earlier admission due to better access to diagnostic testing (i.e., shorter time between symptom onset and admission, from median 4 to 2 days), more effective preventive measures shielding the most vulnerable groups,[16] increased levels of population immunity,[17] as well as possible changes in the virulence of SARS-CoV-2 between delta and omicron viral strains.[4,5,18] Additionally, in line with previous reports, Indonesian patients infected with omicron variant experienced loss of smell and taste less commonly and upper respiratory tract symptoms and fatigue more commonly than with pre-delta and delta.[19,20] Nonetheless, despite its decreased severity, omicron's higher transmissibility has caused greater accumulated numbers of infections resulting in more hospitalisations and other serious outcomes in Indonesia and other countries, than previous VOCs, putting substantial pressure on national health systems.[6]

Our prospective study corroborated previous retrospective analyses in Indonesia that estimated crude hospital mortality at 12–15% for the first (pre-delta) pandemic phase,[1,21] and extended these early findings to report on disparate adverse clinical outcomes for the delta and omicron waves. For the severe clinical disease outcome, the age-adjusted percentage of patients varied from 26.8% (22.7–30.9) for pre-delta, up to 50.1% (44.0–56.2) for delta, and down to 15.2% (9.7–20.7) for omicron overall, and 7.2% (0.2–14.1) for the recent BA.4/BA.5/XBB subvariants, and participants admitted with omicron had 64% (18%–84%) lower odds than delta of developing severe disease, after adjusting for known confounders (i.e., age, sex, comorbidities, vaccination, presence of comorbidity). For the mortality outcome, the age-adjusted mortality varied from 11.8% (8.8–14.8) for pre-delta, up to 23.4% (17.8–29.1) for delta, and down to 8.6% (4.2–13.1) for omicron overall, and 7.2% (0.2–14.1) for the recent BA.4/BA.5/XBB subvariants, and disease severity on admission was the predominant risk factor of death across the variants. When controlling for disease severity on admission as a mediator on the pathway between the variants and death, we found that participants admitted with omicron had a 48% (32%–60%) lower risk of death compared to delta. These findings concur with a recent meta-analysis of cohort studies, mostly from high-income countries in North America and Europe.[5] The meta-analysis by Hu

and colleagues described that compared with delta variant, infection by omicron variant resulted in a 39% (24%–50%) lower risk of ICU admission (20.7% vs 12.9%), a 65% (28%–114%) lower risk of receiving invasive mechanical ventilation (10.9% vs 5.8%), and a 44% (22%–71%) lower risk of death (10.7% vs 7.1%).[5]

With regard to the effects of vaccination, we found that participants who had received at least one inactivated vaccine dose had substantially reduced odds of developing severe clinical disease by 89% (65%–97%) for delta and by 98% (91%–100%) for omicron, and by 99.6% (96%–100%) for BA.1/BA.2/BA.3 and by 90% (0%–99%) for BA.4/BA.5/XBB, compared with unvaccinated participants. When controlling for disease severity at hospital admission as a mediator on the pathway between vaccination and death, we found that vaccinated participants had a lower risk of death overall (51% [38%–61%]), and 56% (38%–69%) for omicron, 46% (–5%–73%) for pre-delta, but could not be estimated for delta. For comparison, studies in the US found that two or three mRNA vaccines reduced progression to invasive ventilation or death by 76% (53%–88%) for alpha variant, 44% (32%–54%) for delta, and 46% (12%–67%) for omicron,[22] and that full vaccination (10.3%) or boosting (7.1%) with mRNA or viral vector vaccines reduced in-hospital mortality from omicron, compared with unvaccinated people (12.8%).[23] Notably, in an observational study in Hong Kong, two doses of either mRNA or inactivated vaccine protected against severe disease and death from the omicron BA.2 subvariant, with higher effectiveness among adults aged 60 years or older for BNT162b2 (vaccine effectiveness 89.3% [86.6%–91.6%]) compared with CoronaVac (69.9% [64.4%–74.6%]), and three doses of either vaccine offered very high levels of protection against severe or fatal outcomes (97.9% [97.3%–98.4%]).[24] This latter finding is in line with our limited observation that none of the 60 participants admitted with a breakthrough omicron (mostly BA.5, and few BA.2, XBB, BA.1, BA.4 or unidentified) infection after receiving a heterologous booster with an mRNA or viral vector vaccine developed a severe or fatal outcome. Available evidence supports administering a heterologous booster dose after primary vaccination with CoronaVac to maintain high antibody responses for patient groups at risk of severe disease,[25,26] and is highly relevant for the Indonesian context.

The estimated vaccine effects in our cohort are likely combined time-dynamic effects of vaccination[9] as well as natural immunity induced by SARS-CoV-2 exposure ("hybrid immunity"), although we could not differentiate each component. Consecutive population surveys in Indonesia have indeed shown an increasing prevalence of anti-S1 SARS-CoV2 antibodies, from 44.5% in March 2021, to 86.6% in November 2021, to 99% in January 2023.[17] A previous UK study found that in unvaccinated individuals documented previous SARS-CoV-2 infection offered some protection against hospitalisation and high protection against death, while in vaccinated individuals only offered additional protection against death.[27] Nonetheless, it should be noted that recently emerged omicron subvariants have been increasingly capable of escaping vaccine-elicited immunity,[7,8] with potential for a new wave of infections such as the one driven by XBB in Singapore in September 2022,[28] and that in our cohort CoronaVac-elicited immune responses were likely to have waned over time, especially in older patients.[11,12]

Although for omicron infection the presence of one or more comorbidities was not independently associated with a severe or fatal outcome, we found that older participants aged ≥60 years had a persistently increased risk of severe clinical disease for the successive variants including omicron than those <50 years, which was independent of other risk factors, also after adjusting for the increased uptake of corticosteroids over time, which has been a WHO-recommended treatment since September 2020.[29] This finding suggests that the COVID-19 pathophysiology in older patients may be insufficiently mitigated by current treatment interventions (mostly corticosteroids), warranting access to optimised regimens with interleukin-6 or Janus kinase inhibitors.

This study has some limitations. First, there were numerous structural and human resource-related challenges during the epidemic peaks. This meant that study site teams were not able to consecutively recruit all patients hospitalised with COVID-19 during the whole study period, and that during the pre-delta and delta peaks some patients could not access potentially life-saving invasive ventilation. This analysis reported real-world findings in a convenient, heterogeneous hospital sample and, although the findings were robust in several additional analysis, they may thus not entirely reflect the rates and risk factors of severe and fatal outcomes in Indonesian hospital populations. Second, some factors related to severe of fatal outcomes could not be captured or accounted for, which means that unmeasured confounding could have influenced the effect estimates. We were not able to correlate previous COVID-19 infection and immunity levels at admission with patient outcomes. We cannot rule out possible confounding by vaccine prioritisation of higher-risk (e.g., older and comorbid) groups,[30] and the possibility of collider bias, given that our analyses were restricted to populations requiring hospital admission (i.e., more severe cases) which could have led to overestimating the effect of vaccination.[31] The effects of pre-existing comorbidities could have been underestimated due to possible under-diagnosis and/or under-management in resource-limited settings. There could be heterogeneity between study populations, in terms of differences in quality of health care services, patient health seeking behaviour and background health risks. Third, the main analyses combined omicron and its subvariants since

low numbers limited statistical power to differentiate any subvariant effects. Fourth, because of the observational design of the study, the associations found do not necessarily demonstrate causality.

In conclusion, SARS-CoV-2 omicron infection in hospitalised patients in Indonesia resulted in less severe and fatal outcomes than delta infection. Nonetheless, the omicron variant still caused substantial public health and patient burdens, with older and unvaccinated individuals remaining at higher risk of adverse outcomes. Emerging variants or subvariants need to be rapidly assessed for their associated risk of hospitalisation and severe or fatal outcomes, to inform vaccine booster strategies and treatment protocols.

Contributors

AK, APP, S, DSa, JKB, AHS and RLH were the principal investigators, and conceptualised the study. AHS, JKB and RLH obtained the funding. AK, APP, VI, DUN, RS, S, MJN, F, MRL, EK, M, HA, HH, PADP, B, YDC, CB, DSa, KL, HIM, SZ, MR, FAD, FW, and DSu established the cohort, and supervised data collection. S, SZ, FAD and NN contributed to data verification. GL and RLH designed the analysis, GL performed the statistical analysis and data visualisations, with critical input from HS, AHS and RLH. AP, APS and MAK conducted and supervised the SARS-CoV-2 whole genome sequencing. GL and RLH drafted the manuscript, with critical input from AK, APP, S, RS, HS, JKB, AHS. GL and RLH had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors critically revised the manuscript for important intellectual content and all authors gave final approval for this version to be published.

Data sharing statement

After publication, the datasets used for this study will be made available to others on reasonable request to the corresponding author. Deidentified participant data will be provided after written approval from the principal investigators.

Editor note

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Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lansea.2023.100348.

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