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Original Article

Real-world effectiveness of full and booster mRNA vaccination for coronavirus disease 2019 against disease severity during the delta- and omicron-dominant phases: A propensity score-matched cohort study using the nationwide registry data in Japan

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Abstract *Background:* To date, few studies from the Asian region have reported the effectiveness of messenger ribonucleic acid coronavirus disease 2019 (COVID-19) vaccines against disease progression and death after hospitalization.
Methods: We evaluated the data from the COVID-19 registry in Japan during the delta- and omicron-dominant phases. A propensity score-matched cohort study was conducted between the incompletely (0—1 dose) and fully (2 doses) vaccinated groups during the delta-dominant phase and among the incompletely, fully, and booster (3 doses) vaccinated groups during the omicron-dominant phase.

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Results: In the delta-dominant phase, 411 pairs were matched. The fully vaccinated group showed a significantly lower oxygen supplementation rate (24.1 % vs. 41.1 %, $p < 0.001$) but little difference in the mortality rate (2.2 % vs. 2.9 %, $p = 0.66$). In the omicron-dominant phase, 1494 pairs from the incompletely and fully vaccinated groups, and 425 pairs from the fully and booster vaccinated groups were matched. Full vaccination reduced both the oxygen supplementation rate (18.6 % vs 25.7 %, $p < 0.001$) and mortality rate (0.7 % vs 2.3 %, $p < 0.001$). Booster vaccination showed little difference in either the rate of oxygen supplementation (21.2 % vs. 24.7 %, $p = 0.25$) or mortality (1.2 % vs. 2.6 %, $p = 0.21$) compared with full vaccination.

Conclusions: Full vaccination reduced disease severity during the delta- and omicron-dominant phases; booster vaccination did not further enhance the protective effects against disease progression during the omicron-dominant phase compared to full vaccination. Future vaccine strategies and policy decisions should consider preventing infection or disease progression in the target population, as well as the characteristics of the dominant variant in that phase.

Introduction

Several years have passed since the coronavirus disease (COVID-19) pandemic, caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), was declared. To date, SARS-CoV-2 has undergone repeated mutations, and different variants have been identified in each pandemic phase. The delta variant has a higher virulence,[1] while the omicron variant is more contagious.[2] Patients infected with the omicron variant were prone to being asymptomatic or having mild disease.[3] In addition to the differences in severity and infectivity, mutations can affect the efficacy of some treatments.[4—6] Hence, the existing messenger ribonucleic acid (mRNA) vaccines proved to be less effective against omicron variants.[7]

The mRNA COVID-19 vaccine[8,9] has substantially contributed to the control of infection during this global pandemic. Its real-world effectiveness has been reported in several countries.[10] However, recent studies mainly focused on investigating the mRNA COVID-19 vaccine's effectiveness in preventing infection. Few studies have reported the effectiveness of preventing COVID-19 progression and death after hospitalization, especially in Asia. As the vaccine effectiveness (VE) is affected by population characteristics and healthcare systems, it should be assessed using real-world data from each country, and subsequent vaccinations should be considered. Many studies investigating the VE have been published in Japan; however, these studies mostly elucidated the COVID-19 vaccine's effectiveness in preventing infections[11—15] and only provided limited data on its effectiveness against hospitalization, progression to severe illness, and death.[16—18] Therefore, the VE in preventing disease severity and death should be assessed to develop more effective vaccination strategies and establish appropriate policies in the future. Thus, we aimed to evaluate the effectiveness of the COVID-19 vaccine in preventing disease severity and death after hospitalization using nationwide registry data from Japan.

Methods

Design and setting

A retrospective cohort study with propensity score matching was conducted using the data from the COVIREGI-JP, a nationwide Japanese registry of hospitalized patients with COVID-19. As of September 1, 2022, 783 hospitals participated in this registry. An overview of this registry has been reported in a previous study.[19] Each hospital registered the patients' background, treatment, clinical course, and other relevant information during hospitalization. The study was completely anonymized at the time of data entry; therefore, the requirement for informed consent was waived. This study was reviewed and approved by the Institutional Review Board of the National Center for Global Health and Medicine (approval number: NCGM-G-003494-0).

In Japan, the policy during the delta-dominant phase was to hospitalize all patients in principle, partly for the purpose of patient isolation. In reality, due to the rapid increase in the number of patients, it was impossible to hospitalize all of them, and those with severe condition or risk factors were prioritized. Notwithstanding, there was a heavy burden on medical facilities, and many patients had to be treated at home due to a shortage of medical capacity. During the Omicron outbreak, the policy of hospitalizing all patients was revised, and only those who needed to be hospitalized were admitted. Notably, due to differences in the virulence of the variants, there were fewer patients with severe conditions during the omicron-dominant phase. On the other hand, many elderly patients requiring nursing care and patients with multiple comorbidities needed to be hospitalized.

Data collection and handling

The data was extracted on September 1, 2022. The data collection began on July 1, 2021, when vaccination status

registration was started. The vaccination status included the total number of vaccinations, date of vaccination, and type of vaccine. Patients for whom the year and month of vaccination were recorded, but not the exact date, were assumed to have been vaccinated on the first day of the subsequent month. This leads to the most conservative estimates concerning the effectiveness of vaccination. Patients were excluded if they received non-mRNA vaccines, had unregistered vaccination status, only had the vaccination year recorded, or lacked essential data for analysis. We assumed that an mRNA vaccine was used when the patients received vaccinations; however, the type of vaccine used was not identified. More than 99 % of vaccinated individuals in Japan received the mRNA vaccines.[20] Through August 2022, for the first two doses of mRNA vaccines administered, 84.2 % and 15.8 % were BNT162b2 [Pfizer/BioNTech] and mRNA-1273 [Moderna], respectively.

Based on the COVID-19 genomic surveillance data in Japan,[21] we defined the period from July 1, 2021, to December 31, 2021, as the delta-dominant phase and the period from January 1, 2022, to August 31, 2022, as the omicron-dominant phase. As of June 2021, alpha and delta variants represented 88.3 % and 10.2 % of cases in Japan, respectively. By July 2021, delta variants rose to 62.3 % and subsequently stayed above 95 %. In December, delta and omicron constituted 52.0 % and 48.0 % of cases, respectively. From January 2022, omicron variants comprised 96.0 % and remained above 99 % until August 2022. Patients with 0 or 1-dose vaccination, or less than 14 days from their second dose to onset, were categorized as incompletely vaccinated. Those with 14 or more days post-second dose, or less than 14 days post-third dose to onset, were deemed fully vaccinated. Individuals with 14 or more days post-third dose to onset were classified as booster vaccinated. All vaccines were monovalent against the original strains. We used propensity score matching to create cohort A, which can be used to compare the symptoms and severity upon admission, and cohort B, which can be used to compare the outcomes after admission. In the delta-dominant phase, patients in the incompletely and fully vaccinated groups were matched to create the delta cohorts A and B. In the omicron-dominant phase, patients in the incompletely and fully vaccinated groups were matched to create the omicron cohorts 1A and 1B, whereas those in the fully and booster vaccinated groups were matched to create the omicron cohorts 2A and 2B.

Statistical analysis

Categorical variables were expressed as numbers (percentages), while continuous variables were expressed as the median [interquartile range]. The chi-square test or Fisher's exact test for binary categorical variables and the Mann−Whitney U test for continuous variables were used to compare the two groups. Propensity score matching was performed using a multivariate logistic regression model, with the number of vaccinations assigned as the objective variable. In cohort A, the explanatory variables were age ($<$60 years in the delta cohort and $<$65 years in the omicron cohort), sex, body mass index (BMI) ($<$30), activities of daily living (ADL) (defined as impaired ADL unless walking ability, self-care ability, and type of meal was all intact), cardiovascular disease, cerebrovascular disease, dementia, chronic respiratory disease, liver disease, hypertension, hyperlipidemia, diabetes, renal dysfunction/dialysis, tumor, leukemia/lymphoma, and human immunodeficiency virus infection. For cohort B, a severe condition (if oxygen supplementation was required or radiological findings of pneumonia were noted) upon admission was also included as an explanatory variable. Furthermore, in omicron cohort 2A and 2B, days from last vaccination to onset were also used as the explanatory variables. Each cohort was matched on a 1:1 ratio using the nearest-neighbor matching method. The caliper width was set to 0.15, and a standardized difference of $\geq$0.1 indicated a meaningful imbalance. For cohort A, the primary outcome was severe condition upon admission, while the secondary outcome was symptoms (fever, cough, headache, etc.) upon admission. For cohort B, the primary outcome was mortality during COVID-19 hospitalization, while the secondary outcome was oxygen supplementation rate during COVID-19 hospitalization. The odds ratios (ORs) for each of the cohort B outcomes were calculated. The VE in the delta and omicron cohorts 1 was calculated as follows:

$$\mathrm{VE} = 1 - \frac{\text{Mortality (or oxygen supplementation rate) in the fully vaccinated group}}{\text{Mortality (or oxygen supplementation rate) in the incompletely vaccinated group}}$$

Meanwhile, the VE in the omicron cohort 2 was calculated as follows:

$$\mathrm{VE} = 1 - \frac{\text{Mortality (or oxygen supplementation rate) in the booster vaccinated group}}{\text{Mortality (or oxygen supplementation rate) in the fully vaccinated group}}$$

The statistical tests were two-tailed, with the p value of <0.05 considered as significant. All analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria), and the Mactchit function from the MatchIt package was used for propensity score matching.

Results

Overall

A total of 22,780 patients were enrolled, of whom 7129 were assigned to the delta-dominant phase and 6608 to the omicron-dominant phase; those missing data required for analysis were excluded. Propensity score matching was then performed. Fig. 1 shows a flowchart of the patient selection process.

Delta cohort A and B (incompletely vs. fully vaccinated)

Table 1 presents the characteristics of the delta cohorts A and B. In both cohorts, 411 pairs were matched. The standardized difference between the factors for matching was ± 0.1 in both cohorts (Supplemental Figs. 1 and 2). Compared to the incompletely vaccinated group, the fully vaccinated group was older, but no significant differences were found in sex, BMI, past COVID-19 history, ADL, or comorbidities between the two groups. In delta cohort B, no significant difference was found in the severity of the condition upon admission.

Table 2 shows the symptoms and conditions upon admission in the delta cohort A. Significantly fewer patients in the fully vaccinated group had a fever (≥ 37.5 °C) upon admission and in a severe condition upon admission.

Table 3 shows the mortality and oxygen supplementation in the delta cohort B. No significant difference was observed in the mortality between the incompletely and fully vaccinated groups. The oxygen supplementation rate was significantly lower in the fully vaccinated group.

Omicron cohort 1 (incompletely vs. fully vaccinated)

Table 4 shows the characteristics of the omicron cohorts 1A (1582 pairs) and 1B (1494 pairs). The standardized difference between the factors for matching was ± 0.1 in both cohorts (Supplemental Figs. 3 and 4). The fully vaccinated group was older and had higher BMI scores than did the incompletely vaccinated group, but no significant differences were observed in the past COVID-19 history, ADL, and comorbidities. In cohort 1B, no significant difference was observed in the incidence of severity upon admission; however, a higher proportion of incompletely vaccinated patients required oxygen therapy.

Table 5 shows the symptoms and conditions upon admission in omicron cohort 1A. On admission, significantly fewer patients in the fully vaccinated group had a fever (≥ 37.5 °C) and in a severe condition upon admission.

Table 6 shows the mortality and oxygen supplementation rates in the omicron cohort 1B. The mortality and oxygen supplementation rate were significantly lower in the fully vaccinated group than in the incompletely vaccinated group.

Omicron cohort 2 (fully vs. booster vaccinated)

Table 7 presents the characteristics of the omicron cohorts 2A and 2B. In both cohorts, 425 pairs were matched. The standardized difference between the factors for matching was ± 0.1 (Supplemental Figs. 5 and 6). The booster vaccinated group was older than the fully vaccinated group, but

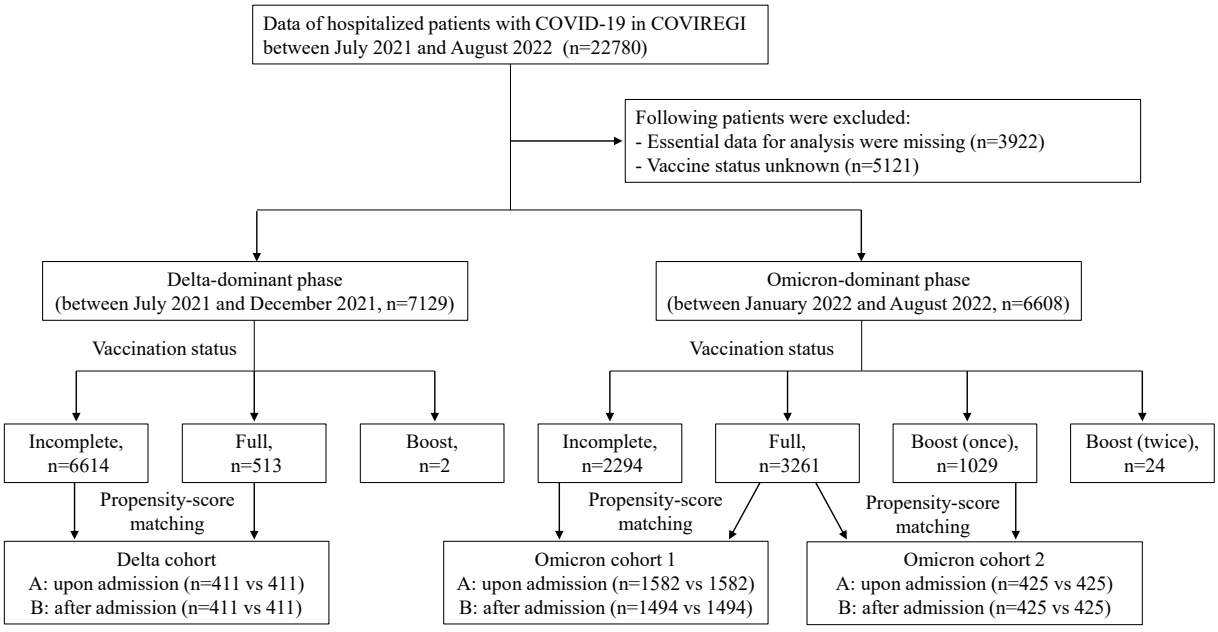

Figure 1. Study flowchart.

Table 1 Characteristics of patients in delta cohort A and B.

	Pre-matched			Delta cohort A: upon admission			Delta cohort B: after admission		
	Incomplete	Full	p value	Incomplete	Full	p value	Incomplete	Full	p value
Number of patients	6614	513		411	411		411	411	
Sex									
Male	4012 (60.7)	276 (53.8)	0.003	222 (54)	224 (54.5)	0.95	227 (55.2)	225 (54.7)	0.95
Female	2602 (39.3)	237 (46.2)		189 (46)	187 (45.5)		184 (44.8)	186 (45.3)	
Age (years old)	47 [32, 57]	72 [55, 82]	<0.001	63 [52, 74]	69 [50.5, 80]	0.003	63 [51, 73]	69 [50.5, 80]	<0.001
BMI (kg/m^2)	23.8 [20.9, 27.3]	22.9 [20.2, 26.0]	<0.001	23.6 [21.0, 26.6]	23.1 [20.5, 26.4]	0.23	23.4 [20.7, 26.3]	23.2 [20.5, 26.4]	0.76
Onset to admission (days)	4 [2, 7]	2 [0, 4]	<0.001	5 [2, 7]	2 [1, 4]	<0.001	4 [2, 6]	2 [1, 4]	<0.001
Last vaccination to onset (days)	8 [3, 19]	64 [37, 107]	<0.001	12 [4, 30]	63 [37, 107]	<0.001	15 [6, 38]	62 [37, 107]	<0.001
Past COVID-19 history	31 (0.5)	7 (1.4)	0.017	2 (0.5)	5 (1.2)	0.451	3 (0.7)	6 (1.5)	0.505
Impaired ADL	379 (5.8)	126 (25)	<0.001	59 (14.4)	63 (15.3)	0.78	53 (12.9)	63 (15.3)	0.38
Cardiovascular disease	142 (2.1)	45 (8.8)	<0.001	31 (7.5)	30 (7.3)	1	29 (7.1)	30 (7.3)	1
Cerebrovascular disease	195 (2.9)	51 (9.9)	<0.001	27 (6.6)	30 (7.3)	0.79	23 (5.6)	29 (7.1)	0.49
Dementia	106 (1.6)	76 (14.8)	<0.001	35 (8.5)	37 (9.0)	0.91	33 (8.0)	37 (9.0)	0.71
Chronic respiratory disease	128 (1.9)	30 (5.8)	<0.001	16 (3.9)	22 (5.4)	0.40	21 (5.1)	21 (5.1)	1
Liver disease	252 (3.8)	15 (2.9)	0.34	10 (2.4)	11 (2.7)	1	10 (2.4)	11 (2.7)	1
Hypertension	1310 (19.8)	234 (45.6)	<0.001	182 (44.3)	176 (42.8)	0.72	185 (45.0)	177 (43.1)	0.62
Hyperlipidemia	700 (10.6)	97 (18.9)	<0.001	88 (21.4)	79 (19.2)	0.47	87 (21.2)	79 (19.2)	0.56
Diabetes	869 (13.1)	102 (19.9)	<0.001	87 (21.2)	85 (20.7)	0.93	92 (22.4)	86 (20.9)	0.67
Renal dysfunction/ Dialysis	83 (1.3)	22 (4.3)	<0.001	14 (3.4)	14 (3.4)	1	14 (3.4)	14 (3.4)	1
Tumor	163 (2.5)	41 (8.0)	<0.001	29 (7.1)	31 (7.5)	0.90	29 (7.1)	30 (7.3)	1
Leukemia/ Lymphoma	36 (0.5)	8 (1.6)	0.014	7 (1.7)	6 (1.5)	1	6 (1.5)	7 (1.7)	1
HIV	10 (0.2)	2 (0.4)	0.21	0 (0)	1 (0.2)	1	1 (0.2)	2 (0.5)	1
Oxygen on admission	1306 (19.8)	73 (14.3)	0.002		See Table 2		50 (12.2)	41 (10.0)	0.40
Severe condition on admission	2600 (39.3)	143 (27.9)	<0.001				93 (22.6)	96 (23.4)	0.87

Normal brackets indicate percentage, and square brackets indicate interquartile range. "Incomplete" includes those who received 0–1 dose vaccination. "Full" includes those who received 2 dose vaccinations. "Severe condition" defines that patient need oxygen supplementation or has radiological findings of pneumonia.
Abbreviations: BMI; body mass index, COVID-19; coronavirus disease 2019, ADL; activity of daily living, HIV; human immunodeficiency virus.

there were no significant difference in sex, BMI, past COVID-19 history, ADL, and comorbidities between groups. In cohort 2B, no significant differences were observed in the number of days between the last vaccination and the disease onset. Moreover, no significant difference was found in the condition severity upon admission.

Table 8 shows the symptoms and conditions upon admission of the omicron cohort 2A. No significant difference was found in the number of patients with a fever (≥37.5 °C) and in a severe condition upon admission.

Table 9 shows the mortality and oxygen supplementation rates of the omicron cohort 2B. No significant difference between the fully and booster vaccinated groups was found in the mortality rate and oxygen supplementation rate.

Discussion

This propensity score-matched cohort study aimed to evaluate the effectiveness of mRNA vaccines in patients hospitalized due to COVID-19 in Japan. During the delta-dominant phase, full vaccination improved the fever, illness severity upon admission, and oxygen supplementation rate during hospitalization for COVID-19 but did not improve the

Table 2 Symptoms and conditions upon admission in delta cohort A.

	Incomplete	Full	p value
Fever (37.5 C°or more)	188 (45.9)	121 (29.4)	<0.001
Cough	268 (65.2)	217 (52.8)	<0.001
Sore throat	78 (19.0)	94 (22.9)	0.004
Runny nose	32 (7.8)	71 (17.3)	<0.001
Shortness of breath	159 (38.7)	49 (11.9)	<0.001
Arthralgia/Myalgia	47 (11.4)	27 (6.6)	0.003
Headache	67 (16.3)	45 (10.9)	<0.001
Fatigue	167 (40.6)	105 (25.5)	<0.001
Dysgeusia	61 (14.8)	27 (6.6)	<0.001
Olfactory dysfunction	55 (13.4)	34 (8.3)	0.029
Oxygen on admission	128 (31.2)	40 (9.7)	<0.001
Severe condition on admission	211 (51.3)	94 (22.9)	<0.001

Brackets indicate percentage. "Incomplete" includes those who received 0—1 dose vaccination. "Full" includes those who received 2 dose vaccinations.

mortality rate. During the omicron-dominant phase, full vaccination improved all of these indicators. However, these indicators were less improved in patients who received a booster vaccination compared with those who were fully vaccinated. Most previous studies focused on investigating the effectiveness of COVID-19 vaccines at solely preventing the infection, while this study focused on determining the effectiveness of these vaccines at reducing severity during admission and hospitalization due to COVID-19. Our study provides unique and valuable information for clinicians to estimate the likelihood of subsequent disease progression among COVID-19 patients depending on their vaccination status.

Full vaccination suppressed the fever (37.5 °C) both in the delta- and omicron-dominant phases and reduced condition severity upon admission, compared with incomplete vaccination. A previous observational study[18] using Japanese epidemiological data showed that full vaccination reduced the hospitalization rates both in the delta- and omicron-dominant phases. Our study showed that full vaccination additionally reduces the incidence of high severity and fever, stabilizing the patient's condition even when an exacerbation leads to hospitalization.

In the fully vaccinated group, no significant difference was observed in the mortality rate among hospitalized COVID-19 patients during the delta-dominant phase, but a significant improvement was observed in the mortality rate during the omicron-dominant phase. A previous test-negative case—control study conducted in the United States[7] showed that patients who received two or more mRNA vaccinations showed reduction in the rate of in-hospital progression of COVID-19 caused by delta variants. The discordance between our results and those of previous studies may have been influenced by the study designs. Once a patient is infected with virulent variants, such as delta, it is difficult to prevent progressions in severity after hospitalization by vaccine alone. However, many previous studies in Japan have reported the effectiveness of full vaccination in preventing infection[11,13,17] and avoiding hospitalization[18] during the delta-dominant phase. Our results suggest the necessity of promoting additional non-vaccine measures, such as early diagnosis and antiviral treatment, along with the implementation of universal vaccination to prevent disease progression after admission.

During the omicron-dominant phase, full vaccination improved not only the oxygen supplementation rate after hospitalization but also the mortality rate. During the delta-dominant phase, the mortality rate did not differ significantly. The median age of the omicron cohort 1 was 42—49 years, which was younger than that of our delta cohort. Our study results should not be used to compare the superiority of VE against the delta and omicron variants as we established different cohorts. Previous studies in Japan have shown that the VE is generally lower during the omicron-dominant phase than during the delta-dominant phase.[12,17] However, considering the large number of people infected in the omicron-dominant phase, the overall number of people who can benefit from the vaccine will significantly increase if full vaccination can reduce infection and prevent disease progression.

Booster vaccination during the omicron-dominant phase did not improve the incidence of fever and severe illness upon admission compared with full vaccination. It did not reduce either the oxygen supplementation or mortality rate during hospitalization. Our results do not deny the importance of booster vaccinations, as previous studies conducted during the omicron-dominant phase in Japan have shown that booster vaccination is effective in reducing infections[22] and hospitalization risk.[18] Because the omicron variants are somewhat unlikely to cause disease progression,[3] low severity and mortality may influence the effectiveness of booster vaccinations in our study. Moreover, the

Table 3 Vaccine effectiveness for death and oxygen supplementation in delta cohort B.

	Incomplete	Full	p value	Odds ratio [95%CI]	VE
Pre-matched population					
Death	140 (2.1)	17 (3.3)	0.084	1.58 [0.89—2.66]	−0.57
Oxygen supplementation	2693 (40.7)	152 (29.6)	<0.001	0.61 [0.50—0.75]	0.27
Matched cohort					
Death	12 (2.9)	9 (2.2)	0.66	0.75 [0.27—1.95]	0.25
Oxygen supplementation	169 (41.1)	99 (24.1)	<0.001	0.46 [0.33—0.62]	0.41

Normal brackets indicate percentage, and square brackets indicate 95 % confidential intervals. "Incomplete" includes those who received 0—1 dose vaccination. "Full" includes those who received 2 dose vaccinations. VE is calculated by 1-(mortality or oxygen supplementation rate in the fully vaccinated group)/(mortality or oxygen supplementation rate in the incompletely vaccinated group). Abbreviations: CI; confidential intervals, VE; vaccine effectiveness.

Table 4 Characteristics of patients in omicron cohort 1A and 1B.

	Pre-matched			Omicron cohort 1A: upon admission			Omicron cohort 1B: after admission		
	Incomplete	Full	p value	Incomplete	Full	p value	Incomplete	Full	p value
Number of patients	2294	3261		1582	1582		1494	1494	
Sex									
Male	1226 (53.4)	1719 (52.7)	0.60	869 (54.9)	792 (50.1)	0.007	805 (53.9)	766 (51.3)	0.17
Female	1068 (46.6)	1542 (47.3)		713 (45.1)	790 (49.9)		689 (46.1)	728 (48.7)	
Age (years old)	38 [10, 71]	70 [45, 81]	<0.001	42 [21, 70]	48 [31, 72]	<0.001	44 [24, 71]	49 [31, 72]	<0.001
BMI (kg/m^2)	21.2 [17.7, 25.0]	22.8 [20.3, 25.9]	<0.001	21.7 [18.4, 25.4]	22.8 [20.3, 25.9]	<0.001	21.9 [18.8, 25.5]	22.9 [20.3, 26.0]	<0.001
Onset to admission (days)	2 [1, 4]	2 [1, 4]	0.751	2 [1, 4]	2 [1, 4]	0.145	2 [1, 4]	2 [1, 4]	0.059
Last vaccination to onset (days)	153.5 [28.8, 221]	184 [139, 214]	<0.001	136 [24, 221]	159 [118, 201]	0.009	151 [26, 218]	161 [118, 201]	0.024
Past COVID-19 history	34 (1.5)	34 (1.0)	0.172	26 (1.6)	18 (1.1)	0.288	27 (1.8)	18 (1.2)	0.229
Impaired ADL	474 (22.5)	875 (27.1)	<0.001	220 (13.9)	217 (13.7)	0.92	238 (15.9)	205 (13.7)	0.10
Cardiovascular disease	141 (6.1)	282 (8.6)	0.001	97 (6.1)	89 (5.6)	0.58	98 (6.6)	82 (5.5)	0.25
Cerebrovascular disease	167 (7.3)	385 (11.8)	<0.001	113 (7.1)	110 (7.0)	0.89	118 (7.9)	110 (7.4)	0.63
Dementia	156 (6.8)	442 (13.6)	<0.001	72 (4.6)	77 (4.9)	0.72	72 (4.8)	74 (5.0)	0.93
Chronic Respiratory Disease	81 (3.5)	230 (7.1)	<0.001	56 (3.5)	57 (3.6)	1	56 (3.7)	49 (3.3)	0.56
Liver disease	70 (3.1)	117 (3.6)	0.30	52 (3.3)	54 (3.4)	0.92	52 (3.5)	45 (3.0)	0.53
Hypertension	449 (19.6)	1361 (41.7)	<0.001	338 (21.4)	322 (20.4)	0.51	338 (22.6)	327 (21.9)	0.67
Hyperlipidemia	188 (8.2)	602 (18.5)	<0.001	152 (9.6)	148 (9.4)	0.85	151 (10.1)	144 (9.6)	0.73
Diabetes	269 (11.7)	688 (21.1)	<0.001	211 (13.3)	233 (14.7)	0.27	208 (13.9)	201 (13.5)	0.74
Renal dysfunction/ Dialysis	72 (3.1)	180 (5.5)	<0.001	57 (3.6)	45 (2.8)	0.26	56 (3.7)	52 (3.5)	0.78
Tumor	113 (4.9)	306 (9.4)	<0.001	90 (5.7)	91 (5.8)	1	88 (5.9)	94 (6.3)	0.70
Leukemia/ Lymphoma	54 (2.4)	100 (3.1)	0.12	46 (2.9)	56 (3.5)	0.38	46 (3.1)	40 (2.7)	0.58
HIV	6 (0.3)	11 (0.3)	0.63	6 (0.4)	7 (0.4)	1	6 (0.4)	2 (0.1)	0.29
Oxygen on admission	319 (14.0)	471 (15.0)	0.60		See Table 5		190 (12.8)	145 (9.7)	0.009
Severe condition on admission	927 (40.4)	975 (29.9)	<0.001				408 (27.3)	381 (25.5)	0.27

Normal brackets indicate percentage, and square brackets indicate interquartile range. "Incomplete" includes those who received 0—1 dose vaccination. "Full" includes those who received 2 dose vaccinations. "Severe condition" defines that patient need oxygen supplementation or has radiological findings of pneumonia.
Abbreviations: BMI; body mass index, COVID-19; coronavirus disease 2019, ADL; activity of daily living, HIV; human immunodeficiency virus.

Table 5 Symptoms and conditions upon admission in omicron cohort 1A.

	Incomplete	Full	p value
Fever (37.5C°or more)	790 (50.0)	564 (35.7)	<0.001
Cough	902 (57.0)	997 (63.0)	<0.001
Sore throat	523 (33.1)	744 (47.0)	<0.001
Runny nose	213 (13.5)	334 (21.1)	<0.001
Shortness of breath	344 (21.8)	238 (15.0)	<0.001
Arthralgia/Myalgia	191 (12.1)	193 (12.2)	0.40
Headache	306 (19.3)	344 (21.7)	0.013
Fatigue	595 (37.6)	551 (34.8)	0.076
Dysgeusia	68 (4.3)	57 (3.6)	0.051
Olfactory dysfunction	48 (3.0)	47 (3.0)	0.071
Oxygen on admission	215 (13.7)	132 (8.4)	<0.001
Severe condition on admission	559 (35.3)	326 (20.6)	<0.001

Brackets indicate percentage. "Incomplete" includes those who received 0—1 dose vaccination. "Full" includes those who received 2 dose vaccinations. "Severe condition" defines that patient need oxygen supplementation or has radiological findings of pneumonia.

Table 6 Vaccine effectiveness for death and oxygen supplementation in omicron cohort 1B.

	Incomplete	Full	p value	Odds ratio [95%CI]	VE
Overall population					
Death	67 (2.9)	101 (3.1)	0.75	1.06 [0.77—1.48]	−0.06
Oxygen supplementation	601 (26.2)	893 (27.4)	0.34	1.06 [0.94—1.20]	−0.05
Matched cohort					
Death	35 (2.3)	10 (0.7)	<0.001	0.28 [0.14—0.57]	0.71
Oxygen supplementation	384 (25.7)	278 (18.6)	<0.001	0.66 [0.56—0.79]	0.28

Normal brackets indicate percentage, and square brackets indicate 95 % confidential intervals. "Incomplete" includes those who received 0—1 dose vaccination. "Full" includes those who received 2 dose vaccinations. VE is calculated by 1-(mortality or oxygen supplementation rate in the fully vaccinated group)/(mortality or oxygen supplementation rate in the incompletely vaccinated group).
Abbreviations: CI; confidential intervals, VE; vaccine effectiveness.

Table 7 Characteristics of patients in omicron cohort 2A and 2B.

	Pre-matched			Omicron cohort 2A: upon admission			Omicron cohort 2B: after admission		
	Full	Boost	p value	Full	Boost	p value	Full	Boost	p value
Number of patients	3261	1029		425	425		425	425	
Sex									
Male	1719 (52.7)	486 (47.2)	0.004	214 (50.4)	209 (49.2)	0.77	201 (47.3)	214 (50.4)	0.41
Female	1542 (47.3)	543 (52.8)		211 (49.6)	216 (50.8)		224 (52.7)	211 (49.6)	
Age (years old)	70 [45, 81]	79 [68, 88]	<0.001	67 [33, 78]	71 [51, 82]	<0.001	68 [33, 79]	71 [50, 82]	<0.001
BMI (kg/m^2)	22.8 [20.3, 25.9]	22 [19.4, 24.5]	<0.001	22.9 [20.3, 25.8]	22.6 [19.9, 25.1]	0.18	22.8 [20.2, 25.8]	22.6 [20.0, 25.1]	0.44
Onset to admission (days)	2 [1, 4]	1 [0, 3]	<0.001	2 [1, 4]	1 [0, 3]	<0.001	2 [1, 3]	1 [0, 3]	<0.001
Last vaccination to onset (days)	184 [139, 214]	89 [46, 133.2]	<0.001	117 [68, 160]	122 [82, 152]	0.91	117 [71, 159]	120 [82, 150]	0.93
Past COVID-19 history	34 (1.0)	12 (1.2)	0.729	6 (1.4)	4 (0.9)	0.752	6 (1.4)	3 (0.7)	0.505
Impaired ADL	875 (27.1)	437 (42.9)	<0.001	94 (22.1)	106 (24.9)	0.38	100 (23.5)	110 (25.9)	0.47
Cardiovascular disease	282 (8.6)	103 (10.0)	0.19	38 (8.9)	35 (8.2)	0.81	38 (8.9)	35 (8.2)	0.82
Cerebrovascular disease	385 (11.8)	187 (18.2)	<0.001	46 (10.8)	44 (10.4)	0.92	43 (10.1)	47 (11.1)	0.72
Dementia	442 (13.6)	248 (24.1)	<0.001	48 (11.3)	56 (13.2)	0.47	46 (10.8)	54 (12.7)	0.45
Chronic Respiratory Disease	230 (7.1)	92 (8.9)	0.057	34 (8.0)	28 (6.6)	0.52	38 (8.9)	33 (7.8)	0.63
Liver Disease	117 (3.6)	33 (3.2)	0.63	9 (2.1)	13 (3.1)	0.52	12 (2.8)	15 (3.5)	0.70
Hypertension	1361 (41.7)	527 (51.2)	<0.001	173 (40.7)	188 (44.2)	0.32	178 (41.9)	195 (45.9)	0.26
Hyperlipidemia	602 (18.5)	198 (19.2)	0.58	71 (16.7)	72 (16.9)	1	73 (17.2)	78 (18.4)	0.73
Diabetes	688 (21.1)	231 (22.4)	0.37	72 (16.9)	79 (18.6)	0.60	82 (19.3)	81 (19.1)	1
Renal dysfunction/ dialysis	180 (5.5)	67 (6.5)	0.24	35 (8.2)	35 (8.2)	1	36 (8.5)	33 (7.8)	0.79
Tumor	306 (9.4)	127 (12.3)	0.006	39 (9.2)	48 (11.3)	0.35	39 (9.2)	43 (10.1)	0.73
Leukemia/ lymphoma	100 (3.1)	46 (4.5)	0.043	25 (5.9)	24 (5.6)	1	24 (5.6)	20 (4.7)	0.65
HIV	11 (0.3)	6 (0.6)	0.39	3 (0.7)	4 (0.9)	1	1 (0.2)	4 (0.9)	0.37
Oxygen on admission	471 (14.5)	168 (16.3)	0.20		See Table 8		48 (11.3)	45 (10.6)	0.80
Severe condition on admission	975 (29.9)	358 (34.8)	0.001				110 (25.9)	122 (28.7)	0.40

Normal brackets indicate percentage, and square brackets indicate interquartile range. "Full" includes those who received 2 dose vaccinations. "Boost" includes those who received 3 dose vaccinations. "Severe condition" defines that patient need oxygen supplementation or has radiological findings of pneumonia.
Abbreviations: BMI; body mass index, COVID-19; coronavirus disease 2019, ADL; activity of daily living, HIV; human immunodeficiency virus.

Table 8 Symptoms and conditions upon admission in omicron cohort 2A.

	Full	Boost	p value
Fever (37.5 C°or more)	144 (34.0)	163 (38.4)	0.21
Cough	260 (61.2)	274 (64.5)	0.41
Sore throat	186 (43.8)	155 (36.5)	0.097
Runny nose	75 (17.6)	65 (15.3)	0.61
Shortness of breath	72 (16.9)	65 (15.3)	0.20
Arthralgia/Myalgia	38 (8.9)	28 (6.6)	0.11
Headache	76 (17.9)	53 (12.5)	0.008
Fatigue	124 (29.2)	122 (28.7)	0.071
Dysgeusia	10 (2.4)	10 (2.4)	0.061
Olfactory dysfunction	7 (1.6)	5 (1.2)	0.075
Oxygen on admission	53 (12.5)	44 (10.4)	0.40
Severe condition on admission	114 (26.8)	121 (28.5)	0.65

Brackets indicate percentage. "Full" includes those who received 2 dose vaccinations. "Boost" includes those who received 3 dose vaccination. "Severe condition" defines that patient need oxygen supplementation or has radiological findings of pneumonia.

Table 9 Vaccine effectiveness for death and oxygen supplementation in omicron cohort 2B.

	Full	Boost	p value	Odds ratio [95%CI]	VE
Overall population					
Death	101 (3.1)	21 (2.0)	0.085	0.65 [0.39−1.06]	0.34
Oxygen supplementation	893 (27.4)	303 (29.4)	0.20	1.11 [0.95−1.30]	−0.08
Matched cohort					
Death	11 (2.6)	5 (1.2)	0.21	0.45 [0.12−1.42]	0.55
Oxygen supplementation	105 (24.7)	90 (21.2)	0.25	0.82 [0.59−1.14]	0.14

Normal brackets indicate percentage, and square brackets indicate 95 % confidential intervals. "Full" includes those who received 2 dose vaccination. "Boost" includes those who received 3 dose vaccinations. VE is calculated by 1-(mortality or oxygen supplementation rate in the booster vaccinated group)/(mortality or oxygen supplementation rate in the fully vaccinated group). Abbreviations: CI; confidential intervals, VE; vaccine effectiveness.

numbers of days since vaccination to onset may have affected the results. Specifically, in this study, the interval from the second or third vaccination to the onset of the disease was approximately 120 days. Thus, the effectiveness of booster vaccines may have waned over this extended period. Regarding the prevention to the severity, because the vaccine was not for omicron variants, there might have been fewer T-cell responses specific to the omicron variant. Moreover, very few patients with past COVID-19 history were included in our cohort, which may have influenced the results. Booster vaccination for preventing progression to severe illness during an epidemic of variants, such as omicron, may be more effective in high-risk patients just before the epidemic than universal vaccination may throughout the year.

By nature, a registry study does not cover all regions and hospitals in Japan. However, the validity of this registry has been examined and its representativeness confirmed.[23] Thus, the analysis using the present data is valid. In delta and omicron cohort 2, the days from onset to admission were significantly shorter in full and boost vaccinated group. This difference might have affected the results. It remains uncertain whether our results will be valid for future virus mutations. However, our results will provide solid information when managing future variants as our analysis included highly virulent and infectious variants. This study only assessed the effectiveness of a single booster vaccination, and data were obtained prior to the development of an mRNA vaccine against the omicron variants. Thus, it is difficult to predict how the indicators will change when the number of booster vaccinations increases or when mRNA vaccines against omicron variants are used. Moreover, we did not evaluate its effectiveness over a longer duration after vaccination. Patients with a history of COVID-19 may show different trends since those who had a history of COVID-19 accounted for <2 % of the study participants.

Conclusion

Full mRNA vaccination against COVID-19 improved the incidence of fever, condition severity upon admission and oxygen supplementation rate among COVID-19 patients in Japan, regardless of the pandemic phase. The use of mRNA vaccines against the omicron variants also improved the mortality rates. Our study did not demonstrate the effectiveness of booster vaccinations in preventing severe illness during the omicron-dominant phase. Booster vaccination would be more effective for those at risk of severe illness than universal vaccination. Future vaccine strategies and policy decisions should consider preventing infection or reducing disease progression in the target population and consider the characteristics of the dominant variant in that phase.

Author contributions

TS, YA, ST, HN, NM, and KH developed the study concept. YA played a chief role in the statistical analysis. TS drafted the manuscript. EK, KH, and NO supervised the experiments. All authors have approved the final version of the manuscript.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.12.002.