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Short Communication

Characteristics and clinical effectiveness of COVID-19 vaccination in hospitalized patients in Omicron-dominated epidemic wave – a nationwide study in Japan

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ABSTRACT

Objectives: COVID-19 was severe in the Delta variant-dominated epidemic wave (fifth wave) in Japan. The clinical characteristics and effectiveness of COVID-19 vaccination are not fully understood in the Omicron variant-dominated wave (sixth and seventh waves), especially in hospitalized patients. We investigated the relationship between vaccination and disease severity in the Omicron-dominated wave and compared these variant-dominated waves.

Methods: The nationwide COVID-19 database (Japan COVID-19 Task Force) was used to compare clinical characteristics and critical outcomes in patients hospitalized with Delta (fifth, N = 735) vs Omicron-dominated waves (sixth, N = 495; seventh, N = 128).

Results: Patients in the sixth and seventh waves had a lower incidence of critical outcomes and respiratory outcomes, and a higher incidence of bacterial infection, although the mortality rate did not differ significantly between waves. In the sixth and seventh waves, 138 (27.9%) and 29 (22.7%) patients with COVID-19 were unvaccinated, respectively. Multivariable analysis adjusted with previously reported factors revealed that the proportion of (1) critical outcomes and (2) respiratory outcomes decreased in a frequency-dependent manner. Thus, (1) (the number of vaccinations): 1-2 times: adjusted odds ratio (aOR) 0.37 (95% confidence interval [CI]; 0.20-0.69); 3-4 times: aOR 0.25 (95% CI; 0.11-0.58); and (2) 1-2 times: aOR 0.43 (95% CI; 0.27-0.66); 3-4 times: aOR 0.36 (95% CI; 0.21-0.60).

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Conclusions: Patients hospitalized with COVID-19 with Omicron infections showed a lower incidence of critical outcomes than those with Delta infections, and COVID-19 vaccination may contribute to preventing respiratory failure.

Introduction

The SARS-CoV-2 pandemic remains a serious problem, and while it continues to acquire mutations, the use of new antiviral/anti-inflammatory drugs and vaccination is evolving. From 2021 to 2022, the major viral mutant strain changed from Delta to Omicron, involved in the fifth to seventh epidemic waves in Japan (Supplementary Figure S1). Vaccination commenced in February 2021, sotrovimab and molnupiravir became newly available as antiviral drugs, and early administration of remdesivir to prevent disease exacerbation became available in the middle of the sixth wave. We compared clinical information on the first five waves in Japan and reported the high severity of the fifth wave, which was mainly caused by the Delta strain [1]. Although there are limited reports on the clinical characteristics and vaccine effects in hospitalized patients during the Omicron epidemic in 2022, we aimed to compare clinical characteristics and outcomes on hospitalized patients from the Delta- vs Omicron-dominated waves and evaluated the association between vaccination and disease severity in the Omicron-dominated wave.

Methods

The Japan COVID-19 Task Force collects clinical information on patients with COVID-19 from multiple centers in Japan [2]. New information on vaccination frequency was collected from patients

Table 1
Comparison of patient backgrounds and outcomes among fifth, sixth, and seventh epidemic waves.

Parameters	Total (n = 1358)	Fifth wave (n = 735)	Sixth wave (n = 495)	Seventh wave (n = 128)	*P*-value
Backgrounds					
Age	57.4 (±17.7)	50.9 (±14.2)	63.5 (±18.4)	72.0 (±16.6)	<0.001
Sex, male	916 (67.5)	526 (71.6)	309 (62.4)	81 (63.3)	0.002
Body mass index	24.9 (±6.4)	25.6 (±5.0)	24.3 (±8.2)	22.8 (±4.5)	<0.001
Smoking, current or former	628 (48.3)	346 (49.4)	220 (45.6)	62 (52.1)	0.300
Medical history					
Hypertension	508 (37.6)	213 (29.1)	224 (45.4)	71 (56.8)	<0.001
Diabetes mellitus	303 (22.4)	146 (20.0)	118 (24.0)	39 (30.5)	0.018
Cardiovascular disease	199 (14.8)	56 (7.7)	106 (21.6)	37 (29.1)	<0.001
Malignancy	124 (9.2)	33 (4.5)	68 (13.8)	23 (18.1)	<0.001
Autoimmune disease	110 (8.1)	29 (4.0)	68 (13.8)	13 (10.2)	<0.001
Chronic obstructive pulmonary disease	63 (4.7)	19 (2.6)	36 (7.4)	8 (6.3)	<0.001
Asthma	110 (8.2)	55 (7.6)	41 (8.4)	14 (11.1)	0.405
Hyperuricemia	134 (10.0)	73 (10.0)	46 (9.5)	15 (11.8)	0.734
Chronic liver disease	57 (4.3)	28 (3.9)	26 (5.3)	3 (2.4)	0.266
Chronic kidney disease	145 (10.8)	37 (5.1)	79 (16.2)	32 (22.7)	<0.001
Outcomes					
Severity					<0.001
Critical	276 (20.3)	206 (28.0)	62 (12.5)	8 (6.3)	
Dead	43 (3.2)	19 (2.6)	20 (4.0)	4 (3.1)	0.360
Oxygen support					<0.001
Invasive mechanical ventilation	124 (9.1)	97 (13.2)	26 (5.3)	1 (0.8)	
High-flow oxygen	138 (10.2)	106 (14.4)	27 (5.5)	5 (3.9)	
Low-flow oxygen	514 (37.9)	296 (40.3)	165 (33.3)	53 (41.4)	
Not requiring oxygen support	582 (42.9)	236 (32.1)	277 (56.0)	69 (53.9)	
Complications					
Bacterial infection	183 (13.6)	80 (11.0)	70 (14.3)	33 (25.8)	<0.001
Heart failure	43 (3.2)	16 (2.2)	20 (4.1)	7 (5.5)	0.062
Cardiomyopathy	14 (1.0)	5 (0.7)	8 (1.6)	1 (0.8)	0.268
Thromboembolism	23 (1.7)	14 (2.0)	9 (1.8)	0 (0.0)	0.289
Liver dysfunction					<0.001
Mild	431 (32.4)	273 (37.8)	125 (26.0)	33 (26.0)	
Moderate	165 (12.4)	132 (18.3)	30 (6.2)	3 (2.4)	
Severe	53 (4.0)	40 (5.5)	12 (2.5)	1 (0.8)	
Kidney dysfunction					0.002
Moderate	219 (16.5)	126 (17.5)	67 (14.0)	26 (20.5)	
Severe	86 (6.5)	30 (4.2)	44 (9.2)	12 (9.4)	
Macrophage activation syndrome	12 (1.0)	5 (0.7)	6 (1.3)	1 (0.8)	0.643
Treatments					
Remdesivir	895 (66.1)	563 (76.9)	239 (48.5)	93 (72.7)	<0.001
Sotrovimab	147 (20.6)	1 (1.1)	145 (29.5)	1 (0.8)	<0.001
Molnupiravir	56 (8.0)	0 (0.0)	39 (8.1)	17 (13.4)	0.002
Corticosteroid	766 (56.6)	552 (75.2)	178 (36.1)	36 (28.3)	<0.001
Tocilizumab	183 (13.6)	154 (21.0)	28 (5.7)	1 (0.8)	<0.001
Baricitinib	223 (16.5)	185 (25.3)	33 (6.7)	5 (3.9)	s

Data are as N (%) or mean (SD).

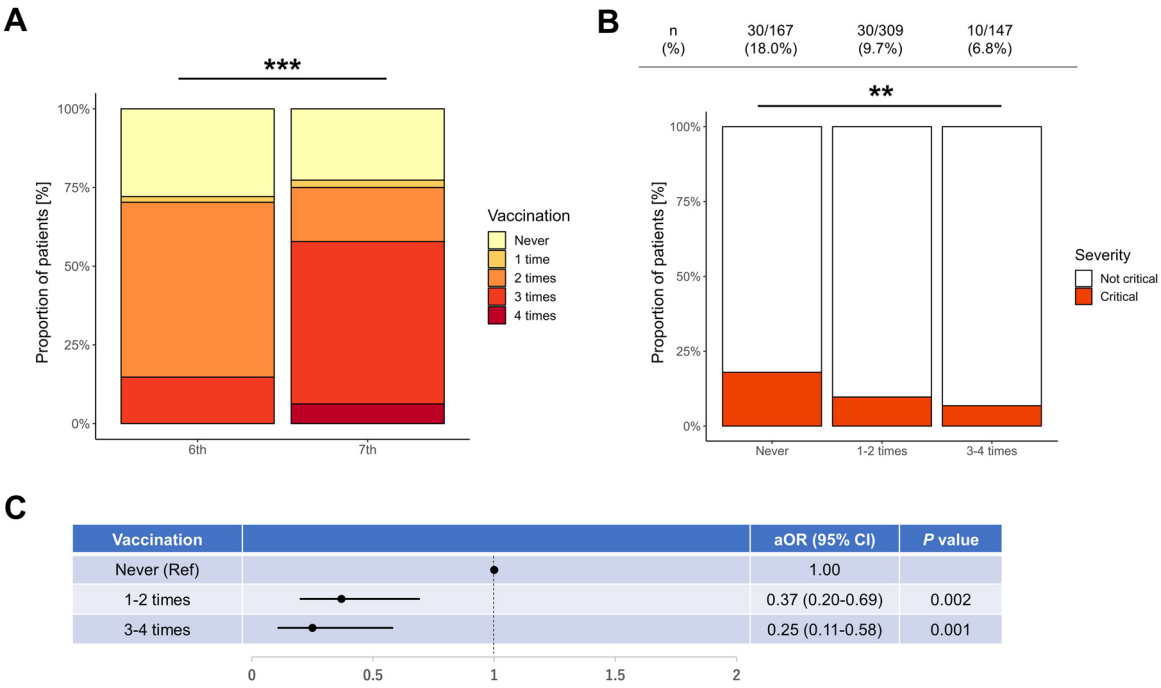

Figure 1. Relationship between vaccination and disease severity of COVID-19 among hospitalized patients in the sixth and seventh (Omicron) epidemic waves in Japan. (a) The comparison of the number of vaccinations between in the sixth and seventh waves. (b) The comparison of the rates of critical outcomes among three groups based on the number of vaccinations. (c) Multivariable analysis for critical outcomes based on the number of vaccinations. aOR; adjusted odds ratio, CI; confidence interval, Ref; reference. **; P <0.01, ***; P <0.001.

since the sixth epidemic wave. A consort diagram is shown in Supplementary Figure S2. We extracted 1414 patients hospitalized with COVID-19: 56 patients with insufficient clinical information, 735 patients in the fifth (June 21, 2021-December 16, 2021), 495 patients in the sixth (December 17, 2021 to June 24, 2022), and 128 patients in the seventh (June 25, 2022 to September 26, 2022) epidemic wave were analyzed. We performed a multivariable analysis adjusted for previously reported factors of age, sex, body mass index, smoking history, hypertension, diabetes, cardiovascular disease, and chronic kidney disease [3,4] to evaluate the relationship between vaccination and (i) critical outcome, defined as conditions requiring the support of a high-flow oxygen device or invasive mechanical ventilation (IMV) or death, and (ii) respiratory outcome, defined as conditions requiring any form of oxygen support. Data were compared using the chi-square test or one-way analysis of variance.

Results

Comparison of clinical backgrounds, treatments, and outcomes of patients between the fifth, sixth, and seventh waves are shown in Table 1. In the sixth and seventh waves, the proportion of older female patients with lower body mass index increased, and with a higher proportion of comorbidities including hypertension, diabetes, cardiovascular disease, and chronic kidney disease than in the fifth wave. Critical outcome decreased from the fifth wave, with an increasing bacterial infection and renal impairment as complications of COVID-19. Compared with the fifth wave, fewer patients in the sixth and seventh waves required IMV or high-flow oxygen support. There were no significant differences in mortality among groups. Remdesivir was more frequently used in the fifth and seventh waves. Sotrovimab was used in 29.5% of patients in the sixth wave, and molnupiravir in 13.4% in the seventh wave. The use of corticosteroids, tocilizumab, and baricitinib was significantly lower in the sixth and seventh waves than in the fifth wave (P <0.001).

The relationship between the number of vaccinations and severity of COVID-19 among patients in the sixth and seventh waves is shown in Figure 1. In the sixth and seventh waves, 138 (27.9%) and 29 (22.7%) patients with COVID-19 were unvaccinated, respectively. (Figure 1a). By contrast, the proportion of patients who received three or more doses of the vaccination increased from 73 (14.8%) in the sixth wave to 74 (57.8%) in the seventh wave. Comparing by vaccination frequency, the proportion of critical outcome decreased as the number of vaccinations increased from never, 1-2 times, to 3-4 times (Figure 1b). A multivariable analysis revealed COVID-19 vaccination was significantly associated with lower critical outcome in a frequency-dependent manner (the number of vaccinations): 1-2 times: adjusted odds ratio (aOR) 0.37 (95% confidence interval [CI]; 0.20-0.69); 3-4 times: aOR 0.25 (95% CI; 0.11-0.58). The incidence of the respiratory outcome was significantly lower in the sixth and seventh waves (Supplementary Figure S3A) than in the fifth wave, and a multivariable analysis showed an association between COVID-19 vaccination and a lower incidence of the respiratory outcome: 1-2 times: aOR 0.43 (95% CI; 0.27-0.66); 3-4 times: aOR 0.36 (95% CI; 0.21-0.60) (Supplementary Figure S3B).

Discussion

To the best of our knowledge, this is the first study comparing clinical characteristics and outcomes in hospitalized patients from the Delta- and Omicron-dominated waves and evaluating the effect of vaccination on disease severity in the recent Omicron-dominated wave. Vaccination against SARS-CoV-2 is known to prevent severe disease [5]. In this study, some hospitalized patients in the sixth and seventh waves were found to be unvaccinated, and multivariable analysis suggested that a lack of vaccination was as-

sociated with the critical outcome and the need for oxygen support. Further, the incidence of critical outcomes decreased as the number of doses of vaccine increased to three or more, suggesting that increasing the number of doses of vaccine may have a protective effect. This result is consistent with the reported booster effect of a third vaccination [6]. The increase in the number of vaccinations may have contributed to the decrease in patients with critical outcomes in the seventh epidemic wave. Because vaccination against the Omicron strain began in Japan on September 20, 2022, almost all the patients in this study did not receive this new vaccine. Therefore, the vaccination may have limited efficacy during the Omicron-dominated wave [7], and the introduction of new antiviral drugs also might affect favorable outcomes.

Although there were fewer cases of critical outcomes and patients requiring IMV or high-flow oxygen support in the sixth and seventh waves compared with the fifth wave, there was no significant difference in mortality rates by wave in this study. Omicron strains are reported to be associated with lower disease severity than Delta strains [8]. Results of a previous study reported that the sixth wave had lower mortality rates than the fifth wave, with similar results in the older patients group [9]. Considering this difference in mortality rates between the previous and our study, it is possible that the participating institutions in the present study were mainly large hospitals that prioritized severe or critical patients with comorbidities. In addition, fewer pneumonia on chest computed tomography were reported during the Omicron-dominated wave [10], suggesting fewer cases of severe pneumonia requiring IMV or high-flow oxygen device support. Therefore, in this study, the severity of COVID-19 pneumonia was lower in patients during the Omicron-dominated waves, as seen by the lower incidence of the respiratory outcome. In contrast, the number of hospitalized patients with underlying diseases increased in the sixth and seventh waves, which may contribute higher rate of complications, such as bacterial infections and renal insufficiency during the disease course. The use of sotrovimab in the sixth wave, and molnupiravir and remdesivir in the seventh wave, mainly in mild cases, may have prevented disease exacerbation.

There are several limitations of this study. First, although the number of patients in Japan was greater in the sixth and seventh waves than in the fifth wave, the study has the largest number of patients in the fifth wave, indicating selection bias. This is caused by the extremely large number of patients in the sixth and seventh waves, which led to a decrease in enrollment in this study due to occupied medical facilities. Second, while many minor cases in the sixth and seventh wave were untreated and resolved with rest at home, patients with underlying background diseases and other comorbidities were selected and admitted to the hospital, making them eligible for this study. Therefore, the patients in the sixth and seventh waves are considered to have milder illnesses in fact than those included in this study. However, even with this bias, we observed differences in the incidence of respiratory outcomes between strain waves in this study. The patients in this study were hospitalized; therefore, the proportion of patients receiving antiviral therapy was high relative to the actual number of patients in the clinical settings. The proportion of unvaccinated patients is also expected to be even lower, but we believe these biases further strengthen the results of this study.

Conclusion

Patients hospitalized with COVID-19 during the Omicron-dominated waves had a lower incidence of critical and respiratory outcomes. COVID-19 vaccination might contribute to prevent infection-induced respiratory failure.

Declarations of competing interests

The authors have no competing interests to declare.

CRediT authorship contribution statement

Hiromu Tanaka: Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Shotaro Chubachi:** Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Takanori Asakura:** Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Ho Namkoong:** Conceptualization, Data curation, Methodology, Visualization, Writing – review & editing. **Shuhei Azekawa:** Data curation, Supervision. **Shiro Otake:** Data curation. **Kensuke Nakagawara:** Data curation. **Takahiro Fukushima:** Data curation. **Ho Lee:** Data curation. **Mayuko Watase:** Data curation. **Kaori Sakurai:** Data curation. **Tatsuya Kusumoto:** Data curation. **Katsunori Masaki:** Conceptualization, Supervision, Writing – review & editing. **Hirofumi Kamata:** Conceptualization, Supervision, Writing – review & editing. **Makoto Ishii:** Conceptualization, Supervision, Writing – review & editing. **Naoki Hasegawa:** Supervision, Writing – review & editing. **Yukinori Okada:** Supervision, Writing – review & editing. **Ryuji Koike:** Supervision, Writing – review & editing, Writing – review & editing. **Yuko Kitagawa:** Supervision, Writing – review & editing. **Akinori Kimura:** Supervision, Writing – review & editing. **Seiya Imoto:** Supervision, Writing – review & editing. **Satoru Miyano:** Supervision, Writing – review & editing. **Seishi Ogawa:** Supervision, Writing – review & editing. **Takanori Kanai:** Supervision, Writing – review & editing. **Koichi Fukunaga:** Conceptualization, Supervision, Writing – review & editing.

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Ethical approval, consent to participate

This study was approved by the ethics committee of the Keio University School of Medicine (20200061) and related research institutions. All participants provided informed consent.

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Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.04.399.

References

[1] Lee H, Chubachi S, Namkoong H, Asakura T, Tanaka H, Otake S, et al. Characteristics of hospitalized patients with COVID-19 during the first to fifth waves of infection: a report from the Japan COVID-19 Task Force. *BMC Infect Dis* 2022;**22**:935. doi:10.1186/s12879-022-07927-w.

[2] Namkoong H, Edahiro R, Takano T, Nishihara H, Shirai Y, Sonehara K, et al. DOCK2 is involved in the host genetics and biology of severe COVID-19. *Nature* 2022;**609**:754–60. doi:10.1038/s41586-022-05163-5.

[3] Fukushima T, Chubachi S, Namkoong H, Asakura T, Tanaka H, Lee H, et al. Clinical significance of prediabetes, undiagnosed diabetes and diagnosed diabetes on critical outcomes in COVID-19: integrative analysis from the Japan COVID-19 task force. *Diabetes Obes Metab* 2023;**25**:144–55. doi:10.1111/dom.14857.

[4] Watase M, Masaki K, Chubachi S, Namkoong H, Tanaka H, Lee H, et al. Impact of accumulative smoking exposure and chronic obstructive pulmonary disease on COVID-19 outcomes: report based on findings from the Japan COVID-19 task force. *Int J Infect Dis* 2023;**128**:121–7. doi:10.1016/j.ijid.2022.12.019.

[5] El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. *N Engl J Med* 2021;**385**:1774–85. doi:10.1056/NEJMoa2113017.

[6] Patalon T, Gazit S, Pitzer VE, Prunas O, Warren JL, Weinberger DM. Odds of testing positive for SARS-CoV-2 following receipt of 3 vs 2 doses of the BNT162b2 mRNA vaccine. *JAMA Intern Med* 2022;**182**:179–84. doi:10.1001/jamainternmed.2021.7382.

[7] Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. *N Engl J Med* 2022;**386**:1532–46. doi:10.1056/NEJMoa2119451.

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

[9] Baba H, Ikumi S, Aoyama S, Ishikawa T, Asai Y, Matsunaga N, et al. Statistical analysis of mortality rates of coronavirus disease 2019 (COVID-19) patients in Japan across the 4C mortality score risk groups, age groups, and epidemiological waves: a report from the nationwide COVID-19 cohort. *Open Forum Infect Dis* 2023;**10**:ofac638. doi:10.1093/ofid/ofac638.

[10] Ito N, Kitahara Y, Miwata K, Okimoto M, Takafuta T. Comparison of COVID-19 pneumonia during the SARS-CoV-2 Omicron wave and the previous non-Omicron wave in a single facility. *Respir Investig* 2022;**60**:772–8. doi:10.1016/j.resinv.2022.08.001.