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Alpha and Delta variants and vaccination effectiveness against severity in COVID-19 inpatients based on medical claims in Japan

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Abstract: Some mutated strains of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presumably have high infectivity and pathogenicity. Using Japanese medical claims data, we assessed the pathogenicity of Alpha and Delta variants and vaccine effectiveness by severity. Inpatient records from the Medical Information Analysis Databank for the National Hospital Organization were used. Severity was defined as the proportion of inpatients using respiratory ventilators among inpatients with oxygen administration. We regressed severity and fatality on the proportion of patients with Alpha or Delta variant and on vaccination coverage, while allowing for some lag to reflect development from infection to hospitalization. We also examined results obtained when using data for all new inpatients, instead of inpatients with oxygen administration, as the denominator for severity. Estimation results were better when using severity defined by inpatients with oxygen administration as the denominator than when using all new inpatients. Especially for severity measures for inpatients 65 years old or older with oxygen administration, we confirmed an association of vaccination with lower severity and an association of Delta variant infection with high severity. Vaccines were most effective for people 65 years old or older. The age distributions of inpatients and confirmed patients were greater than for people younger than 65 years old. Vaccination reduced severity and fatality and Alpha and Delta variants might increase severity and fatality among inpatients 65 years old or older receiving oxygen therapy.

***Keywords*:** COVID-19, mutated strains, fatality, medical claim data, vaccine

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19). COVID-19 spread throughout Japan from January 2020. The number of COVID-19 patients increased and decreased due to individual infection prevention and some political policies such as a state of emergency (*1-4*).

Some mutated strains such as Alpha and Delta variants including B.1.1.7 (Alpha variant) and B.1.617.2 (Delta variant) are likely to induce severe symptoms (*5-7*). In Japan, an epidemic of the Alpha variant occurred from March 2021 (Weeks 9–13, Wave 4). An epidemic of the Delta variant was reported from July 2021 (Weeks 27–30, 2021, Wave 5).

Development of vaccination against SARS-CoV-2 was initiated around the world after the emergence of COVID-19 (*8*). Vaccination in Japan started from 17 February 2021 (Week 7, 2021, Wave 3) using BNT162b2 mRNA (Pfizer Inc., BioNTech SE) and mRNA-1273 (Moderna, Inc.). Clinical trials proved the vaccines' efficacy for preventing infection against Alpha and Delta variants (*9*). Therefore, the object of this study was evaluation of the severity of Alpha and Delta variants while considering vaccine effectiveness.

Japan's National Hospital Organization (NHO), an organization of regional core hospitals and 140 medical facilities with about 52,000 beds, represents about 3.4% of all beds in Japan (*10*).The NHO provides a database, the Medical Information Analysis Databank (MIA), which contains medical claims from 60 representative NHO hospitals, including data related to the numbers of inpatients and outpatients, diagnoses, medical interventions including oxygen administration and the use of respiratory ventilators, in addition to outcomes such as discharge and death (*11*). Representative 60 hospitals were the hospitals whose data on medical claim were available as MIA data at the beginning of this study. They locate in each region and we regarded and assumed that they are representative of patients in each region. The database does not include data related to the vaccination history or causative strain. COVID-19 had a significant impact on the medical setting for outpatients and inpatients (*12-14*). The number of patients of COVID-19

increased rapidly from July 2021 (Weeks 26–30, 2021, Wave 5) because of the spreading Delta variant. In the period during which the Delta variant spread, nationwide demand for medical resources such as hospital beds and respiratory ventilators threatened to exceed the capacity of medical resources allocated for COVID-19 patients. Therefore, asymptomatic patients and some patients with mild symptoms were not hospitalized during that period, even though such patients had been hospitalized earlier during the pandemic. In other words, the COVID-19 patient criteria for hospitalization changed to reflect the outbreak scale and the available capacity of medical resources. For that reason, when examining COVID-19 pathogenicity, the fraction of patients with severe symptoms or cases of fatality beyond the hospitalized cases might not be appropriate to evaluate pathogenicity because the criteria for hospitalization were not constant. The criteria were not based solely on medical necessity. To avoid inconsistency in the data, the number of hospitalizations had to be adjusted. Therefore, this study specifically examined patients who required oxygen therapy.

Materials and Methods

Data source

This study used MIA data from the NHO such as the number of inpatients with oxygen therapy, ventilation, and deaths from 1 January 2020 (Week 1, 2020, Wave 1) to 21 November 2021 (Week 46, 2021, Wave 5). All MIA data for patients were counted based on the week of admission.

Additionally, we used background COVID-19 patient data nationwide, including the number of newly confirmed patients and deaths, published between 1 January 2020 (Week 1, 2020, Wave 1) and 21 November 2021 (Week 46, 2021, Wave 5) from the Ministry of Health, Labour and Welfare (MHLW) (*15*). Hereinafter, we designate data from MHLW as "national data". Data related to vaccine administration (such as the number of people receiving at least one dose, which means one or two doses, and those who had received the second dose) were published by the Cabinet Secretariat (*16*). For the study period, the third and subsequent doses were not available. Data related to the Alpha and Delta variants were referred from a monitoring meeting in Tokyo (*17*).

Definition of waves

As of November 2021, Japan experienced five waves, which mean movements of the number of COVID-19 patients shown as Figure 1. In this study, the COVID-19 outbreak waves in Japan were classified by the number of newly confirmed patients from the trough of the prior wave to the trough of the current wave (*4*). That method clearly distinguished five waves through the end of November 2021: the wave 1 extended from week 1 of 2020 through week 23 of 2020; the wave 2 lasted from week 24 of 2020 through week 39 of 2020; the wave 3

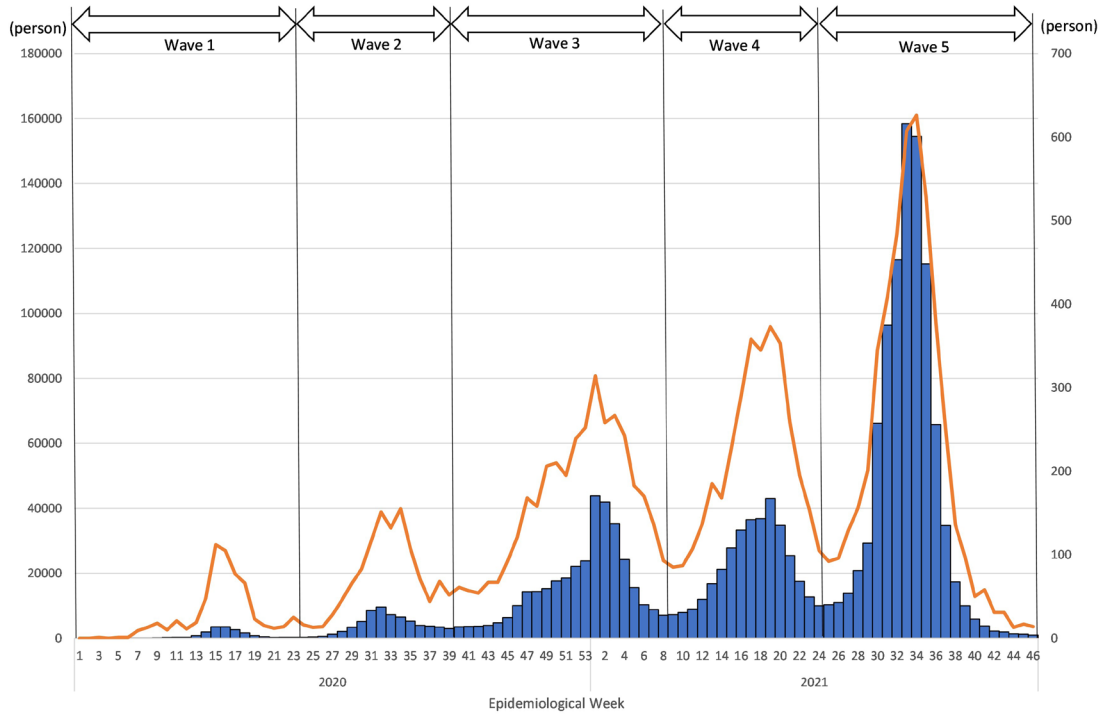

Figure 1. Newly confirmed COVID-19 patients in national data and new COVID-19 hospitalizations in MIA data. Notes: Bars show the numbers of newly confirmed COVID-19 patients in national data (left scale). The line shows the numbers of new COVID-19 hospitalizations in MIA data (right scale).

was recorded from week 40 of 2020 through week 8 of 2021; the wave 4 occurred from week 9 of 2021 through week 24 of 2021; and the wave 5 was from week 25 of 2021 through week 46 of 2021.

Design

Associations between the severity or fatality rate among inpatients with oxygen therapy and the vaccination coverage and/or the proportions of Alpha and Delta variants were examined. Additionally, we sought to ascertain the most appropriate length from infection to hospitalization by adjusting the delay in the timing of vaccination coverage two weeks prior and the proportions of Alpha and Delta variants. Specifically, we examined no delay and 1–4 or more weeks' delay. For no delay, vaccination coverage was recorded for two weeks before hospitalization; the proportions of Alpha and Delta variants were measured the same week of hospitalization. For 1–4 weeks' delay, the vaccination coverage 3–6 weeks before hospitalization or the proportions of Alpha and Delta variants were measured at 1–4 weeks before hospitalization.

The study period for analysis was from the first week of 2021 (Wave 1) through the 46th week of 2021 (Wave 5) because vaccination against COVID-19 had not started and Alpha and Delta variants had not emerged before the study period.

Definitions

Patients were limited to hospitalized patients with a COVID-19 infection confirmed by PCR test or antigen test and those who received oxygen therapy during their hospitalization. It is noteworthy that the timing of oxygen therapy did not matter: only that it was administered during their hospitalization. Furthermore, comorbidities did not matter for the patient definitions or outcome measures presented below.

The severity rate among patients was defined as the number of patients with ventilation during their hospitalization among patients who were admitted during a week, by the number of patients administered oxygen therapy who had been admitted during the same week. The timing of ventilation use did not matter: only that it was administered their hospitalization. The fatality rate among patients was defined as the number of fatalities among patients who were admitted in a week, divided by the number of patients administered oxygen therapy who had been admitted during the same week. The main or direct cause of death does not matter: only that they had been diagnosed as COVID-19-infected.

Hypothesis

Results of earlier studies have demonstrated that vaccination decreased severity and fatality rates. They have also demonstrated that Alpha and Delta variants are associated with increased severity and higher fatality rates (*5-7*,*18*,*19*). Therefore, we expected to find a positive association among severity, fatality, and vaccination, and a negative association for the proportion of Alpha and Delta variants.

Statistical analysis

We applied ordinary least squares regression, with dependent variables of the severity rate among patients with oxygen therapy and the fatality rate among patients who had received oxygen therapy. Vaccination coverage and the proportions of Alpha and Delta variants were used as explanatory variables.

Statistical analyses were also performed after patient data were divided into those for age groups, with patients who were 65 years old or older and patients younger than 65 years. First, we identified the optimal period from infection to hospitalization for all ages, and by age classification, by outcome, severity rate, and fatality rate. Then, we discussed estimation results under the optimal period for each category. We adopted 5% as the significance level. All statistical analyses were conducted using software (STATA SE 17.0; Stata Corp.).

Ethical considerations

This study was approved by the Ethics Committee of Mie Hospital (Approval No. 2020-89). Permission to use MIA data was obtained from the NHO (Registration No. 1201003).

Results

Figure 1 presents the number of newly confirmed COVID-19 patients from national data and the number of new COVID-19 hospitalizations from MIA data. Figure 2 presents the number of fatalities attributed to COVID-19 from national data and the number of fatalities from MIA data. The number of newly confirmed COVID-19 patients from national data was shown by the diagnosed week. The number of new hospitalizations from MIA data is shown by the hospitalized week. The numbers of fatalities from national data and MIA data are shown by their death and discharge weeks. Vertical lines in Figures 1–5 represent periods between waves. Figure 1 shows similar trends obtained from the number of newly confirmed COVID-19 patients and the number of newly hospitalized patients. Figure 2 also shows that the number of fatalities from national data presents a similar trend to that of the number of fatalities from MIA data. Correlation between them was 0.8830, which was inferred as significant. The wave 5 showed the greatest number of newly confirmed cases (Figure 1). The wave 4 showed the greatest number of fatalities (Figure 2).

Figure 3 and Figure 4 respectively portray the

severity rate with ventilator usage among patients with oxygen therapy and the fatality rate among patients with oxygen therapy for all ages, and by age classification. At first glance, all lines were declining in the latter period of the study period when bottom from wave 5 to 6. Figure 5 shows vaccination coverage with at least one dose in the entire population, younger than 65 years old, and 65 years old or older, in addition to the proportions of Alpha and Delta variants in Tokyo. The proportions of the Delta variant showed a similar increase to that of vaccination

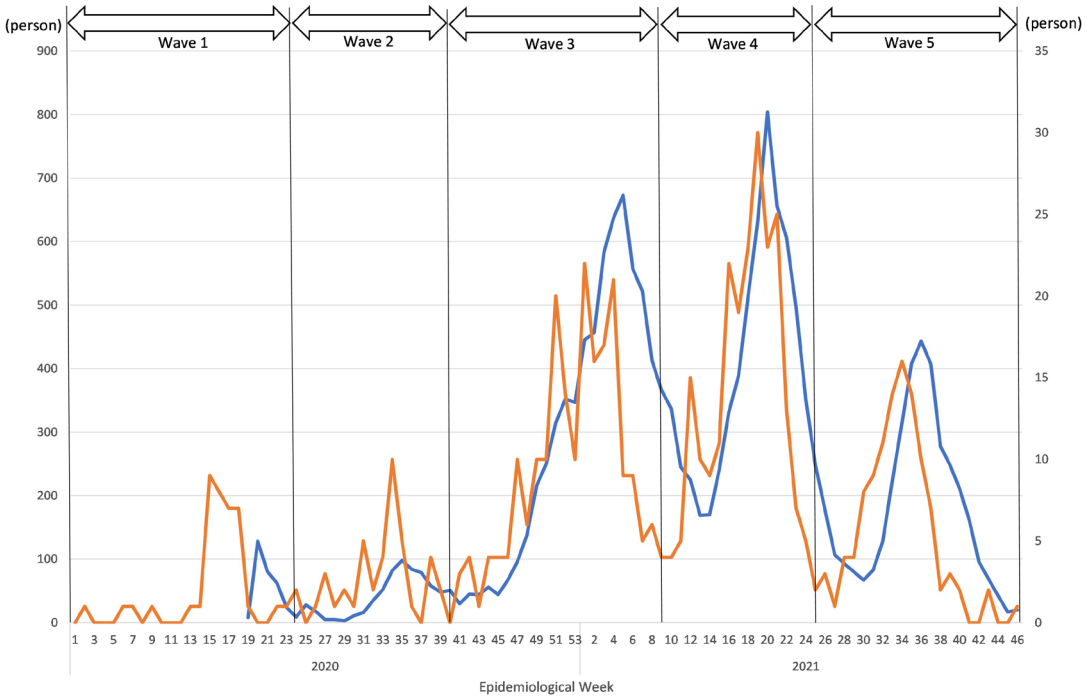

Figure 2. Fatalities with COVID-19 in national data and in MIA data. Notes: The blue line denotes the number of fatalities with COVID-19 in National data (left scale). Orange line denotes the numbers of fatalities by hospitalized week in MIA data (right scale).

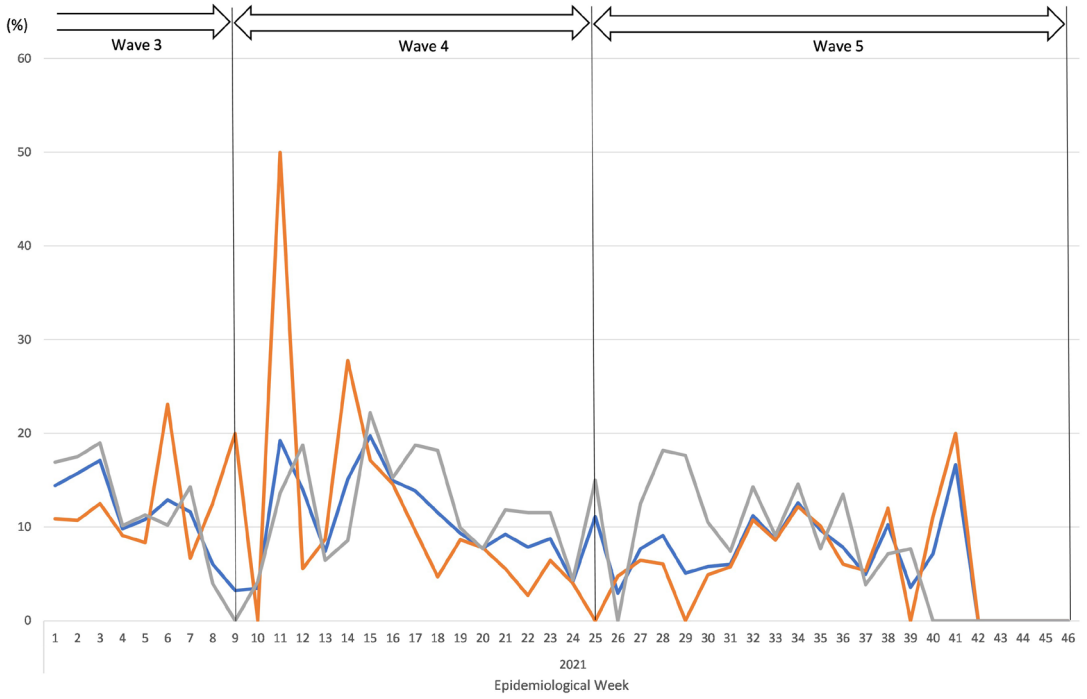

Figure 3. Severity rate among inpatients administered oxygen therapy. Notes: Blue, orange, and gray lines respectively show the severity rate with ventilator use among inpatients with oxygen therapy in the entire population, younger than 65 years old, and 65 years old or older. Severity was defined as the proportion of ventilator use. All data were sourced from MIA data.

coverage for patients 65 years old or older.

Table 1 presents coefficients of determination using proportions of Alpha and Delta variants and vaccination coverage in the hospitalized week, or 1–4 weeks before hospitalization for all ages and by age classification. The findings indicate the highest coefficients of determination for three weeks before for severity and one week before for fatality for all ages.

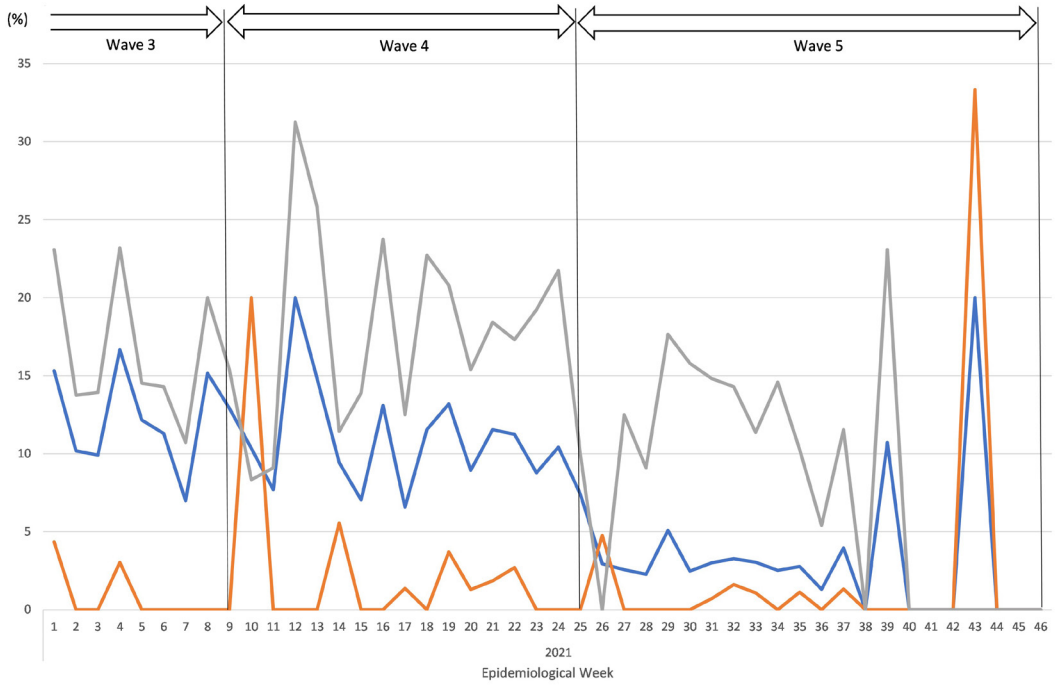

Figure 4. Fatality rate among inpatients administered oxygen therapy. Notes: Blue, orange, and gray lines respectively represent the fatality rate among inpatients with oxygen therapy in the entire population, younger than 65 years old, and 65 years old or older. All data sources were MIA data.

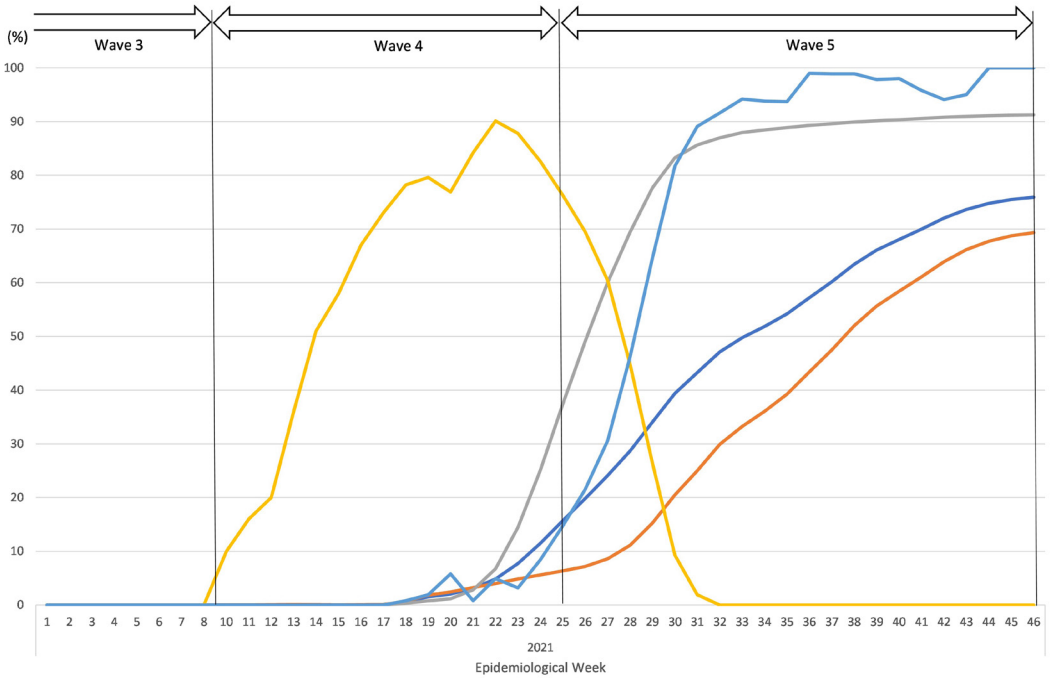

Figure 5. Vaccination coverage with at least one dose in Japan, in addition to proportions of Alpha and Delta variants in Tokyo. Notes: Yellow and light blue lines respectively represent the proportions of the Alpha and Delta variants. Data of the proportions of the Alpha and Delta variants were published by the Cabinet Secretariat. Blue, orange, and gray lines respectively represent vaccination coverage with at least one dose in the entire population, younger than 65 years old, and 65 years old or older. Data of the vaccination coverage were published by the monitoring meeting in Tokyo.

Among inpatients 65 years old or older, the highest coefficients of determination for the severity rate and for the fatality rate were the same: one week. Conversely, among inpatients younger than 65 years old, although the highest coefficients of determination for the fatality rate were the same week with hospitalization, it was six weeks for the severity rate.

Table 2 presents estimation results obtained from multivariable analyses of the association between the severity and fatality rates among inpatients with oxygen therapy and vaccination coverage or Alpha and Delta variant proportions for all ages and by age class. Each estimation result was obtained under the optimal period for each category shown in Table 1. For patients of all ages, at least one dose vaccination and the proportion of Delta variant were found to be associated significantly with the severity rate. Also, the proportion of Alpha variant was associated significantly with the fatality rate. The results were mixed: the negative sign of the proportion of Alpha variant was unexpected from the hypothesis defined in Method. However, the negative sign of at least one dose vaccination and the positive sign of the proportion of Delta variant were expected. For patients younger than 65 years old, the proportion of the Alpha variant and Delta variant showed negative association with the severity rate significantly, which were unexpected. For all age patients, at least one dose vaccination was negatively associated with the severity and fatality rates. The proportion of Delta variant was positively associated with the severity and fatality rates.

Discussion

All COVID-19 patients, including asymptomatic patients, be admitted mandatory to medical facilities through March 2020. Subsequently, asymptomatic

Table 1. Coefficients of determination obtained using proportions of Alpha and Delta variants and vaccination coverage in the hospitalized week, or 1–4 weeks before hospitalization in all age and by age classification

Length of delay in vaccination coverage and Proportion of Alpha and Delta variants	0	1	2	3	4
All ages with oxygen therapy					
Severity rate	0.33	0.37	0.40	0.43	0.42
Fatality rate	0.17	0.49	0.47	0.47	0.48
Among patients younger than 65 years old					
Severity rate	0.17	0.18	0.23	0.24	0.25
Fatality rate	0.07	0.05	0.06	0.07	0.07
Among patients 65 years old or older					
Severity rate	0.21	0.42	0.40	0.40	0.38
Fatality rate	0.36	0.52	0.51	0.49	0.48

Note: The highest coefficient of determination for the severity rate among inpatients younger than 65 years old with oxygen therapy was 0.2779 when vaccination coverage and the prevalence of the mutated strains were measured six weeks before.

Table 2. Results of multivariate analysis of the association between severity/ fatality and vaccination coverage or proportion of variants among inpatients with oxygen therapy for cases of vaccination coverage two weeks prior and the proportion of Alpha and Delta variants measured several weeks before their hospitalized week determined by Table 1

Variables	Severity Rate		Fatality Rate	
	Estimated coefficient	*p* value	Estimated coefficient	*p* value
All ages				
At least one dose vaccination 14 days prior	-0.40	0.00	0.03	0.79
Alpha variant	-0.03	0.10	-0.05	0.04
Delta variant	0.18	0.02	-0.12	0.09
Constant	12.21	0.00	12.57	0.00
Younger than 65 years old				
At least one dose vaccination 14 days prior	1.55	0.07	0.16	0.10
Alpha variant	-0.16	0.00	-0.01	0. 73
Delta variant	-0.21	0.01	-0.08	0.14
Constant	14.59	0.000	2.27	0.19
65 years old or older				
At least one dose vaccination 14 days prior	-0.12	0.00	-0.14	0.00
Alpha variant	0.02	0.50	0.00	0.89
Delta variant	0.18	0.01	0.18	0.03
Constant	11.54	0.00	16.69	0.00

Notes: Vaccination coverage and proportions of Alpha and Delta variants were measured three weeks before the hospitalized week for severity rates for all ages. These lags for inpatients younger than 65 years old were zero for severity and six for fatality. For inpatients 65 years old or older, these were one for both dependent variables. The severity rate was defined as the rate of patients who used a respiratory ventilator during their hospital stay among all infected inpatients who were hospitalized the same week. The fatality rate was defined as the rate of inpatients who died among all infected inpatients who were hospitalized the same week. The study period was from week 1 (Wave 1) through week 46, 2021 (Wave 5). The parts highlighted in yellow are significant except for constant terms.

patients or patients with mild symptoms who required no oxygen therapy were admitted optionally based on medical criteria for high risk of exacerbation. They were allowed to stay at home if the number of COVID-19 patients was increasing (*20*). Furthermore, in cases of an explosive increase, the criteria of hospitalization for asymptomatic patients or patients with mild symptoms who did not require oxygen therapy were probably affected heavily by the scarcity of medical resources or social situations such as support for their staying at home and recuperation at home, aside from pure medical criteria. Under these circumstances, we evaluated the pathogenicity of Alpha and Delta variants and vaccine effectiveness in 2021.

Because the criteria of hospitalization for patients with COVID-19 might have differed for the wave 5, we defined the severity and fatality rates for inpatients with oxygen therapy. From a medical perspective, the criteria for oxygen therapy might be less affected by social situations such as scarcity of medical resources than by criteria for hospitalization. Because the number of inpatients with oxygen therapy was not published in general, we had to use database covering several hospitals and thus covering a sufficient number of inpatients potentially to evaluate of the severity of Alpha and Delta variants and vaccine effectiveness.

As shown in Table 2, the severity and fatality rates for patients 65 years old or older showed negative association with vaccination coverage and positive association with the Delta variant. Findings indicate that vaccination reduced the severity and that the proportion of the Delta variant increased severity, which findings are consistent with those obtained from earlier studies (*5-7*,*18*,*19*).

However, some results were not consistent with those reported from earlier studies. For example, the proportion of the Alpha variant and Delta variant were negatively associated with the severity rate for patients younger than 65 years old. However, no report of the relevant literature has described a study of lower pathogenicity for Alpha and Delta variants.

Some results in severity and fatality were not consistent. This difference might indicate that patients who finally died became more severely ill even in a few weeks than patients who eventually survived, but who received oxygen therapy.

For patients younger than 65 years old, the proportions of Alpha and Delta variant showed significantly negative association with the severity rate, which means that the Alpha and Delta variants had less pathogenicity for patients younger than 65 years old. These results were unexpected. In Table 1, the highest coefficient of determination for severity was six weeks before. It might be too long a period from infection to hospitalization for inpatients with oxygen therapy. Overall, coefficients of determination among younger patients were lower than they were among older inpatients. In this sense, the estimation for severity among younger inpatients might not be credible. This might be the reason that these results for patients younger than 65 years old were unexpected. Furthermore, one potential reason for the lower pathogenicity of Alpha and Delta variants might be differences of the age distribution of patients with oxygen therapy between waves for which the original strain was dominant and ones for which Alpha and Delta variants were dominant. One potential reason for the lower pathogenicity of Alpha and Delta variants might be differences of age distributions of patients with oxygen therapy among waves dominated by the original or Alpha and Delta variants. The proportion of inpatients younger than 65 years old with oxygen therapy in the wave 3, which was dominated by the original variant, was 28.0%. Their proportion in the wave 4, which was dominated by the Alpha variant, was 43.9%. However, their proportion in the wave 5, which was dominated by the Delta variant, became to be 78.7%. Consequently, the proportion of inpatients younger than 65 years old with oxygen therapy increased. If the severity and fatality rates were lower for patients younger than 65 years old than for patients 65 years old or older, then the results of the Alpha and Delta variants would not be significantly positive for patients of all ages and for patients younger than 65 years old. Whichever might be true, because the results were those of mixed association among Alpha and Delta variants and pathogenicity, more sophisticated analyses using more data must be done to reach a definitive conclusion.

An earlier study investigating the effectiveness of vaccination against Alpha and Delta variants showed that vaccination reduced hospitalizations or deaths. Moreover, its effectiveness for patients 60 years old or older was lower than that for patients younger than 60 years old in test-negative design (*19*). Another study presented that the case fatality rate was decreasing, and Japan achieved high vaccination rate (*21*). In our study, the vaccination coverage for all ages and for patients 65 years old or older was found to be significant, as shown in Table 2. These findings might depend on the vaccination strategy pursued in Japan. Vaccination for healthcare workers started on 17 February 2021 (Week 7, 2021, Wave 3). Later, vaccination for patients 65 years old or older started on 12 April 2021 (Week 15, 2021, Wave 4). The proportion of that age group who had at least one vaccination was about 80% by July, as presented in Figure 5. The severity and mortality rates for patients 65 years old or older appears to be declining in Figures 3 and 4, possibly because the starting vaccination was in the same period as the Delta variant emerged, as presented in Figure 5. For all ages, vaccination coverage with at least one vaccination was only 40–50% by late August, when the Delta variant emerged. Vaccination coverage was not associated significantly with severity or fatality for patients younger than 65 years old, probably because vaccination had started for patients 65 years

old or older. Most patients younger than 65 years old were not vaccinated at that time. Results might reflect vaccine effects for patients 65 years old or older. The age distribution of inpatients and of confirmed patients came to reflect more patients younger than 65 years old, for whom the severity and fatality risk were lower than for other patients.

Definition of severity as extracorporeal membrane oxygenation (ECMO) using instead of ventilator using in this study might be possible potentially. However, limitation in capacity of ECMO system in a hospital might be tight especially in the latter study period. If so, severity should be downward biased during capacity of ECMO system was insufficient. Therefore, we avoided the definition of severity by ECMO using.

This study has three limitations. First, as explanatory variables, we considered only the vaccination coverage and the proportions of Alpha and Delta variants. Other factors such as treatment must also be considered. For example, some types of drugs (*22*) such as remdesivir (*23*), dexamethasone (*24*), baricitinib (*25*), casirivimab/imdevimab (*26*,*27*) and sotrovimab (*28*) were approved for COVID-19 in the study period and more widely administered in the latter period. These drugs may decrease severity and fatality and thus create lower severity and fatality in younger patients during the mutated variants strain dominated. Unfortunately, we cannot use some information of the administered drug in this study. Pathogenicity of the mutated strain and vaccine effectiveness controlled drug administration remained as the next challenge.

Second, although we confirmed the representativeness of fatality cases from MIA data, the exact numbers of patients with oxygen therapy and ventilation in Japan have not been published. Therefore, the representativeness of case severity could not be confirmed.

Third, the only targets of this study were hospitalized patients, for whom "severity rates" and "fatality" might differ from people of the general public. This point must be interpreted carefully because MIA data did not include patients who were not hospitalized.

Even in controlling inpatients' condition as necessary for oxygen therapy, we confirmed that vaccination reduced severity and fatality, and that the Alpha variant and Delta variant might increase severity and fatality among inpatients 65 years old or older, as earlier studies have shown, though such a controlling patients' condition had been never examined.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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