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ORIGINAL RESEARCH

Risk of Underlying Diseases and Effectiveness of Drugs on COVID-19 Inpatients Assessed Using Medical Claims in Japan: Retrospective Observational Study

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Background: Results of earlier studies have demonstrated underlying diseases such as cancer, diabetes mellitus, immunodeficiency, hypertension and heart failure to be risk factors for severe outcomes and mortality. Furthermore, clinical trials have shown that drugs such as antiviral drugs, antibody cocktails, steroids and anti-inflammatory drugs can be expected to prevent severe COVID-19 outcomes and death.

Methods: This study, using inpatient records from the Medical Information Analysis Databank covering national hospital organizations in Japan, was conducted to evaluate the effects of underlying diseases and/or administered drugs on mortality. Subjects were all inpatients receiving oxygen administration and inpatients using respiratory ventilators, categorized by three age classes: all ages, patients 65 years old or older, and patients younger than 65 years old. We used logistic regression to analyze outcomes for underlying diseases, administered drugs, age, sex, the proportion of the mutated strains, and vaccine coverage.

Results: Patients with hypertension, except for younger inpatients, have a lower risk of mortality (estimated coefficient 0.67 among all inpatients ($p < 0.01$): 0.77 among inpatients with oxygen therapy ($p = 0.02$) and 0.57 among inpatients with respiratory ventilation w ($p = 0.01$)). Except for younger inpatients, antibody cocktail (casirivimab/imdevimab or sotrovimab) administration was associated with a higher probability of survival (estimated coefficient 0.27 among all inpatients ($p < 0.01$)). It raised the survival probability consistently, although other drugs might have reduced the probability of survival.

Conclusion: These findings suggest that antiviral drugs (remdesivir, estimated coefficient 1.44 ($p < 0.01$)), steroids (dexamethasone, estimated coefficient 1.85 ($p < 0.01$)), and anti-inflammatory drugs (baricitinib, estimated coefficient 1.62 ($p < 0.01$), and tocilizumab, estimated coefficient 2.73 ($p < 0.01$)) might not contribute to survival. These results have not been reported from earlier studies. More sophisticated estimation procedures, such as treatment effect models, are necessary to obtain conclusive results.

Keywords: antibody cocktail, anti-inflammatory drug, antiviral drug, hypertension, steroid, variant strains

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for coronavirus disease 2019 (COVID-19), emerged at the end of December 2019 in China and quickly spread worldwide. Human-to-human transmission was observed. This transmission is through spike protein receptor binding domain and receptor angiotensin-converting enzyme 2 (ACE2). ACE2 is related to the SARS-CoV-2 entry to the host cells and replication.[1] Japan had one of the lowest fatality rates in the world in 2020.[2]

Results of earlier studies have shown underlying diseases such as cancer,[3–7] diabetes mellitus,[4,8–14] immunodeficiency,[10] hypertension,[4,8–11,15–17] and heart failure[9,11,15] as risk factors for severe outcomes or mortality for COVID-19 patients.

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Vaccination against SARS-CoV-2 was expected to prevent severe or mortality of COVID-19. In Japan, vaccination for people 65 years old and older started in April 2021. The proportion of one or more dose vaccinations reached about 90% by the end of March 2022. Vaccination for people younger than 65 years old started in July 2021. The proportion of one or more dose vaccinations reached about 70% by the end of March 2022.[18] Elderly people showed a higher proportion of one or more dose vaccinations than younger people, as an earlier study showed.[19]

Moreover, earlier studies and clinical trials have demonstrated that drugs used against COVID-19 such as antiviral drugs (remdesivir),[20] antibody cocktails (casirivimab/imdevimab or sotrovimab),[21,22] steroids (dexamethasone),[23] and anti-inflammatory drugs (baricitinib and tocilizumab)[24–26] can be expected to prevent severe COVID-19 outcomes and death. Other drugs have been used against COVID-19 such as statins,[27,28] RNA-dependent RNA polymerase inhibitors (molnupiravir and favipiravir),[29,30,34,35] protease inhibitors (nirmatrelvir/ritonavir),[29,31] and JAK inhibitor (ruxolitinib),[36] but none of those was evaluated for this study.

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.[32] One or more NHO hospitals are located in each prefecture. The NHO provides the Medical Information Analysis Databank (MIA), which collects data on medical insurance claims for outpatients and inpatients of NHO hospitals from 2010. The secondary use of MIA for epidemiological studies is available. MIA includes data related to patient characteristics and underlying diseases, medical interventions including oxygen administration and the use of respiratory ventilators, received therapy including administration of drugs, and outcomes such as discharge or death.[33] The database does not include data related to a patient's vaccination history or the causative strain. For this study, we analyzed data from 60 representative NHO hospitals with available data.

The object of this study was examination of risk factors among underlying diseases for severe COVID-19 outcomes and evaluation of the effectiveness of drugs against COVID-19 in Japan using MIA.

Methods

Data Source

This study used MIA data from the NHO for SARS-CoV-2 confirmed inpatients, including their age, sex, underlying diseases, hospitalized week, whether they received oxygen therapy and/or ventilation, administered drugs, and outcomes. Unfortunately, MIA includes no information about patient vaccine status or subtype of SARS-CoV-2. Therefore, we used data that include vaccine administration published by the Cabinet Secretariat (https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html). Moreover, the prevalence situations of Alpha, Delta and Omicron variant strains, Alpha, Delta, and Omicron variant strains, were referred from a monitoring meeting in Tokyo (https://www.bousai.metro.tokyo.lg.jp/taisaku/saigai/1013388/index.html).

The study period was January 2020 through the end of March 2022, as of May 2022. The study area was the entirety of Japan.

Definitions of Variables

Data related to the patients' physical condition included age and sex.

As underlying diseases, we examined cancer (C00-C96 in ICD10), hypertension (I10-I15), heart failure (I50, I51), and diabetes mellitus (DM) (E10-E14). It is noteworthy that a patient could have several of the considered underlying diseases. We examined effects of antiviral drug (remdesivir), antibody cocktails (casirivimab/imdevimab and sotrovimab), steroids (dexamethasone), and anti-inflammatory drugs (baricitinib and tocilizumab). Because the number of cases with antibody cocktails was insufficiently large, we did not divide it according to the drug name, either casirivimab/imdevimab or sotrovimab, and instead considered the effects of antibody cocktails overall. We selected these drugs from drugs of 15 types specified as COVID-19 treatments: remdesivir, casirivimab/imdevimab and sotrovimab, dexamethasone, baricitinib and tocilizumab. Some drugs that were shown to be ineffective in earlier studies were excluded from this examination.[37–42] Among 9737 cases of administration, remdesivir was used for 18% of inpatients, antibody cocktails including it for 4%, dexamethasone for 54%, baricitinib for 10%, and tocilizumab for 5%. These were the top five drugs used for inpatients. Therefore, we limited our analyses to these major drugs. Some patients were administered multiple

considered drugs during their hospitalization. Unfortunately, data about the timing of administration of the drug during their hospitalization were not available for this study.

Vaccine coverage was defined as the rate of completion of second-dose administration two weeks prior by age class: younger than 65 years old, or 65 years old or older.

Regarding variant strains, they were measured by percentage in the same week of admission. Omicron included BA.2 or later sublineage. Moreover, to check robustness, we used a dummy variable for data during waves 4–6 instead of the proportion of the mutated strains as an explanatory variable. By this specification, the Alpha variant strain emerged and then dominated in the fourth wave, defined as 1 March through 20 June, 2021 when the Alpha variant strain emerged and became dominant. Similarly, the Delta variant strain emerged and then dominated in the fifth wave defined as 21 June through 21 November, 2021. Omicron, BA.1 strain emerged and then became dominant in the sixth wave, defined as 22 November, 2021 to the end of study period.

The outcome was defined as death during hospitalization. Because our data are based on medical claims, we identified completely whether a patient had the considered underlying diseases and had been administered the considered drugs, or not. There were no missing data for underlying diseases or drugs. Moreover, we used the national averages as information about vaccine coverage and the mutant strains.

Patients

We presumed that all patients, as inpatients, had been infected by SARS-CoV-2. However, the criteria for hospitalization used for asymptomatic patients or patients with mild symptoms who did not require oxygen therapy were probably affected strongly by the scarcity of medical resources or social circumstances such as support for their stay at home and recuperation at home. Therefore, aside from pure medical criteria, we also limited scope of the subjects to inpatients who had received oxygen therapy or respiratory ventilation.

Statistical Analysis

To evaluate the effects of underlying diseases and/or pharmaceutical therapy, we used logistic regression to regress outcomes, whether death or not as dependent variable, on the patient physical condition, underlying diseases, pharmaceutical therapy, vaccine coverage, and prevalence in the variant strains as independent variables such as:

$$D_i = \alpha_0 + \alpha_1 A_i + \alpha_2 G_i + \sum \alpha_{3j} U_{ij} + \sum \alpha_{4j} P_{ij} + \alpha_5 V_{t(i)-3} + \alpha_6 M_{t(i)-1}$$

where subscript i denotes the ith inpatient, $t(i)$ stands for the hospitalized week of the ith inpatient, A_i denotes the age on $t(i)$, G_i is a sex dummy, U_{ij} are dummy variables for the jth underlying diseases on $t(i)$, P_{ij} are dummy variables for the administered drug during their hospitalization period, $V_{t(i)-3}$ expresses the vaccine coverage on $t(i) - 3$ week, and $M_{t(i)-1}$ signifies the proportion of the mutated strain for $t(i) - 1$week. We assumed to take one week from infection to be hospitalized and two weeks for being immune after immunization.

Moreover, because drug administration was based endogenously on the inpatient condition. Some bias might be attributable to simultaneous determination in the specification above. Therefore, we also regressed it as explanatory variables were, without administered drugs as

$$D_i = \beta_0 + \beta_1 A_i + \beta_2 G_i + \sum \beta_{3j} U_{ij} + \beta_5 V_{t(i)-3} + \beta_6 M_{t(i)-1}$$

Finally, we regressed the outcome on the same explanatory variables, but using the wave period instead of the proportion of the variant strains: Alpha, Delta and Omicron such as

$$D_i = \gamma_0 + \gamma_1 A_i + \gamma_2 G_i + \sum \gamma_{3j} U_{ij} + \sum \gamma_{4j} P_{ij} + \gamma_5 V_{t(i)-3} + \gamma_6 M_{t(i)-1,\ or}$$

$$D_i = \delta_0 + \delta_1 A_i + \delta_2 G_i + \sum \delta_{3j} U_{ij} + \delta_5 V_{t(i)-3} + \delta_6 M_{t(i)-1}$$

All statistical analyses were conducted using software (SE 17.0; Stata Corp.). We adopted 5% as significance level.

Ethical Considerations

Individual informed consent was not required to conduct this study because the dataset was provided as anonymized data by NHO.[33] This study was approved by the Ethics Committee of Mie Hospital (Approval No. 2020-89). Specific permission to use MIA data was obtained from the NHO (Registration No. 1201003).

Results

Figure 1 presents the number of new COVID-19 hospitalizations from MIA data and the number of patients who had been administered drugs for treatment of COVID-19 during their hospitalization by the hospitalized week. The findings indicate that the most administered drug against COVID-19 in 2020 and 2021 was dexamethasone, but it was remdesivir in 2022. The numbers of patients who had been administered drugs closely paralleled the numbers of new COVID-19 hospitalizations.

Figure 2 shows the number of underlying diseases of SARS-CoV-2 infected inpatients in MIA data at their hospitalization. The number of all underlying diseases changed according to the increasing and decreasing of inpatients who had been infected by SARS-CoV-2. Throughout the study period, there were more inpatients with hypertension and diabetes mellitus than inpatients with cancer and heart failure.

Table 1 presents the estimation results obtained for all inpatients, inpatients receiving oxygen therapy and inpatients who used ventilators of all ages, 65 years old and older, or younger than 65 years old. Common results among these populations were odds of age greater than one, ie, rising risk of mortality by age, even in younger people.

Regarding underlying diseases, hypertension was associated with reduced risk of mortality, except for younger inpatients treated with oxygen therapy or a ventilator. That finding suggests that patients with hypertension have a higher probability of survival. Heart failure and cancer were associated with significantly elevated risk in some

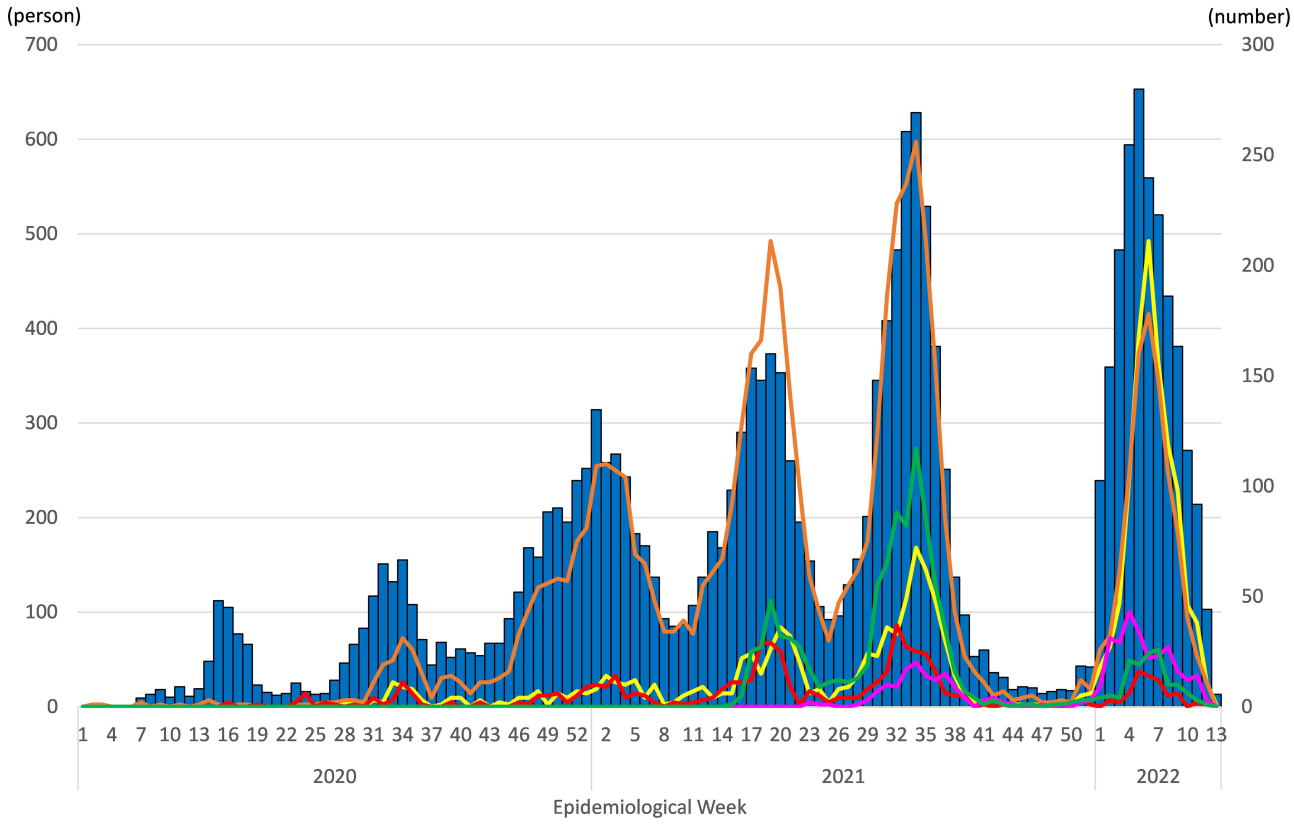

Figure 1 Number of new hospitalizations in MIA data and number of drugs used against COVID-19.
Notes: Blue bars show the numbers of newly COVID-19 hospitalizations in MIA data by their hospitalized week measured by the left scale. Yellow, orange, red, green, and pink lines, respectively, represent the number of inpatients who had been administered remdesivir, dexamethasone, tocilizumab, baricitinib and casirivimab/imdevimab or sotrovimab by their hospitalized week, as shown on the right scale. A single patient could have been administered several of the considered drugs.

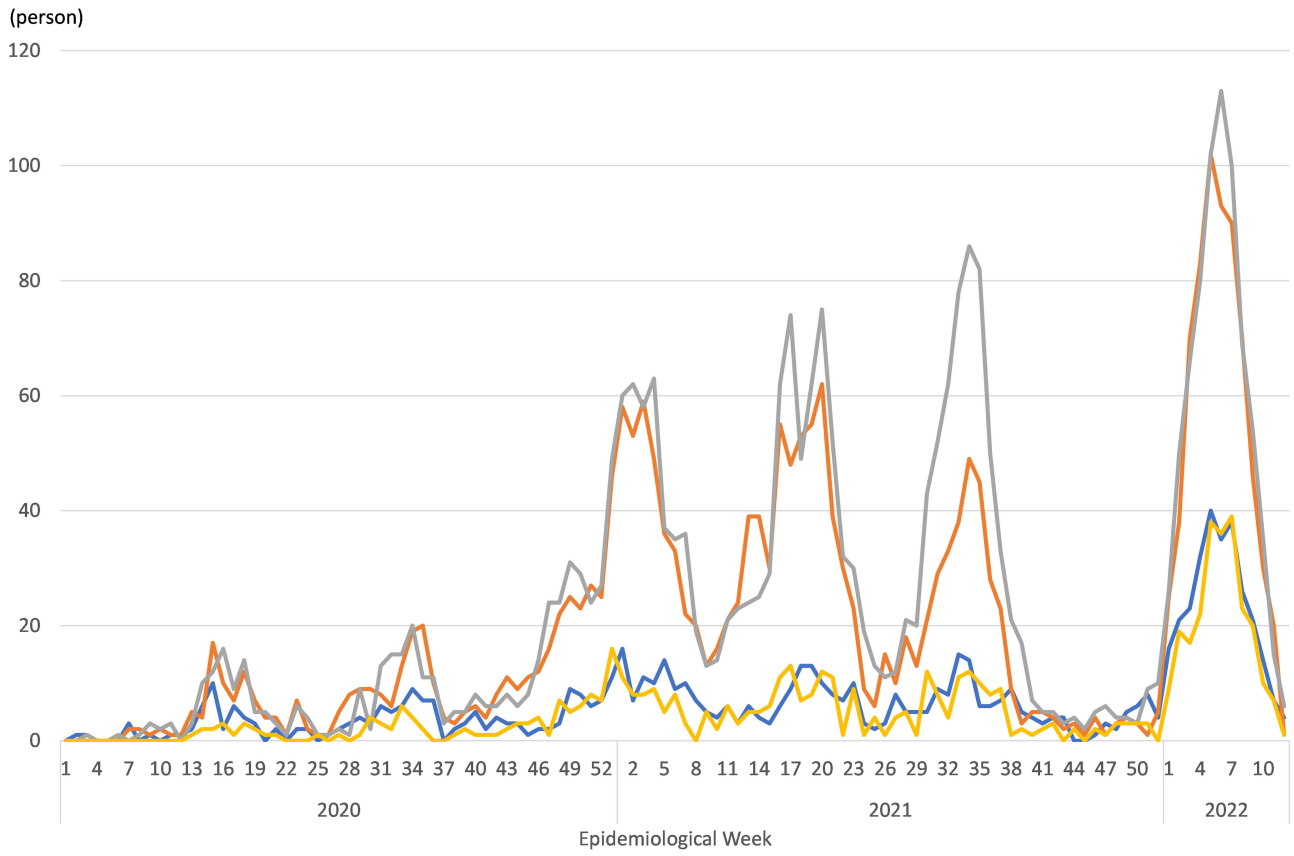

Figure 2 Number of underlying diseases of SARS-CoV-2 infected inpatients, by MIA data.
Notes: Blue, orange, gray, and yellow lines, respectively, represent the numbers of underlying diseases in which inpatients with cancer, hypertension, diabetes mellitus, and heart failure by their hospitalized week. One patient could have multiple considered underlying diseases.

estimations. Most results for DM were not significant. However, it might be associated with higher survival among younger inpatients, including those without oxygen therapy or a ventilator and older inpatients with a ventilator.

Regarding the administered drugs, the odds of casirivimab/imdevimab or sotrovimab administration, except for younger inpatients, were significantly lower than one in some estimations, indicating that patients administered casirivimab/imdevimab or sotrovimab have a higher probability of survival. Odds of the other examined drugs are greater than one, suggesting that these drugs reduced patients' probability of survival.

Results related to mutated strains were mixed. Among all inpatients, the proportions of mutated strains, whether Alpha, Delta or Omicron, were not different from those of the original strain. However, among inpatients of all ages who had received oxygen therapy, Delta and Omicron variant strains showed lower mortality than for the original strain. That finding was not shown by age class. By contrast, the Alpha variant strain was associated with higher mortality than the original strain among inpatients of all ages and those younger than 65 years old who had used a ventilator.

Table 2 presents estimation results excluding drugs from explanatory variables: DM among all inpatients of all ages was found to be significant. However, for hypertension among inpatients 65 years old or older who had received oxygen therapy, the proportion of Omicron among inpatients receiving oxygen therapy in all ages, and DM among inpatients 65 years old or older with ventilator use was not significant. Differences in the estimated coefficients of these variables were less than 10% in absolute terms.

Table 3 presents estimation results obtained using dummy variables during waves 4–6 instead of the proportions of the mutated strains. The results were almost identical to those presented in Table 1. Exceptions were baricitinib among inpatients receiving oxygen therapy in patients of all age. No variable shown in Table 1 is significantly different from the estimated sign. Therefore, using the period instead of the proportion of the mutated strains confirmed the estimated results shown in Table 1.

Table 1 Estimation Results of Logistic Regression for Death with the Administered Drug and Proportion of Mutated Strains

	All Ages		65 Years Old or Older		Younger Than 65 Years Old	
	Estimated Coefficient	***p***	**Estimated Coefficient**	***p***	**Estimated Coefficient**	***p***
All inpatients						
Age	1.09	0.00	1.08	0.00	1.09	0.00
Gender	0.56	0.00	0.56	0.00	0.53	0.01
Cancer	2.05	0.00	1.74	0.00	6.18	0.00
Hypertension	0.67	0.00	0.70	0.00	0.40	0.01
DM	1.12	0.18	1.01	0.93	2.10	0.00
Heart failure	1.67	0.00	1.57	0.00	4.64	0.00
Completed two-dose vaccination 14 days prior	1.00	1.00	0.99	0.43	1.02	0.21
Proportion of Alpha variant strain (%)	1.00	0.09	1.00	0.22	1.00	0.37
Proportion of Delta variant strain (%)	1.00	0.54	1.01	0.50	1.00	0.58
Proportion of Omicron variant strain (%)	1.00	0.39	1.01	0.54	0.99	0.23
Remdesivir	1.44	0.00	1.47	0.00	1.11	0.74
Casirivimab/imdevimab or sotrovimab	0.27	0.00	0.25	0.00	0.52	0.52
Dexamethasone	1.85	0.00	1.91	0.00	1.44	0.11
Baricitinib	1.62	0.00	1.79	0.00	1.00	0.99
Tocilizumab	2.73	0.00	2.66	0.00	3.05	0.00
Constant	0.00	0.00	0.00	0.00	0.00	0.00
Number of samples	18,566		7224		11,332	
Adjusted coefficient of determination (R^2)	0.24		0.11		0.18	
Inpatients receiving oxygen therapy						
Age	1.09	0.00	1.09	0.00	1.05	0.02
Gender	0.71	0.00	0.68	0.00	1.01	0.98
Cancer	2.81	0.00	2.20	0.00	20.05	0.00
Hypertension	0.77	0.02	0.79	0.05	0.50	0.22
DM	0.86	0.16	0.85	0.16	0.95	0.90
Heart failure	1.44	0.01	1.40	0.02	3.10	0.11
Completed two-dose vaccination 14 days prior	1.01	0.11	1.00	0.86	1.00	0.89
Proportion of Alpha variant strain (%)	1.00	0.22	1.00	0.18	1.00	0.57
Proportion of Delta variant strain (%)	0.99	0.01	1.00	0.99	0.99	0.27
Proportion of Omicron variant strain (%)	0.99	0.04	1.00	0.95	0.99	0.57
Remdesivir	1.25	0.06	1.22	0.10	1.38	0.46

(*Continued*)

Table 1 (Continued).

	All Ages		65 Years Old or Older		Younger Than 65 Years Old	
	Estimated Coefficient	***p***	**Estimated Coefficient**	***p***	**Estimated Coefficient**	***p***
Casirivimab/imdevimab or sotrovimab	0.43	0.06	0.37	0.04	2.12	0.53
Dexamethasone	1.27	0.02	1.32	0.01	0.95	0.89
Baricitinib	1.37	0.06	1.43	0.04	0.93	0.89
Tocilizumab	2.41	0.00	2.46	0.00	2.17	0.16
Constant	0.00	0.00	0.00	0.00	0.00	0.00
Number of samples	6403		3612		2791	
Adjusted coefficient of determination (R^2)	0.20		0.09		0.20	
Inpatients receiving respiratory ventilation						
Age	1.07	0.00	1.08	0.00	1.05	0.01
Gender	0.90	0.53	0.95	0.79	0.60	0.22
Cancer	0.86	0.66	0.69	0.32	4.37	0.14
Hypertension	0.57	0.01	0.59	0.02	0.40	0.06
DM	0.82	0.23	0.67	0.05	1.43	0.28
Heart failure	1.25	0.48	0.99	0.97	7.44	0.02
Completed two-dose vaccination 14 days prior	1.00	0.68	0.93	0.10	1.03	0.20
Proportion of Alpha variant strain (%)	1.01	0.00	1.01	0.08	1.01	0.03
Proportion of Delta variant strain (%)	1.01	0.20	1.07	0.09	1.00	0.54
Proportion of Omicron variant strain (%)	1.01	0.13	1.08	0.08	0.99	0.70
Remdesivir	1.00	0.98	1.06	0.81	0.71	0.45
Casirivimab/imdevimab or sotrovimab	0.09	0.03	0.09	0.03	NA	NA
Dexamethasone	0.83	0.25	0.76	0.15	1.05	0.89
Baricitinib	0.91	0.70	1.20	0.58	0.51	0.11
Tocilizumab	1.28	0.29	1.47	0.18	0.74	0.51
Constant	0.01	0.00	0.00	0.00	0.01	0.00
Number of samples	923		571		352	
Adjusted coefficient of determination (R^2)	0.12		0.08		0.09	

Note: Yellow denotes significance.
Abbreviation: DM, diabetes mellitus.

As shown in Table 1 and Table 3, no inference about casirivimab/imdevimab or sotrovimab could be made because of the small number of so-treated younger inpatients with a ventilator. The tables show estimation results excluding those for casirivimab/imdevimab or sotrovimab in the explanatory variables.

Table 2 Estimation Results of Logistic Regression for Death with Proportion of the Mutated Strains and with and without Administered Drugs

	All Ages		65 Years Old or Older		Younger Than 65 Years Old	
	Estimated Coefficient	***p***	**Estimated Coefficient**	***p***	**Estimated Coefficient**	***p***
All inpatients						
Age	1.09	0.00	1.08	0.00	1.10	0.00
Gender	0.51	0.00	0.52	0.00	0.52	0.01
Cancer	2.01	0.00	1.69	0.00	5.96	0.00
Hypertension	0.67	0.00	0.71	0.00	0.40	0.01
DM	1.23	0.01	1.10	0.31	2.28	0.00
Heart failure	1.63	0.00	1.55	0.00	4.32	0.00
Completed two-dose vaccination 14 days prior	1.00	0.18	0.98	0.34	1.01	0.39
Proportion of Alpha variant strain (%)	1.01	0.00	1.01	0.00	1.01	0.18
Proportion of Delta variant strain (%)	1.00	0.39	1.02	0.39	1.00	0.93
Proportion of Omicron variant strain (%)	1.00	0.64	1.01	0.42	0.99	0.38
Constant	0.00	0.00	0.00	0.00	0.00	0.00
Number of samples	18,566		7224		11,332	
Adjusted coefficient of determination (R^2)	0.21		0.07		0.17	
Inpatients receiving oxygen therapy						
Age	1.09	0.00	1.08	0.00	1.06	0.01
Gender	0.68	0.00	0.66	0.00	1.01	0.99
Cancer	2.76	0.00	2.14	0.00	20.72	0.00
Hypertension	0.77	0.02	0.80	0.05	0.50	0.22
DM	0.89	0.29	0.89	0.29	1.00	1.00
Heart failure	1.38	0.03	1.35	0.04	2.65	0.17
Completed two-dose vaccination 14 days prior	1.01	0.21	1.00	0.86	1.00	0.89
Proportion of Alpha variant strain (%)	1.00	0.05	1.00	0.04	1.00	0.53
Proportion of Delta variant strain (%)	0.99	0.03	1.00	0.98	0.99	0.26
Proportion of Omicron variant strain (%)	0.99	0.09	1.00	0.94	0.99	0.62
Constant	0.00	0.00	0.00	0.00	0.00	0.00
Number of samples	6403		3612		2791	
Adjusted coefficient of determination (R^2)	0.19		0.07		0.20	

(*Continued*)

Table 2 (Continued).

	All Ages		65 Years Old or Older		Younger Than 65 Years Old	
	Estimated Coefficient	***p***	**Estimated Coefficient**	***p***	**Estimated Coefficient**	***p***
Inpatients receiving respiratory ventilation						
Age	1.07	0.00	1.07	0.00	1.05	0.01
Gender	0.89	0.51	0.96	0.85	0.59	0.21
Cancer	0.83	0.60	0.67	0.28	4.18	0.15
Hypertension	0.57	0.01	0.59	0.02	0.41	0.07
DM	0.84	0.30	0.70	0.08	1.37	0.33
Heart failure	1.14	0.67	0.88	0.70	7.59	0.02
Completed two-dose vaccination 14 days prior	1.00	0.72	0.94	0.13	1.03	0.12
Proportion of Alpha variant strain (%)	1.01	0.01	1.01	0.10	1.01	0.05
Proportion of Delta variant strain (%)	1.01	0.22	1.07	0.11	1.00	0.99
Proportion of Omicron variant strain (%)	1.01	0.15	1.07	0.10	0.99	0.48
Constant	0.01	0.00	0.00	0.00	0.01	0.00
Number of samples	923		571		352	
Adjusted coefficient of determination (R^2)	0.11		0.07		0.08	

Note: Yellow denotes significance.
Abbreviation: DM, diabetes mellitus.

Table 3 Estimation Results of Logistic Regression for Death with Administered Drugs and Periods of Waves When the Mutated Strains Were Dominant

	All Ages		65 Years Old or Older		Younger Than 65 Years Old	
	Estimated Coefficient	***p***	**Estimated Coefficient**	***p***	**Estimated Coefficient**	***p***
All inpatients						
Age	1.09	0.00	1.08	0.00	1.09	0.00
Gender	0.56	0.00	0.57	0.00	0.53	0.01
Cancer	2.05	0.00	1.75	0.00	6.39	0.00
Hypertension	0.67	0.00	0.70	0.00	0.39	0.01
DM	1.12	0.19	1.01	0.92	2.11	0.00
Heart failure	1.67	0.00	1.57	0.00	4.65	0.00
Completed two-dose vaccination 14 days prior	1.00	0.82	1.00	0.93	1.02	0.21
4th wave	1.19	0.08	1.17	0.15	1.53	0.16

(*Continued*)

Table 3 (Continued).

	All Ages		65 Years Old or Older		Younger Than 65 Years Old	
	Estimated Coefficient	***p***	**Estimated Coefficient**	***p***	**Estimated Coefficient**	***p***
5th wave	0.80	0.34	0.80	0.63	0.86	0.73
6th wave	0.70	0.25	0.70	0.49	0.32	0.27
Remdesivir	1.44	0.00	1.46	0.00	1.10	0.76
Casirivimab/imdevimab or sotrovimab	0.27	0.00	0.25	0.00	0.50	0.51
Dexamethasone	1.85	0.00	1.91	0.00	1.40	0.14
Baricitinib	1.66	0.00	1.85	0.00	1.01	0.98
Tocilizumab	2.74	0.00	2.68	0.00	3.04	0.00
Constant	0.00	0.00	0.00	0.00	0.00	0.00
Number of samples	18,566		7224		11,332	
Adjusted coefficient of determination (R^2)	0.24		0.11		0.18	
Inpatients receiving oxygen therapy						
Age	1.09	0.00	1.09	0.00	1.05	0.02
Gender	0.70	0.00	0.68	0.00	1.00	0.99
Cancer	2.83	0.00	2.20	0.00	20.54	0.00
Hypertension	0.77	0.02	0.79	0.05	0.50	0.22
DM	0.86	0.16	0.85	0.16	0.94	0.88
Heart failure	1.43	0.02	1.40	0.03	3.12	0.11
Completed two-dose vaccination 14 days prior	1.01	0.16	1.00	0.78	1.01	0.79
4th wave	1.14	0.30	1.20	0.16	0.79	0.61
5th wave	0.39	0.01	0.61	0.41	0.38	0.21
6th wave	0.39	0.04	0.64	0.51	0.23	0.45
Remdesivir	1.26	0.05	1.23	0.10	1.40	0.44
Casirivimab/imdevimab or sotrovimab	0.44	0.06	0.37	0.04	2.09	0.53
Dexamethasone	1.27	0.02	1.32	0.01	0.94	0.88
Baricitinib	1.39	0.04	1.47	0.03	0.90	0.85
Tocilizumab	2.39	0.00	2.46	0.00	2.10	0.18
Constant	0.00	0.00	0.00	0.00	0.00	0.00
Number of samples	6403		3612		2791	
Adjusted coefficient of determination (R^2)	0.20		0.09		0.20	

(*Continued*)

Table 3 (Continued).

	All Ages		65 Years Old or Older		Younger Than 65 Years Old	
	Estimated Coefficient	***p***	**Estimated Coefficient**	***p***	**Estimated Coefficient**	***p***
Inpatients receiving respiratory ventilation						
Age	1.07	0.00	1.08	0.00	1.05	0.01
Gender	0.90	0.56	0.95	0.79	0.65	0.29
Cancer	0.87	0.69	0.71	0.35	4.14	0.16
Hypertension	0.57	0.01	0.57	0.01	0.43	0.09
DM	0.81	0.20	0.65	0.04	1.40	0.30
Heart failure	1.23	0.51	0.98	0.96	7.49	0.02
Completed two-dose vaccination 14 days prior	1.00	0.58	1.00	0.89	1.01	0.67
4th wave	1.85	0.00	1.80	0.01	2.65	0.05
5th wave	1.80	0.12	1.44	0.70	2.51	0.19
6th wave	2.72	0.09	1.84	0.58	2.58	0.58
Remdesivir	1.00	0.99	1.06	0.81	0.67	0.39
Casirivimab/imdevimab or sotrovimab	0.09	0.03	0.11	0.05	N.A.	N.A.
Dexamethasone	0.84	0.26	0.77	0.18	0.99	0.97
Baricitinib	0.93	0.78	1.31	0.40	0.52	0.12
Tocilizumab	1.28	0.29	1.48	0.17	0.72	0.47
Constant	0.01	0.00	0.00	0.00	0.01	0.00
Number of samples	923		571		352	
Adjusted coefficient of determination (R^2)	0.12		0.08		0.09	

Notes: Yellow denotes significance. The fourth wave was defined as 1 March through 20 June, 2021, when the Alpha variant strain emerged and became dominant. Similarly, the fifth wave was defined as 21 June through 21 November, 2021, when the Delta variant strain emerged and then became dominant. The sixth wave was defined as 22 November, 2021 to the end of the study period, when the Omicron, BA.1 strain emerged and then became dominant.
Abbreviation: DM, diabetes mellitus.

Discussion

Findings indicated that antibody cocktails (casirivimab/imdevimab or sotrovimab) raised the probability of survival, but other drugs might have reduced the probability of survival. These counterintuitive indications might be attributable to reverse causality: higher risk of mortality led to the use of these drugs. In other words, the selection of who had been administered these drugs, or not, is expected to be endogenous and determined by the patient condition. In this sense, drug administration might be inappropriate as an explanatory variable to explain outcomes. To resolve this difficulty, patients with almost identical conditions must be compared, with one patient coincidentally using the drug and another patient not using the drug. For such an experiment, we would be able to assign the drug randomly. However, when using these observational data after the fact, such experiments are impossible. Under these circumstances, propensity score matching provides a statistical experiment.[43–45] That is expected to be a challenge for future study.

Similarly, findings indicate that patients with hypertension have a higher probability of survival than patients without cancer, hypertension, DM, or heart failure. At first glance, this result was inconsistent with those of earlier studies

indicating hypertension as a risk factor for developing COVID-19.[4,8–11,15–17] In 2020, COVID-19 patients who were taking angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin-receptor blockers (ARB) were suspected to be severely ill because the SARS-CoV-2 receptor is angiotensin-converting enzyme 2. However, some reports have described that taking ACE-I or ARB did not increase the risk of severe COVID-19 outcome or death.[46,47] In fact, reports of some studies have suggested ACE-I or ARB as effective for preventing a severe COVID-19 outcome or death.[48–52] Therefore, the risk posed by hypertension might be controversial. Our results might support the effectiveness of ACE-I or ARB because many patients are taking these medicines. This finding might partially explain the result that patients with hypertension tended to avoid a severe COVID-19 outcome or death. Furthermore, this finding also suggests that patients with hypertension, because they were characterized as high-risk patients, received more cautiously administered care than patients with no underlying disease. Consequently, they had a higher probability of survival. However, we defined hypertension based on the diagnosis. We did not depend on blood pressure test results. Therefore, this definition for hypertension might include patients with very mild hypertension. For that reason, their probability of survival was estimated as greater than for inpatients without hypertension. Whichever happened to be the case, more careful analysis is needed before one could conclude that hypertension was not a risk factor for COVID-19.

Patients with cancer have a significantly high risk of mortality among all inpatients and inpatients with oxygen therapy. This result is consistent with those of earlier studies.[3–7] However, they have a low risk of mortality among inpatients receiving respiratory ventilation, although it was not significant. This might be true because inpatients with cancer, especially elderly inpatients, tend to avoid intensive care. Only inpatients with better condition might receive respiratory ventilation. Then the risk of mortality might be low. Inpatients with heart failure might have the same reason for low risk of mortality among inpatients receiving respiratory ventilation. Data from the MIA with more cases might provide detailed results such as indications of breakthrough infection, and detailed risk factors in each disease for mortality.[53]

The obtained results showed that vaccination coverage did not contribute to survival. Vaccine for COVID-19 was expected to reduce infection and severity when recipients were infected.[54] Vaccination might not be expected to improve the probability for survival. For this study, we examined vaccine effects among all inpatients or inpatients receiving oxygen therapy or ventilator use. Therefore, the subjects were presumed to be severe cases. For that reason, vaccine effectiveness might not be confirmed by our data. Additionally, we used vaccine coverage instead of the vaccination history of the patients themselves because the latter was not available in our data. If the vaccine history of the patients was available, then the results might differ.

One earlier study examined social predictors of receiving vaccination.[55] Even for COVID-19, such as study was conducted.[56] If social factors affect vaccination and if vaccines were effective to prevent severe COVID-19, then the social backgrounds of inpatients might differ before and after the initiation of vaccination. For instance, because vaccination had started for old persons at first, the average age among new hospitalized patients can be expected to be lower. This changing age distribution of inpatients might affect the results. In general, younger inpatients have a higher probability of survival than older patients with the same condition other than age. Assuming those effects and knowing that some drugs had been approved later during the study period, the effects of drug administration can be expected to be biased upwardly by the changing age distribution attributable to vaccination initiation. Therefore, their effectiveness might be lower than the obtained result. Other social factors such as income, health insurance status or religion are not recorded in medical claim data. Therefore, we cannot examine the effects of these factors. Particularly, vaccination and treatment for COVID-19 required no payment for patients. All costs were paid by the government of Japan. Income and health insurance status were presumed to be independent of decisions about receiving vaccinations or visiting a doctor. No report describes a study of vaccination against COVID-19 in Japan examining that point. Moreover, decisions about drug administration and using oxygen therapy or respiratory ventilation were made by doctors. Therefore, these social factors other than age were presumed not to affect the results of this study.

We did not find the Delta and Omicron variant strain to have higher pathogenicity than the original or Alpha variant strain. One excess mortality study showed higher excess mortality during Delta and Omicron variant strain dominance in Japan.[57] Our obtained result might be inconsistent with that study which found excess mortality. Nevertheless, it is noteworthy that this study examined the rate of mortality among inpatients, whereas the excess mortality study cited

above examined the number of mortality cases attributable to all causes. Even if the mortality rate among inpatients was smaller, if the number of infected persons was much larger, then the number of mortalities could be larger. Therefore, our result might not be inconsistent with those of the excess mortality study.

Different timing of treatment initiation among patients might have affected the results. For example, patients with severe pneumonia but who had not been treated yet might have died before being administered the appropriate drug. If so, time-immortal bias might be severe.[58] An example of this bias was death before operation, even though an operation had been planned. In such a case, these biases increase the risk of no-operation and therefore overestimate the benefits of the operation. However, because this study considered the administration of drugs, the period from decision-to-use to actual administration was not long, unlike the case of a surgical or other operation. We also examined these points for inpatients receiving oxygen therapy or respiratory ventilation. In these estimations, the inpatient condition was better-controlled than estimation among all inpatients: time-immortal bias was expected to be smaller, perhaps even negligible. Actually, results for drugs for severe patients (remdesivir, dexamethasone, baricitinib, and tocilizumab) showed that they did not contribute to survival. Therefore, time-immortal bias, which overestimates of treatment effectiveness, was not large. By contrast, antibody cocktails showed effectiveness. However, because these drugs were typically used for patients who were less severely ill, time-immortal bias might not be strongly applicable.

If test data such as oxygen saturation over time were used, then it would be possible to use survival analysis or a marginal structural model to evaluate drug effectiveness and to model the dynamics of development of the illness.[59] However, our data did not include such time-varying data or test data. Therefore, we must limit the information at hospitalization, except for drug administration. We confirmed that estimation results were not affected heavily, whether drug administration was included among the explanatory variables, or not.

Limitations

First, we defined severity as the mortality rate among inpatients, or inpatients receiving oxygen therapy or ventilation. Therefore, the results might differ from those found for the case-fatality rate, which has been more commonly used to indicate the pathogen severity. In general, the case-fatality rate was defined as the number of cases of mortality among all infected patients, including moderate cases, with patients were not hospitalized, or asymptomatic cases. This study did not include those moderate cases or asymptomatic cases.

Second, although the selection of drugs and decisions to use drugs were endogenous by the patient situation and drugs available at that time, we treat them as exogenous variables of the estimation model. To address this difficulty, we must use a treatment effect model with propensity score matching.

Third, because no information was available to us about the vaccination histories of the patients and strains infecting the patients, we relied on the circumstances of the vaccine coverage or prevailing strain when the patients were presumed to have been infected. This indirect information and the consequent estimation results might have been affected if the patients' vaccine history or infected strain had been available.

Fourth, because MIA is a database of medical claims, the data of MIA, especially data of the prior few weeks, might be revised slightly over a few months. For this study, we collected and analyzed MIA data from January 2020 to the end of March 2022 as of May 2022. Data and therefore estimation results might differ over time if the study period were extended. Further examinations must be undertaken with an extended period of study and a greater number of patients. Some ambiguity might result from the number of patients, which was insufficient to yield clear results. However, our MIA data were the widest dataset for inpatients including long-term outcomes and therapy in Japan. Therefore, we cannot expand the number of inpatients for improvement of the estimation, except by extending the study period. Of course, international comparisons through meta-analyses might overcome this difficulty, but such methods are beyond the scope of this study.

Fifth, we exclude camostat from analysis because it was shown to be ineffective in an earlier study.[39] However, it was administered more than antibody cocktails. Therefore, we might analyze its effectiveness in the framework of this study. It might play a role as a negative control and might evaluate the precision of estimation procedures used for this study.

Conclusion

The obtained results demonstrated that patients with hypertension have a lower risk of mortality, except for younger patients, which suggests that hypertension might not pose a risk to survival. Results also show that only antibody cocktails (casirivimab/imdevimab or sotrovimab) raise the probability of survival consistently, although other drugs might reduce the probability of survival. In other words, other drugs such as antiviral drugs (remdesivir), steroids (dexamethasone), and anti-inflammatory drugs (baricitinib and tocilizumab) might not contribute to survival. These results have not been reported from any earlier study. More sophisticated estimation procedures such as treatment effect models must be used to obtain conclusive results.

Data Sharing Statement

The data in this study are available from the National Hospital Organization, but the availability of these data is restricted because of privacy reasons. These data were used under license for this study and are therefore not available to the public. Data are available from the authors with permission of the National Hospital Organization.

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Disclosure

The authors report no conflicts of interest related to this work.

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