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Drug Effectiveness for COVID-19 by Average Treatment Effects with Multiple Choice using Medical Claim Data of the Largest Hospital Network in Japan: Retrospective Study

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Abstract

During the COVID-19 pandemic, several drugs were developed, including steroids, antiviral drugs, anti-inflammatory drugs, and monoclonal antibodies, which have shown potential in preventing severe COVID-19. Notably, monoclonal antibodies were targeted for mild to moderate cases, while anti-inflammatory drugs and antiviral drugs were intended for severe cases. Analysing drug effectiveness using medical claim data, especially with propensity score matching, becomes challenging due to this drug-specific treatment assignment. This could lead to biased results and hinder accurate evaluation of drug effects. To assess drug effectiveness, we employed an estimated model of drug choice using observational data from Japan. The study population comprised 21,727 hospitalized COVID-19 patients in hospitals under the National Hospital Organization (NHO), divided into three age groups: all ages (21,727 patients), ≥ 65 years old (8,734), and < 65 years old (12,993). By applying an average treatment effect model with multiple drug choices, we analysed the database to evaluate the simultaneous effect of provided drugs. The explanatory variables included demographic characteristics, underlying diseases, provided drugs, proportion of variants, and vaccine coverage. The first logistic regression analysed drug choice, and the secondary logistic regression estimated the average treatment effect for the outcome of death during hospitalization. The results indicated a higher probability of survival with monoclonal antibodies in older patients receiving oxygen therapy significantly (-0.094 in three choice model, -0.091 in four choice model), while other drugs did not show significant survival benefits. The model highlighted the effectiveness of monoclonal antibodies for patients aged 65 years or older in improving survival.

Keywords: COVID-19, Monoclonal antibody, Antiviral drug, Average treatment effect, Multiple choice.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19). From January 2020, COVID-19 spread worldwide and caused a pandemic. Several drugs for other diseases such as rheumatoid arthritis were used to treat COVID-19. Some drugs were newly developed during the pandemic. The COVID-19 mortality rate in Japan has declined because of various factors such as vaccination, mutated strains, and drugs [1].

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Several drugs have been shown to be effective against COVID-19 in previous studies. For example, antiviral drugs (remdesivir), steroids (dexamethasone), statins, anti-inflammatory drugs (baricitinib and tocilizumab), protease inhibitors (nirmatrelvir, ritonavir), RNA-dependent RNA polymerase inhibitor (molnupiravir), and monoclonal antibodies (casirivimab/imdevimab and sotrovimab) are demonstrated to prevent severe COVID-19 and death due to COVID-19 [2-13]. However, changes in the outbreak situation such as the emergence of mutated strains, immunization, development of therapy could influence the drug's effectiveness. Therefore, it is important to evaluate effectiveness of drugs constantly using observational data. Random assignment after drug approval to assess its effectiveness is difficult because of ethical reason. Moreover, patients who are more likely to develop severe illness have higher probability of being administered drugs generally.

We evaluated the effectiveness of several drugs in our earlier studies [14,15]. However, these drugs were not always administered to patients with the same severity. For instance, monoclonal antibodies were administered to patients with less-severe symptoms, whereas dexamethasone, baricitinib, and tocilizumab were administered to patients with severe symptoms [16].

We strove to model the choice of drug because decision-making about what drug was administered should not be independent of the type of drug. The drug choice was determined simultaneously over all available drugs. In this study, we estimated the average treatment effect with multiple drug choices for mortality using inverse probability weighted regression adjustment to consider the use of drug combinations or switching from one drug to another.

Materials and Methods

Data sources

The National Hospital Organization (NHO) of Japan, a large organization of regional core hospitals accounting for about 3.4% of all beds in Japan, provides the Medical Information Analysis Databank (MIA), a database consisting of medical claims received from 60 representative NHO hospitals. It includes outpatients' and hospitalized patients' demographical characteristics, underlying diseases, medical interventions including oxygen therapy, administration of drugs, and outcomes such as discharge or death [17,18]. In this study, we used MIA sourced from hospitalized patients diagnosed as COVID-19 to verify drug effectiveness. We examined data on hospitalized patients encompassing variables such as age, gender, underlying diseases, date of hospitalization, date of discharge, date of death, provided drug, outcome and whether they received oxygen therapy and/or respiratory ventilation. The data on vaccination utilized in this study was sourced from publications released by the Cabinet Secretariat and prevalence data regarding mutated strains were obtained from a monitoring meeting in Tokyo as MIA includes no data related to patients' vaccination history or the causative strain of disease [19,20].

This study included the period from January 2020 to March 2022, utilizing data collected and recorded as of May 2022. The geographical scope of this study encompassed the entirety of Japan.

Subjects

The study population were all hospitalized patients diagnosed with COVID-19 between January 2020 and March 2022. We extracted data on all hospitalized patients with COVID-19 from MIA. However, we excluded some patients who were still hospitalized at the end of the study period.

In the summer of 2021, some asymptomatic or mild patients who did not require oxygen therapy could not hospitalize due to lack of medical resources in Japan [21]. In other words, the criterion for hospitalization changed during the COVID-19 pandemic influenced by social condition. Therefore, we assumed that all patients requiring oxygen therapy could be admitted to the hospital throughout the COVID-19 pandemic, and we considered not only the inclusion of all subjects but also the limitation of patients with oxygen therapy to standardize hospitalization criterion.

Definitions of variables

Drugs were considered as antiviral drugs such as remdesivir, steroids such as dexamethasone, anti-inflammatory drugs such as baricitinib and tocilizumab, and monoclonal antibodies such as sotrovimab and casirivimab/imdevimab. Since the number of patients receiving monoclonal antibodies was insufficiently large, they were not divided according to the name of the drug as sotrovimab, casirivimab/imdevimab. We considered the overall effects of monoclonal antibodies.

To use a choice model with multiple logistic regression, we classified drugs of some types: drugs for severely ill patients including antiviral drug, a steroid, and anti-inflammatory drugs; and drugs for moderately ill patients as monoclonal antibodies [2,3,6-8,12,13,16]. By this classification, drugs of three types were defined as below three types.

- Monoclonal antibodies only (sotrovimab and casirivimab/imdevimab)
- Only drugs for severe patients (remdesivir, dexamethasone, baricitinib, and tocilizumab)
- No drug considered for this study
- However, because remdesivir was sometimes administered for both severe and moderate patients, we also examined drugs of four types.
- Monoclonal antibodies only (sotrovimab and casirivimab/imdevimab)
- Antiviral drug only (remdesivir)
- Other drugs only (dexamethasone, baricitinib, and tocilizumab)
- No drug considered for this study
- The demographical characteristic in our study was defined as age and gender. Underlying diseases examined included cancer (C00-C90 in ICD10), hypertension (I10), heart failure (I50), diabetes mellitus (E10), asthma (J45), and chronic obstructive pulmonary disease (J44). Vaccine

coverage data was defined as the proportion of patients who received the second dose of the vaccine two weeks' prior, categorized into two age groups: < 65 years old and ≥ 65 years old, which is because people aged ≥ 65 are considered elderly in Japan, and various statistics and laws often use this classification [19,22]. The prevalence of mutated strains was measured as a percentage one week before admission, and the Omicron variant encompassed sublineages starting from BA.1. However, for robustness assessment, we employed a wave variable instead of relying on the proportion of mutated strains. Throughout the study period, there were six distinct waves in the number of patients observed in Japan. The wave periods were defined based on the lowest patient count from the preceding wave to the lowest count in the current wave, utilizing national data [23]. The dominant variants observed during the fourth, fifth, and sixth waves were different from each other. The fourth wave, spanning from March 1, 2021, to June 20, 2021, was characterized by the dominance of the Alpha variant. In the fifth wave, which occurred from June 21, 2021, to November 21, 2021, the Delta variant became prevalent. The sixth wave, caused by the Omicron variant, extended from November 22, 2021, until the end of the study period. We also defined the outcome as death during hospitalization.

Statistical analysis

Initially, we conducted multiple logistic regression analyses, employing explanatory variables such as demographical characteristics, underlying diseases, provided drugs, vaccine coverage, and prevalence of mutated strains, to estimate the drug choice in both the three-choice and four-choice models [24]. Subsequently, logistic regression was performed, weighting the fatality outcome by the inverse probability obtained in the first step. The same set of explanatory variables, along with a binary variable indicating the administration of the considered drugs, was used in this second step. We adopted 5% as the significance level and performed all statistical analyses using Stata Corp's Stata SE 17.0 software.

Ethical considerations

Approval for this study was obtained from the Ethics Committee of Mie Hospital (Approval No. 2020-89). The utilization of MIA was permitted by NHO, with a registration number of 1201003.

Results

Figure 1 shows the number of hospitalized patients, hospitalized patients with oxygen therapy, hospitalized patients with respiratory ventilation who were diagnosed as COVID-19 in MIA during this study period. The maximum number of hospitalized patients was 653 (February, 2022), the maximum number of hospitalized patients with oxygen therapy was 279 (August 2021), and the maximum number of hospitalized patients with respiratory ventilation was 46 (August, 2021). Table 1 demonstrates demographic characteristics of the study population by medical intervention such as oxygen therapy and respiratory ventilation. Among all hospitalized patients, there were a total of 21,727 patients, with 7,180 (33.0%) requiring oxygen therapy and 995 (4.6%) requiring respiratory ventilation. The most prevalent underlying disease was diabetes mellitus in 3,241 (14.9%), followed by hypertension in 2,828 (13.0%). Among the prescribed medications, dexamethasone in 6,041 (27.8%) was the most commonly prescribed, followed by remdesivir in 1,910 (8.8%) and baricitinib in 1,087 (5.0%).

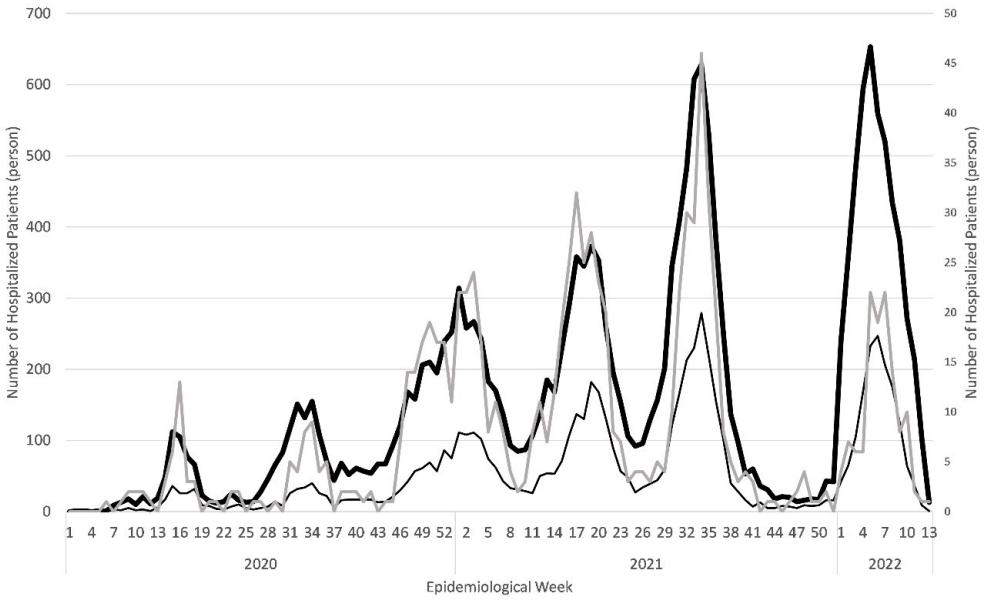

Figure 1: The number of hospitalized patients, hospitalized patients with oxygen therapy, hospitalized patients with respiratory ventilation who were diagnosed as COVID-19.
Notes: Black thick line and black thin line show the numbers of hospitalized patients and hospitalized patients with oxygen therapy (left scale). Gray line presents the number of hospitalized patients with respiratory ventilator (right scale). All these hospitalized patients were diagnosed as COVID-19 in Medical Information Analysis Databank. These data were aggregated by hospitalized week.

Characteristics	All Ages		≥ 65 years old		< 65 years old	
	n	%	n	%	n	%
All inpatients	n=21727		n=8734		n=12993	
Age						
Mean (SD)	54.3 (25.6)		79.4 (8.6)		37.4 (18.3)	
Sex						
Female	10083	46.4	4256	48.7	5827	44.8
Outcome						
Death	1028	4.7	917	10.5	111	0.9
Underlying diseases						
Cancer	1036	4.8	783	9.0	253	1.9
Hypertension	2820	13.0	2025	23.2	795	6.1
Diabetes mellitus	3241	14.9	1982	22.7	1259	9.7
Heart failure	825	3.8	672	7.7	143	1.1
Asthma	575	2.6	217	2.5	358	2.8
COPD	217	1.0	181	2.1	36	0.3
Drugs against COVID-19						
Remdesivir	1910	8.8	1121	12.8	789	6.1
Dexamethasone	6041	27.8	2928	33.5	3113	24.0
Tocilizumab	562	2.6	274	3.1	288	2.2
Baricitinib	1087	5.0	378	4.3	709	5.5
Antibody cocktails	525	2.4	349	4.0	176	1.4
Patients with oxygen therapy	n=7180		n=4240		n=2940	
Age						
Mean (SD)	67.3 (18.8)		80.2 (8.7)		48.5 (12.7)	
Sex						
Female	2822	39.3	1935	45.6	887	30.2
Outcome						
Death	701	9.8	656	15.5	45	1.5
Underlying diseases						
Cancer	501	7.0	418	9.9	83	2.8
Hypertension	1402	19.5	1044	24.6	358	12.2
Diabetes mellitus	1716	23.9	1120	26.4	596	20.3
Heart failure	493	6.9	427	10.1	5880	200.0
Asthma	236	3.3	126	3.0	110	3.7
COPD	142	2.0	120	2.8	22	0.7
Drugs against COVID-19						

Remdesivir	1333	18.6	836	19.7	497	16.9
Dexamethasone	4235	59.0	2265	53.4	1970	67.0
Tocilizumab	380	5.3	188	4.4	192	6.5
Baricitinib	962	13.4	334	7.9	628	21.4
Antibody cocktails	127	1.8	99	2.3	28	1.0
Patients with respiratory ventilator	n=995		n=617		n=378	
Age						
Mean (SD)	66.8 (14.3)		75.9 (7.0)		52.1 (10.4)	
Sex						
Female	281	28.2	207	33.5	74	19.6
Outcome						
Death	311	31.3	249	40.4	62	16.4
Underlying diseases						
Cancer	50	5.0	44	7.1	6	1.6
Hypertension	218	21.9	154	25.0	64	16.9
Diabetes mellitus	322	32.4	209	33.9	113	29.9
Heart failure	72	7.2	61	9.9	11	2.9
Asthma	31	3.1	20	3.2	11	2.9
COPD	21	2.1	16	2.6	5	1.3
Drugs against COVID-19						
Remdesivir	162	16.3	113	18.3	49	13.0
Dexamethasone	540	54.3	333	54.0	207	54.8
Tocilizumab	130	13.1	65	10.5	65	17.2
Baricitinib	149	15.0	64	10.4	85	22.5
Antibody cocktails	9	0.9	8	1.3	1	0.3

Table 1: Characteristics of study population.
Abbreviation: SD: standard deviation, COPD: chronic obstructive pulmonary disease, COVID-19: coronavirus disease 2019.

Notably, antibody cocktails in 525 (2.4%) was the least frequently prescribed drug, particularly among patients requiring respiratory ventilation (9 patients, 0.9%). There were 8,734 (40.2%) patients 65 years old and older, and 12,993 (59.8%) patients younger than 65 years old. Among the group aged 65 years old and older, the number of deaths (917 patients, 10.5%) was higher compared to the group younger than 65 years old (111 patients, 0.9%). In both age groups, hypertension (2,025 (23.2%) patients in ≥ 65 years old, 795 (6.1%) in <65 years old) and diabetes mellitus (1,982 (22.7%) patients in ≥ 65 years old, 1,259 (9.7%) in <65 years old) were the most prevalent underlying diseases, and the prescribed medications followed a similar trend to all age group. Supplementary tables present summaries of the estimation results of multinomial logit estimation obtained from the first step logistic regression with three and four choices model. Table 2 presents the estimation results of average treatment effects. Overall, in both the three-choice and four-choice models, many average treatment effects that were found to be significant have a positive sign, which means that the drugs showed lower survival probability compared to no administration of the considered drugs. Exceptional results were found for monoclonal antibodies for older hospitalized patients with oxygen therapy. In those patients, administration of the monoclonal antibodies was associated with higher survival probability than with no administration of the considered drugs. Among older patients with oxygen therapy, the utilization of other drugs such as remdesivir, dexamethasone, baricitinib, and tocilizumab demonstrated positive and significant both in the three-choice and four-choice models.

	All age		≥ 65 years old		< 65 years old	
	difference	p value	difference	p value	difference	p value
Three Choice Model						
All hospitalized patients						
Difference between monoclonal antibody only vs. None	0.353	0.000	0.240	0.769	0.4134	0.561
Difference between drug other than monoclonal antibody vs. None	0.046	0.000	0.108	0.568	0.014	0.000
Mortality rate among patients with none	0.026	0.000	0.058	0.000	-0.006	0.000
Hospitalized patients with oxygen therapy						
Difference between monoclonal antibody only vs. None	N/A	N/A	-0.094	0.000	N/A	N/A
Difference between drug other than monoclonal antibody vs. None	N/A	N/A	0.074	0.000	N/A	N/A
Mortality rate among patients with none	0.070	0.000	0.113	0.000	N/A	N/A
Four Choice Model						
All hospitalized patients						
Difference between monoclonal antibody only vs. None	0.390	0.000	N/A	N/A	N/A	N/A
Difference between Remdesivir only vs. None	0.025	0.001	N/A	N/A	0.006	0.000
Difference between drug other than monoclonal antibody or Remdesivir vs. None	0.040	0.000	N/A	N/A	0.006	0.000
Mortality rate among patients with none	0.030	0.000	N/A	N/A	0.004	0.000
Hospitalized patients with oxygen therapy						
Difference between monoclonal antibody only vs. None	0.017	0.999	-0.091	0.000	N/A	N/A
Difference between remdesivir only vs. none	0.034	0.059	0.057	0.054	N/A	N/A
Drug other than monoclonal antibody or Remdesivir vs. None	0.037	0.000	0.060	0.000	N/A	N/A
Mortality rate among patients with none	0.070	0.000	0.113	0.000	N/A	N/A

Table 2: Estimation Results of Average Treatment for mortality.

Notes: Yellow denotes significance in difference. "N/A." signifies not available. "drug other than monoclonal antibody" in a three-choice model included remdesivir, dexamethasone, baricitinib, and tocilizumab. "drug other than monoclonal antibody or remdesivir" in a four-choice model included dexamethasone, baricitinib, and tocilizumab.

Discussion

Patients in less-severe cases might not have been administered any of the considered drugs and had a higher probability of survival. Consequently, the likelihood of a positive average treatment effect of the drugs, which means that drugs did not contribute to survival, might be higher among all hospitalized patients than among hospitalized patients with oxygen therapy. Therefore, limitation of the subjects to hospitalized patients with an oxygen therapy control condition among all subjects might lead to derivation of more appropriate results indicating drug effectiveness. In this sense, we must mainly evaluate the obtained results among hospitalized patients who had oxygen therapy.

We evaluated lower to positive coefficients in monoclonal antibodies among all hospitalized patients or all older hospitalized patients in both of three-choice and four-choice models. The findings indicate that monoclonal antibodies for older hospitalized patients with oxygen therapy increased probability of survival. We were unable to ascertain whether other drugs, including remdesivir, dexamethasone, baricitinib, and tocilizumab, contributed to increase probability of survival. These results might be attributed to situations such as emerging mutated strains, immunization, or poor matching.

The findings indicate that monoclonal antibodies were effective, but other drugs were not found to be effective even when using other previous studies. For instance, to ascertain whether drug administration was effective, or not, simple logistic regression for fatality on dummy variables in addition to the explanatory variables was done, demonstrated similar results [25]. Moreover, studies using propensity score matching and an average treatment effect model produced the similar results [14,15]. Prior study showed that monoclonal antibodies reduced viral load [12]. Typically, monoclonal antibodies are administered to patients with mild COVID-19 before a significant increase in viral load occurs. Consequently, they may exhibit greater efficacy against COVID-19 when compared to drugs administered to patients with severe patients. Therefore, our finding from this study, that only monoclonal antibodies were effective for survival, was robust with respect to the estimation procedure. The previous study on casirivimab/ imdevimab showed a worse prognosis in patients receiving oxygen therapy, but the present study showed that monoclonal antibodies contributed to increase probability of survival for only patients with oxygen therapy, which was the opposite result of the clinical trial. This might because of not considering the order of drug administration and oxygen initiation.

There were several limitations in this study. First, the most recent data might change during a few months as MIA is based on medical claims. The data collection period for this study encompassed January 2020 to March 2022, with data

recorded as of May 2022. It should be recognized that if the study period were extended, which could lead to different estimation results.

Second, this study was conducted using medical claim data, and it does not include vaccination history, causative strain of disease, the severity of underlying diseases or direct causes of death. The results could be different if this information were available. Third, we ignored data of hospitalized patients who received both monoclonal antibodies and some other drugs. If we were to introduce their data for analyses, then we would have to add one more choice to represent that both monoclonal antibodies and some other drugs were administered to a three-choice or four-choice model. Using such data for this study might make estimation much more difficult. Actually, very few hospitalized patients were treated with both drugs and therefore could not be identified adequately as one choice. Data accumulation by extension of the study period might resolve this difficulty.

Fourth, we were unable to consider the order of drug initiation, oxygen therapy, or respiratory ventilation when evaluating drug effectiveness. If we had access to this information, we could differentiate between patients who initiated drug treatment before oxygen therapy or respiratory ventilation and those who initiated drug treatment after. This additional information would have facilitated a more careful assessment of drug effectiveness.

Finally, bed availability varied by period. It might have affected hospitalization rates due to COVID-19, but this study did not take that into account.

The findings of this study indicated that the administration of monoclonal antibodies to older hospitalized patients receiving oxygen therapy significantly increased the likelihood of survival and potentially contributed to life-saving efforts in this and future pandemics. Conversely, other drugs such as remdesivir, dexamethasone, baricitinib, and tocilizumab might not have a substantial impact on life-saving interventions. It is important to obtain more comprehensive information, including examination results, to achieve better patient matching and draw definitive conclusions.

Data availability

The data used in this study were sourced from the National Hospital Organization and are not publicly accessible due to privacy concerns. However, the authors have been granted permission by the Ethics Committee and the National Hospital Organization to share this data.

Conflict of Interest

The author reports no conflicts of interest in this work.

Contributors

KT was responsible for organizing and coordinating the study. KT was the chief investigator, responsible for the data setting. SM and KT developed the estimation model. All authors contributed to composition of the final manuscript.

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