Real-world clinical outcomes of treatment with molnupiravir for patients with mild- to-moderate coronavirus disease 2019 during the Omicron variant pandemic

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Research Article

Keywords: molnupiravir, COVID-19, Omicron variant, real-world, effectiveness

Posted Date: October 5th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2118653/v1

Abstract

Background

It is unclear whether molnupiravir has a beneficial effect on vaccinated patients infected with the Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We here evaluated the efficacy of molnupiravir in patients with mild-to-moderate coronavirus disease 2019 (COVID-19) during the Omicron variant surge in Fukushima Prefecture, Japan.

Methods

We enrolled patients with mild-to-moderate COVID-19 who were admitted to hospitals between January and April, 2022. Clinical deterioration after admission was compared between molnupiravir users (n = 281) and non-users (n = 1,636).

Results

The molnupiravir users were older (P < 0.0001), and had greater rates of history of chronic respiratory disease (P = 0.039), hypertension (P < 0.0001), dyslipidemia (P < 0.0001), diabetes mellitus (P < 0.0001), and cardiac disease (P = 0.003) than the non-users. The clinical deterioration rate was significantly lower in the molnupiravir users compared to the non-users (3.92% vs 7.46%; P = 0.021). Multivariate logistic regression analysis demonstrated that receiving molnupiravir was a factor for preventing deterioration (odds ratio 0.426; 95% confidence interval 0.208–0.871; P = 0.019), independent of receiving the SARS-CoV-2 vaccine. Furthermore, in 259 patients who were selected from each group after matching on the propensity score, the rate of deterioration was significantly lower among those receiving molnupiravir compared to those not receiving molnupiravir (3.86% vs 9.65%; p = 0.008).

Conclusion

This real-world study demonstrates that molnupiravir contributes to the prevention of deterioration in COVID-19 patients after hospitalization during the Omicron variant phase.

Introduction

The coronavirus disease 2019 (COVID-19), which originated in Wuhan, China in 2019, remains a serious concern worldwide. Until now, several neutralizing monoclonal antibody products and antiviral agents against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been developed and authorized by the United States Food and Drug Administration for treatment of high-risk patients with mild-to-moderate COVID-19 [1–4]. However, these drugs have been authorized based on double-blind, placebo-controlled randomized clinical trials [1–4], including trials that targeted only unvaccinated

patients with COVID-19 [3, 4]. Therefore, it is important to evaluate the efficacy of these drugs for cases of COVID-19 in real-world settings, where most people are vaccinated.

Newly emerging variants have mutations in the spike protein of SARS-CoV-2 and show high infectivity [5]. The B.1.1.529 (Omicron) variant of SARS-CoV-2, which was first identified on November 25, 2021, in South Africa [6], has attained global dominance with a higher infectivity, transmissibility and immune evasion [7]. Indeed, cases of the Omicron variant have spread throughout Japan from November 2021 [8].

The Omicron variant contains approximately 30 mutations in the spike protein and, in vitro, escapes some neutralizing monoclonal antibodies [9, 10]. To date, few investigations have reported the real-world effect of molnupiravir and nirmatrelvir/ritonavir on COVID-19 during the Omicron variant phase, and in such an investigation by Wong et al. the rate of vaccination was low [11]. It remains unclear whether molnupiravir has a beneficial effect on vaccinated patients infected with the Omicron variant of SARS-CoV-2, as the vaccine is effective in controlling disease exacerbations.

Starting in March 2020, we have been gathering the medical information of patients with COVID-19, who were hospitalized in 27 medical institutes in Fukushima Prefecture, in our electronic database. A total of 6,657 COVID-19 patients were registered by the end of April 2022. Even in Fukushima Prefecture, the Omicron variant was widely spread, and from January 2022, the most frequently detected variant of SARS-CoV-2 was the Omicron variant [12]. Furthermore, sotrovimab and molnupiravir were approved in Japan, and their administration was started in September 2021 and December 2021, respectively, for treating mild-to-moderate COVID-19 patients who are at high-risk of deterioration. Hence, with the use of our database, it was possible to evaluate the clinical efficacy of the above-mentioned new drugs against SARS-CoV-2 including the Omicron variant in the real-world setting. Molnupiravir can be used for outpatients with COVID-19 because it is an oral antiviral drug and is easier to prescribe than monoclonal antibodies such as sotrovimab. Thus, it is important to evaluate the effectiveness of molnupiravir for the Omicron variant of SARS-CoV-2, considering the status of the current pandemic situation.

To the best of our knowledge, the present study is the first real-world retrospective study to evaluate the efficacy of molnupiravir for mostly vaccinated patients with mild-to-moderate COVID-19 caused by the Omicron variant of SARS-CoV-2. We compared the clinical outcomes of the patients treated with and without molnupiravir.

Material And Methods

Patient Consent Statement

The need for informed consent was waived because the study is retrospective. This study was approved by the Ethics Committee of Fukushima Medical University (approval number 2020 – 118, approved on August 3, 2020, updated September 01, 2021).

Study Design And Population

This is a retrospective cohort study conducted using an electronic database. Among 27 hospitals participating in this study, we excluded 4 hospitals whose data on at least 60% of patients were not input into the database. A total of 6,657 COVID-19 patients (as of the end of April 2022) admitted to 23 hospitals in Fukushima Prefecture were enrolled. The 23 hospitals participated in the web conferences organized by the Department of Pulmonary Medicine, Fukushima Medical University. Among the 6,657 patients, the data of 4,323 were excluded, because those patients were admitted before January 1, 2022 (before the Omicron variant pandemic). Among the remaining 2,334 patients, we excluded 405 who were 19 years old or younger and who were pregnant. Finally, we analyzed the data of 1,929 patients, including those who had been vaccinated against SARS-CoV-2. The clinical characteristics, including comorbidities, examination results, medications, as well as clinical course and outcomes of the subjects, were obtained from the electronic database of each hospital. Clinical characteristics including severity of all patients were evaluated on the day of admission. The administration of molnupiravir was started on admission in almost all cases.

The diagnosis of COVID-19 was made by positive results for SARS-CoV-2 polymerase chain reaction on nasopharyngeal swab or saliva samples. Assessment of COVID-19 severity was performed according to the definition issued by the Japanese Ministry of Health, Labor and Welfare: mild, patients without pneumonia or respiratory failure; moderate-1, patients with pneumonia but without respiratory failure; moderate-2, patients with pneumonia and respiratory failure (percutaneous oxygen saturation < 94% on room air) but do not require mechanical ventilation/extracorporeal membrane oxygenation (ECMO); or severe, patients with pneumonia and respiratory failure who require mechanical ventilation/ECMO [13, 14].

Retrospectively, the patients were divided into two groups: (1) those treated with molnupiravir; and (2) those not treated with molnupiravir (controls). If a patient's condition deteriorated during the clinical course after the administration of molnupiravir, other therapies for COVID-19, including antiviral drugs or immunomodulatory agents (remdesivir, systemic corticosteroid, baricitinib, or tocilizumab), were prescribed and administered at the attending doctor's discretion.

Patient Eligibility Criteria

The inclusion criteria for treatment with molnupiravir were guided by those for the MOVe-OUT trial [3], and the recommendation of the Japanese Ministry of Health, Labor and Welfare [13]. In particular, patients who were aged ≥ 18 years were eligible for molnupiravir treatment if they had symptoms of COVID-19 (e.g., cough, sore throat, fever, and constitutional symptoms), and were within 5 days of symptom onset, and had at least one of the following criteria for high-risk aggravation: an age of > 60 years, body mass index of ≥ 30 kg/m^2, active cancer, chronic kidney disease (CKD), chronic obstructive pulmonary disease, and presence of serious cardiovascular disease (such as heart failure and coronary artery disease), diabetes mellitus and/or chronic liver disease.

Outcomes Of Interest

The primary outcomes of interest were any clinical deterioration, need for mechanical ventilation, and all-cause death after initiation of molnupiravir. The secondary outcomes included the association between treatments and clinical deterioration after hospitalization.

The definition of clinical deterioration in the present study was a worsened respiratory condition requiring additional medications such as systemic corticosteroid, tocilizumab, and baricitinib, or that requiring respiratory therapy (use of inhalation oxygen or, mechanical ventilation) after the first day of hospitalization.

Statistical Analyses

Continuous variables are shown as median with interquartile range, and they are shown as mean ± standard deviation when approximately normally distributed. Categorical variables are shown as numbers and percentages. Comparisons between groups for the continuous variables and categorical variables were performed using Mann-Whitney U test and chi-square test, respectively. Among the comorbidities, those with a prevalence of ≥ 2% were applied to the analyses. The variables that had statistically significant differences between the molnupiravir users and non-users were used to identify independent risk factors for predicting deterioration a day or later after admission via multivariate logistic regression analysis. Adjusted odds ratios (OR) with 95% confidence interval (CI) were calculated. In addition, we compared the risk of exacerbation between the molnupiravir users and non-users using the DOATS score. The DOATS score is a simple predictive model that we established and reported in a previous study [15]. It consists of four items: 1) having the comorbidity of diabetes or obesity (2 points), 2) being aged ≥ 40 years (1 points), 3) having high body temperature (≥ 38°C) (1 points), and 4) having oxygen saturation < 96% (1 points). The DOATS score range is 0–5 points, and a high DOATS score (optimal cutoff point is 2) denotes a higher possibility of deterioration in non-elderly COVID-19 patients who do not have respiratory failure on admission.

Furthermore, multivariate logistic regression was performed to estimate the association between treatments and clinical deterioration after hospitalization, including 9 confounders that are related to deterioration risk (age, sex, severity, vaccination state, DOATS score, respiratory disease, malignancy, need for nursing care/bedridden, and chronic kidney disease). Additionally, we used the propensity score technique to match the molnupiravir users and non-users. The score was made by 9 parameters (age, sex, severity, vaccination state, DOATS score, respiratory disease, malignancy, need for nursing care/bedridden, and chronic kidney disease) that used in the multivariate logistic regression analysis [16]. We then matched subjects on the logit of the propensity score using a caliper of width equal to 0.2 of the standard deviation of logit of the propensity score [17]. Moreover, we compared the odds for deterioration during hospitalization among treatment options, namely molnupiravir alone, sotrovimab alone and combination of molnupiravir and sotrovimab, using the multivariate logistic regression analysis.

All statistical analyses were performed using JMP 13 (SAS Institute Inc, Cary NC) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). A two-tailed p-value of < 0.05 was considered statistically significant.

Results

Characteristics of participants and clinical outcomes of treatment with molnupiravir

The patient selection flowchart is shown in Fig. 1. Among the 1,929 COVID-19 patients enrolled in the current study, 281 were administered molnupiravir. The differences in characteristics between the molnupiravir users and non-users are demonstrated in Table 1. The use of molnupiravir was unknown in 12 subjects due to missing inputs by researchers. The molnupiravir users were significantly older ($P < 0.0001$), and had a lower prevalence of pneumonia diagnosed by computed tomography (CT) scan ($P < 0.0001$) compared to the non-users. The disease severity was significantly higher in the non-users compared to the molnupiravir users ($P < 0.0001$). Regarding comorbidities, in the molnupiravir users, there was a significantly higher prevalence of chronic respiratory disease ($P = 0.039$), hypertension ($P < 0.0001$), dyslipidemia ($P < 0.0001$), diabetes mellitus ($P < 0.0001$), and cardiac disease ($P = 0.003$). There were no significant differences in sex, malignancies, CKD, obesity, stroke, autoimmune disease, need for nursing care/bedridden, and number of vaccinations between the two groups. With regard to physical and laboratory examinations, DOATS score ($P < 0.0001$) and D-dimer ($P = 0.002$) were significantly higher in the molnupiravir users than in the non-users. On the other hand, white blood cells, neutrophil percentage, lymphocyte percentage, C-reactive protein (CRP), lactate dehydrogenase (LDH), or ferritin did not significantly differ between the groups. Furthermore, the concomitant administration of sotrovimab was significantly higher in the molnupiravir users compared to the non-users ($P < 0.0001$).

Table 1
Comparison of baseline clinical characteristics and outcomes between the molnupiravir users and non-users

	All subjects	Molnupiravir non-users	Molnupiravir users	*P* value
	n = 1929	n = 1636	n = 281	
Age, years	59.7 ± 22.2	58.6 ± 22.5	66.0 ± 19.3	< 0.0001
Male sex	947 (49.2)	789 (48.3)	150 (53.6)	0.102
Current smoker	334 (17.7)	290 (18.1)	44 (16.0)	0.692
Received vaccine twice or more	1487 (77.1)	1260 (77.0)	220 (78.3)	0.448
Severity, Mild/Mod-1/Mod-2/Severe	1346/408/153/12	1113/352/151/10	225/52/2/2	< 0.0001
DOATS score	1 [1, 2]	1 [1, 2]	2 [1, 3]	< 0.0001
Pneumonia diagnosed by CT scan	549 (31.8)	487 (33.8)	58 (21.2)	< 0.0001
Chronic respiratory disease	209 (11.8)	166 (11.1)	42 (15.7)	0.039
Chronic kidney disease	118 (6.70)	89 (6.00)	23 (8.70)	0.111
Need for nursing care/Bedridden	149 (8.40)	122 (8.10)	27 (10.2)	0.288
Malignancies	123 (6.90)	95 (6.40)	26 (9.60)	0.062
Hypertension	669 (37.2)	509 (33.6)	154 (57.0)	< 0.0001

Information about usage of molnupiravir was not available in 12 subjects.

Continuous variables are shown as medians with interquartile range except for age, WBC, neutrophil, and lymphocyte. Age, WBC, neutrophil, and lymphocyte are shown as mean ± standard deviation. Categorical variables are shown as numbers with percentages. COVID-19 severity grade: mild, subjects without pneumonia or respiratory failure; moderate-1, subjects with pneumonia but without having respiratory failure; moderate-2, subjects with pneumonia and respiratory failure (oxygen saturation < 94% on room air) but who do not require mechanical ventilation/extracorporeal membrane oxygenation (ECMO); and severe, subjects with pneumonia and respiratory failure who require mechanical ventilation/ECMO.

Definition of abbreviations: CRP, C-reactive protein; CT, computed tomography; DOATS score, a predictive model for clinical deterioration in mild-to-moderate COVID-19 patients using 4 items, having diabetes or obesity, age ≥ 40 years, high body temperature (≥ 38°C) and oxygen saturation < 96% (Details are described in the manuscript), LDH, lactate dehydrogenase; Mod-1, moderate-1; Mod-2, Moderate-2; WBC, white blood cell.

	All subjects	Molnupiravir non-users	Molnupiravir users	*P* value
	n = 1929	n = 1636	n = 281	
Dyslipidemia	213 (12.1)	156 (10.5)	56 (21.1)	< 0.0001
Diabetes mellitus	342 (19.3)	262 (17.5)	76 (28.3)	< 0.0001
Obesity	232 (13.2)	190 (12.8)	42 (15.8)	0.194
Cardiac disease	255 (14.3)	199 (13.3)	55 (20.5)	0.003
Stroke	114 (6.40)	96 (6.40)	18 (6.70)	0.843
Autoimmune disease	51 (2.90)	40 (2.70)	11 (4.10)	0.226
WBC, /uL	5604 ± 3095	5600 ± 2649	5589 ± 4860	0.954
Neutrophil, %	63.5 ± 13.8	63.6 ± 13.8	62.6 ± 13.4	0.273
Lymphocyte, %	25.2 ± 12.0	25.4 ± 12.1	24.6 ± 11.9	0.361
LDH, IU/L	191 [165, 223]	191 [165, 225]	191 [168, 217]	0.614
CRP, mg/dL	0.98 [0.35, 2.52]	0.97 [0.34, 2.52]	0.98 [0.40, 2.45]	0.976
Ferritin, ng/mL	156 [77, 284]	157 [74.3, 297]	147 [81.2, 241]	0.347
D-dimer, ug/mL	0.70 [0.30, 1.30]	0.63 [0.30, 1.20]	0.80 [0.50, 1.30]	0.002
Any worsening	133 (6.89)	122 (7.46)	11 (3.92)	0.021
Mechanical ventilation	5 (0.26)	5 (0.31)	0 (0.00)	0.208
Death	24 (1.24)	21 (1.28)	3 (1.07)	0.759

Information about usage of molnupiravir was not available in 12 subjects.

Continuous variables are shown as medians with interquartile range except for age, WBC, neutrophil, and lymphocyte. Age, WBC, neutrophil, and lymphocyte are shown as mean ± standard deviation. Categorical variables are shown as numbers with percentages. COVID-19 severity grade: mild, subjects without pneumonia or respiratory failure; moderate-1, subjects with pneumonia but without having respiratory failure; moderate-2, subjects with pneumonia and respiratory failure (oxygen saturation < 94% on room air) but who do not require mechanical ventilation/extracorporeal membrane oxygenation (ECMO); and severe, subjects with pneumonia and respiratory failure who require mechanical ventilation/ECMO.

Definition of abbreviations: CRP, C-reactive protein; CT, computed tomography; DOATS score, a predictive model for clinical deterioration in mild-to-moderate COVID-19 patients using 4 items, having diabetes or obesity, age ≥ 40 years, high body temperature (≥ 38°C) and oxygen saturation < 96% (Details are described in the manuscript), LDH, lactate dehydrogenase; Mod-1, moderate-1; Mod-2, Moderate-2; WBC, white blood cell.

	All subjects	Molnupiravir non-users	Molnupiravir users	*P* value
	n = 1929	n = 1636	n = 281	
Sotrovimab	672 (34.8)	494 (30.2)	169 (60.1)	< 0.0001
Information about usage of molnupiravir was not available in 12 subjects.				
Continuous variables are shown as medians with interquartile range except for age, WBC, neutrophil, and lymphocyte. Age, WBC, neutrophil, and lymphocyte are shown as mean ± standard deviation. Categorical variables are shown as numbers with percentages. COVID-19 severity grade: mild, subjects without pneumonia or respiratory failure; moderate-1, subjects with pneumonia but without having respiratory failure; moderate-2, subjects with pneumonia and respiratory failure (oxygen saturation < 94% on room air) but who do not require mechanical ventilation/extracorporeal membrane oxygenation (ECMO); and severe, subjects with pneumonia and respiratory failure who require mechanical ventilation/ECMO.				
Definition of abbreviations: CRP, C-reactive protein; CT, computed tomography; DOATS score, a predictive model for clinical deterioration in mild-to-moderate COVID-19 patients using 4 items, having diabetes or obesity, age ≥ 40 years, high body temperature (≥ 38°C) and oxygen saturation < 96% (Details are described in the manuscript), LDH, lactate dehydrogenase; Mod-1, moderate-1; Mod-2, Moderate-2; WBC, white blood cell.				

Among all patients analyzed in the present study, 133 experienced deterioration a day after admission or later. The primary endpoints of the rates of clinical deterioration, need for mechanical ventilation, and death for the total population were 6.89%, 0.26%, and 1.24%, respectively. The clinical deterioration rate was significantly lower in the molnupiravir users compared to the non-users (3.92% vs 7.46%; P = 0.021). Five molnupiravir non-user required mechanical ventilation, but there was no significant difference between the two groups. Twenty-one molnupiravir non-users and 3 molnupiravir users died, but there was no significant difference regarding the death rate between the two groups (Table 1).

Independent Risk Factors Of Deterioration After Hospitalization

The results of multivariate logistic regression analysis of the association of COVID-19 deterioration during hospitalization are shown in Table 2. According to this analysis, not receiving molnupiravir was a risk factor related to the clinical deterioration of COVID-19 (OR 0.426; 95% CI 0.208–0.871; P = 0.019), independent of other covariates including the use of sotrovimab. We compared the odds for any deterioration among treatment options using the multivariate logistic regression analysis adjusted for age, sex, vaccination, severity, DOATS score, having comorbidities such as chronic respiratory disease, malignancy and CKD, and need for nursing care/bedridden. Odds ratio of molnupiravir vs. combination of molnupiravir and sotrovimab and that of sotrovimab vs. the combination were 0.371 (95% CI: 0.044 to 3.125, P = 0.362) and 1.047 (95% CI: 0.386 to 2.843, P = 0.928), respectively, indicating that additive effect of sotrovimab to molnupiravir was not observed.

Table 2
Multivariate logistic regression analysis of deterioration among patients with COVID-19 after hospitalization*

	OR	95% CI	*P* value
Age, per 1 year-increase	1.014	1.002–1.027	0.026
Male sex	0.738	0.476–1.146	0.177
Received vaccine twice or more	0.521	0.317–0.854	0.161
Chronic respiratory disease	0.939	0.506–1.742	0.843
DOATS score, per 1 point-increase	1.581	1.329–1.880	< 0.0001
Severity, per 1 grade-increase	1.498	1.122–2.000	0.007
Malignancies	1.002	0.455–2.205	0.996
Need for nursing care/Bedridden	2.668	1.510–4.712	0.001
Chronic kidney disease	1.456	0.742–2.857	0.275
Molnupiravir	0.426	0.208–0.871	0.019
Sotrovimab	1.083	0.690–1.699	0.729
*Adjusted for age, gender, severity, received vaccination, DOATS score, chronic respiratory disease, malignancies, needing nursing care/bedridden, and chronic kidney disease.			
COVID-19 severity grade: mild, subjects without pneumonia or respiratory failure; moderate-1, subjects with pneumonia but without having respiratory failure; moderate-2, subjects with pneumonia and respiratory failure (oxygen saturation < 94% on room air) but who do not require mechanical ventilation/extracorporeal membrane oxygenation (ECMO); and severe, subjects with pneumonia and respiratory failure who require mechanical ventilation/ECMO.			
Definition of abbreviations: CI, confidence interval; DOATS score, a predictive model for clinical deterioration in mild-to-moderate COVID-19 patients using 4 items, having diabetes or obesity, age ≥ 40 years, high body temperature (≥ 38°C) and oxygen saturation < 96%; OR, odds ratio.			

The Clinical Deterioration Rate In Molnupiravir Users And Non-users After Propensity Score Matching

Using the propensity score matching method, 259 patients were selected from each group. The baseline clinical characteristics after adjusting for propensity score are summarized in Table 3. There were no significant differences between the two groups, except for the presence of hypertension. The clinical deterioration rate was significantly lower in the molnupiravir users compared to the non-users (3.86% vs 9.65%; P = 0.008). One of the non-users required mechanical ventilation, which, however, showed no significant difference between the two groups. Two patients in each group died, and there was no

significant difference regarding the death rate between the two groups (Table 4). Univariate logistic regression analysis of deterioration after hospitalization demonstrated that receiving molnupiravir was an independent factor for preventing deterioration (OR 0.376; 95% CI 0.177–0.800; P = 0.008).

Table 3
Comparison of baseline clinical characteristics between the molnupiravir users and non-users after adjustment with propensity score

	Molnupiravir non-users	Molnupiravir users	*P* value
	n = 259	n = 259	
Age, years	65.1 ± 19.6	65.9 ± 19.7	0.482
Male sex	145 (56.0)	140 (54.1)	0.659
Current smoker	33 (12.9)	42 (16.5)	0.372
Received vaccine twice or more	214 (82.6)	205 (79.2)	0.592
Severity, Mild/Mod-1/Mod-2/Severe	209/46/3/1	207/49/2/1	0.959
DOATS score	2 [1, 3]	2 [1, 3]	0.882
Pneumonia diagnosed by CT scan	53 (22.4)	51 (20.2)	0.551
Chronic respiratory disease	29 (11.2)	41 (15.8)	0.122
Chronic kidney disease	28 (10.8)	23 (8.90)	0.461
Need for nursing care/Bedridden	27 (10.4)	27 (10.4)	1.000
Malignancies	19 (7.34)	22 (8.50)	0.625
Hypertension	113 (43.6)	143 (55.6)	0.006
Dyslipidemia	42 (16.2)	52 (20.1)	0.254
Diabetes mellitus	66 (25.5)	69 (26.6)	0.764
Obesity	37 (14.3)	40 (15.4)	0.711
Cardiac disease	43 (16.7)	51 (19.7)	0.372
Stroke	25 (9.70)	14 (5.40)	0.067
Autoimmune disease	8 (3.10)	10 (3.90)	0.631

Continuous variables are shown as medians with interquartile range except for age, WBC, neutrophil, and lymphocyte. Age, WBC, neutrophil, and lymphocyte are shown as mean ± standard deviation. Categorical variables are shown as numbers with percentages. COVID-19 severity grade: mild, subjects without pneumonia or respiratory failure; moderate-1, subjects with pneumonia but without having respiratory failure; moderate-2, subjects with pneumonia and respiratory failure (oxygen saturation < 94% on room air) but who do not require mechanical ventilation/extracorporeal membrane oxygenation (ECMO); and severe, subjects with pneumonia and respiratory failure who require mechanical ventilation/ECMO.

Definition of abbreviations: CRP, C-reactive protein; CT, computed Tomography; DOATS score, a predictive model for clinical deterioration in mild-to-moderate COVID-19 patients using 4 items, having diabetes or obesity, age ≥ 40 years, high body temperature (≥ 38°C) and oxygen saturation < 96%; LDH, lactate dehydrogenase; Mod-1, moderate-1; Mod-2, Moderate-2; WBC, white blood cell.

	Molnupiravir non-users	Molnupiravir users	*P* value
	n = 259	n = 259	
WBC, /uL	5621 ± 2367	5331 ± 2256	0.159
Neutrophil, %	64.1 ± 13.6	62.6 ± 13.3	0.214
Lymphocyte, %	24.5 ± 11.6	24.7 ± 12.0	0.550
LDH, IU/L	194 [169, 228]	192 [169, 217]	0.317
CRP, mg/dL	0.92 [0.34, 2.17]	0.995 [0.44, 2.47]	0.550
Ferritin, ng/mL	163 [81.4, 333]	143 [81.3, 228]	0.052
D-dimer, ug/mL	0.75 [0.30, 1.30]	0.80 [0.50, 1.30]	0.159

Continuous variables are shown as medians with interquartile range except for age, WBC, neutrophil, and lymphocyte. Age, WBC, neutrophil, and lymphocyte are shown as mean ± standard deviation. Categorical variables are shown as numbers with percentages. COVID-19 severity grade: mild, subjects without pneumonia or respiratory failure; moderate-1, subjects with pneumonia but without having respiratory failure; moderate-2, subjects with pneumonia and respiratory failure (oxygen saturation < 94% on room air) but who do not require mechanical ventilation/extracorporeal membrane oxygenation (ECMO); and severe, subjects with pneumonia and respiratory failure who require mechanical ventilation/ECMO.

Definition of abbreviations: CRP, C-reactive protein; CT, computed Tomography; DOATS score, a predictive model for clinical deterioration in mild-to-moderate COVID-19 patients using 4 items, having diabetes or obesity, age ≥ 40 years, high body temperature (≥ 38°C) and oxygen saturation < 96%; LDH, lactate dehydrogenase; Mod-1, moderate-1; Mod-2, Moderate-2; WBC, white blood cell.

Table 4
Comparison of the clinical outcomes between the molnupiravir users and non-users after adjustment with propensity score

	Molnupiravir non-user	Molnupiravir user	*P* value
	n = 259	n = 259	
Any deterioration	25 (9.65)	10 (3.86)	0.008
Mechanical ventilation	1 (0.39)	0 (0.00)	0.239
Death	2 (0.77)	2 (0.77)	1.000

Discussion

In the present study, we utilized real-world data from 1,929 COVID-19 patients admitted to hospitals in Fukushima Prefecture between January 2022 and April 2022, during the Omicron variant pandemic, in order to investigate the efficacy of molnupiravir. The disease severity was significantly lower in the molnupiravir users than the non-users. On the other hand, the patients taking molnupiravir were older, and

had more frequent comorbidities such as hypertension, chronic respiratory disease, and dyslipidemia, compared to those who were not receiving molnupiravir. The eligibility criteria for treatment with molnupiravir may have caused these differences. Therefore, it is not surprising that the DOATS score [15], a predictor of COVID-19 exacerbation was higher in the molnupiravir users than in non-users. There was a significant difference in clinical outcomes (deterioration) between the two groups in the univariate analysis (Table 1). However, we also performed a multivariate logistic regression analysis that included the confounding factors as explanatory variables because of several significant differences in clinical characteristics between the two groups. The results showed that not taking molnupiravir was an independent risk factor for deterioration of COVID-19. In addition, the efficacy of molnupiravir hiding behind confounders was revealed by propensity score matching analysis of mild-to-moderate patients. These results are similar to a previous clinical trial that showed that molnupiravir treatment was associated with significant reductions in hospitalization as well as in the mortality of non-hospitalized patients who are at high risk of mild-to-moderate COVID-19 [3].

Detailed information about the SARS-CoV-2 variants of individual cases was not available in the current study. However, the Fukushima Prefectural Institute of Public Health reported that the proportion of Omicron variant cases reached 70% by the beginning of January 2022, and reached 100% after mid-February [12]. Therefore, we believe that almost all cases analyzed in this study were the Omicron variant. Therefore, the present study supports the efficacy of molnupiravir against SARS-CoV-2 Omicron variants.

In vitro and in vivo, molnupiravir retains antiviral potency against SARS-CoV-2 variants including B.1.1.529 (Omicron) [18, 19], B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta), and P.1 (Gamma), and may prevent the selection of drug-resistant variants [20, 21]. Recently, Wong et al. [11]. reported in a retrospective cohort study in Hong Kong that the use of molnupiravir or nirmatrelvir/ritonavir for treating SARS-CoV-2 patients infected with the Omicron variant reduced the all-cause mortality rate along with reduced viral loads compared with control groups (not receiving molnupiravir or nirmatrelvir/ritonaviroral). Although their results support the present study results, the details regarding the disease severity, comorbidity and deterioration rate in the patients treated with molnupiravir in their study are unknown. In addition, the rate of vaccination in their study subjects treated with molnupiravir after propensity score matching is low (about 6%). The vaccination rate of the subjects in our study was high (about 80%), and we demonstrated that molnupiravir is effective for preventing deterioration independently of vaccination. Taking our real-world results together with those from Wong et al., molnupiravior is suggested to be effective for the treatment of the SARS-CoV-2 Omicron variant.

Simultaneously, our study showed that the effectiveness of molnupiravir in preventing deterioration was independent of receiving sotrovimab. On the other hand, in the current study, there was no significant difference regarding deterioration between sotrovimab users and non-users (Table 2). In addition, we could not observe any additive effect of sotrovimab to molnupiravir (see text in the Results section). Recent studies have demonstrated that sotrovimab was effective in reducing hospitalization and mortality among patients with COVID-19 in real-world settings during the Delta variant pandemic [22, 23]. However, there is no report evaluating the effect of sotrovimab for patients with COVID-19 during the

Omicron variant pandemic. The surge of the BA.2 Omicron subvariant [24] can be considered as one of the reasons for sotrovimab not to show a preventive effect on exacerbation. Takashita et al. [19] have reported that sotrovimab had less neutralizing activity against the BA.2 Omicron subvariant than against the ancestral strain and other variants of concern. The proportion of BA.2 subvariant cases reached about 40% by the beginning of April 2022 in Fukushima Prefecture [25]. Thus, the results of the effect of sotrovimab against SARS-CoV-2 Omicron variants including the BA.2 subvariant in the present study are reasonable. Although further investigation is still required, combination use of molnupiravir and sotrovimab may not be superior to mono use of molnupiravir for high-risk SARS-CoV-2 patients infected with the Omicron variant, especially the BA.2 subvariant.

The strength of the current study is that its results are considered to be highly reliable because the population was comprised of inpatients at major 23 institutions in Fukushima Prefecture that handle COVID-19 inpatient treatment. In addition, this retrospective cohort study analyzed the population with a high vaccination rate. Therefore, our study reflects the current real world of the COVID-19 pandemic.

There are several limitations to the present study. First, this was an observational and retrospective study. Therefore, the results of this study cannot be equated with those obtained from a randomized control trial. Furthermore, clinical deterioration, which was set as the primary outcome in this study, is less objective than hard endpoints such as mechanical ventilation and death. However, it is essential to evaluate clinical deterioration from various perspectives, such as individual disease burden, concerns about post COVID-19 condition, and health economics. Second, the information about the duration between COVID-19 symptom onset and the administration of molnupiravir and the day of exacerbation was not available in our database. The difference in clinical time course may influence the clinical outcomes. Third, we could not assess whether molnupiravir contributes to shortening the length of hospital stay due to the lack of information. Fourth, concomitant use of molnupiravir and sotrovimab was decided by the discretion of attending doctors. It is possible that more severe patients were treated with this combination therapy, which may affect our present results. Fifth, regarding the vaccinated patients, it was unknown on what day after the vaccination was completed that the inoculator was infected. It can be estimated that almost all healthy individuals obtained the full efficacy of vaccination against SARS-CoV-2 at least 7 days after second vaccination [26]. Some subjects may have been infected with the virus shortly after their injection before acquiring immunity against the virus.

In conclusion, this real-world retrospective study of high-risk mild-to-moderate COVID-19 patients, who had a high vaccination rate, during the Omicron variant pandemic demonstrated a low rate of clinical deterioration after treatment with molnupiravir. Treatment with molnupiravir should be considered to prevent deterioration in high-risk patients with mild-to-moderate COVID-19.

Abbreviations

CI: confidence interval

CKD: chronic kidney disease

COVID-19: coronavirus disease 2019

CRP: C-reactive protein

CT: computed tomography

ECMO: extracorporeal membrane oxygenation

LDH: lactate dehydrogenase

OR: odds ratio

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Declarations

Acknowledgements

We thank the Scientific English Editing Section of Fukushima Medical University for their fruitful discussion and linguistic assistance in proofreading the manuscript.

Funding

This study was funded by Japanese Society for the Promotion of Science (JSPS) KAKENHI grant number 19K08658 and 22K10560. Funder did not play any roles in this study.

Conflicts of interest

Y Shibata and H Minemura received lecture fees and research grants from Chugai Pharmaceutical Co., Ltd. Y Shibata and J Saito received lecture fees from GlaxoSmithKline K.K. The other authors report no conflicts of interest related to this study.

Author contribution

Conception and design: Yasuhito Suzuki and Yoko Shibata. Analysis and drafting the manuscript: Yasuhito Suzuki and Yoko Shibata. Data curation: all authors. Final approval of the manuscript: all authors.

Ethic approval

This study was performed in line with the principles of the Declaration of Helsinki. The protocol was approved by the local ethical committee.

Consent to publication

The authors have seen the final version of the manuscript and approved submission for publication.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available due to our institutional policy but are available from the corresponding author on reasonable request.

References

1. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med 2021; 384(3):238-51. https://doi.org/10.1056/NEJMoa2035002.
2. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Effect of Sotrovimab on Hospitalization or Death Among High-risk Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. Jama 2022; 327:1236-46. https://doi.org/10.1001/jama.2022.2832.
3. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med 2022; 386:509-20. https://doi.org/10.1056/NEJMoa2116044.
4. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med 2022; 386:1397-408. https://doi.org/10.1056/NEJMoa2118542.
5. Korber B, Fischer WM, Gnanakaran S, et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. Cell 2020; 182:812-27.e19. https://doi.org/10.1016/j.cell.2020.06.043.
6. Callaway E. Heavily mutated Omicron variant puts scientists on alert. Nature 2021; 600:21. https://doi.org/10.1038/d41586-021-03552-w.
7. Liu Y, Rocklöv J. The effective reproductive number of the Omicron variant of SARS-CoV-2 is several times relative to Delta. J Travel Med 2022; 29. https://doi.org/10.1093/jtm/taac037.
8. Ren Z, Nishimura M, Tjan LH, et al. Large-scale serosurveillance of COVID-19 in Japan: Acquisition of neutralizing antibodies for Delta but not for Omicron and requirement of booster vaccination to overcome the Omicron's outbreak. PLoS One 2022; 17:e0266270. https://doi.org/10.1371/journal.pone.0266270.
9. Hoffmann M, Krüger N, Schulz S, et al. The Omicron variant is highly resistant against antibody-mediated neutralization: Implications for control of the COVID-19 pandemic. Cell 2022; 185:447-56.e11. https://doi.org/10.1016/j.cell.2021.12.032.
10. VanBlargan LA, Errico JM, Halfmann PJ, et al. An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by therapeutic monoclonal antibodies. Nat Med 2022; 28:490-5. https://doi.org/10.1038/s41591-021-01678-y.
11. Carlos K.H. Wong ICHA, Kristy T.K. Lau, Eric H. Y. Lau, Benjamin J. Cowling, Gabriel M. Leung. Real-world effectiveness of early molnupiravir or nirmatrelvir-ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave:

a retrospective cohort study. Lancet Infect Dis 2022. https://doi.org/10.1016/S1473-3099(22)00507-2.

12. The official website of Fukushima Prefecture. The variant of COVID-19 in Fukushima from January 2022 (in Japanese). https://www.pref.fukushima.lg.jp/site/covid19-portal/variant.html. Accessed 1 June 2022.
13. Japan Ministry of Health Labor and Welfare. Clinical Management of patients with COVID-19: A guide for front-line healthcare workers (in Japanese). Available at: https://www.niph.go.jp/h-crisis/wp-content/uploads/2020/07/20200706103735_content_000646531.pdf. Accessed 1 June 2022.
14. Yamamoto A, Wada H, Ichikawa Y, et al. Evaluation of Biomarkers of Severity in Patients with COVID-19 Infection. J Clin Med 2021; 10:3775. https://doi.org/10.3390/jcm10173775.
15. Shibata Y, Minemura H, Suzuki Y, et al. Development and external validation of the DOAT and DOATS scores: simple decision support tools to identify disease progression among nonelderly patients with mild/moderate COVID-19. medRxiv [Preprint] December 14 2021. Available from: https://www.medrxiv.org/content/10.1101/2021.12.13.21267698v1.
16. Shiba K, Kawahara T. Using Propensity Scores for Causal Inference: Pitfalls and Tips. J Epidemiol 2021; 31:457-63. https://doi.org/10.2188/jea.JE20210145.
17. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011; 10:150-61. https://doi.org/10.1002/pst.433.
18. Bojkova D, Widera M, Ciesek S, Wass MN, Michaelis M, Cinatl J Jr. Reduced interferon antagonism but similar drug sensitivity in Omicron variant compared to Delta variant of SARS-CoV-2 isolates. Cell Res 2022: 32:319-21. https://doi.org/10.1038/s41422-022-00619-9.
19. Takashita E, Kinoshita N, Yamayoshi S, et al. Efficacy of Antiviral Agents against the SARS-CoV-2 Omicron Subvariant BA.2. N Engl J Med 2022; 386:1475-7. https://doi.org/10.1056/NEJMc2201933.
20. Ohashi H, Hishiki T, Akazawa D, et al. Different efficacies of neutralizing antibodies and antiviral drugs on SARS-CoV-2 Omicron subvariants, BA.1 and BA.2 Antiviral Res. 2022. https://doi.org/10.1016/j.antiviral.2022.105372.
21. Rosenke K, Okumura A, Lewis MC, et al. Molnupiravir (MK-4482) is efficacious against Omicron and other SARS-CoV-2 variants in the Syrian hamster COVID-19 model. medRxiv [Preprint] February 24 2022 Available from: https://www.biorxiv.org/content/10.1101/2022.02.22.481491v1.
22. Ong SWX, Ren D, Lee PH, et al. Real-World Use of Sotrovimab for Pre-Emptive Treatment in High-Risk Hospitalized COVID-19 Patients: An Observational Cross-Sectional Study. Antibiotics (Basel) 2022; 11:345. https://doi.org/10.3390/antibiotics11030345.
23. Aggarwal NR, Beaty LE, Bennett TD, et al. Real World Evidence of the Neutralizing Monoclonal Antibody Sotrovimab for Preventing Hospitalization and Mortality in COVID-19 Outpatients. J Infect Dis 2022; 16;jiac206. https://doi.org/10.1093/infdis/jiac206.

24. Hirotsu Y, Maejima M, Shibusawa M, et al. SARS-CoV-2 Omicron sublineage BA.2 replaces BA.1.1: Genomic surveillance in Japan from September 2021 to March 2022. J Infect 2022; 85:174-211. https://doi.org/10.1016/j.jinf.2022.04.040.
25. The proportion of SARS-CoV-2 Omicron Subvariant BA.2 in Fukushima in April 2022 (in Japanese). https://www.minpo.jp/news/moredetail/2022041296103. Accessed 1 June 2022.
26. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020; 383:2603-15. https://doi.org/10.1056/NEJMoa2034577.

Figures

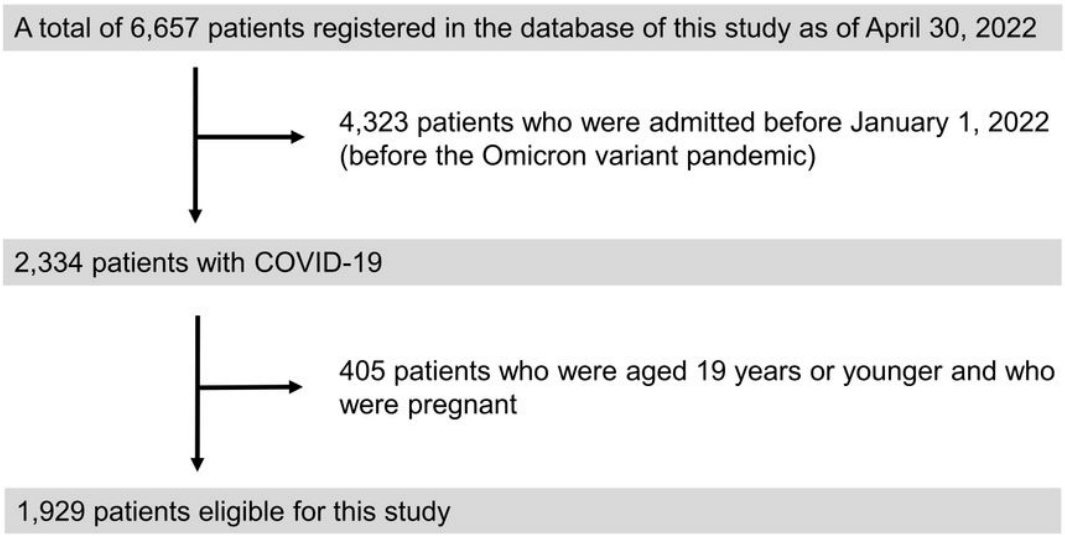

Figure 1

Flowchart of patients' recruitment in this study

Among a total of 6,657 registered COVID-19 patients in our electronic database, 1,929 were selected for the present study.