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Original Article

Changes in Prescribing Patterns of Antiviral Drugs before and after Public Coverage Termination among Hospitalized COVID-19 Patients in Regional Hospitals in Japan: A Retrospective, Multicenter Study

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In Japan, antiviral agents for COVID-19 were freely available until September 2023 as part of national policy. This study evaluated changes in these agents' prescribing patterns and the patient outcomes following the policy shift. We conducted a multicenter retrospective study at four hospitals in Japan's Okayama and Kagawa prefectures from January 2022 to March 2024. The study period was divided into the public-expenditure phase (January 2022 to September 2023) and the post-expenditure phase (October 2023 to March 2024). We extracted the hospitalized patients' clinical data from the electronic database. The study's primary outcome was the antiviral prescription rate; the secondary outcome was in-hospital mortality. Among the 302 hospitalized patients (median age 85 years), 52.0% were classified as having a mild condition. Of the patients with mild conditions, 37.7% were diagnosed in outpatient settings prior to hospitalization. During the public-expenditure phase, 47.4% of the patients received antivirals as outpatients, mainly molnupiravir (80.9%). In the post-expenditure period, 80.0% of the patients were prescribed antivirals, mostly molnupiravir (91.7%). The antiviral prescription rate was significantly higher after the policy change. The overall in-hospital mortality was 15.8%, with no significant difference between the two periods (17.0% vs. 10.5%). Despite the termination of government funding, antiviral prescriptions remained frequent at community hospitals located in highly aging regions of western Japan such as Okayama and Kagawa prefectures. Mortality remains high among the elderly, highlighting the need for continued antiviral therapy and booster vaccinations.

Key words: coronavirus disease 2019, public expenditure, prescribing pattern, prognosis, Japan

Coronavirus disease 2019 (COVID-19), first reported in Wuhan, China, is a respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), [1,2]. COVID-19 can progress to severe and fatal pneumonia in elderly individuals with underlying conditions such as cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus, and cancer [3-6]. Messenger (m)RNA vaccines for COVID-19 were developed in 2021 and have demonstrated promising effectiveness for preventing severe cases, with efficacy rates ranging from 67% to 95% [7-10]. Even during the surge of the Omicron variant of

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COVID-19, intensive care unit (ICU) admissions for this disease were reduced by 70-80% due to the widespread use of vaccines [11], and the hospitalization-to-infection ratio was less than half of that observed at the peak in 2020 [12]. However, with the emergence of COVID variants that are capable of evading vaccine-induced antibodies, the efficacy of the available vaccines has waned over time following immunization [13, 14]. High-risk populations thus remain vulnerable to developing severe disease, underscoring the importance of effective treatments for COVID-19.

Several antiviral agents for the treatment of COVID-19 have been introduced to the market, including remdesivir as an intravenous treatment and ensitrelvir, molnupiravir, and nirmatrelvir/ritonavir as oral medications, in accordance with current treatment recommendations issued by the Infectious Diseases Society of America and the Japanese Ministry of Health, Labour and Welfare, as described on their official websites (IDSA, https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/, accessed September 17, 2024; MLHW, https://www.mhlw.go.jp/content/001248424. pdf, accessed September 17, 2024) [15]. The clinical efficacy of remdesivir has been well established through a series of clinical studies, and a meta-analysis of randomized controlled trials demonstrated that remdesivir reduced the mortality rate in patients hospitalized with COVID-19, with an adjusted odds ratio (OR) at 0.88 (95% confidence interval [CI]: 0.78-1.00) [16]. Ensitrelvir can alleviate clinical symptoms, but no study has yet corroborated its efficacy in preventing severe disease [17]. Molnupiravir has been shown to reduce the risks of hospital admission for COVID with a relative risk (RR) value at 0.67 (95%CI: 0.45-0.99) and death with an RR value at 0.43 (95%CI: 0.20-0.94) in adult patients with mild or moderate COVID-19 [18]. Nirmatrelvir reduced the risk of hospitalization or death by 88.9% in high-risk, non-hospitalized patients [19], making it the first-line oral therapy for outpatients with COVID-19 (IDSA, https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/, accessed September 17, 2024; MLHW, https://www.mhlw.go.jp/content/001248424. pdf, accessed September 17, 2024) [15].

In Japan, these drugs were available free of charge as part of the national policy combatting COVID-19 until September 2023. Following the widespread distribution of vaccines and the official declaration of the end of the COVID-19 pandemic (WHO, https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing---5-may-2023, accessed July 29, 2024), the country's public expenditure system was discontinued. From October 2023 onward, the national policy was revised: partial copayments were introduced based on the recipient's income level, and financial support for inpatient care was reduced, including a decrease in the copayment ceiling reduction under the high-cost medical expense benefit system from 20,000 JPY to 10,000 JPY (yen). Our research group hypothesized that treatment practices for COVID-19 patients in Japan may thus have changed, and we conducted the present study to investigate the shifts in the prescribing patterns of the anti-COVID-19 drugs from before to after the September 2023 modifications to Japan's government policy for COVID-19 treatment. We also examined the clinical impact of COVID-19 on patient outcomes by calculating the hospitalization and mortality rates.

Patients and Methods

Study design and setting. The study was conducted at four community-based hospitals in two of Japan's 47 prefectures: Okayama and Kagawa: Watanabe Hospital (88 beds, Niimi City), Kasaoka City Hospital (99 beds, Kasaoka City), Takahashi Central Hospital (160 beds, Takahashi City), and Marugame Medical Center (300 beds, Marugame City). These hospitals are located in areas with some of the highest percentages of individuals aged ≥65 in Japan (41.4%, 41.0%, 38.3%, and 29.0%, respectively) (e-Stat, https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00200521&tstat=000001049104&cycle=0&tclass1=000001049105&tclass2val=0, accessed September 10, 2025). The hospitals were selected because they are affiliated with general medicine departments that have been collaborating with our research group and expressed willingness to participate in the study.

The study period was set from January 1, 2022 to March 31, 2024 and was divided into two phases: (*i*) during the public expenditure system (from Jan. 1, 2022 to Sept. 2023) and (*ii*) the post-expenditure period (from Oct. 2023 to March 2024). The study period ended in March 2024, corresponding to the end of the

Japanese fiscal year. This provided a practical time point for evaluating the short-term impact of the policy change implemented in October 2023.

Inclusion criteria and data collection. The enrolled cases were only those of the patients who had been newly hospitalized with a diagnosis of COVID-19 during the study period. We collected the following data from the patients' medical records in an electronic database: age, gender, date of disease onset, visit(s) as an outpatient before admission, the prescription of an antiviral drug at an outpatient visit, the number of days from the onset to hospitalization, the disease severity at the time of hospitalization, vaccination history, and treatment outcomes (hospital transfer and overall in-hospital mortality). We defined the period from the onset to the hospitalization as the number of days from the development of symptoms to the patient's admission to the hospital.

Clinical disease severity was classified according to the guidelines provided by the Japanese Ministry of Health, Labour and Welfare as follows: mild (SpO2 ≥96% on room air, with no or mild respiratory symptoms), moderate I (SpO2 93-96% on room air, with dyspnea or pneumonia), moderate II (SpO2 ≤93% on room air, requiring oxygen therapy), and severe (requiring ICU admission and/or mechanical ventilation) (MLHW, https://www.mhlw.go.jp/content/001248424. pdf, accessed September 17, 2024). The patients' vaccination status was based on self-reporting and was categorized into the following five groups: no vaccination, 1-2 doses, ≥3 doses, vaccinated with an unknown number of doses, and unknown.

Outcome measures. The primary outcome of the study was the prescription rate of antiviral drugs at the time of the outpatient visit among the patients who were subsequently hospitalized for COVID-19. The study's secondary outcome was the in-hospital mortality of the included patients. Transfer cases were excluded from the prognosis analysis because their prognosis could not be followed up.

Statistical analyses. Continuous variables are presented as medians and interquartile ranges (IQRs) and were assessed using the Kruskal–Wallis test and the Mann–Whitney *U*-test as appropriate. Categorical variables are reported as numbers and percentages and were assessed using the χ^2-test or Fisher's exact test, or the two-proportion Wald test. For key study outcomes such as the outpatient antiviral prescriptions and in-hospital mortality, effect sizes are presented as risk differences (RDs) and odds ratios (ORs) with 95% confidence intervals (CIs), in addition to probability (p)-values. The data were analyzed using EZR software, a graphic user interface for the R 3.5.2 software (The R Foundation for Statistical Computing, Vienna, Austria) [20]. All p-values < 0.05 were considered significant.

Ethical approval. Ethical approval for this study was obtained from the Institutional Review Board of Okayama University Hospital (No. 2406-029). The requirement for informed consent was waived due to the retrospective nature of the study and the use of routinely collected, fully anonymized data.

Results

A total of 302 patients were hospitalized and treated for COVID-19 during the study period, comprising 162 men (53.6%) and 140 women (46.4%) (Table 1). During the earlier period under the public expenditure system, 245 patients were hospitalized, including 132 men (53.9%). After the cessation of the publicly funded system, 57 patients were hospitalized, of whom 30 were men (52.6%). The overall median age of the patients was 85 years (IQR: 76-90 years), with no significant difference between the patients in the public-expenditure and post-expenditure groups. The median number of days from symptom onset to hospitalization was comparable; 1 day for both patient groups (IQRs: 1 to 3 days). Overall, over half (52.0%) of the hospitalized patients were classified as having a mild condition, followed by moderate I (29.1%) and moderate II (17.5%). There was no significant difference in the distribution of disease severity between the public-expenditure and post-expenditure patient groups.

The vaccination history was unknown for 54.6% of the patients. Among the patients with a known vaccination history, 16.8% had never been immunized. The proportions of never-vaccinated individuals in the public-expenditure and post-expenditure groups were 17.6% and 8.3% and the proportions of those who had received three or more vaccine doses were 78.6% and 63.6%, respectively. Among the 302 hospitalized patients, 114 (37.7%) were diagnosed with COVID-19 in an outpatient setting prior to hospitalization, with 40.4% during the public-expenditure period and 26.3% in the subsequent period.

The prescribing patterns of antiviral drugs in outpa-

Table 1 Baseline characteristics of hospitalized patients with COVID-19

	Entire study period	During the PE system	Post-expenditure period	*P*-value
Period	2022/01/01–2024/03/31 (27 months)	2022/01/01–2023/09/30 (21 months)	2023/10/01–2024/03/31 (6 months)	
Number of the patient	302	245	57	
Sex, male, n (%)	162 (53.6%)	132 (53.9%)	30 (52.6%)	0.88
Age, years (median [IQR])	85 [76–90]	84 [75–90]	87 [80–90]	0.10
Days from onset to hospitalization	1 [1–3]	1 [1–3]	1 [1–3]	0.45
Severity at hospitalization				0.37
—No symptom, n (%)	4 (1.3%)	3 (1.2%)	1 (1.8%)	
—Mild, n (%)	157 (52.0%)	122 (49.8%)	35 (61.4%)	
—Moderate Ⅰ, n (%)	88 (29.1%)	75 (30.6%)	13 (22.8%)	
—Moderate Ⅱ, n (%)	53 (17.5%)	45 (18.4%)	8 (14.0%)	
—Severe, n (%)	0 (0%)	0 (0%)	0 (0%)	
Vaccination history				—
Unknown, n (%)	165 (54.6%)	120 (49.0%)	45 (78.9%)	
Known, n (%)	137 (45.4%)	125 (51.0%)	12 (21.1%)	
Never vaccinated, n (%)	23/137 (16.8%)	22/125 (17.6%)	1/12 (8.3%)	
At least one dose, n (%)	114/137 (83.2%)	103/125 (82.4%)	11/12 (91.7%)	
—1–2 doses	—19/114 (16.7%)	—18/103 (17.5%)	— 1/11 (9.1%)	
—3 or more doses	—88/114 (77.2%)	—81/103 (78.6%)	— 7/11 (63.6%)	
—unknown number of doses	— 7/114 (6.1%)	— 4/103 (3.9%)	— 3/11 (27.3%)	
Diagnosed with COVID-19 in outpatient settings prior to hospitalization	114 (37.7%)	99 (40.4%)	15 (26.3%)	0.05

PE, public expenditure. Continuous variables are denoted in median and interquartile ranges.

tient settings are illustrated in Fig. 1. During the public-expenditure period, 47 of the 99 patients (47.5%) diagnosed with COVID-19 prior to hospitalization received antiviral medications, most commonly molnupiravir (38 patients, 80.9%), with nirmatrelvir/ritonavir, sotrovimab, and remdesivir prescribed to three patients each. In the subsequent post-expenditure period, 12 of the 15 patients (80.0%) received antivirals, including molnupiravir (11 patients, 91.7%) and ensitrelvir (1 patient, 8.3%). The proportion of patients who had been prescribed antivirals as outpatients was significantly higher in the post-expenditure period ($p=0.026$), with a risk difference of 32.5% (95%CI: 7.9-57.0%), and the OR of 4.43 (95%CI: 1.14-17.2).

The patients' clinical outcomes are presented in Table 2. The number of transferred cases was four during the public-expenditure period, whereas none were recorded in the post-expenditure period. The overall in-hospital mortality rate was 15.4%. The mortality rate was 16.6% (40/241) in the first period and 10.5% (6/57) in the second period, with no significant between-group difference ($p=0.31$). The risk difference was 5.8% (95%CI: −3.4% to 15.0%), and the OR was 1.66 (95%CI: 0.67-4.13).

The mortality rates by age group were 7.7% (3/39) in the patients aged 20-69 years, 10.2% (6/59) among those in their 70s, 17.5% (21/120) in their 80s, 19.2% (14/73) in their 90s, and 28.6% (2/7) in the patients aged ≥100 years. The causes of death included COVID-19 in 32.6% (15 of the 46) patients, aspiration pneumonia in 15.2% (7/46), senility in 10.9% (5/46), choking and bacterial pneumonia in 6.5% each (3/46), and heart failure in 4.3% (2/46). Other causes comprised lung cancer, myocardial infarction, upper gastrointestinal bleeding, exacerbation of interstitial pneumonia, and acute kidney injury, one case each. In the remaining six cases, the cause of death was not specified. The characteristics of each of the four hospitals, along with the facility-specific prescription and mortality rates, are presented in Table 3.

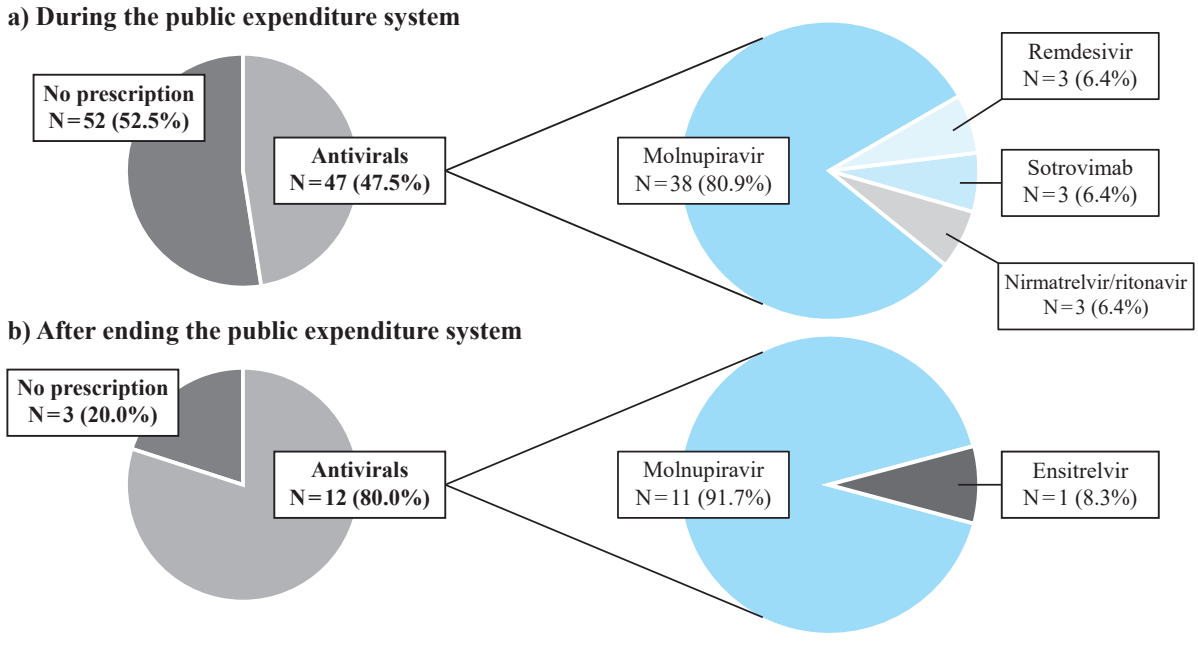

Fig. 1 The prescribing patterns of antiviral drugs in outpatient settings during the study period.

Table 2 Outcomes of COVID-19 patients

	Entire study period	During the PE system	Post-expenditure period	*P*-value
Transferred cases	4	4	0	—
Overall in-hospital death	46/298 (15.4%)	40/241 (16.6%)	6/57 (10.5%)	0.31

PE, public expenditure.

Table 3 Facility characteristics

	Watanabe Hospital (n=40)	Kasaoka City Hospital (n=135)	Takahashi Central Hospital (n=87)	Marugame Medical Center (n=40)
Number of hospital beds, n	88	99	160	300
Age, years (median [IQR])	88 [82–91]	83 [73–89]	86 [79–91]	83 [75–87]
Diagnosed in outpatient settings, n	10	60	37	7
Outpatient prescriptions, n (%)	6 (60%)	26 (43.3%)	26 (70.3%)	1 (14.3%)
Overall in-hospital death, n (%)	7 (17.5%)	29 (21.5%)	8 (9.2%)	2 (5%)
Age at death, years (median [IQR])	87 [85–89]	87 [82–93]	89 [84–95]	72 [69–74]

Discussion

We investigated the changes in COVID-19 treatment and consequent patient outcomes following the termination of public financial support in Japan. Our search of the relevant literature identified no prior assessments of the impact of changes in a public subsidy on clinical practice for COVID-19. Contrary to our expectations, our analyses revealed that antiviral drugs for the treatment of COVID-19 were prescribed significantly more often in the post-expenditure period (80% vs. 47.5% in the public-expenditure period), with molnupiravir being the most commonly prescribed drug. The overall in-hospital mortality rates were comparable between the

public-expenditure and post-expenditure patient groups; however, the rates remained surprisingly high at > 10% (17.0% and 10.5%, respectively).

The results of this study demonstrated that the proportion of outpatients receiving antiviral treatment for COVID-19 increased even after the discontinuation of the public expenditure system. Due to the small sample size, definitive conclusions cannot be drawn from this study. However, one plausible reason for this preferable shift may be the prevailing influence of clinical guidelines and recommendations among general practitioners at regional hospitals.

In addition to the prescribing proportions, the frequencies of each antiviral drug selected as treatment also warrant discussion. Molnupiravir was prescribed in 80.9% and 91.7% of the outpatients during the public-expenditure and the post-expenditure periods, respectively. The clinical effectiveness of molnupiravir in reducing the risk of hospital admission and death has been corroborated [18]. In addition, molnupiravir does not require renal dose adjustment and has fewer concerns regarding drug-drug interactions, making it relatively safe to prescribe to elderly individuals in outpatient settings. However, according to a randomized controlled trial, molnupiravir does not reduce the severity or mortality rates in high-risk populations who have completed three doses of a COVID-19 vaccine [21]. Molnupiravir is thus not recommended for clinical use in European countries and Australia. In the United States, molnupiravir is positioned as an alternative therapy to nirmatrelvir/ritonavir, rather than as a first-line treatment [22].

The Japanese practice guide also defines molnupiravir as a second-line COVID-19 therapy for patients with underlying risk factors (MLHW, https://www.mhlw.go.jp/content/001248424. pdf, accessed September 17, 2024). Nirmatrelvir/ritonavir is currently the global standard first-line drug for vulnerable patients with COVID-19 (IDSA, https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/, accessed September 17, 2024; MLHW, https://www.mhlw.go.jp/content/001248424. pdf, accessed September 17, 2024; WHO, https://iris.who.int/bitstream/handle/10665/373975/WHO-2019-nCoV-therapeutics-2023.2-eng.pdf?sequence=1, accessed September 18, 2024) [22]. Its cost-effectiveness for patients aged ≥ 60 years was suggested by a recent simulation study conducted in Japan [23]. Collectively, these findings indicate that nirmatrelvir/ritonavir, rather than molnupiravir, should have been prescribed more frequently, but this was not reflected in the real-world practice examined herein.

Our findings confirm that the high mortality rate of COVID-19 among super-aged populations remains a significant concern. A reported all-cause mortality rate of COVID-19 among people aged ≥ 80 years who received three doses of vaccine was 2.6% [24]. In our present patient population the in-hospital mortality rate exceeded 10%, highlighting the persistent threat posed by COVID-19. The high age of our study population, with a median at 85 years, could be the most strongly associated factor contributing to the increased mortality. Older individuals often have underlying medical conditions as well as physiological and anatomical problems [25], and they therefore have a high likelihood of developing secondary complications after hospitalization such as aspiration pneumonia, resulting in the higher overall mortality [26].

To mitigate the mortality risk of COVID-19 in elderly populations, vaccination coverage continues to be crucial. A newly developed mRNA vaccine exerted a surprisingly high preventive efficacy, with a vaccine efficacy at 91.3% (95%CI: 89.0-93.2) over a 6-month period [27]. However, with the emergence of new COVID variants that evade human immunity, the effectiveness of the original vaccine has waned over time. Currently, even the XBB variant-targeted vaccine has exhibited limited efficacy in reducing hospitalization rates or preventing emergency outpatient visits following booster doses [28]. The most updated mRNA vaccine targeting the JN. 1 variant can elicit a stronger neutralizing response compared to earlier vaccines [29], raising expectations for its potential effectiveness in humans. Vulnerable patient populations, including those at advanced ages, may achieve improved outcomes with these updated vaccines.

Several limitations of this study must be acknowledged. As this was a retrospective study, there were instances of missing data, particularly regarding the patients' vaccination status, which was self-reported and unavailable in 54.6% of the cases. The number of study participants was limited, particularly in the subset of patients diagnosed in outpatient settings during the post-expenditure period, which reduced the study's statistical power and limited the precision of estimates for risk differences and odds ratios. A multivariate

analysis and adjustments for potential confounding factors such as age, disease severity, and vaccination status could therefore not be performed. In addition, the calculated data may not accurately represent the overall population.

Another study limitation is that the specific subvariants circulating during the public-expenditure and post-expenditure periods were unknown, and the potential impact of these variant differences was not considered. Moreover, the study was conducted in small-scale hospitals, and severe cases might have been transferred to higher-level medical institutions, which underestimates the severity of COVID-19. The post-expenditure phase spanned only 6 months compared to 21 months in the public-expenditure phase, resulting in an imbalanced observation period. This was due to the study's design focusing on the impact of the termination of public expenditure support for COVID-19. Lastly, the number of outpatient-diagnosed cases during the post-policy phase was extremely limited (n = 15), which restricts the study's statistical power and the generalizability of comparisons between the two phases. Despite these limitations, the implications of this study are significant, especially in a world facing an aging population and an ongoing battle against COVID-19.

In conclusion, our analyses revealed that anti-COVID-19 drugs were frequently prescribed to patients with COVID-19 at regional hospitals in Japan, even after the termination of public financial support. Molnupiravir has continued to be the most commonly prescribed drug throughout the study period, despite its lower recommendation in clinical guidelines. The mortality rate remains undeniably high among super-aged individuals, underscoring the critical role of appropriate antiviral therapy as well as booster vaccinations in the mitigation of severe outcomes.

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