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Original Article

Favipiravir for symptomatic COVID-19: A nationwide observational cohort study

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ABSTRACT

Introduction: Favipiravir, an antiviral agent with activity against SARS-CoV-2, was made available to hospitals in Japan for off-label use among COVID-19 patients between 2020 and 2021.

Methods: A nationwide observational cohort study was conducted on patients who received favipiravir as part of clinical care between February 2020 and December 2021. Information was collected on demographics, comorbidities, severity of illness, use of favipiravir and other medications targeting COVID-19, adverse events, clinical status at 7 and 14 days and clinical outcome one month after admission to the hospital.

Results: A total of 17,508 hospitalized patients who received favipiravir were registered from 884 hospitals. In terms of demographics, 55.9% were age ≥ 60 years, and 62.3% were male. At least one of the four surveyed comorbidities was present in 45.5% of the patients. The rates of clinical improvement at 7 and 14 days were 72.4% and 87.5%, 61.4% and 76.6%, and 45.4% and 59.5% for mild, moderate, and severe diseases, respectively. The case fatality rates within a month from hospitalization were 3.3%, 12.6%, and 29.1% for mild, moderate, and severe diseases, respectively. Significant correlations were observed between death and advanced age, male sex, moderate or severe disease, diabetes, cardiovascular diseases, and immunosuppression. Commonly reported adverse events included uric acid level increase or hyperuricemia (16.8%), liver function abnormalities (6.9%), and rash (1.0%).

Conclusions: Favipiravir was well tolerated among COVID-19 patients. The study provides insights into the use of this agent at hospitals across Japan in the early phase of the pandemic.

1. Introduction

Favipiravir is a nucleoside analog antiviral agent that inhibits RNA-dependent RNA polymerase and demonstrates a wide spectrum of activity against RNA viruses. In Japan, favipiravir has been approved for the treatment of patients with novel or re-emerging pandemic influenza against which other treatments are ineffective, but the inventory is managed by the government and the drug is not routinely available for prescription. Given its *in vitro* activity against SARS-CoV-2, favipiravir was made available to hospitals for off-label use among patients with

COVID-19 between February 2020 and December 2021, the period during which approved oral antiviral treatment options for COVID-19 were not yet available. Hospitals were asked to register the cases to this observational cohort study after it was administered to patients. This was the first occasion in which a large number of patients received favipiravir for the treatment of a viral infection in Japan. Here, we report the final dataset from the cohort, with a focus on demographics, disease course, and safety of favipiravir.

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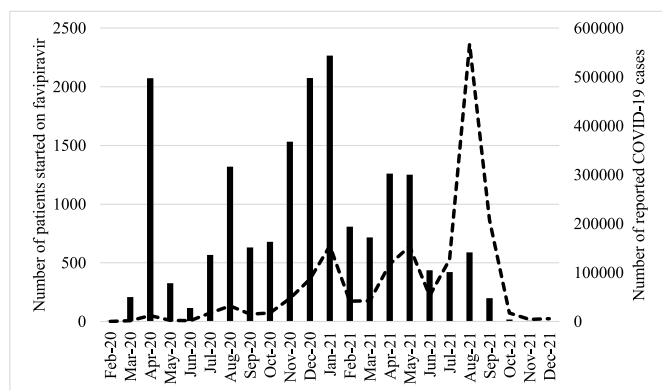


Fig. 1. Number of patients started on favipiravir based on month.

2. Methods

2.1. Off-label use of favipiravir

Favipiravir was made available to hospitals between February 2020 and December 2021 from FUJIFILM Toyama Chemical Co., Ltd., the manufacturer of favipiravir, after a request for off-label use of the agent was made by the hospitals to the Ministry of Health, Labour and Welfare and the requirements for close management of the medication were met, which practically restricted its use to hospitalized patients. The physicians prescribed favipiravir to patients with a confirmed diagnosis of COVID-19 upon consent in accordance with institutional regulations governing off-label use at each hospital.

2.2. Study design

This study was conducted as a retrospective study to collect clinical information after favipiravir was administered to patients as part of clinical care. Informed consent was on an opt-out basis given the non-interventional nature of the study. The hospitals were asked to provide anonymized information regarding the patient demographics, comorbidities, severity of illness, location of patient (inpatient or outpatient), dose and duration of favipiravir, use of other medications targeting COVID-19, adverse events likely related to favipiravir use, clinical status 7 and 14 days from the start of the use of favipiravir and clinical outcome approximately one month after admission to the hospital. This study was approved by the Institutional Review Board of Fujita Health University.

2.3. Data collection and analysis

The data were collected using the survey function of REDCap. Query and data cleaning was conducted to address apparent errors such as duplicate record entry, missing values and outliers. Site monitoring was not conducted.

Continuous variables were described using median and interquartile range and categorical variables using frequencies. For the analysis of prognosis, the Kaplan-Meier estimate and Cox proportional hazards model were used. The date of the first dose of favipiravir was used as the baseline date, and a period up to the date of entry of clinical outcome was handled as the follow-up period. Only the clinical outcome recorded as died in hospital was defined as death. Age, sex, severity of illness, and underlying diseases (diabetes, cardiovascular diseases, chronic lung diseases, and immunosuppression) were considered to possibly affect death, and each of these factors was selected as explanatory variables of the Cox proportional hazards model. No correlations suspected of multicollinearity were noted between each variable. The proportional hazards assumption was confirmed using Schoenfeld's partial residuals of the independent variables included in the model. Age was handled as a

Table 1

Demographics and concomitant COVID-19-related medications of patients with COVID-19 who received favipiravir.

Variables	Categories	n (%)
Demographics		
Age group (n = 17,508)	<10	1 (0.0%)
	10–19	67 (0.4%)
	20–29	694 (4.0%)
	30–39	1074 (6.1%)
	40–49	2383 (13.6%)
	50–59	3501 (20.0%)
	60–69	3134 (17.9%)
	70–79	3499 (20.0%)
	80–89	2491 (14.2%)
	≥90	664 (3.8%)
Sex (n = 17,508)	Female	6597 (37.7%)
	Male	10,911 (62.3%)
Diabetes (n = 17,429)	Present	4070 (23.4%)
	Absent	13,359 (76.6%)
Cardiovascular diseases (n = 17,440)	Present	4034 (23.1%)
	Absent	13,406 (76.9%)
Chronic lung diseases (n = 17,415)	Present	1611 (9.3%)
	Absent	15,804 (90.7%)
Immunosuppression (n = 17,410)	Present	775 (4.5%)
	Absent	16,635 (95.5%)
Any of the above comorbidities (n = 17,457)	Present	7951 (45.5%)
	Absent	9506 (54.5%)
Concomitant COVID-19-related medications		
Ciclesonide (n = 17,508)	Given	4289 (24.5%)
	Not given	13,219 (75.5%)
Lopinavir–ritonavir (n = 17,508)	Given	72 (0.4%)
	Not given	17,436 (99.6%)
Hydroxychloroquine (n = 17,508)	Given	198 (1.1%)
	Not given	17,310 (98.9%)
Nafamostat (n = 17,508)	Given	1084 (6.2%)
	Not given	16,424 (93.8%)
Camostat (n = 17,508)	Given	702 (4.0%)
	Not given	16,806 (96.0%)
Remdesivir (n = 17,508)	Given	2312 (13.2%)
	Not given	15,196 (86.8%)
Dexamethasone (n = 17,508)	Given	7012 (40.1%)
	Not given	10,496 (59.9%)
Methylprednisolone (n = 17,508)	Given	2064 (11.8%)
	Not given	15,444 (88.2%)
Outcome (n = 17,461)	Died in hospital	1203 (6.9%)
	Transferred for escalation of care	934 (5.3%)
	Still in hospital (alive)	179 (1.0%)
	Transferred for de-escalation of care	1303 (7.5%)
	Discharged alive	13,842 (79.3%)

Table 2
Administration of favipiravir.

(a) Dosing of favipiravir				
n	Dosing	n (%)		
17,478	2 doses of 1600 mg followed by 600 mg twice a day	550 (3.1%)		
	2 doses of 1800 mg followed by 800 mg twice a day	16564 (94.8%)		
	Others	364 (2.1%)		
(b) Duration of favipiravir				
n	Median	Q1 (25%)	Q3 (75%)	
17,508	8	5	10	
(c) Days from first positive test to first dose of favipiravir				
n	Median	Q1 (25%)	Q3 (75%)	
17,508	2	1	4	
(d) Days from hospital admission to first dose of favipiravir				
n	Median	Q1 (25%)	Q3 (75%)	
17,508	0	0	1	

continuous variable, and other variables were handled as categorical variables. We used R (version 4.1.3 patched) for all statistical analyses. A two-sided $p < 0.05$ was considered statistically significant.

Interim reports of the study have previously been released on the Japanese Association of Infectious Diseases website (<https://www.kansensho.or.jp/modules/en/>) in May and September 2020, and April and November 2021.

3. Results

3.1. Overview

A total of 17,508 hospitalized patients who received favipiravir were registered from 884 hospitals. Of these patients, the patient demographics, clinical status at Day 7, clinical status at Day 14, and clinical outcome at approximately one month after hospital admission were available for 17,366, 16,512, 13,425, and 17,461 patients, respectively. Fig. 1 shows the number of patients started on favipiravir by month. Over two thousand patients were treated with favipiravir in April 2020 at the height of the first surge. Its use then increased again in the summer and winter of 2020, corresponding to the second and third surges, respectively, then decreased in 2021 over the course of the fourth and fifth surges. Since the cohort only includes patients who received favipiravir, clinical effectiveness of this agent cannot be evaluated from this dataset. Rather, below describes the general features of patients who opted into this off-label use program.

3.2. Patient demographics

The age distribution, sex, presence or absence of underlying disease (diabetes, cardiovascular diseases, chronic lung diseases, and immunosuppression), and use of other antiviral agents are shown in Table 1. In

terms of demographics, 55.9% were age ≥ 60 years, and 62.3% were male. At least one of the four surveyed comorbidities (diabetes, cardiovascular diseases, chronic lung diseases, and immunosuppression) was present in 45.5% of the patients.

3.3. Administration of favipiravir

Administration of favipiravir is shown in Table 2. In 94.8% of the patients, favipiravir was dosed at two doses of 1800 mg followed by 800 mg twice a day. The median days from the first positive COVID-19 test and hospital admission to the initiation of favipiravir therapy were 2 and 0 days, respectively. The median duration of treatment was 8 days.

3.4. Severity of illness

For this study, mild, moderate, and severe diseases at the start of favipiravir were defined as those not requiring supplemental oxygen, those breathing spontaneously but requiring supplemental oxygen, and those requiring mechanical ventilation or extracorporeal membrane oxygenation, respectively. By this definition, 11,680 patients (66.7%) had mild disease, 5303 patients (30.3%) had moderate disease, and 525 patients (3%) had severe disease.

3.5. Clinical course and outcome by severity of disease

The clinical course at 7 and 14 days after the start of favipiravir therapy was evaluated as improved, worsened, or unchanged by the treating physicians. The rates of clinical improvement at 7 and 14 days were 72.4% and 87.5%, 61.4% and 76.6%, and 45.4% and 59.5% for mild, moderate, and severe diseases, respectively (Table 3). The rates of clinical worsening at 7 and 14 days were 14.5% and 6.8%, 24.4% and 16%, and 28% and 25.5% for mild, moderate, and severe diseases, respectively.

The clinical outcome was assessed at approximately one month from hospitalization as discharged alive, died in hospital, transferred for de-escalation of care, transferred for escalation of care, or still in hospital. The case fatality rates within a month from hospitalization were 3.3%, 12.6%, and 29.1% for mild, moderate, and severe diseases, respectively.

3.6. Clinical course and outcome by age group

The clinical course and outcome based on age groups are shown in Table 4. Both the clinical course and outcome were worse in older patients. The case fatality rate was 1.2% in the 50–59 age group, whereas the rates were 3.7%, 9.4%, 21%, and 27.6% in the 60–69, 70–79, 80–89, and ≥ 90 age groups, respectively.

Table 3
Clinical status and outcome stratified by severity of illness in patients who received favipiravir.

(a) At 7 days after start of favipiravir						
Day 7 (n = 16,512)		Improved		Unchanged	Worsened	
		Mild	8057 (72.4%)	1449 (13%)	1618 (14.5%)	
	Moderate	3010 (61.4%)	697 (14.2%)	1199 (24.4%)		
	Severe	219 (45.4%)	128 (26.6%)	135 (28%)		
(b) At 14 days after start of favipiravir						
Day 14 (n = 13,425)		Improved		Unchanged	Worsened	
		Mild	7753 (87.5%)	512 (5.8%)	600 (6.8%)	
	Moderate	3161 (76.6%)	305 (7.4%)	659 (16%)		
	Severe	259 (59.5%)	65 (14.9%)	111 (25.5%)		
(c) Clinical outcome one month from hospital admission						
Outcome (n = 17,461)		Died in hospital	Transferred for escalation of care	Still in hospital (alive)	Transferred for de-escalation of care	Discharged alive
		Mild	386 (3.3%)	475 (4.1%)	86 (0.7%)	621 (5.3%)
	Moderate	665 (12.6%)	438 (8.3%)	75 (1.4%)	534 (10.1%)	3585 (67.7%)
	Severe	152 (29.1%)	21 (4%)	18 (3.4%)	148 (28.4%)	183 (35.1%)

Table 4
Clinical status and outcome stratified by age group in patients who received favipiravir.

(a) At 7 days after start of favipiravir		Improved	Unchanged	Worsened
Day 7 (n = 16,512)	<10	1 (100%)	0 (0%)	0 (0%)
	10-19	58 (89.2%)	6 (9.2%)	1 (1.5%)
	20-29	587 (89.1%)	49 (7.4%)	23 (3.5%)
	30-39	863 (83.2%)	101 (9.7%)	73 (7%)
	40-49	1820 (80%)	243 (10.7%)	211 (9.3%)
	50-59	2485 (75.4%)	339 (10.3%)	473 (14.3%)
	60-69	2005 (68.2%)	398 (13.5%)	539 (18.3%)
	70-79	1950 (59.5%)	550 (16.8%)	775 (23.7%)
	80-89	1224 (52.3%)	438 (18.7%)	678 (29%)
	≥90	293 (47.1%)	150 (24.1%)	179 (28.8%)

(b) At 14 days after start of favipiravir		Improved	Unchanged	Worsened
Day 14 (n = 13,425)	<10	1 (100%)	0 (0%)	0 (0%)
	10-19	37 (90.2%)	3 (7.3%)	1 (2.4%)
	20-29	484 (94.5%)	20 (3.9%)	8 (1.6%)
	30-39	758 (93.6%)	32 (4%)	20 (2.5%)
	40-49	1660 (93.4%)	65 (3.7%)	52 (2.9%)
	50-59	2430 (91.1%)	119 (4.5%)	118 (4.4%)
	60-69	2022 (85.7%)	129 (5.5%)	209 (8.9%)
	70-79	2111 (77.6%)	226 (8.3%)	382 (14%)
	80-89	1352 (67.6%)	201 (10.1%)	447 (22.4%)
	≥90	318 (59.1%)	87 (16.2%)	133 (24.7%)

(c) Clinical outcome one month from hospital admission		Died in hospital	Transferred for escalation of care	Still in hospital (alive)	Transferred for de-escalation of care	Discharged alive
Outcome (n = 17,461)	<10	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
	10-19	0 (0%)	0 (0%)	1 (1.5%)	1 (1.5%)	65 (97%)
	20-29	2 (0.3%)	10 (1.4%)	2 (0.3%)	28 (4%)	652 (93.9%)
	30-39	2 (0.2%)	35 (3.3%)	4 (0.4%)	31 (2.9%)	1001 (93.3%)
	40-49	10 (0.4%)	88 (3.7%)	3 (0.1%)	74 (3.1%)	2200 (92.6%)
	50-59	43 (1.2%)	185 (5.3%)	11 (0.3%)	144 (4.1%)	3106 (89%)
	60-69	116 (3.7%)	233 (7.5%)	24 (0.8%)	188 (6%)	2566 (82.1%)
	70-79	327 (9.4%)	268 (7.7%)	64 (1.8%)	336 (9.6%)	2495 (71.5%)
	80-89	520 (21%)	102 (4.1%)	44 (1.8%)	374 (15.1%)	1442 (58.1%)
	≥90	183 (27.6%)	13 (2%)	26 (3.9%)	127 (19.2%)	314 (47.4%)

Table 5
Predictors of death in hospital (univariable analysis).

Variables	Hazard ratio	Lower limit of 95% CI	Upper limit of 95% CI	P-value
Age	1.07	1.06	1.07	<0.001
Male (vs. female)	1.12	0.99	1.25	0.068
Moderate (vs. mild)	2.78	2.45	3.15	<0.001
Severe (vs. mild)	3.66	3.02	4.43	<0.001
Diabetes	1.39	1.23	1.56	<0.001
Cardiovascular diseases	1.82	1.62	2.05	<0.001
Chronic lung diseases	1.61	1.38	1.86	<0.001
Immunosuppression	1.75	1.46	2.11	<0.001

Table 6
Predictors of death in hospital (multivariable analysis).

Variables	Hazard ratio	Lower limit of 95% CI	Upper limit of 95% CI	P-value
Age	1.08	1.07	1.08	<0.001
Male (vs. female)	1.62	1.43	1.83	<0.001
Moderate (vs. mild)	2.32	2.05	2.64	<0.001
Severe (vs. mild)	4.45	3.66	5.4	<0.001
Diabetes	1.26	1.12	1.42	<0.001
Cardiovascular diseases	1.15	1.02	1.29	0.022
Chronic lung diseases	1.15	0.99	1.34	0.067
Immunosuppression	1.91	1.58	2.3	<0.001

3.7. Prognostic factors

Univariable analysis showed significant correlations between death and advanced age, moderate or severe disease, diabetes, cardiovascular

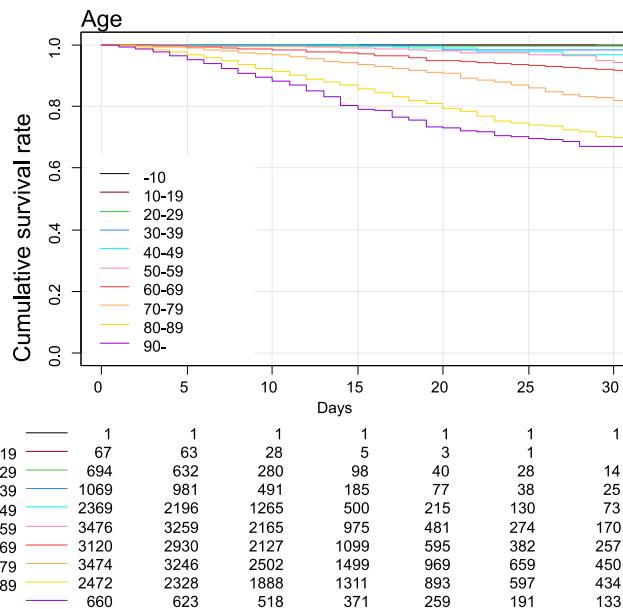


Fig. 2. Survival by age group.

diseases, chronic lung diseases, and immunosuppression (Table 5). A multivariable analysis showed significant correlations between death and advanced age, male sex, moderate or severe disease, diabetes, cardiovascular diseases, and immunosuppression (Table 6). Figs. 2-8 show survival curves stratified by each factor.

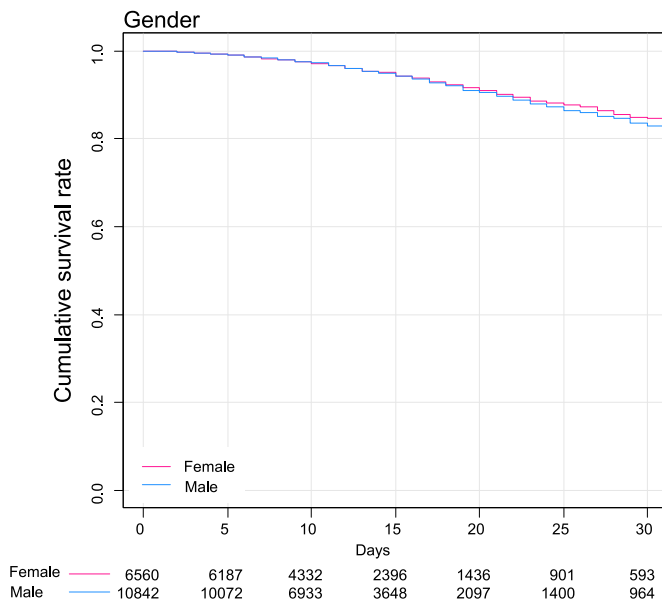


Fig. 3. Survival by gender.

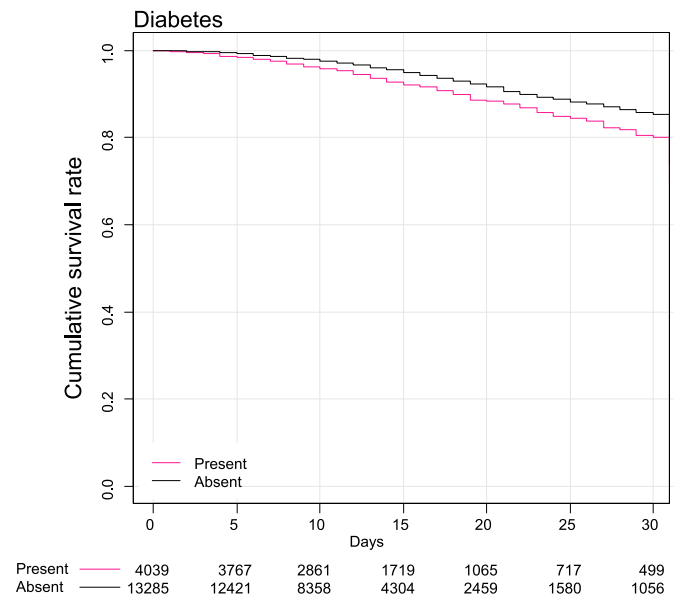


Fig. 5. Survival by presence or absence of diabetes.

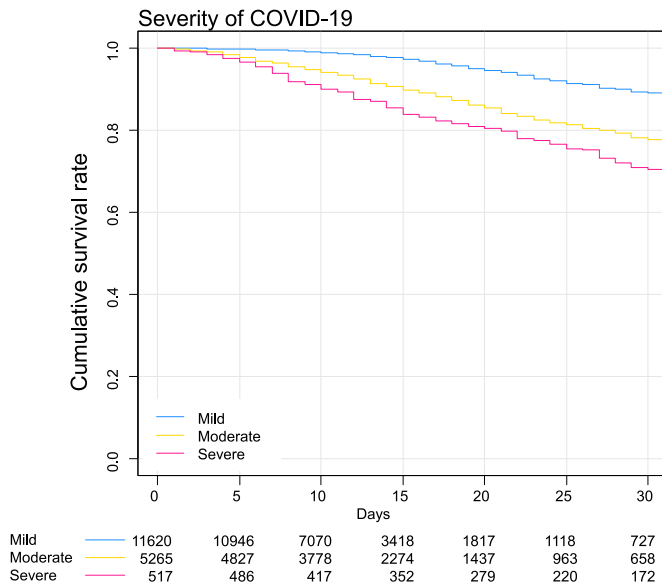


Fig. 4. Survival by severity of COVID-19.

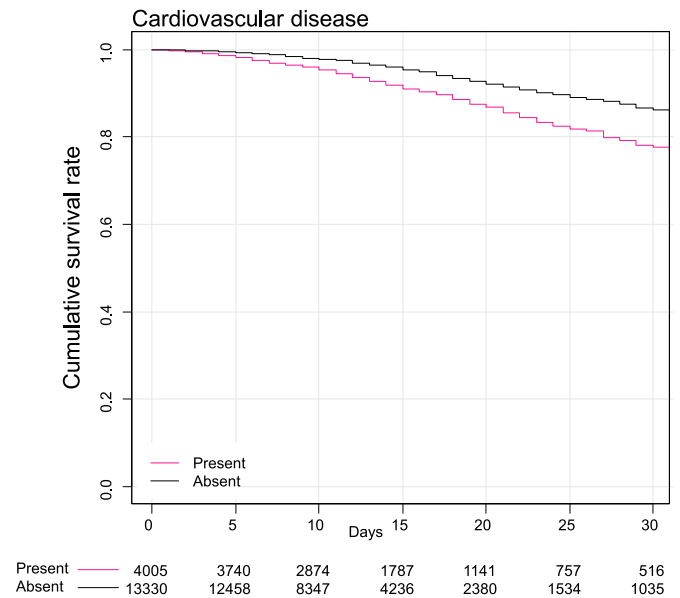


Fig. 6. Survival by presence or absence of cardiovascular disease.

3.8. Adverse events

A total of 4312 (24.6%) patients had probable or possible adverse events in association with favipiravir use recorded based on the treating physicians' assessment (Table 7). Commonly reported adverse events included uric acid level increase or hyperuricemia in 2934 patients, liver function abnormalities in 1205 patients, and rash in 170 patients. The adverse event rates by age groups are shown in Fig. 9. They were reported more commonly in younger age groups, and hyperuricemia or increase in serum uric acid level was reported most frequently in those between 30 and 39.

3.9. Outpatients

Separate from the data shown on hospitalized patients above, 219 patients from 19 hospitals were recorded as having been started on favipiravir in an outpatient setting. As information on location of care

was not collected otherwise, they may have been hospitalized subsequently or followed up as outpatients. These patients were younger than inpatients with 71.7% less than 60 years of age. Males accounted for 53.9%, and at least one of the four surveyed comorbidities was present in 25.3%. The median day from the first positive COVID-19 test to the initiation of favipiravir was 1 day, and the median duration of treatment was 6 days. Among these patients, 216 patients (98.6%) had mild disease, 3 patients (1.4%) had moderate disease, and none had severe disease. The combined rates of clinical improvement at 7 and 14 days were 79.1% and 86.7%, respectively. At approximately one month, 89.0% of the patients had improved, 1.4% had not improved and the outcome was unknown for 2.7%. Adverse events reported were uric acid level increase or hyperuricemia (13 patients), liver function abnormalities (3 patients), and palpitation (1 patient).

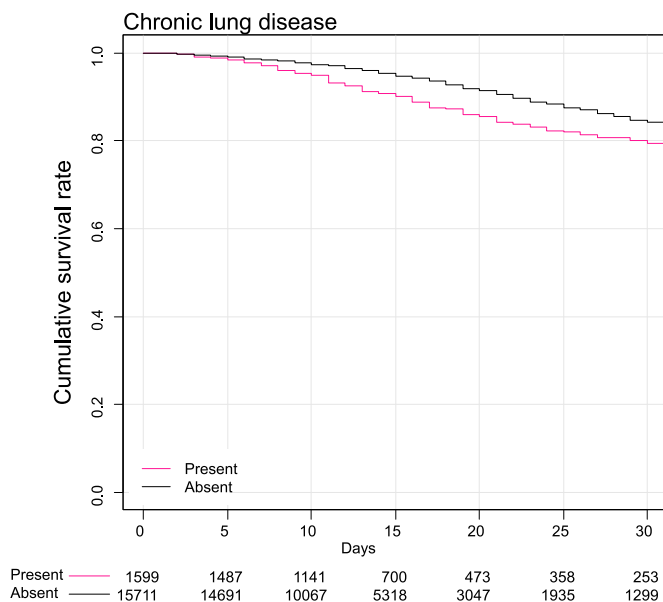


Fig. 7. Survival by presence or absence of chronic lung disease.

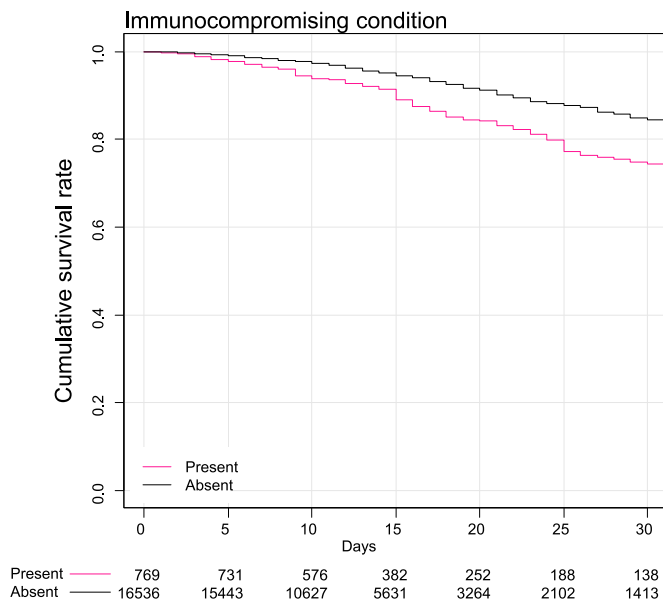


Fig. 8. Survival by presence or absence of immunocompromising condition.

4. Discussion

Favipiravir became available for off-label use in the treatment of COVID-19 in Japan beginning in February 2020 in response to the unprecedented pandemic which was quickly unfolding at the time. The off-label use program was coordinated through the Ministry of Health, Labour and Welfare, and the hospitals participating in this off-label use program were invited to register the cases to this observational cohort study in order to monitor its use, safety and patient outcomes. As the incidence of COVID-19 decreased and other oral antiviral treatment options became available, the off-label use program was concluded at the end of December 2021. Prior to this final report, four interim reports from this study have been published on the website of the Japanese Association of Infectious Diseases. In this final report, over seventeen thousand patients were registered, making it one of the largest cohorts of patients who received favipiravir.

Favipiravir shows variable degrees of *in vitro* activity against SARS-

Table 7

Adverse events associated with favipiravir use.

Adverse event	Number of events
Hyperuricemia, increase in serum uric acid level	2934
Liver function abnormalities	1205
Fever	161
Rash (toxicoderma, eczema, purpura, erythema)	170
Renal dysfunction, increase in serum creatinine level	57
Diarrhea, loose stool	56
Hypoxemia	53
Nausea	52
Bradycardia	39
Dyslipidemia	19
Leukopenia	18
Anorexia	18
Hyperkalemia	13
Gout	13
Coagulation abnormalities	13
Rhabdomyolysis, increase in serum creatine kinase level	12
Neutropenia	11
Dizziness	10
Increase in serum inflammatory marker level	9
Thrombocytopenia	8
Pruritus	8
Constipation	7
Laboratory abnormalities relating to biliary tract	7
Increase in serum amylase level	6
Eosinophilia	6
Heartburn	6
Hyperglycemia	6
Fatigue	5
Thrombocytosis	5
Pneumonia, worsening thereof	5
Headache	4
Increase in serum blood urea nitrogen level	4
Anemia	4
Increase in serum lactate dehydrogenase level	3
Worsening of COVID-19 symptoms	3
Hypernatremia	3
Abdominal pain	3
Lymphocytopenia	3
Gastrointestinal symptoms	3
Melena	3
Hypertension	2
Stomatitis	2
Worsening of laboratory values	2
Altered mental status	2
Stroke	2
Increase in serum ferritin level	2
Agitation	2
Seizure	2
Cough, worsening thereof	2
Arthritis, arthralgia	2
Acute pancreatitis	2
Cytopenia	2
Thromboembolism	2
Increase in serum aldolase level	1
Increase in estimated glomerular filtration rate	1
QT prolongation	1
Allergic reaction	1
Increase in SARS-CoV-2 viral load	1
Stevens-Johnson syndrome	1
Lymphadenopathy	1
Jaundice	1
Lower extremity numbness	1
Eye mucus	1
Hiccup	1
Angina pectoris	1
Hyperkalemia	1
Hematuria	1
Hematochezia	1
Visual field defect	1
Gum bleeding	1
Premature ventricular contraction	1
Psychiatric symptoms	1
Cramps in the groin	1
Secondary pneumothorax	1
Dehydration	1

(continued on next page)

Table 7 (continued)

Hyponatremia	1
Diaphoresis	1
Eye floater	1
Dysgeusia	1
Drowsiness	1
Lacrimation	1
Splenic infarction	1

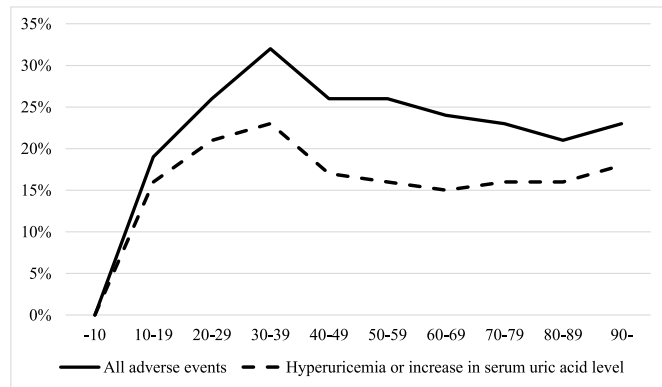


Fig. 9. Adverse event rates by age group.

CoV-2 depending on the cells and experimental conditions [1–3], and has demonstrated efficacy in hamster models [4,5]. A large number of clinical trials have also been conducted and reported. A recent meta-analysis suggested potential modest clinical benefit of favipiravir over standard of care in terms of faster viral clearance, defervescence, radiographic improvement, hospital discharge and clinical improvement among hospitalized patients, however no difference was observed on mortality [6]. Furthermore, clinical trials conducted among outpatients have not demonstrated clinical or virological benefit of favipiravir [7–9]. The present study was not designed to evaluate effectiveness, and the study covered periods with variable admission criteria, SARS-CoV-2 variants, vaccination rates and availability of additional treatment options, such as use of corticosteroids for patients requiring oxygen. It is also conceivable that the outcomes may have been confounded by indication in that those perceived to be at an elevated risk of suboptimal clinical outcomes were preferentially considered for treatment with favipiravir.

The common adverse events associated with favipiravir use were uric acid level increase and liver function test abnormalities. Elevation of uric acid levels, believed to be caused by its reduced excretion into the urine, have been observed among patients receiving favipiravir across clinical studies, and are known to normalize after discontinuation of the agent [10,11]. The reason for the higher frequencies of uric acid elevation in younger age groups was unclear. Importantly, there were no unanticipated safety signals in this large cohort of patients who received favipiravir.

The study has several key limitations to be acknowledged. As this was an observational cohort study, not all patients who received favipiravir on an off-label basis were captured. Also, the study used the survey function of RedCap to minimize data entry effort on the part of the hospitals. This meant that the assessment of clinical improvement or worsening was delegated to the treating physicians, and data cleaning was also kept to a minimum. Underreporting of adverse events is another possibility. Despite these caveats, the study provides unique insights into how favipiravir was utilized in the management of COVID-

19 at Japanese hospitals in the early phase of the pandemic.

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Availability of data and materials

The data will not be shared because of participant confidentiality.

Authors' contributions

YD was the principal investigator and responsible for the data analysis. SB and MK contributed to the study design and ethical approval. TI conducted the statistical analysis. MA conducted quality control of the database. YD drafted the manuscript, and all authors contributed substantially to its revision.

Declaration of competing interest

YD has served on a scientific advisory board of FujiFilm, the manufacturer of favipiravir, for an unrelated study. All other authors declare no competing interests.

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References

- [1] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020;30(3):269–71.
- [2] Shannon A, Selisko B, Le NT, Huchting J, Touret F, Piorkowski G, et al. Rapid incorporation of Favipiravir by the fast and permissive viral RNA polymerase complex results in SARS-CoV-2 lethal mutagenesis. *Nat Commun* 2020;11(1):4682.
- [3] Jeon S, Ko M, Lee J, Choi I, Byun SY, Park S, et al. Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs. *Antimicrob Agents Chemother* 2020;64(7):e00819–20.
- [4] Kaptein SJF, Jacobs S, Langendries L, Seldeslachts L, Ter Horst S, Liesenborghs L, et al. Favipiravir at high doses has potent antiviral activity in SARS-CoV-2-infected hamsters, whereas hydroxychloroquine lacks activity. *Proc Natl Acad Sci U S A* 2020;117(43):26955–65.
- [5] Driouch JS, Cochlin M, Lingas G, Moureau G, Touret F, Petit PR, et al. Favipiravir antiviral efficacy against SARS-CoV-2 in a hamster model. *Nat Commun* 2021;12(1):1735.
- [6] Hung DT, Ghula S, Aziz JMA, Makram AM, Tawfik GM, Abozaid AA, et al. The efficacy and adverse effects of favipiravir on patients with COVID-19: a systematic review and meta-analysis of published clinical trials and observational studies. *Int J Infect Dis* 2022;120:217–27.
- [7] Bosaeed M, Alharbi A, Mahmoud E, Alrehily S, Bahlaq M, Gaifer Z, et al. Efficacy of favipiravir in adults with mild COVID-19: a randomized, double-blind, multicentre, placebo-controlled clinical trial. *Clin Microbiol Infect* 2022;28(4):602–8.
- [8] Holubar M, Subramanian A, Purington N, Hedlin H, Bunning B, Walter KS, et al. Favipiravir for treatment of outpatients with asymptomatic or uncomplicated COVID-19: a double-blind randomized, placebo-controlled, phase 2 trial. *Clin Infect Dis* 2022. <https://doi.org/10.1093/cid/ciac312>.
- [9] Golan Y, Campos JAS, Woolson R, Cilla D, Hanabergh R, Gonzales-Rojas Y, et al. Favipiravir in patients with early mild-to-moderate COVID-19: a randomized controlled trial. *Clin Infect Dis* 2022. <https://doi.org/10.1093/cid/ciac712>.
- [10] Mishima E, Anzai N, Miyazaki M, Abe T. Uric acid elevation by favipiravir, an antiviral drug. *Tohoku J Exp Med* 2020;251(2):87–90.
- [11] Doi Y, Hibino M, Hase R, Yamamoto M, Kasamatsu Y, Hirose M, et al. A prospective, randomized, open-label trial of early versus late favipiravir therapy in hospitalized patients with COVID-19. *Antimicrob Agents Chemother* 2020;64(12):e01897–20.