Favipiravir Observational Study Interim Report 2
(as of June 26, 2020)

Favipiravir Observational Study Group, Fujita Health University

Introduction

Favipiravir (brand name: Avigan), an anti-influenza agent, is known to exert the antiviral activity against the new coronavirus (SARS-CoV-2), which is also an RNA virus[1]. Among clinical studies of favipiravir for the coronavirus infectious disease 2019 (COVID-19), a Chinese nonrandomized clinical study reported that patients who received favipiravir in combination with interferon-α for 14 days achieved PCR negativity faster than those who received lopinavir–ritonavir (brand name: Kaletra), an anti-HIV agent, in combination with interferon-α for 14 days[2]. A non-peer-reviewed report on a randomized clinical study in patients with COVID-19, also conducted in China, reported that patients who received favipiravir for 10 days showed a higher symptom improvement rate at 7 days and shorter durations of fever and cough compared with those who received umifenovir, an anti-influenza agent, for 10 days[3]. Furthermore, a Japanese randomized clinical study of early and delayed treatment of favipiravir in asymptomatic patients and patients with mild COVID-19 reported that the PCR negativity rate and duration of fever were more favorable in the early treatment group compared with those in the delayed treatment group[4], and a preliminary report of a Russian randomized clinical trial of favipiravir vs standard of care showed PCR negativity rates of 62.5% for the favipiravir group and 30.0% for the standard of care group by the fifth day, respectively[5].

In Japan, compassionate use of favipiravir to hospitalized patients with COVID-19 is allowed at the discretion of the medical institutions since February 2020. For off-label use, it is recommended to refer to the "Guidelines for Drug Therapy for COVID-19 4th Edition (May 28, 2020)" published by the Japanese Association for Infectious Diseases[6]. Medical institutions are asked to registered cases for which favipiravir was administered to a registry study (retrospective observational study) managed by the National Center for Global Health and Medicine (NCGM) and the antiviral agent observational study conducted by Fujita Health University. This report is the second report of the latter study (the antiviral agent observational study).

Methods

Favipiravir is provided to medical institutions admitting patients who are eligible for the off-label use from the manufacturer and vendor FUJIFILM Toyama Chemical Co., Ltd., after a request for off-label use of favipiravir is made to the Ministry of Health, Labour and Welfare by medical institutions and the requirements are met[7]. This study is conducted as a retrospective study to collect clinical information when favipiravir is administered as part of clinical practice. Participating medical institutions are asked to enter the patient demographics, comorbidities, severity of illness at the start of favipiravir, dosage and duration of favipiravir, concomitant medications, adverse events, and clinical outcome at the start of favipiravir and approximately 1 month after hospital admission.

Administration of favipiravir is contingent upon obtaining informed consent from the patient in accordance with the protocols in place at the participating institution, and any serious adverse events would be collected through this observational study.

The Kaplan–Meier estimate and Cox proportional hazards model were used for the analysis of prognosis in this report. 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 entered as died in hospital was defined as death, and the clinical outcomes entered as transferred for escalation of care or died in hospital were defined as exacerbation. Age, sex, severity of illness, and underlying diseases (diabetes, cardiovascular diseases, chronic lung diseases, and immunosuppression) were considered to possibly affect death or exacerbation, 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. Age was handled as a continuous variable, and other variables were handled as categorical variables.

This study was approved by the Institutional Review Board of Fujita Health University.

Results

【Overview】

As of June 28, 2020, at 24:00, a total of 2,970 patients who received favipiravir were registered from 497 medical institutions. Of these patients, the patient demographics, clinical status at Day 7, clinical status at Day 14, and clinical outcome at approximately 1 month after hospital admission were available for 2,951, 2,670, 2,256, and 2,913 patients, respectively. This study utilizes a survey function in an effort to prioritize speed of report and ease of data entry at each medical institution, and only limited data cleaning has been performed.

【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% were age ≥60 years, and 65.4% were male. At least one of the four surveyed comorbidities (diabetes, cardiovascular diseases, chronic lung diseases, and immunosuppression) was present in 49.8% of the patients. Ciclesonide, which has been approved for treatment of bronchial asthma and shown to possess the antiviral activity against SARS-CoV-2[8], was co-administered in 42.1% of the patients. There are few changes from the first report in these ratios.

Table 1. Demographics of patients with COVID-19 who received favipiravir

Variables	Categories	n	(%)
Age group (n = 2,969)	<10	1	(0%)
	10–19	3	(0.1%)
	20–29	99	(3.3%)
	30–39	168	(5.7%)
	40–49	392	(13.2%)
	50–59	673	(22.7%)
	60–69	593	(20%)
	70–79	567	(19.1%)
	80–89	370	(12.5%)
	≥90	103	(3.5%)
Sex (n = 2,970)	Male	1,942	(67.1%)
	Female	1,028	(65.4%)
Diabetes (n = 2,959)	Present	731	(24.7%)
	Absent	1,028	(75.3%)
Cardiovascular diseases (n = 2,959)	Present	755	(25.5%)
	Absent	2,204	(74.5%)
Diabetes or cardiovascular diseases (n = 2,964)	Present	1,209	(40.8%)
	Absent	1,755	(59.2%)
Chronic lung diseases (n = 2,961)	Present	328	(11.1%)
	Absent	2,633	(88.9%)
Immunosuppression (n = 2,959)	Present	1,478	(49.8%)
	Absent	1,487	(50.2%)
Any of the above comorbidities (n = 2,965)	Present	1,053	(49.2%)
	Absent	1,087	(50.8%)
Ciclesonide (n = 2,899)	Given	1,220	(42.1%)
	Not given	1,679	(57.9%)
Lopinavir–ritonavir (n = 2,841)	Given	81	(2.9%)
	Not given	2,760	(97.1%)
Nafamostat (n = 2,970)	Given	256	(8.6%)
	Not given	2,714	(91.4%)
Tocilizumab (n = 2,970)	Given	45	(1.5%)
	Not given	2,925	(98.5%)
Systemic steroid (n = 2,970)	Given	91	(3.1%)
	Not given	2,879	(96.9%)
Other therapy related to COVID-19 (n = 2,870)	Given	702	(24.5%)
	Not given	2,168	(75.5%)
Outcome (n = 2,913)	Died in hospital	348	(11.9%)
	Transferred for escalation of care	155	(5.3%)
	Still in hospital (alive)	286	(9.8%)
	Transferred for de-escalation of care	345	(11.8%)
	Discharged alive	1,799	(61.1%)

【Administration of favipiravir】

Administration of favipiravir is shown in Table 2. In 93.6% of the patients, favipiravir was dosed at two doses of 1,800 mg followed by 800 mg twice a day. The median duration of treatment was 12 days. The median days from the positive PCR test and hospital admission to the

initiation of favipiravir therapy were 2 and 1 days, respectively. There were few changes from the first report.

Table 2. Administration of favipiravir

(a) Dosing of favipiravir

n	Dosing	n(%)
2,957	2 doses of 1,600 mg followed by 600 mg twice a day	136 (4.6%)
	2 doses of 1,800 mg followed by 800 mg twice a day	2,769 (93.6%)
	Others	52 (1.8%)

(b) Duration of favipiravir

n	Mean	SD	Median	Q1 (25%)	Q3 (75%)
2,665	10.6	5.6	12	7	13

(c) Days from positive PCR to first dose of favipiravir

n	Mean	SD	Median	Q1 (25%)	Q3 (75%)
2,937	2.9	3.3	2	1	4

(d) Days from hospital admission to first dose of favipiravir

n	Mean	SD	Median	Q1 (25%)	Q3 (75%)
2,948	3.1	10.5	1	0	2

【Severity of illness】

In this study, mild, moderate, and severe diseases at the start of favipiravir were defined as those not requiring supplemental oxygen, those with spontaneous respiration but requiring supplemental oxygen, and those requiring artificial respiration or extracorporeal membrane oxygenation, respectively. By this definition, 1,342 patients (45.2%) had mild disease, 1,284 patients (43.2%) had moderate disease, and 344 patients (11.6%) had severe disease. This severity classification is based solely on oxygen requirement and does not necessarily reflect the overall severity of disease.

【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. The rates of clinical improvement at 7 and 14 days were 74.3% and 86%, 65.6% and 81.2%, and 44.5% and 58.1% for mild, moderate, and severe diseases, respectively (Table 3). The rates of clinical worsening at 7 and 14 days were 12.2% and 6%, 22.9% and 13.2%, and 26.8% and 26.2% for mild, moderate, and severe diseases, respectively.

The clinical outcome was assessed at approximately 1 month into hospitalization as discharged alive, died in hospital, transferred for de-escalation of care, transferred for escalation of care, or still in hospital. The mortality rates at the time of entry of outcome were 4.3%, 14.9%, and 30.2% for mild, moderate, and severe diseases, respectively. There were no significant changes from the first report.

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

(a) At 7 days after start of favipiravir

		Improved	Unchanged	Worsened
Day 7 (n=2,670)	Mild	921 (74.3%)	168 (13.5%)	151 (12.2%)
	Moderate	735 (65.6%)	128 (11.4%)	257 (22.9%)
	Severe	138 (44.5%)	89 (28.7%)	83 (26.8%)

(b) At 14 days after start of favipiravir

		Improved	Unchanged	Worsened
Day 14 (n=2,256)	Mild	871 (86%)	81 (8%)	61 (6%)
	Moderate	783 (81.2%)	54 (5.6%)	127 (13.2%)
	Severe	162 (58.1%)	44 (15.8%)	73 (26.2%)

(c) Clinical outcome 1 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=2,913)	Mild	56 (4.3%)	50 (3.8%)	84 (6.4%)	143 (10.9%)	973 (74.5%)
	Moderate	189 (14.9%)	86 (6.8%)	149 (11.8%)	132 (10.4%)	710 (56.1%)
	Severe	103 (30.2%)	19 (5.6%)	53 (15.5%)	70 (20.5%)	96 (28.2%)

【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 poor in older patients. The rate of died in hospital was 2.7% in the 50–59 age group, whereas the rates were 10.1%, 19.1%, 34.6%, and 33.3% in the 60–69, 70–79, 80–89, and ≥90 age groups, respectively, showing a sharp increase with increasing age. This trend is consistent with reports from overseas.[9]

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=2,670)	<10	1 (100%)	0 (0%)	0 (0%)
	10–19	2 (66.7%)	1 (33.3%)	0 (0%)
	20–29	78 (84.8%)	8 (8.7%)	6 (6.5%)
	30–39	129 (81.6%)	22 (13.9%)	7 (4.4%)
	40–49	272 (77.1%)	49 (13.9%)	32 (9.1%)
	50–59	487 (78%)	64 (10.3%)	73 (11.7%)
	60–69	350 (66.3%)	72 (13.6%)	106 (20.1%)
	70–79	292 (57.3%)	93 (18.2%)	125 (24.5%)
	80–89	145 (46.5%)	58 (18.6%)	109 (34.9%)
	≥90	38 (42.7%)	18 (20.2%)	33 (37.1%)

(b) At 14 days after start of favipiravir

		Improved	Unchanged	Worsened
Day 14 (n=2,256)	<10	1 (100%)	0 (0%)	0 (0%)
	10–19	2 (66.7%)	1 (33.3%)	0 (0%)
	20–29	61 (91%)	3 (4.5%)	3 (4.5%)
	30–39	113 (94.2%)	6 (5%)	1 (0.8%)
	40–49	255 (90.4%)	19 (6.7%)	8 (2.8%)
	50–59	492 (90.3%)	31 (5.7%)	22 (4%)
	60–69	357 (80.4%)	33 (7.4%)	54 (12.2%)
	70–79	331 (73.6%)	45 (10%)	74 (16.4%)
	80–89	163 (61%)	25 (9.4%)	79 (29.6%)
	≥90	41 (53.2%)	16 (20.8%)	20 (26%)

(c) Clinical outcome 1 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=2,913)	<10	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
	10–19	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)
	20–29	1 (1%)	0 (0%)	3 (3.1%)	15 (15.3%)	79 (80.6%)
	30–39	0 (0%)	5 (3%)	13 (7.8%)	21 (12.6%)	128 (76.6%)
	40–49	5 (1.3%)	23 (6%)	14 (3.6%)	47 (12.2%)	295 (76.8%)
	50–59	18 (2.7%)	34 (5.2%)	34 (5.2%)	70 (10.6%)	504 (76.4%)
	60–69	58 (10.1%)	41 (7.1%)	70 (12.1%)	70 (12.1%)	338 (58.6%)
	70–79	107 (19.1%)	36 (6.4%)	70 (12.5%)	58 (10.4%)	289 (51.6%)
	80–89	12 6(34.6%)	16 (4.4%)	57 (15.7%)	44 (12.1%)	121 (33.2%)
	≥90	33 (33.3%)	0 (0%)	24 (24.2%)	20 (20.2%)	22 (22.2%)

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

Variables (n = 2,892)	Hazard ratio	Lower limit of 95% CI	Upper limit of 95% CI	P-value
Age	1.07	1.06	1.08	<0.001
Male (vs. female)	1.2	0.95	1.51	0.12
Moderate (vs. mild)	3.51	2.6	4.74	<0.001
Severe (vs. mild)	5.52	3.97	7.68	<0.001
Diabetes	1.78	1.43	2.2	<0.001
Cardiovascular diseases	2.48	2.01	3.07	<0.001
Chronic lung diseases	1.46	1.09	1.94	0.01
Immunosuppression	2.38	1.8	3.15	<0.001

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

Variables (n = 2,892)	Hazard ratio	Lower limit of 95% CI	Upper limit of 95% CI	P-value
Age	1.07	1.06	1.09	<0.001
Male (vs. female)	1.56	1.22	1.99	<0.001
Moderate (vs. mild)	2.7	1.99	3.66	<0.001
Severe (vs. mild)	5.31	3.78	7.44	<0.001
Diabetes	1.33	1.07	1.65	0.01
Cardiovascular diseases	1.31	1.05	1.63	0.015
Chronic lung diseases	1.04	0.78	1.39	0.798
Immunosuppression	2.2	1.66	2.92	<0.001

Table 7. Predictors of death in hospital or discharge with exacerbation (univariate analysis)

Variables (n = 2,892)	Hazard ratio	Lower limit of 95% CI	Upper limit of 95% CI	P-value
Age	1.04	1.04	1.05	<0.001
Male (vs. female)	1.31	1.08	1.59	0.006
Moderate (vs. mild)	2.71	2.16	3.39	<0.001
Severe (vs. mild)	3.67	2.82	4.77	<0.001
Diabetes	1.5	1.25	1.81	<0.001
Cardiovascular diseases	2.03	1.7	2.43	<0.001
Chronic lung diseases	1.39	1.09	1.77	0.009
Immunosuppression	2.09	1.64	2.68	<0.001

Table 8. Predictors of death in hospital or discharged with exacerbation (multivariate analysis)

Variables (n = 2,892)	Hazard ratio	Lower limit of 95% CI	Upper limit of 95% CI	P-value
Age	1.04	1.03	1.05	<0.001
Male (vs. female)	1.48	1.21	1.82	<0.001
Moderate (vs. mild)	2.19	1.74	2.75	<0.001
Severe (vs. mild)	3.15	2.41	4.13	<0.001
Diabetes	1.13	0.93	1.36	0.215
Cardiovascular diseases	1.28	1.06	1.55	0.009
Chronic lung diseases	1.02	0.79	1.31	0.903
Immunosuppression	1.89	1.47	2.42	<0.001

【Prognostic factors】

Univariate analysis showed significant correlations between in-hospital death and advanced age, moderate or severe disease, diabetes, cardiovascular diseases, chronic lung diseases, and immunosuppression (Table 5). A multivariate analysis showed significant correlations between in-hospital death and advanced age, male sex, moderate or severe disease, diabetes, cardiovascular diseases, and immunosuppression (Table 6).

Univariate analysis showed significant correlations between in-hospital death or discharge with exacerbation and advanced age, male sex, moderate or severe disease, diabetes, cardiovascular diseases, chronic lung diseases, and immunosuppression (Table 7). A multivariate analysis

showed significant correlations between in-hospital death or discharge with exacerbation with advanced age, male sex, moderate or severe disease, cardiovascular diseases, and immunosuppression (Table 8).

Figures 1–8 show survival curves of in-hospital death for the overall and stratified groups by each factor.

Figures 9–16 show survival curves of exacerbation (in-hospital death and discharge with exacerbation) for the overall group and groups stratified by each factor.

Fig.1-8. Thirty-day cumulative mortality rate in patients who received favipiravir (died in hospital)

A cumulative survival rate that considers censored data is calculated using the Kaplan–Meier estimate. Therefore, the data do not necessarily coincide with the ratio of in-hospital mortality that does not consider censored cases and the follow-up period.

Fig.1 Overall survival

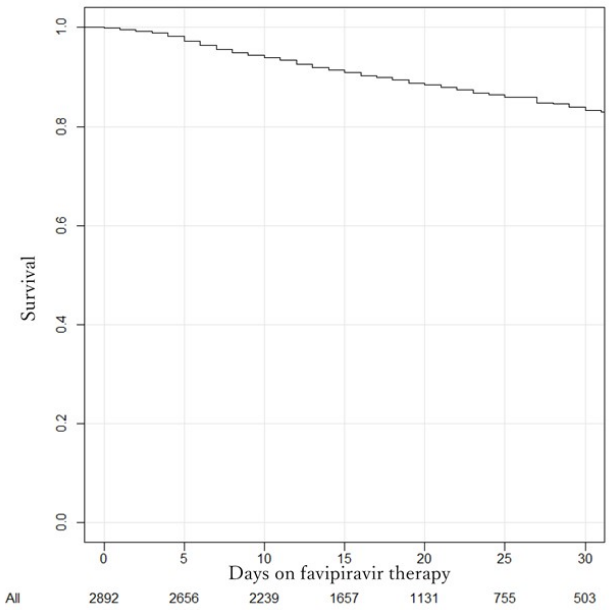


Fig.2 Survival by age group

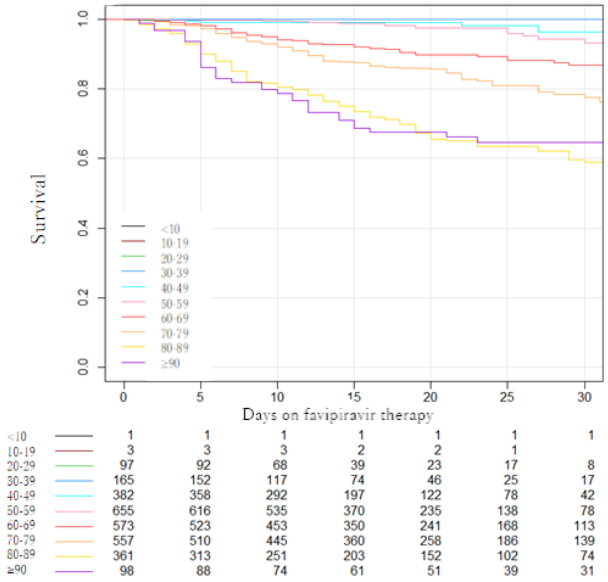


Fig.3 Survival by sex

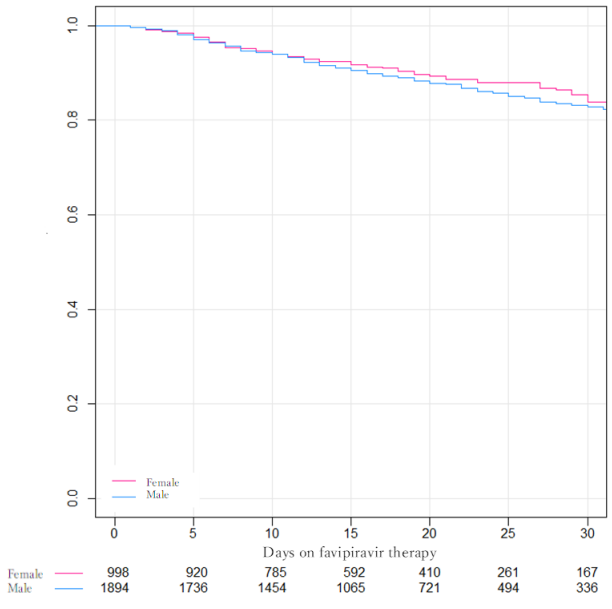


Fig.4 Survival by severity disease at start of favipiravir

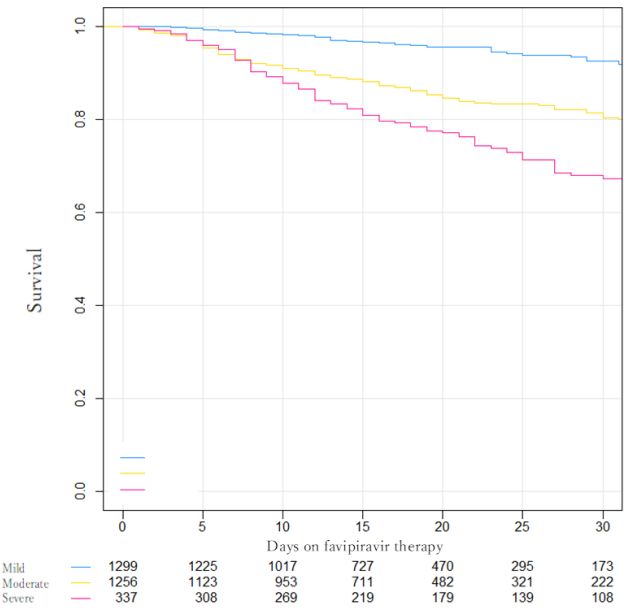


Fig.5　Survival by presence or absence of diabetes

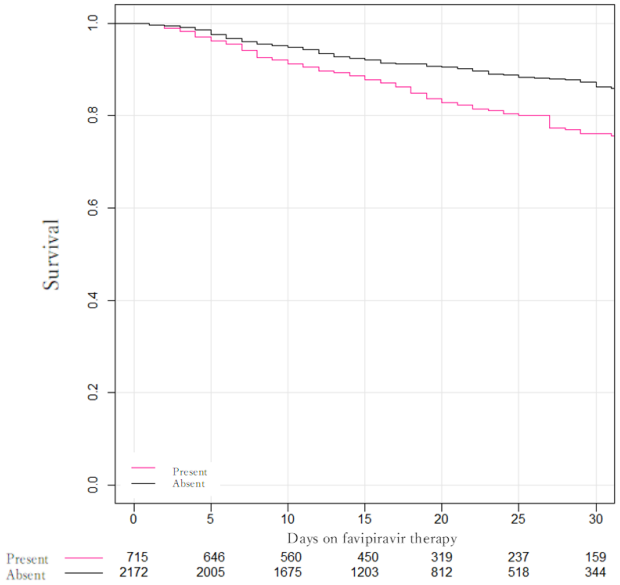


Fig.6　Survival by presence or absence of cardiovascular disease

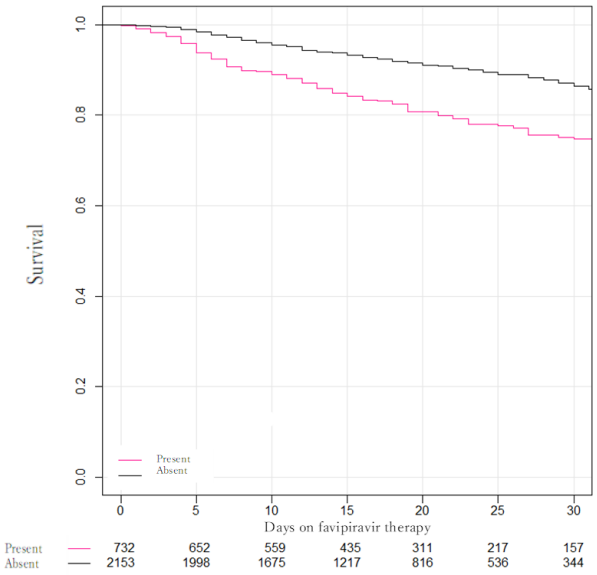


Fig.7　Survival by presence or absence of chronic lung disease

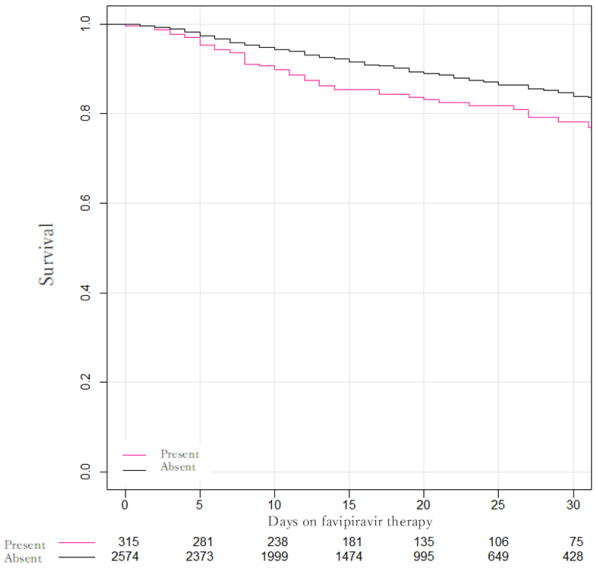


Fig.8　Survival by presence or absence of immunosuppression

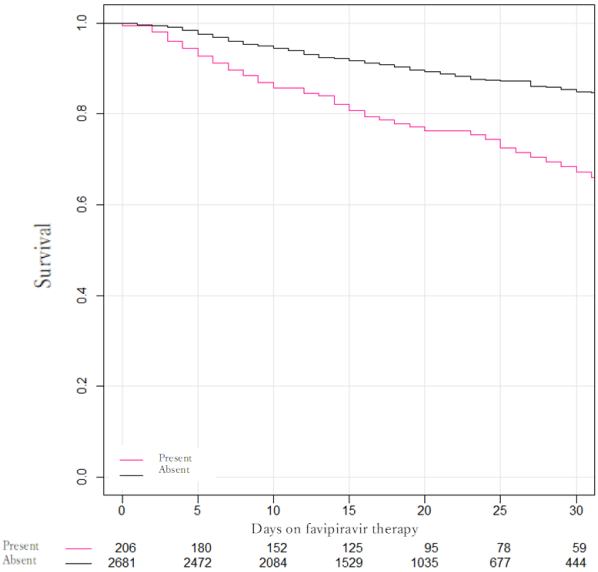


Fig.9-16. Thirty-day cumulative exacerbation rate in patients who received favipiravir (died in hospital + discharged with exacerbation)

A cumulative survival rate that considers censored data is calculated using the Kaplan–Meier estimate. Therefore, the data do not necessarily coincide with the ratio of in-hospital mortality and discharge with exacerbation that does not consider censored cases and the follow-up period.

Fig.9 Overall exacerbation

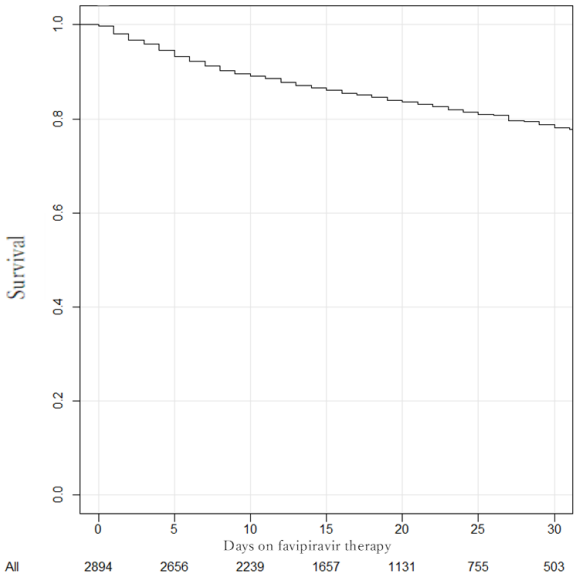


Fig.10 Exacerbation by age group

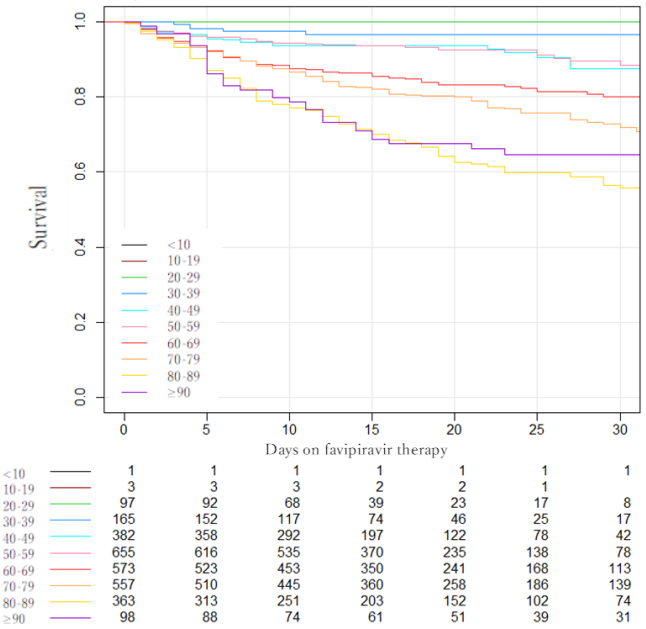


Fig.11 Exacerbation by sex

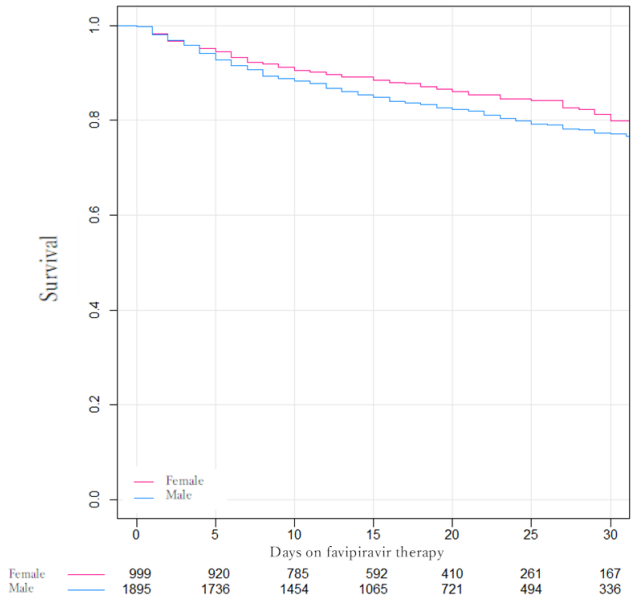


Fig.12 Exacerbation by severity of disease at start of favipiravir

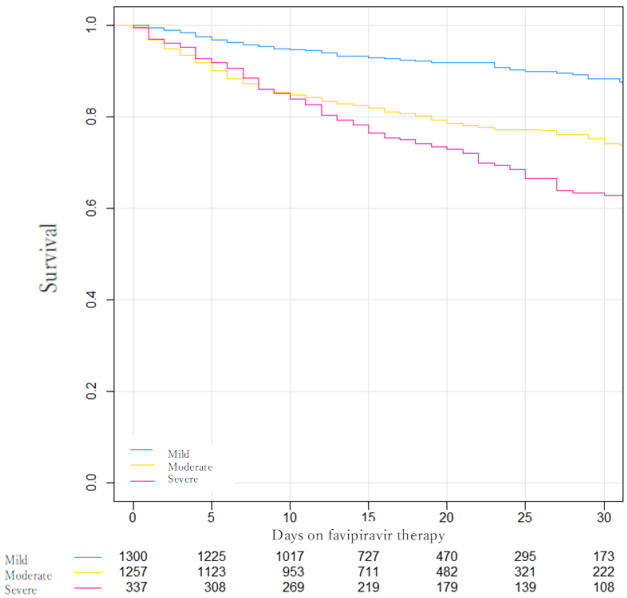


Fig.13　Exacerbation by presence or absence of diabetes

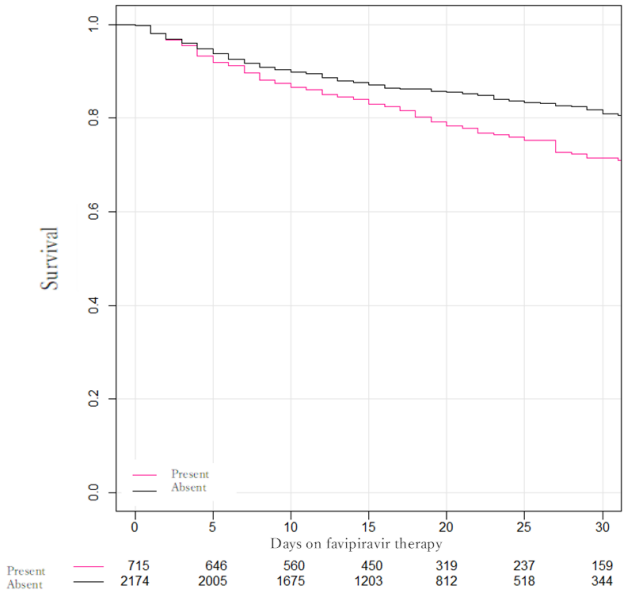


Fig.14　Exacerbation by presence or absence of cardiovascular disease

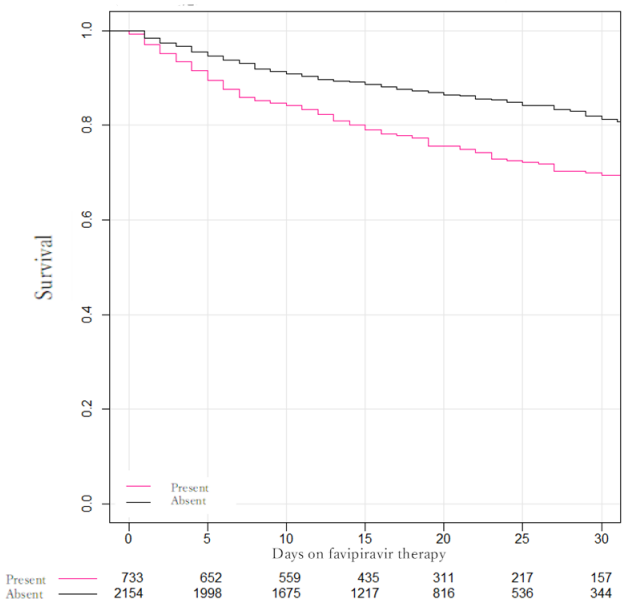


Fig.15　Exacerbation by presence or absence of chronic lung disease

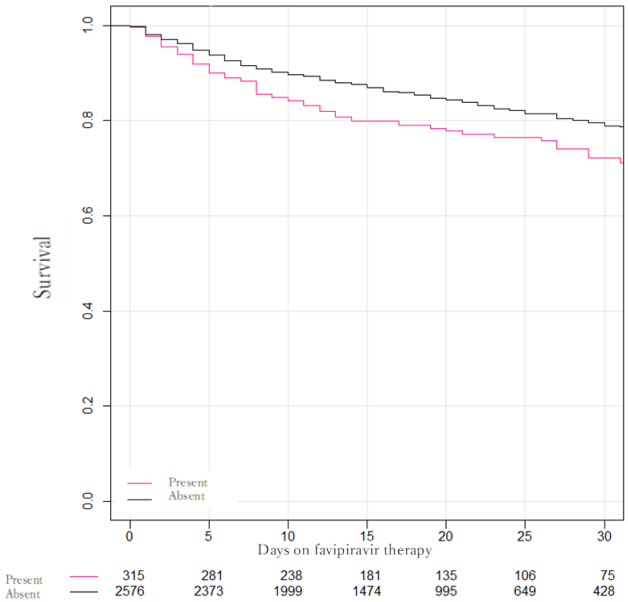
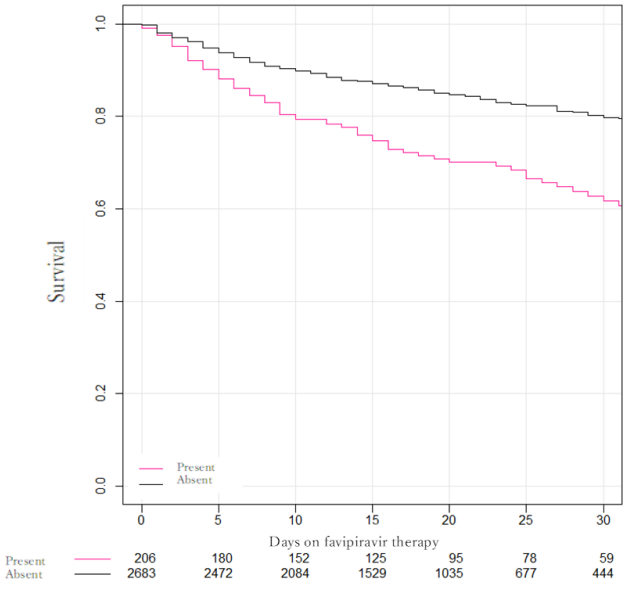


Fig.16　Exacerbation by presence or absence of immunosuppression



【Adverse events】

A total of 1,005 adverse events were reported in association with favipiravir use in 826 of 2,970 patients (Table 9). Adverse events reported in >1% of the patients were uric acid level increase or hyperuricemia in 524 patients (17.6%), liver disorder or liver function enzyme increase in 240 patients (8.1%), and skin eruption or toxicoderma in 56 patients (1.9%). There were no changes from the first report in the trend of adverse events. No deaths directly related to death were reported.

Table 9. Adverse events associated with favipiravir use

n=2,970		
Number of patients with adverse events associated with favipiravir use	826	(28.5%)
Number of adverse events associated with favipiravir use	1,005	
(breakdown)		
Hyperuricemia/elevated uric acid levels	524	(17.6%)
Hepatic function disorder/elevated liver function enzyme levels	240	(8.1%)
Skin eruption/toxicoderma	56	(1.9%)
Renal impairment/elevated creatinine levels	25	(0.8%)
Diarrhea/soft stool	20	(0.7%)
Fever	19	(0.6%)
Vomiting/nausea	16	(0.5%)
Gout	9	(0.3%)
Rhabdomyolysis/elevated creatine kinase levels	5	(0.2%)
Hyperkalemia	5	(0.2%)*
Bradycardia	4	(0.1%)
Pruritus	4	(0.1%)
Leukocytopenia	4	(0.1%)
Abnormal coagulation test values	4	(0.1%)
Thrombocytopenia	3	(0.1%)
Inappetence	3	(0.1%)
Worsening of pneumonia	3	(0.1%)
Dizziness	2	(0.1%)
Lymphopenia	2	(0.1%)
Worsening of underlying disease	2	(0.1%)
Hypernatremia	2	(0.1%)
Hyperbilirubinemia	2	(0.1%)
Thromboembolism	2	(0.1%)
Convulsion	2	(0.1%)
High blood sugar	2	(0.1%)
Malaise	2	(0.1%)
Abdominal pain/stomach discomfort	2	(0.1%)
Elevated blood urea nitrogen levels	1	(0%)
Elevated inflammatory reaction levels	1	(0%)
Jaundice	1	(0%)
Numbness of lower extremities	1	(0%)
Arthritis/enthesitis	1	(0%)
Arthralgia	1	(0%)
Redness of face	1	(0%)
Hypertension	1	(0%)
Thrombocytosis	1	(0%)
Bloody stool	1	(0%)
Worsening of respiratory failure	1	(0%)
Oral candidiasis	1	(0%)
Circumoral swelling	1	(0%)
Stomatitis	1	(0%)
Eosinophilia	1	(0%)
Hyperamylasemia	1	(0%)
Visual field defect	1	(0%)
Poor appetite	1	(0%)
Hyponatremia	1	(0%)
Cerebral infarction	1	(0%)
Sepsis	1	(0%)
Redness	1	(0%)
Pancytopenia	1	(0%)
Anemia	1	(0%)
Unrest	1	(0%)
Constipation	1	(0%)

* The number of patients with hyperkalemia was seven in the first report because "potassium elevated" in two patients was counted in duplicate.

Discussion

The observational study is being conducted to overview the safety and efficacy of favipiravir against COVID-19 in patients who were administered the agent as off-label use. The number of registrations has been increased by over 800 patients in this second report; there are no significant changes from the first report in the overall trend including the patient demographics and treatment outcomes.

In the multivariate analysis of prognostic factors, advanced age, male sex, moderate or severe disease, diabetes, cardiovascular diseases, and immunosuppression were significantly correlated with the rates of in-hospital death. A marked increase in mortality in the elderly is commonly seen across the world[9], and as discussed later, it affected the overall rates of death in hospital in this study in which many elderly patients were registered. Moreover, the finding that underlying diseases such as diabetes, cardiovascular diseases, and immunosuppression are poor prognostic factors is in line with published reports[10-12].

Because the new coronavirus infection is associated with a wide range of clinical presentations from asymptomatic to severe, attributes of the infected cases, which is the denominator, need to be scrutinized in estimating case fatality rates. It should be also noted that there are approximately 2- to 4-week gaps between increases in the number of infection cases and increases in the number of deaths from infection, therefore the number of deaths, which is the numerator, is calculated in a delayed manner.

The report "New Coronavirus Infection Situation and Measures Taken at the Ministry of Health, Labour and Welfare (July 27, 2020 version)," which exhaustively captures and summarizes patients with COVID-19 in Japan, calculates the total number of patients/asymptomatic carriers/confirmed positive PCR to be 29,989 cases, the number of deaths to be 996 cases, and the case fatality rate to be 3.3%. On the other hand, the case fatality rates of COVID-19 outside Japan vary significantly ranging from 9.3% in Italy to 0.7% in Germany. Most of these differences can be explained by

age distribution of patients[9]. The ratio (55%) of age ≥60 years in this observational study is close to that in Italy (55.7%) in the aforementioned study. The observational study collects information by asking medical institutions to provide information on patients who have been administered favipiravir as off-label compassionate use at the discretion of the medical institutions. It is recommended that providers refer to the document "Guidelines for Drug Therapy for COVID-19" published by the Japanese Association for Infectious Diseases when deciding whether favipiravir should be administered on a compassionate use basis:

1. Pharmacotherapy may be considered for patients with hypoxemia who require supplemental oxygen, invasive ventilation, extracorporeal membrane oxygenation (ECMO), or those who have oxygen saturation of 94% or lower at room air.
2. Patients with advanced age (approximately 60 years or greater), diabetes, cardiovascular disease, chronic lung disease, malignancy, COPD from smoking, immunosuppression are at elevated risk of severe disease and death thus pharmacotherapy may be considered upon careful observation of the clinical course.
3. Pharmacotherapy is not recommended for patients without symptoms or hypoxemia.
4. Pharmacotherapy is not indicated for patients without a definitive diagnosis of COVID-19 by PCR test or other means.

The majority of patients who are eligible for compassionate use tend to have a poor prognosis even with the optimal supportive therapy and are biased to elderly patients or patients with underlying disease(s) for whom off-label use of favipiravir is considered ethically appropriate by the providers. Therefore, they differ from the target populations used to estimate case fatality rates among infected patients in epidemiological studies. The mortality rate in compassionate use of remdesivir, which was emergently approved for the treatment of the new coronavirus infection in Japan, was 13%[13]. Although the compassionate use of remdesivir was limited to patients who had been approved by the manufacturer Gilead, the mortality rate was similar to that seen in this observational study. A randomized, placebo-controlled study of remdesivir was conducted in a broad range of patient populations including mild cases, and its preliminary analysis has been published[14]. In the placebo-treated patients, who required no supplemental oxygen, the mortality rate at 14 days was 2.5% (1 patient). It should be noted, however, that the mortality rate was assessed at 14 days not at 1 month, and the upper limit of 95% confidence interval reached 16.5%. Moreover, this remdesivir study only captured patients who were deemed to survive for ≥3 days. It is known that randomized controlled studies tend to generally exclude high-risk patients due to inclusion/exclusion criteria and difficulty obtaining informed consent1[5]. In the randomized controlled study of favipiravir in asymptomatic patients and patients with mild COVID-19 led by Fujita Health University conducted in a study design that orally administered favipiravir to both treatment groups, all patients had clinical resolution by Day 28, and no deaths were reported[4]. These considerations preclude direct comparison of mortality rates in compassionate use with those in epidemiological research or randomized controlled studies.

Severity of disease in this observational study is classified simply as no oxygen required (mild), oxygen required (moderate), or mechanical ventilation required (severe) due to limited information collected. In guidelines and literatures, severity of disease classification typically takes into account the presence or absence of pneumonia and blood oxygen saturation[16,17], and especially if pneumonia is present radiographically, severity is assessed to be moderate or higher at that point in many instances. This means that some of the patients defined as having mild disease in this observational study may be defined as having moderate disease in other studies. The common adverse events associated with favipiravir use were uric acid level increase and liver function enzyme increase, which is unchanged from the first report. These adverse events are foreseeable from findings in the clinical studies and trials conducted at the development of favipiravir as an anti-influenza agent. Nevertheless, the

dosage and duration of therapy are expected to be higher and longer, respectively, in many cases when used for COVID-19, and close monitoring of these adverse events is recommended for this reason. Early embryonic lethality and teratogenicity due to favipiravir have been observed in animal models. Pregnant women therefore must be excluded, and all patients and their sexual partners should practice effective contraception during and after the treatment period in reference to the "Guidelines for Drug Therapy for COVID-19."

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Favipiravir Observational Study Group, Fujita Health University

Yohei Doi and Masashi Kondo (Faculty of Medicine, Fujita Health University)

Masahiko Ando and Yachiyo Kuwatsuka (Department of Advanced Medicine, Nagoya University Hospital)

Takuma Ishihara (Innovative and Clinical Research Promotion Center, Gifu University Hospital)

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