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ORIGINAL RESEARCH

Effectiveness of Favipiravir on Nonsevere, Early-Stage COVID-19 in Japan: A Large Observational Study Using the COVID-19 Registry Japan

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ABSTRACT

Introduction: Several randomized controlled trials have compared the effectiveness of favipiravir with that of placebo. However, evidence regarding its effect on nonsevere, early-stage coronavirus disease 2019 (COVID-19) remains insufficient.
Methods: We used the COVID-19 Registry Japan, a nationwide registry of inpatients with COVID-19, for evaluating the effectiveness of favipiravir on patients with nonsevere, early-stage COVID-19. Eligible patients, who did not need supplementary oxygen therapy at admission, were classified according to two regimens (starting favipiravir therapy within 4 days from admission vs. no favipiravir during hospitalization) and were then compared using a three-step method (cloning, censoring, and

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weighting). The primary outcome was supplementary oxygen requirement during hospitalization, and the secondary outcomes were the need for invasive mechanical ventilation or extracorporeal membrane oxygenation (IMV/ECMO) and overall mortality at 30 days.
Results: A total of 7654 cases were analyzed. The "start favipiravir" regimen did not show substantial differences in the primary outcome [hazard ratio 0.825, 95% confidence interval (CI) 0.657–1.04, $p = 0.098$] and both of the secondary outcomes [need for IMV/ECMO and overall 30-day mortality, hazard ratio 1.02 (95% CI 0.649–1.60) and 0.869 (95% CI 0.519–1.46), $p = 0.929$ and 0.594, respectively].
Conclusions: In this large cohort from a COVID-19 registry, favipiravir was not associated with a positive effect on the clinical outcome on patients with nonsevere, early-stage COVID-19, suggesting that it is not an essential drug for COVID-19 treatment.

Keywords: Favipiravir; COVID-19; Inpatients

Key Summary Points

Why carry out this study?

Japan has been using favipiravir as a drug option for COVID-19 treatment.

The clinical evidence on its effectiveness for nonsevere, early-stage COVID-19 remains insufficient.

Considering its mechanism of action, favipiravir might be useful for nonsevere, early-stage COVID-19 cases.

What was learned from the study?

National registry data in Japan did not show substantial differences in oxygen requirement, introduction of invasive mechanical ventilation or extracorporeal membrane oxygenation (IMV/ECMO), and 30-day fatality.

The efficacy of favipiravir on nonsevere, early-stage COVID-19 cases is not sufficient.

Favipiravir might not be an essential drug for the treatment of COVID-19 cases.

INTRODUCTION

Although the evidence on coronavirus disease 2019 (COVID-19) management is accumulating day by day, treatments including antiviral drugs are yet to be improved. The antiviral drug favipiravir inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses [1]. This drug was initially discovered and developed as an oral anti-influenza drug; however, given its inhibitory effect on wide-ranging RNA viruses, such as hemorrhagic fever virus, it may play a role in eliminating RNA virus infections, which currently still have no established treatment [1].

Favipiravir was approved in Japan in 2014 under the brand name AVIGAN for the treatment of new or re-emerging influenza virus infections that do not respond to other anti-influenza virus drugs [2]. Favipiravir was also used as one of the treatment options for Ebola

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virus disease in other countries, although its effect was controversial [3, 4]. Similarly, this antiviral drug was expected as one of the potential treatment options for the current COVID-19 pandemic in Japan [5, 6].

Several trials have examined the efficacy of favipiravir on COVID-19, but their results have remained inconclusive. In the pilot stage of a phase II/III clinical trial in Russia, favipiravir (AVIFAVIR) enabled SARS-CoV-2 viral clearance in 62.5% of patients within 4 days [7]. However, a randomized controlled trial conducted in Japan found that favipiravir did not significantly improve viral clearance by day 6, although its use was associated with reduced time to defervescence [5]. According to Shinkai et al., this drug may shorten the time from moderate pneumonia to recovery but increase the risk of developing adverse events [8]. Udwadia et al. also concluded that the time to clinical cure was shorter in the treatment group than in the control group, suggesting that favipiravir might be beneficial in mild-to-moderate COVID-19 cases [9]. In the Fluids and Catheters Treatment Trial, the combination therapy of favipiravir and hydroxychloroquine did not show any clinical benefit in patients with moderate-to-severe COVID-19 [10]. A systematic review of such randomized controlled trials had suggested that favipiravir was only marginally effective [11]. So far, only a few studies have investigated the effectiveness of this drug in the early stages of the disease. Bosaeed et al. revealed that favipiravir did not reduce the time to viral clearance in mild COVID-19 cases [12]. Finberg et al. reported that it did [13].

Of note, these studies did not demonstrate substantial benefit in the direct outcome (i.e., death) of patients with COVID-19, and some of them dealt with severe illnesses. The results so far suggest that the efficacy of favipiravir might be comparatively low. Nevertheless, considering its mechanism of action [1], favipiravir might be more useful in patients with early phase of the disease compared to patients who have already progressed to severe disease.

The present study aimed to investigate the clinical effectiveness of favipiravir for nonsevere, early-stage COVID-19 infection by using a nationwide registry of COVID-19 inpatient data in Japan, named COVID-19 Registry Japan (COVIREGI-JP).

METHODS

Study Population and Data

This study used patient data derived from COVIREGI-JP [14], which started enrollment on March 2, 2020. The inclusion criteria for case enrollment in COVIREGI-JP include (1) a positive SARS-CoV-2 test and (2) inpatient treatment at a healthcare facility. Details regarding the COVIREGI-JP and case report form have been described in a previous study [14]. The study data were collected and managed using Research Electronic Data Capture, a secure, web-based data capture application hosted by the JCRAC data center at the National Center for Global Health and Medicine [15].

We used data from cases for which all of the following major items had been entered as of April 30, 2021: basic information at admission (demographics and epidemiological characteristics), comorbidities, signs and symptoms during admission (including conditions at admission), outcome at discharge, supportive treatment during hospitalization, medication history during hospitalization, and complications during hospitalization.

Study Design

Eligibility for the Analysis Set

To specifically evaluate favipiravir effectiveness in the early stages of treatment in a Japanese cohort, we excluded patients who had non-Japanese nationality, already had severe disease, had already received supplementary oxygen therapy by the fourth day of hospitalization, and/or had been hospitalized for more than 4 days before the day of symptom onset. Additionally, we excluded patients younger than 45 years old because favipiravir is not recommended for women in their reproductive age and both sexes in this age group have a low risk for severe COVID-19 infection. We also

excluded patients treated with favipiravir at a dose not recommended by the Japanese clinical guideline for COVID-19 (1800 mg twice daily [BID] on day 1 and 800 mg BID from day 2) [16].

Endpoints, Treatment Strategies of Interest, and Follow-up

The primary outcome was oxygen requirement within 30 days of hospitalization. The secondary outcomes were overall mortality and need for invasive mechanical ventilation or extracorporeal membrane oxygenation (IMV/ECMO). We compared the following treatment regimens: regimen 1, starting favipiravir therapy within 4 days from the day of admission for at least 3 days and at most 15 days without any of the following: systemic steroids, tocilizumab, baricitinib, and remdesivir; regimen 2, not using favipiravir, other immunosuppressive agents or antivirals (tocilizumab, baricitinib, and remdesivir), and systemic steroids during hospitalization. Other supportive treatments were allowed in both regimens.

Each patient was observed until hospital day 30, event of interest (oxygen therapy initiation for primary outcome analysis; death or IMV/ECMO initiation during 30 days from admission for secondary outcome analysis), or discharge, whichever came first. As mentioned, we selected patients from both regimen groups who had not been placed on supplementary oxygen therapy for 4 days since admission to evaluate favipiravir effectiveness among patients who did not require intensive therapy at admission; otherwise, they were excluded from the study. The possible time-related biases associated with such exclusion after hospitalization (the start of follow-up) [17, 18] were addressed using a novel statistical approach, similar to our previous study [19], which is described in the next section.

Statistical Analysis

To compare the effectiveness of favipiravir from time-varying data in an unbiased manner, we used the three-step method: cloning, censoring, and weighting [20]. First, we prepared clones (or data copies) of patients to assign them to the two regimens on a person-day basis. With consideration of the eligibility criteria for enrollment, patients treated with favipiravir on day 1 were assigned to the "start favipiravir" regimen arm, and the other patients were assigned to both regimens. Assigning a patient to both arms simultaneously means having two clones of that patient in the data set, with one copy assigned to each arm. The cloning process was done only once before censoring.

Second, clones that deviated from their assigned regimen during the follow-up period were artificially censored. For instance, in a patient who began to receive favipiravir between days 1 and 4, their clone assigned to regimen 2 ("no favipiravir") was censored at that time, but the clone assigned to regimen 1 ("start favipiravir") was followed up thereafter. Conversely, for a patient who still did not receive favipiravir on day 5, their clone assigned to regimen 1 was censored on day 5, but the clone assigned to regimen 2 was followed up thereafter. Clones were also censored at any time when the following conditions were met: (1) supported by supplementary oxygen before day 4 of admission, (2) treated with systemic steroids, tocilizumab, baricitinib, or remdesivir, (3) treated with favipiravir for less than 3 days (patients were censored when they discontinued favipiravir before 3 days from treatment initiation), and (4) treated with favipiravir for more than 15 days (patients were censored at 15 days if they were continued on favipiravir). In comparing the primary outcome (supplementary oxygen requirement), patients who were started on oxygen therapy were excluded from the risk set on the following day. Similarly, when we compared the secondary outcomes, patients who were introduced to IMV/ECMO or died within 30 days from admission were censored. Furthermore, discharged patients were censored from the day following discharge. Inpatients were observed for 30 days, and all were censored thereafter. Figure 1 shows a flow diagram of the cloning and censoring process.

Third, selection bias caused by the aforementioned artificial censoring was eliminated using the inverse probability of censoring/discharge weights [21]. The weights of each person-day were calculated using pooled logistic

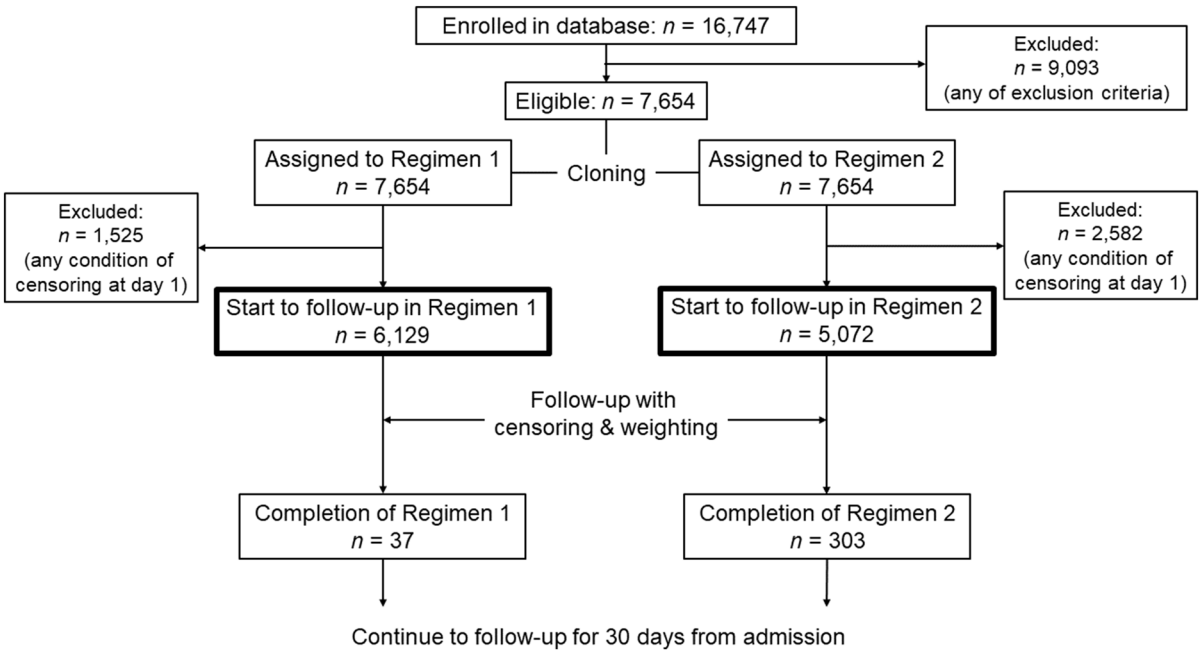

Fig. 1 Flow diagram of the cloning process

regression models for being censored or discharged, such as age, sex, cardiovascular diseases, chronic respiratory diseases, diabetes mellitus, severe renal diseases (serum creatinine level of 3 mg/dL or higher) or dialysis, hypertension, hyperlipidemia, obesity (all of which should be diagnosed by physicians), solid tumor, days from symptom onset to admission, corticosteroid use, anticoagulant use (time-independent variables), and National Early Warning Score (NEWS, time-dependent variable) [22]. The models were fitted separately according to the regimens and follow-up days. The weights were stabilized according to the regimen-day-specific "uncensored" or "not discharged" probability without covariates and were multiplied until each follow-up day. We had only collected intermittent data on the patients' clinical course on days 1, 4, 8, 15, 22, and 29. For example, a patient's record indicating oxygen administration on day 8 implied that oxygen support began between days 5 and 8. In other words, the exact day was unknown. We used NEWS on day 1 as that of day 1; NEWS on day 4 as that of days 2, 3, and 4; NEWS on day 8 as that of days 5, 6, 7, and 8; and NEWS on day 15 as that of days 9, 10, 11, 12, 13, 14, and 15, NEWS on days 22 and 29 were assigned likewise. These possible confounders were selected for their potential association with the outcome of interest on the basis of clinical knowledge and previous studies [23–28].

Finally, we estimated the discrete-time hazard ratio of primary and secondary outcomes between the two regimens through weighted pooled logistic regression, with primary, secondary, and tertiary terms of days included as covariates. Given that each patient has multiple lines in the data set (each day and each regimen of the same patient until being censored), we used cluster-robust standard errors regarding each patient as a cluster to estimate the 95% confidence intervals (CIs). Moreover, cumulative incidence rates under the two regimens were estimated by multiplying the weighted probabilities of no-event using the Kaplan–Meier method. The pointwise 95% CIs on each day were based on 2.5 and 97.5 percentiles of 1000 bootstrap estimates. All statistical data were analyzed through the software R, version 4.1.2 [29].

Table 1 Basic characteristics of patients who met the inclusion criteria

	Case (n = 2532)	Control (n = 5122)	Total (n = 7654)	P value[a]
Age	68 [56–78]	66 [54–79]	67 [55–79]	< 0.001
Male	1495 (59.1%)	2510 (49.0%)	4005 (52.3%)	< 0.001
Cardiovascular disease	196 (7.7%)	373 (7.3%)	569 (7.4%)	0.501
Respiratory disease	130 (5.1%)	159 (3.1%)	289 (3.8%)	< 0.001
Diabetes mellitus	580 (22.9%)	891 (17.4%)	1,471 (19.2%)	< 0.001
Severe renal disease or dialysis	101 (4.0%)	92 (1.8%)	193 (2.5%)	< 0.001
Hypertension	1079 (42.6%)	1939 (37.9%)	3018 (39.4%)	< 0.001
Obesity	201 (7.7%)	296 (5.8%)	490 (6.4%)	< 0.001
Charlson comorbidity index	0 [0–1]	0 [0–1]	0 [0–1]	< 0.001
NEWS at day 1	1 [0–2]	1 [0–2]	1 [0–2]	< 0.001
NEWS at day 4	1 [0–3]	1 [0–2]	1 [0–3]	< 0.001
NEWS at day 8	1 [0–3]	1 [0–2]	1 [0–3]	< 0.001
NEWS at day 15	1 [0–3]	1 [0–3]	1 [0–3]	0.336
NEWS at day 22	2 [0–4]	1 [0–3]	1 [0–3]	0.416
NEWS at day 29	9.5 [9–11]	9 [9–11]	9 [9–11]	0.519
Fatal cases	173 (6.8%)	165 (3.2%)	338 (4.4%)	< 0.001
Oxygen administration during hospitalization[b]	1066 (42.1%)	1071 (20.9%)	2137 (27.9%)	< 0.001
IMV/ECMO during hospitalization	91 (3.6%)	44 (0.9%)	135 (1.8%)	< 0.001
Days from symptom onset to hospitalization	3 [1–4]	3 [1–4]	3 [1–4]	0.172
Systemic steroid use	1243 (49.1%)	984 (19.2%)	2227 (29.1%)	< 0.001
Remdesivir use	244 (9.6%)	520 (10.2%)	764 (10.0%)	0.500
Tocilizumab use	96 (3.8%)	32 (0.6%)	128 (1.7%)	< 0.001
Baricitinib use	0 (0%)	0 (0%)	0 (0%)	1.0
Days from onset to favipiravir administration	4 [2–5]	NA	NA	NA
Days from admission to favipiravir administration	1 [0–3]	NA	NA	NA
Ten-day or longer duration of favipiravir administration	1358 (54.1%)	NA	NA	NA

Numbers in the brackets represent percentage and interquartile range

NA not available, *NEWS* National Early Warning Score, *IMV/ECMO* invasive mechanical ventilation/extracorporeal membrane oxygenation

[a]Results of the Mann–Whitney *U* test for continuous variables and chi-square test for categorical variables (comparison between case group and control group)

[b]Indication for supplementary oxygen was judged by each physician

Table 2 Characteristics of patients after being weighted by inverse probability of censoring/discharge at the beginning of the observation

	Regimen 1 (treated with favipiravir)	Regimen 2 (treated without favipiravir)	Standardized mean difference
Number	6129	5072	
Age (years)	66.4 (14.2)	66.3 (14.5)	0.008
Male	51.4%	50.1%	0.025
Cardiovascular disease	7.0%	7.1%	0.003
Respiratory disease	3.5%	3.3%	0.007
Diabetes mellitus	17.7%	16.7%	0.029
Severe renal disease or dialysis	2.2%	2.1%	0.005
Hypertension	37.5%	36.5%	0.014
Obesity	5.9%	5.6%	0.012
Charlson comorbidity index	0.75 (1.14)	0.75 (1.15)	< 0.001
NEWS at day 1	1.04 (1.22)	1.02 (1.21)	0.020
NEWS at day 4	1.30 (1.47)	1.31 (1.48)	0.009
NEWS at day 8	1.42 (1.77)	1.42 (1.78)	< 0.001
NEWS at day 15	1.70 (2.08)	1.74 (2.13)	0.021
NEWS at day 22	2.0 (2.50)	2.0 (2.48)	0.014
NEWS at day 29	10.22 (1.99)	10.18 [1.99]	0.017
Fatal cases	2.9%	3.0%	0.007
Oxygen administration during hospitalization[a]	17.3%	16.1%	0.031
IMV/ECMO during hospitalization	1.0%	0.8%	0.013
Days from symptom onset to hospitalization	2.52 (1.64)	2.48 (1.64)	0.021
Systemic steroid use	18.2%	15.9%	0.061
Remdesivir use	6.0%	5.8%	0.008
Tocilizumab use	1.2%	0.6%	0.061
Baricitinib use	0 (0%)	0 (0%)	< 0.001

Regimen 1: treated with favipiravir. Regimen 2: treated without favipiravir. Continuous valuables are presented in mean (standard deviation). Categorical variables are presented in percentage

NEWS National Early Warning Score, *IMV/ECMO* invasive mechanical ventilation/extracorporeal membrane oxygenation

[a]Indication for supplementary oxygen was judged by each physician

Ethics

The NCGM ethics review approved this study (NCGM-G-003494-0). Informed consent from each patient was obtained in the form of opt-out and information regarding the opt-out approach of our study is available on the registry website.

RESULTS

Out of 16,747 patients who had been enrolled to the registry as of April 30, 2021, 7654 were included. Table 1 describes their basic characteristics. A total of 2532 patients were treated with favipiravir; only 450 (17.9%) completed the recommended 10-day regimen, whereas 908 (36.1%) were treated for more than 10 days. Patients in the case group were older, more frequently male, and more severely ill both at the time of admission and during hospitalization, and died more frequently than those in the control group.

Table 2 shows the characteristics of the patients at the beginning of the observation (i.e., the first day of hospitalization), after being weighted by the inverse probability of censoring or discharge.

Compared with regimen 2 (treated without favipiravir), regimen 1 (treated with favipiravir within 4 days of admission) did not show a difference in oxygen requirement [adjusted hazard ratio 0.825 (95% CIs 0.657–1.04), $p = 0.098$]. The risks for IMV/ECMO introduction and overall 30-day mortality were also not different between the two groups [adjusted hazard ratio 1.02 (95% CIs 0.649–1.60) and 0.869 (95% CIs 0.519–1.46), $p = 0.929$ and 0.594, respectively]. Table 3 shows the details of primary and secondary outcomes.

Figure 2 shows the daily cumulative probability of meeting the primary and secondary outcomes. Most of the colored areas overlapped for both groups. Regarding the primary outcome, the longer the hospitalization duration, the more patients were supplemented with oxygen. As for the secondary outcomes, the proportions of patients who died and who required IMV/ECMO did not increase significantly.

Regarding the safety of favipiravir treatment, adverse events were reported for 735 (29.0%) of 2532 patients (Table 4), and 365 (49.7%) of them had probable relevance to favipiravir. Only one patient experienced favipiravir dose reduction and treatment suspension. The most common adverse event was uric acid elevation (438, 59.6%), followed by liver dysfunction or liver enzyme elevation (182, 24.8%), rash (30,

Table 3 Results of pooled logistic regression analysis on the effect of favipiravir on the primary and secondary outcomes

	Person-days	Event	Weighted event rate (per 1000 person-day)	Hazard ratio	95% CI	*P* value
Oxygen requirement						
Regimen 1	31,990	119	3.69	0.825	0.657–1.04	0.098
Regimen 2	50,161	308	6.12	1	Reference	
30-day fatality risk						
Regimen 1	32,726	14	0.411	0.869	0.519–1.46	0.594
Regimen 2	53,209	41	0.759	1	Reference	
IMV/ECMO						
Regimen 1	32,713	23	0.682	1.02	0.649–1.60	0.929
Regimen 2	53,145	55	1.02	1	Reference	

IMV/ECMO invasive mechanical ventilation/extracorporeal membrane oxygenation

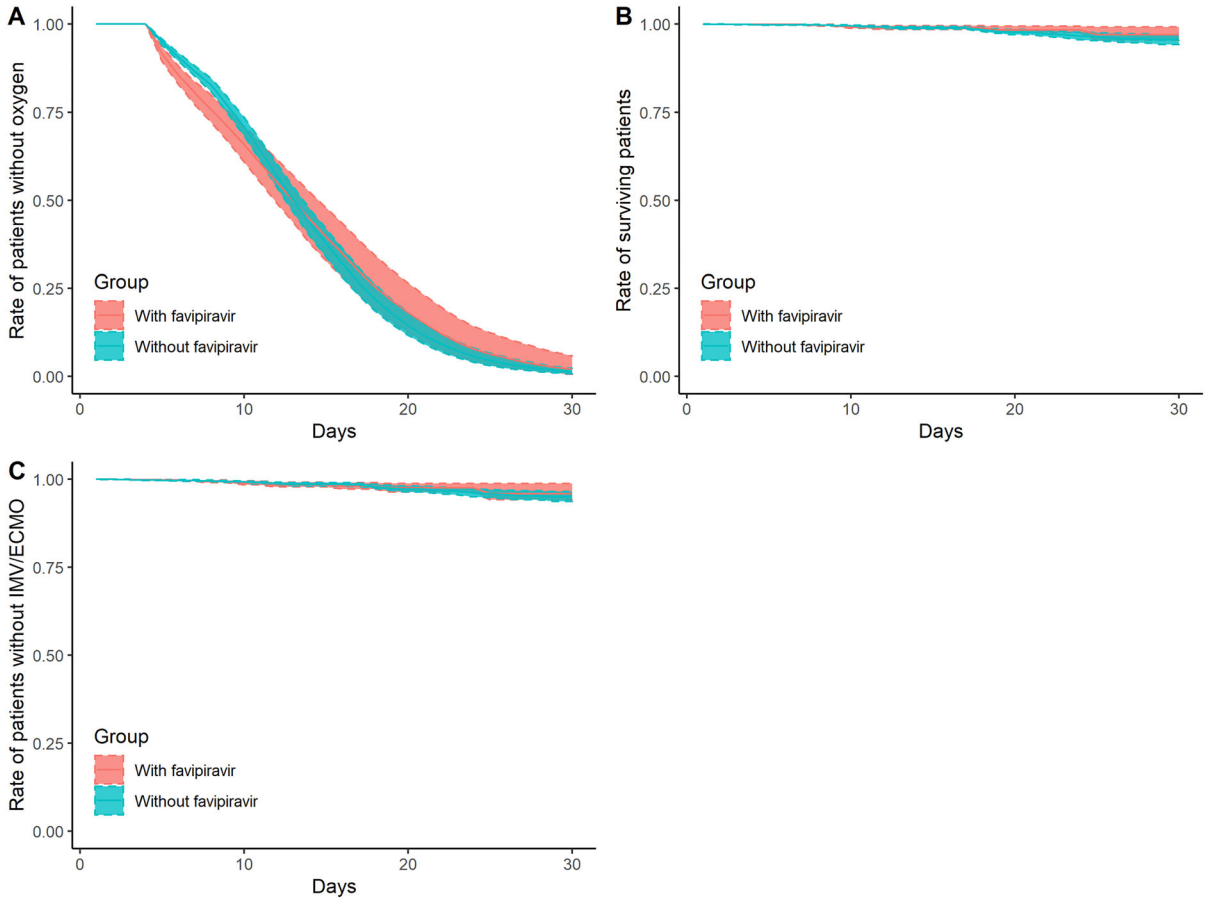

Fig. 2 Daily cumulative probability of presenting the primary/secondary outcomes. **a** Daily cumulative probability of not being supported by oxygen. **b** Daily cumulative probability of survival. **c** Daily cumulative probability of not being supported by invasive mechanical ventilation (IMV)/extracorporeal membrane oxygenation (ECMO). Red bands represent patients treated with favipiravir and blue bands represent patients treated without favipiravir. Shaded zones represent 95% confidence intervals by bootstrapping

Table 4 Adverse events of favipiravir

Severity	Number of cases	Probable relevance to favipiravir	Cessation of favipiravir	Sequelae
Mild	530 (20.9%[a])	245 (46.2%)	1 (0.2%)	0 (0%)
Moderate	202 (8.0%[a])	119 (58.9%)	0 (0%)	0 (0%)
Serious	3 (0.1%[a])	1 (33.3%)	0 (0%)	0 (0%)

Mild: adverse events need no treatment or presented no symptom. Moderate: adverse events need noninvasive treatment. Serious: eminent adverse events need invasive treatment

[a]Denominators are the total number of cases treated with favipiravir (n = 2532)

4.1%), nausea and vomiting (14, 1.9%), and renal dysfunction (8, 1.1%).

DISCUSSION

This study suggested that favipiravir did not have a significant effect in preventing progression to respiratory failure among patients with non-severe, early-stage COVID-19 when initiated in the early stage of hospitalization. As mentioned earlier, the clinical evidence of favipiravir effectiveness on nonsevere, early-stage COVID-19 is still insufficient. According to the preliminary report of the Predictors of Severe COVID-19 Outcomes (PRESCO) study, the trial did not achieve statistical significance on the primary endpoint of time to sustained clinical recovery for the treatment of mild-to-moderate COVID-19 [30]. Our results are consistent with this topline result and suggest the lack of clinically relevant therapeutic benefit of favipiravir in patients with non-severe COVID-19. In addition, Bosaeed et al. reported no significant difference in the time of viral clearance between the favipiravir and placebo groups, which also supports our results to some extent, although its primary endpoint was not a clinical improvement or outcome.

Favipiravir has been used in the management of patients with COVID-19 on a compassionate use basis from the early phase of the pandemic in Japan. However, the management of non-severe disease has already been gradually established [16, 31–33]. Additionally, vaccine coverage has exceeded 80% of the total population in Japan [34, 35]. Currently available data suggest a limited, if any, role of favipiravir in the management of COVID-19.

Adverse events associated with favipiravir were recorded in 29.0% of the patients treated by this agent. An observational study from Japan reported adverse events in 3878 out of 15,245 (25.4%) patients who received favipiravir. Although most of them were noncritical events, the frequency appears higher than with other treatment options. For instance, our previous study showed that remdesivir was associated with adverse events in 92 out of 828 (11.1%) patients who were treated with this drug [19]. Moreover, potential teratogenicity of favipiravir should also be considered [36–38].

Several limitations of this study should be noted. First, this was a retrospective cohort study and not a randomized controlled trial. Although we adjusted for numerous factors that affect clinical outcomes, our three-step method could not adjust for all confounding factors [39]. Though our method allowed us to adjust for time-dependent factors and immortal time bias [18, 20], we could not include time-dependent variables other than NEWS. Given that COVID-19 is an acute infectious disease, its clinical severity varies on a daily basis. Including a larger number of more detailed time-dependent variables would be desirable for more reliable results. Second, several items were difficult to interpret because our data were based on a registry system. For instance, "mortality" in our data implied that a patient died within the 30-day observation period, i.e., during hospitalization in our study. Even when the patients died after discharge, they were still labeled as survivors. The cause of death was also unavailable from our data. When a fatal case had a serious comorbidity, we could not distinguish the disease critical to the patient. Third, our registry determines the clinical status of each patient on an intermittent rather than a daily basis. Fourth, the adverse events of favipiravir were reported at the discretion of each physician, suggesting the possibility of underreporting. Fifth, our primary outcome includes some ambiguity. Although oxygen administration is an effective noninvasive treatment for respiratory failure, its indication is not strictly defined and as at the discretion of the treating physician. Nevertheless, oxygen administration is likely to be a better indicator than other clinical outcomes: persistence of fever, length of stay, antibiotic use during admission, and so forth. However, fever is not an appropriate indicator of COVID-19 severity given that low fever does not represent the mild condition. Similarly, the length of stay may also not be an ideal outcome because a large number of patients in Japan were admitted for the purpose of isolation (e.g., patients early in the pandemic had to remain hospitalized until they had a negative PCR result twice, despite being asymptomatic).

CONCLUSIONS

Favipiravir was not associated with reduced risk of progression to respiratory failure among patients with non-severe COVID-19 when started early in the disease course. Despite several limitations due to study design, our findings suggest that favipiravir is not an essential drug for the management of COVID-19 infection, particularly when balanced against the frequency of adverse events.

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Author Contributions. Shinya Tsuzuki, Kayoko Hayakawa, Yohei Doi, Wataru Sugiura, and Norio Ohmagari conceived the study. Tomohiro Shinozaki and Yukari Uemura designed analysis. Nobuaki Matsunaga, Mari Terada, Setsuko Suzuki, Yusuke Asai, Taro Shibata, Masahi Kondo, Kazuo Izumi, Masahiro Hojo, Tetsuya Mizoue, Kazuhisa Yokota, Fukumi Nakamura-Uchiyama, and Fumitake Saito collected the data. Shinya Tsuzuki, Kayoko Hayakawa, Yohei Doi, Tomohiro Shinozaki, Yukari Uemura, Sho Saito, and Gen Yamada analyzed and interpreted the data. Shinya Tsuzuki wrote the first draft, which was subsequently revised by all authors. All authors read and approved the final manuscript.

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Data Availability. The data sets generated during and/or analyzed during the current study are not publicly available due to the regulation of COVIREGI-JP. A portion of the data would be available upon reasonable request to the corresponding author.

REFERENCES

1. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci. 2017;93:449–63.

2. Information of Avigan Tablet in relation to Covid-19 | FUJIFILM Toyama Chemical Co.. https://www.fujifilm.com/fftc/en/avigan. Accessed 8 Nov 2021.

3. Bai C-Q, Mu J-S, Kargbo D, et al. Clinical and virological characteristics of Ebola virus disease patients treated with favipiravir (T-705)-Sierra Leone, 2014. Clin Infect Dis. 2016;63:1288–94.

4. Sissoko D, Laouenan C, Folkesson E, et al. Experimental treatment with favipiravir for Ebola virus disease (the JIKI Trial): a historically controlled, single-arm proof-of-concept trial in guinea. PLoS Med. 2016;13:e1001967.

5. Doi Y, Hibino M, Hase R, 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:e01897-20.

6. Ito K, Ohmagari N, Mikami A, Sugiura W. Major ongoing clinical trials for COVID-19 treatment and studies currently being conducted or scheduled in Japan. Glob Health Med. 2020;2:96–101.

7. Ivashchenko AA, Dmitriev KA, Vostokova NV, et al. AVIFAVIR for treatment of patients with moderate coronavirus disease 2019 (COVID-19): interim results of a phase II/III multicenter randomized clinical trial. Clin Infect Dis. 2021;73:531–4.

8. Shinkai M, Tsushima K, Tanaka S, et al. Efficacy and safety of favipiravir in moderate COVID-19 pneumonia patients without oxygen therapy: a randomized, phase III clinical trial. Infect Dis Ther. 2021;10:2489–509.

9. Udwadia ZF, Singh P, Barkate H, et al. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: a randomized, comparative, open-label, multicenter, phase 3 clinical trial. Int J Infect Dis. 2021;103:62–71.

10. Bosaeed M, Mahmoud E, Alharbi A, et al. Favipiravir and hydroxychloroquine combination therapy in patients with moderate to severe COVID-19 (FACCT Trial): an open-label, multicenter, randomized, controlled trial. Infect Dis Ther. 2021;10:2291–307.

11. Lai C-C, Chao C-M, Hsueh P-R. Clinical efficacy of antiviral agents against coronavirus disease 2019: a systematic review of randomized controlled trials. J Microbiol Immunol Infect. 2021;54:767–75.

12. Bosaeed M, Alharbi A, Mahmoud E, et al. Efficacy of favipiravir in adults with mild COVID-19: a randomized, double-blind, multicentre, placebo-controlled clinical trial. Clin Microbiol Infect. 2022. https://doi.org/10.1016/j.cmi.2021.12.026.

13. Finberg RW, Ashraf M, Julg B, et al. US201 study: a phase 2, randomized proof-of-concept trial of favipiravir for the treatment of COVID-19. Open Forum Infect Dis. 2021;8:ofab563.

14. Matsunaga N, Hayakawa K, Terada M, et al. Clinical epidemiology of hospitalized patients with COVID-19 in Japan: report of the COVID-19 Registry Japan. Clin Infect Dis. 2020;73:e3677–89.

15. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377–81.

16. Ministry of Health, Labour and Welfare. Clinical Guideline for COVID-19. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00111.html. Accessed 12 Aug 2021.

17. Suissa S, Dell'Aniello S. Time-related biases in pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2020;29:1101–10.

18. Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol. 2016;79:70–5.

19. Tsuzuki S, Hayakawa K, Uemura Y, et al. Efficacy of remdesivir in hospitalised COVID-19 patients in Japan: a large observational study using the COVID-19 Registry Japan. medRxiv. 2021. https://doi.org/10.1101/2021.03.09.21253183v2.

20. Hernán MA. How to estimate the effect of treatment duration on survival outcomes using observational data. BMJ. 2018;360:k182.

21. Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS clinical trial with inverse probability of censoring weighted (IPCW) log-rank tests. Biometrics. 2000;56:779–88.

22. The National Health Service England. National Early Warning Score (NEWS). https://www.england.nhs.uk/ourwork/clinical-policy/sepsis/nationalearlywarningscore/. Accessed 28 Jan 2021.

23. Wu Z, McGoogan JM. Characteristics of and Important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323:1239.

24. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020;369:m1966.

25. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584:430–6.

26. Cunningham JW, Vaduganathan M, Claggett BL, et al. Clinical outcomes in young US adults hospitalized with COVID-19. JAMA Intern Med. 2020;181:379–81.

27. Lighter J, Phillips M, Hochman S, et al. Obesity in patients younger than 60 years is a risk factor for COVID-19 hospital admission. Clin Infect Dis. 2020;71:896–7.

28. Tartof SY, Qian L, Hong V, et al. Obesity and mortality among patients diagnosed with COVID-19:

results from an integrated health care organization. Ann Intern Med. 2020;173:773–81.

29. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2018.

30. Appili Therapeutics provides update on phase 3 PRESECO clinical trial evaluating Avigan®/Reeqonus™. Appili—LIVE. https://www.appilitherapeutics.com/newsfeed/Appili-Therapeutics-Provides-Update-on-Phase-3-PRESECO-Clinical-Trial-Evaluating-Avigan%C2%AE%2FReeqonus%E2%84%A2. Accessed 17 Nov 2021.

31. National Institutes of Health. Information on COVID-19 treatment, prevention and research. COVID-19 treatment guidelines. https://www.covid19treatmentguidelines.nih.gov/. Accessed 27 Jan 2021.

32. World Health Organization. Therapeutics and COVID-19: living guideline. https://www.who.int/publications-detail-redirect/therapeutics-and-covid-19-living-guideline. Accessed 27 Jan 2021.

33. CDC. Coronavirus disease 2019 (COVID-19). Centers for Disease Control and Prevention. 2020. https://www.cdc.gov/coronavirus/2019-ncov/index.html. Accessed 12 Aug 2021.

34. Prime Minister's Office of Japan. About novel coronavirus vaccine. https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html. Accessed 18 Nov 2021.

35. Ritchie H, Mathieu E, Rodés-Guirao L, et al. Coronavirus pandemic (COVID-19). Our world in data. 2020. https://ourworldindata.org/covid-vaccinations. Accessed 18 Nov 2021.

36. Delang L, Abdelnabi R, Neyts J. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. Antivir Res. 2018;153:85–94.

37. Pilkington V, Pepperrell T, Hill A. A review of the safety of favipiravir—a potential treatment in the COVID-19 pandemic? J Virus Erad. 2020;6:45–51.

38. Hashemian SM, Farhadi T, Velayati AA. A review on favipiravir: the properties, function, and usefulness to treat COVID-19. Expert Rev Anti Infect Ther. 2021;19:1029–37.

39. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrilca. 1983;70:41–55.

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