Triple Combination of Favipiravir, Chloroquine-based Agents and Protease Inhibitors for Treatment of COVID-19 Patients With Pulmonary Involvements: a Multicenter, Non-controlled Observational Study

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Abstract

Background. Presently, data on effectiveness of triple combination of favipiravir, chloroquine-based agents and protease inhibitors for treatment of covid-19 patients with pulmonary involvements is limited.

Method. We conducted a retrospective observational study of hospitalized adult COVID-19 patients at five tertiary care hospitals in Thailand.

Results. Among 247 COVID-19 patients, 63 patients met the study criteria for pulmonary involvements and were prescribed favipiravir according to the Thai National guidelines. Nearly all (61/63,96.8%) were concomitantly treated with chloroquine-based agent and protease inhibitors. The median baseline NEWS2 score was 5 (0–16) and four patients (4/63,6.4%) required invasive mechanical ventilation upon hospitalization. The Day-7 clinical improvement rate [95%CI] was 66.7%[53.7–78.0%] in all patients, 92.5%[75.7%–99.1%] in patients who did not require O_2-supplementation, and 47.2%[0.4%–64.5%] in patients who required O_2-supplementation. No life-threatening adverse events were identified. The 28-day mortality rate was 4.8%. Multivariate analysis revealed three poor prognostic factors for Day-7 clinical improvement [odds ratio (95%CI);*p*-value]: older age [0.94(0.89–0.99);*p*=0.04], higher baseline NEWS2 score [0.64(0.47–0.88);*p*=0.006], and lower favipiravir loading dose (≤45 mg/kg/day) [0.04 (0.005–0.4);*p*=0.006].

Conclusion. Our study preliminary reports the acceptable effectiveness of triple combination regimen for treating COVID-19 patients. In addition to older age and a high baseline NEWS2 score, a low loading dose of favipiravir (≤45 mg/kg/day) was also identified as a poor prognostic factor for early clinical improvement. Further studies with the control group to confirm the effectiveness of triple combination and optimal dose of favipiravir should be performed.

Background

As of July 26, 2020, a total of 15,785,641 COVID-19 cases with 640,016 deaths have been reported globally [1]. This pandemic disease is caused by a novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a single-stranded RNA beta-coronavirus encoding an RNA-dependent RNA polymerase (RdRp) and proteases. Both RdRp and viral proteases are considered important targets for potentially therapeutic agents. Hundreds of clinical studies are actively investigating a variety of promising agents (e.g., remdesivir, favipiravir, lopinavir, hydroxychloroquine, and interferon-alpha)[2]; however, data on the efficacy of these potentially therapeutic agents are still limited.

Favipiravir, a purine nucleic acid analog, is a broad-spectrum oral antiviral agent that inhibits the *RdRp* of RNA viruses [3]. This agent shows in vitro activity against many RNA viruses, including arenaviruses, bunyaviruses, flaviviruses, Ebola virus, and influenza virus, as well as SARS-CoV-2 [4, 5]. Currently, two registered clinical studies of favipiravir among COVID-19 patients have already reported their results [6]. The first study (ChiCTR2000029600) was a small, open-label, nonrandomized control study of 80 patients with COVID-19 conducted to compare the efficacy of favipiravir plus aerosolized interferon-alpha

with that of lopinavir/ritonavir plus aerosolized interferon-alpha. In that study, the favipiravir group showed a significantly shorter time to viral clearance and a significantly higher improvement rate in chest imaging, after adjustment for potential confounders [7]. The second study (ChiCTR200030254) was a randomized control trial (RCT) of 240 patients with COVID-19 pneumonia. That study reported a significantly higher clinical recovery rate on Day 7 in the favipiravir group compared with the arbidol group (71.43% vs. 55.86%; $p = 0.02$) [8].

In February 2020, favipiravir was made available for use in Thailand under emergency procurement by the Department of Disease Control of Thailand. The latest Thailand national clinical practice guidelines (CPG) for COVID-19 management (updated on 1 May 2020) recommended the combination therapy of chloroquine-based agent and protease inhibitors in all symptomatic COVID-19 patients. Favipiravir therapy is recommended only in patients with evidence of pulmonary involvements (i.e., abnormal chest-imaging without desaturation, O2-saturation of ≤94% without oxygen supplementation).

The standard dose of favipiravir for treating influenza infection is 1600 mg twice daily on Day 1, followed by 600 mg twice daily on Days 2–5 [9]. A maximal loading dose of 3000 mg twice daily on Day 1 and a maintenance dose of 1200 mg twice daily on Days 2–9 were safely used in a previous Ebola study [10]. Given that the optimal dose of favipiravir for treating COVID-19 is still uncertain, the Thailand national CPG recommend a fixed loading dose of 1600 mg twice daily on Day 1, followed by 600 mg twice daily on Days 2–10. A higher loading dose (60 mg/kg/day, MKD) and maintenance dose (20 MKD) are recommended in patients with a body mass index (BMI) of ≥35.

Presently, data on the effectiveness of triple combination of favipiravir, chloroquine-based agents and protease inhibitors and optimal dosage of favipiravir for treating COVID-19 is limited. Therefore, we conducted a retrospective study to explore these issues.

Materials And Methods

Study Design

We conducted a retrospective observational study of COVID-19 patients who were hospitalized at any of five tertiary care hospitals in Thailand (i.e., Siriraj, Taksin, Vachira Phuket, Lerdsin, and Central hospitals) during January 1–April 30, 2020.

Inclusion and exclusion criteria

We enrolled all hospitalized patients aged at least 18 years who had reverse transcription PCR-confirmed SARS-CoV-2 based on a respiratory specimen (nasopharyngeal, oropharyngeal, sputum, endotracheal aspirate, or bronchoalveolar lavage sample) and had evidence of pulmonary involvements (abnormal chest imaging and/or O2-saturation of ≤94% without oxygen supplementation). Patients who early expired or were discharged from the hospital within 24 hours after hospitalization were excluded.

Data collection and study definition

We reviewed patient charts to obtain all necessary data, including demographic data, clinical data, laboratory data, and the hospital stay length. We also recorded the daily National Early Warning Score 2 (NEWS2 score). Details regarding the NEWS2 score have been published elsewhere [11]. The primary outcome was the rate of clinical improvement within seven days of favipiravir therapy (Day-7 clinical improvement), and the secondary outcomes were the Day-14 and Day-28 clinical improvement rates.

Clinical improvement was defined as a one-point reduction in baseline status (on the first day of favipiravir therapy) on a six-point disease severity scale at the time of evaluation. The six-point disease severity scale was categorized as follows: 6-death; 5-hospitalization for extracorporeal membrane oxygenation (ECMO) or mechanical ventilation; 4-hospitalization for non-invasive ventilation or high-flow O_2-therapy; 3-hospitalization for supplemental O_2; 2-hospitalization without the need for O_2-supplementation but requiring ongoing medical care; and 1-discharge or normalization of all vital signs and saturation of peripheral O_2 of >94% on room air for at least 24 hours.

Statistical analysis

Categorical variables are summarized by frequency and percentage, whereas continuous variables are summarized by the median and range. Univariate analyses were performed using the Fisher-exact test for categorical data. The Mann-Whitney U test was used for continuous data. To identify the factors independently associated with the Day-7 clinical improvement, we performed a subsequent multivariate analysis including all potentially significant variables with a *p*-value of ≤ 0.20 in a stepwise fashion.

For all calculations, a two-tailed *p*-value of <0.05 was considered statistically significant. All calculations were performed using STATA version 14.1 (Stata Corp, College Station TX).

Results

During the study period, there were a total of 274 COVID-19 patients hospitalized in the

participating hospitals, of which 63 patients (23.0%) had evidence of pulmonary involvements. All of them received favipiravir therapy according to the Thai national clinical practice guidelines. The total of 63 patients were enrolled into the study. The baseline demographics and characteristics of all patients are listed in Table 1.

The median age of patients was 48 (22–85) years, and 39 of these patients (61.9%) were male. Most patients had fever (87.3%), sore throat (69.8%), or cough (74.6%) as the clinical presentation. The median duration between the symptom onset and the admission date was 6 (0–28) days, while the median duration between the symptom onset and the first day of favipiravir therapy was 8 (0–28) days.

At baseline (Day 1 of favipiravir therapy), 17 patients (27.0%) required O_2-supplementation via nasal cannula, 6 patients (9.5%) required non-invasive ventilation and/or high-flow O_2-therapy, and 4 patients

(6.4%) required invasive mechanical ventilation and/or ECMO, while the remainder did not required O_2-supplementation. The median baseline NEWS2 score was 5 (0–16).

The median loading dose of favipiravir was 47.4 (29.1–71.1) MKD, and one-third of enrolled patients (33.3%) received a loading dose of ≤45 MKD. The median maintenance dose of favipiravir was 17.9 (10.9–26.7) MKD, and 76.2% of the subjects received a maintenance dose of ≤15 MKD. The median duration of favipiravir therapy was 12 (2–17) days. Within two days of initiating favipiravir treatment, nearly all patients were prescribed a chloroquine-based agent (98.4%) and a protease inhibitor (96.8%); half of them also received azithromycin (49.2%). Only a few patients received a steroid (12.7%) or tocilizumab (6.4%) at this time.

Hospital course and treatment outcomes

Details regarding the hospital course and treatment outcomes are shown in Table 2. The Day-7, Day-14, and Day-28 clinical improvement rates, stratified by the requirement for O_2-supplementation are depicted in Figure 1. The Day-7 clinical improvement rate [95%CI] was 66.7% [53.7–78.0%] in all patients, 92.5% [75.7–99.1%] in patients who did not require O_2-supplementation (a six-point disease severity scale score of 1–2), and 47.2% [0.4–64.5%] in patients who required O_2-supplementation (a six-point severity scale score of 3–5). The Day-14 clinical improvement rates for all patients, those who did not require O_2-supplementation, and those who required O_2-supplementation were 85.7% [74.6%–93.2%], 100.0% [87.2%–1.00%], and 75.0% [57.8%–87.9%], respectively. Nearly all patients who required O_2-supplementation (96.1%) had clinical improvement within 28 days.

Of these 63 study patients, four patients required invasive mechanical ventilation or ECMO on Day 1 of therapy, and four more cases subsequently required invasive mechanical ventilation (two cases on Day 6 and two cases on Day 9 of therapy). The 14-day, 28-day, and in-hospital mortality rates were 1.6%, 4.8%, and 7.9%, respectively. The major cause of death was superimposed infection.

The most common adverse event was diarrhea (54.0%), follow by nausea/vomit (7.9%), hepatitis (6.4%), and QT interval prolongation in EKG (6.4%). None of these adverse events were life-threatening.

Factors associated with Day-7 clinical improvement

To determine the factors associated with Day-7 clinical improvement, we compared patients

with Day-7 clinical improvement (cases) with patients without Day-7 clinical improvement (controls). The characteristics of both groups are shown Table 1. The cases had a significantly lower age (47 vs. 59 years; $p = 0.02$), a significantly lower BMI (25.0 vs. 27.9; $p = 0.04$), a significantly lower baseline NEWS2 score (4 vs. 5; $p = 0.003$), and a significantly lower baseline six-point disease severity scale score (2 vs. 3; $p < 0.001$). Additionally, the baseline white blood cell count was significantly lower in the case group (5420 vs. 6810; $p = 0.03$). Although the median loading and maintenance doses of favipiravir were not statistically different between these groups, the proportion of patients in the control group who received a

lower loading dose of favipiravir (≤45 MKD) trended higher compared with the case group (26.2% vs. 47.6%; $p < 0.10$).

Table 3 shows the results of multivariate analysis. A multivariate analysis revealed three factors that were negatively associated with Day-7 clinical improvement [odds ratio (95%CI); *p*-value]: older age [0.94 (0.89–0.99); $p = 0.04$], higher baseline NEWS2 score [0.64 (0.47–0.88); $p = 0.006$], and a lower prescribed loading dose of favipiravir (≤45 MKD) [0.04 (0.005–0.4); $p = 0.006$].

Discussion

The Day-7 clinical improvement rate from our study was 67.7%, which is slightly lower than the Day-7 clinical recovery rate from an unpublished RCT of favipiravir (71.4%) [8]. However, there were a few differences between these two studies. First, the definition of clinical recovery used in the unpublished RCT was based mainly on clinical symptoms (e.g., fever, cough), whereas the definition of clinical improvement used in our study was based on improvement in oxygenation status. Our study included sicker patients with a higher proportion of patients who required mechanical ventilation (6.4%) as compared with the subjects of the unpublished RCT (0.9%). These differences may explain the slightly lower rate of favorable clinical responses observed in the present study.

Among the COVID-19 patients with abnormal chest-imaging but did not require O_2-supplementation, nearly all patients (92.6%) had clinical improvement within the first seven days of favipiravir therapy. However, only half of the patients who required O_2-supplementation (47.2%) had clinical improvement within the first seven days of therapy. The rate of clinical improvement in these patients finally reached 75% on Day 14 and 83.3% on Day 28. Of the eight patients who required invasive mechanical ventilation or ECMO during their hospitalization, one patient died within the first 14 days. Therefore, the calculated 14-day mortality among this group was 12.5%. This number is similar to the 14-day mortality reported by a preliminary remdesivir RCT, in which 13 (10.4%) out of 125 patients who required mechanical ventilation or ECMO died [12]. Based on these findings, the effectiveness of favipiravir for treating COVID-19 is promising, but this drug can be slow acting in more severe cases.

Our study identified older age and a higher baseline NEWS2 scale as poor prognostic factors for early clinical response. These findings are compatible with the results from many previous publications [13-15]. We also explored other baseline variables (e.g., BMI, comorbidities); however the impact of those factors disappeared after the data were adjusted by the baseline NEWS2 scale.

Given that the optimal dose of favipiravir is still uncertain, we carefully explored the association between favipiravir dosage and patient outcome. Our study confirmed that a loading dose of favipiravir of ≤45 MKD was a poor prognostic factor for early clinical response. Therefore, a fixed favipiravir loading dose of 1600 mg twice daily for all patients with a BMI of <35 may be suboptimal for patients with a BMI of <35 but a body weight of ≥70 kg. Some might argue that this significant association may be a reflection of patients' obesity, which was also known as a poor prognostic factor in COVID-19. However, our study

did not find any association between the patient's baseline BMI or body weight and the treatment outcome in the adjusted analysis.

Our study has several strengths. First, this study was a very early study to explore the

effectiveness of triple combination of favipiravir, chloroquine-based agents and protease inhibitors in active clinical cases of COVID-19. Second, this study included

patients with differing disease severities; the patients ranged from mild pneumonia cases who had abnormal chest imaging but did not require O_2-supplementation to patients with life-threatening pneumonia who required mechanical ventilation or ECMO. This diverse subject pool allowed us to thoroughly explore the effectiveness of such combination and the clinical course of COVID-19 disease in various degrees of severity. Lastly, the daily NEWS2 scores and six-point disease severity scale scores were carefully collected and analyzed. Consequently, we can report nearly all important clinical outcomes and compare our findings with those of other clinical trials [7, 8, 12].

Our study also has some limitations. First, the retrospective design resulted in a significant amount of missing data, especially for laboratory values. To resolve this issue, when performing the multivariate analysis, missing data was replaced by the mean value of a given variable. Second, majority of our patients received triple combination of favipiravir, chloroquine-based agents and protease inhibitors. Therefore, the good treatment response among our patients may be the synergistic results of triple combination or one of any agents. Furthermore, a high rate (54.0%) of diarrhea of the patients having favipiravir was probably related to protease inhibitor rather than favipiravir. Third, a sample size of 63 patients with COVID-19 pneumonia is not large enough to detect other associated factors with a low prevalence. Lastly, the generalizability of our findings may be an issue. Given that the study was conducted in tertiary care hospitals in Thailand, results may not be applicable to primary or secondary care settings or to COVID-19 patients in other countries.

In conclusion, our study preliminary reports the effectiveness of triple combination of favipiravir, chloroquine-based agents and protease inhibitors for treating COVID-19 patients with pulmonary involvements in a tertiary care hospital setting. No life-threatening adverse events were identified. In addition to older age and a high baseline NEWS2 score, a low loading dose of favipiravir (≤45 mg/kg/day) was also identified as a poor prognostic factor for early clinical improvement. Further studies with a controlled group to explore the effectiveness of triple combination regimen and optimal dose of favipiravir should be performed.

Declarations

Ethics approval and consent to participate. The study protocol was approved with a waiver of informed consent by the institutional review boards of all involved hospitals.

Consent to publication. Written permission for publication has been obtained from all authors.

Availability of data and material. Available upon request.

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Potential conflicts of interest. The authors have no conflicts of interest to declare.

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Tables

Table 1. Baseline demographics and characteristics of all patients.

Variables	All (n = 63)	Day 7 Clinical improvement		*p*-value
		Yes (n = 42)	No (n = 21)	
Age, median (range), year	48 (22–85)	47 (23–72)	59 (22-85)	0.02
Male sex	39 (61.9%)	25 (59.5%)	14 (66.7%)	0.78
Body weight, median (range), kg	69 (45–125)	68 (51–125)	76 (45–120)	0.08
Body mass index median (range), kg/m^2	26.1 (19.0–43.8)	25.0 (19.0–43.8)	27.9 (20.8–39.2)	0.04
Duration between, median (range), day				
Symptom onset and admission date	6 (0–28)	6 (0–28)	8 (0–15)	0.08
Admission date and Day-1 of favipiravir therapy	1 (-8–10)	1 (-3–10)	0 (-8–5)	0.002
Symptom onset and Day-1 of favipiravir therapy	8 (0–28)	8 (2–28)	8 (0–11)	0.60
Exposure risk				
Contact with confirmed COVID-19 cases	26 (41.3%)	19 (45.2%)	7 (33.3%)	0.42
Travel abroad	7 (11.1%)	5 (11.2%)	2 (9.5%)	1.00
Contact with a foreigner	11 (17.5%)	8 (19.1%)	3 (14.3%)	0.74
Travel to a local area with clustered cases	38 (60.3%)	28 (66.7%)	10 (47.6%)	0.18
Underlying diseases				
Heart disease and hypertension	9 (14.3%)	7 (16.7%)	2 (9.5%)	0.71
Diabetes mellitus	17 (27.0%)	11 (26.2%)	6 (28.6%)	1.00
Chronic lung disease	4 (6.4%)	2 (7.1%)	1 (4.8%)	1.00
Chronic kidney disease	4 (6.4%)	3 (7.1%)	1 (4.8%)	1.00
Chronic liver disease	3 (4.8%)	3 (7.1%)	0 (0%)	0.55
Solid cancer	4 (6.4%)	2 (7.1%)	1 (4.8%)	1.00
Others	4 (6.4%)	2 (7.1%)	2 (9.5%)	0.60

Clinical presentation upon admission				
Fever or body temperature of >37.5 °C	55 (87.3%)	36 (85.7%)	19 (90.5%)	0.71
Sore throat	44 (69.8%)	27 (64.3%)	17 (81.0%)	0.25
Rhinorrhea	16 (25.4%)	13 (31.0%)	3 (14.3%)	0.22
Cough	47 (74.6%)	30 (71.4%)	17 (81.0%)	0.54
Headache	11 (17.5%)	8 (19.1%)	3 (14.3%)	0.74
Myalgia	17 (27.0%)	12 (28.6%)	5 (23.8%)	0.77
Diarrhea	8 (12.7%)	6 (14.3%)	2 (9.5%)	0.71
Shortness of breath	27 (42.9%)	14 (33.3%)	13 (61.9%)	0.06
Illness severity at the time of favipiravir initiation				
NEWS2 score, median (range)	5 (0–16)	4 (0–11)	5 (0–16)	0.003
Six-point disease severity scale, median (range)	2.5 (1–5)	2 (1–4)	3 (2–5)	<0.001
1 – No O_2-supplementation with O_2-saturation of >94%	4 (6.4%)	4 (6.4%)	0 (0)	<0.001
2 – No O_2-supplementation with O_2-saturation of ≤94%	23 (36.4%)	21 (50.0%)	2 (9.5%)	
3 –Requiring O_2-supplementation	28 (44.4%)	16 (40.1%)	12 (57.1%)	
4 –Requiring high-flow O_2-supplementation or non-invasive mechanical ventilation	4 (6.4%)	1 (2.4%)	3 (14.3%)	
5 –Requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation	4 (6.4%)	0 (0%)	4 (19.1%)	
Baseline laboratory values*				
Hemoglobin, median (range), (mg/dl)	14.0 (8.0–18.0)	14.0 (9.0–17.0)	13.5 (8.0–18.0)	0.48
White blood cell count, median (range), (cell/mm^3)	5735 (2910–41300)	5420 (2910–41300)	6810 (3180–15750)	0.03

Serum creatinine, median (range), (mg/dl)	0.9 (0.3–22.9) (n = 58)	0.9 (0.4–22.9) (n = 27)	0.9 (0.33–5.1) (n = 21)	0.67
Serum albumin, median (range), (mg/dl)	4.0 (1.8–4.9) (n = 53)	4.2 (1.8–5.0) (n = 33)	3.5 (2.6–4.1) (n = 20)	0.002
Serum lactate dehydrogenase, median (range), (mg/dl)	404 (145–1094) (n = 30)	382 (145–567) (n = 17)	453 (313–1094) (n = 13)	0.03
Indication of favipiravir therapy				
Abnormal chest imagining only	26 (41.3%)	24 (57.1%)	2 (9.5%)	<0.001
Required O_2-supplementation only	3 (4.7%)	2 (4.7%)	1 (4.8%)	
Abnormal chest imaging and required O_2-supplementation	34 (54.0%)	16 (38.1%)	18 (85.7%)	
Favipiravir regimen				
Dose per bw, median (range), mg/kg/day				
Loading dose	47.4 (29.1–71.1)	49.2 (29.1–62.7)	45.7 (29.6–71.1)	0.47
Maintenance dose	17.9 (10.9–26.7)	18.5 (10.9–23.5)	17.1 (11.1–26.7)	0.37
Potentially sub-therapeutic dose				
Loading dose of ≤45 MKD	21 (33.3%)	11 (26.2%)	10 (47.6%)	0.10
Maintenance dose of ≤15 MKD	48 (76.2%)	33 (78.6%)	15 (71.4%)	0.55
Duration of therapy, median (range), day	12 (2–17)	11.5 (2–16)	12 (2–17)	0.02
Other medications used**				
Any chloroquine-based agent	62 (98.4%)	41 (97.6%)	21 (100%)	1.00
Hydroxychloroquine	54 (85.7%)	36 (85.7%)	18 (85.7%)	1.00

Chloroquine	14 (22.2%)	8 (19.1%)	6 (28.6%)	0.52
Any protease inhibitor	61 (96.8%)	40 (95.2%)	21 (100.0%)	0.55
Darunavir/ritonavir	51 (81.0%)	35 (83.3%)	16 (76.2%)	0.51
Lopinavir/ritonavir	22 (34.9%)	13 (31.0%)	9 (42.9%)	0.26
Azithromycin	31 (49.2%)	17 (40.5%)	14 (66.7%)	0.06
Steroid	8 (12.7%)	5 (11.9%)	3 (14.3%)	1.00
Tocilizumab	4 (6.4%)	1 (2.4%)	3 (14.3%)	0.10

Note. *Earliest results of a test obtained within the first 7 days of admission (missing data was replaced by the mean value of the variable)

** Medications used within 2 days before or after the initiation of favipiravir therapy

Table 2. Hospital course and treatment outcomes

Variables	All patients (n = 63)
Clinical improvement	
Day-7 clinical improvement	42 (66.7%)
Patients who did not require O_2-supplementation (n = 27)	25 (92.6%)
Patients who required O_2-supplementation (n = 36)	17 (47.2%)
Day-14 clinical improvement	54 (85.7%)
Patients who did not require O_2-supplementation (n = 27)	27 (100.0%)
Patients who required O_2-supplementation (n = 36)	27 (75.0%)
Day-28 clinical improvement	57 (90.5%)
Patients who did not require O_2-supplementation (n = 27)	27 (100.0%)
Patients who required O_2-supplementation (n = 36)	30 (83.3%)
ICU duration, median (range), day	0 (0–46)
Required invasive mechanical ventilation or ECMO* during hospitalization	8 (12.7%)
Before initiation of favipiravir	4 (6.3%)
After initiation of favipiravir	4 (6.3%)
14-day mortality rate	1 (1.6%)
28-day mortality rate	3 (4.8%)
In-hospital mortality rate	5 (7.9%)
Length of hospital stay, median (range), day	15 (2–47)
Adverse drug reactions	39 (61.9%)
Diarrhea	34 (54.0%)
Hepatitis	4 (6.4%)
QT interval prolongation	4 (6.4%)
Nausea and vomit	5 (7.9%)
Superimposed bacterial infection	8 (12.7%)

Note. *ECMO: extracorporeal membrane oxygenation

Table 3. Factors associated with Day-7 clinical improvement

Variables	Unadjusted Odd Ratio [95%CI ; *p*-value]	Adjusted Odd Ratio [95%CI ; *p*-value]
Age, year	0.95 [0.92 -099; p=0.02]	0.94 [0.89–0.99; p=0.04]
Baseline NEWS2 score	0.77 [0.65-0.92;p=0.004]	0.64 [0.47 – 0.88; p=0.006]
Low loading dose of favipiravir	0.39 [0.13-1.17;p=0.09]	0.04 [0.005–0.41; p=0.006]

Figures

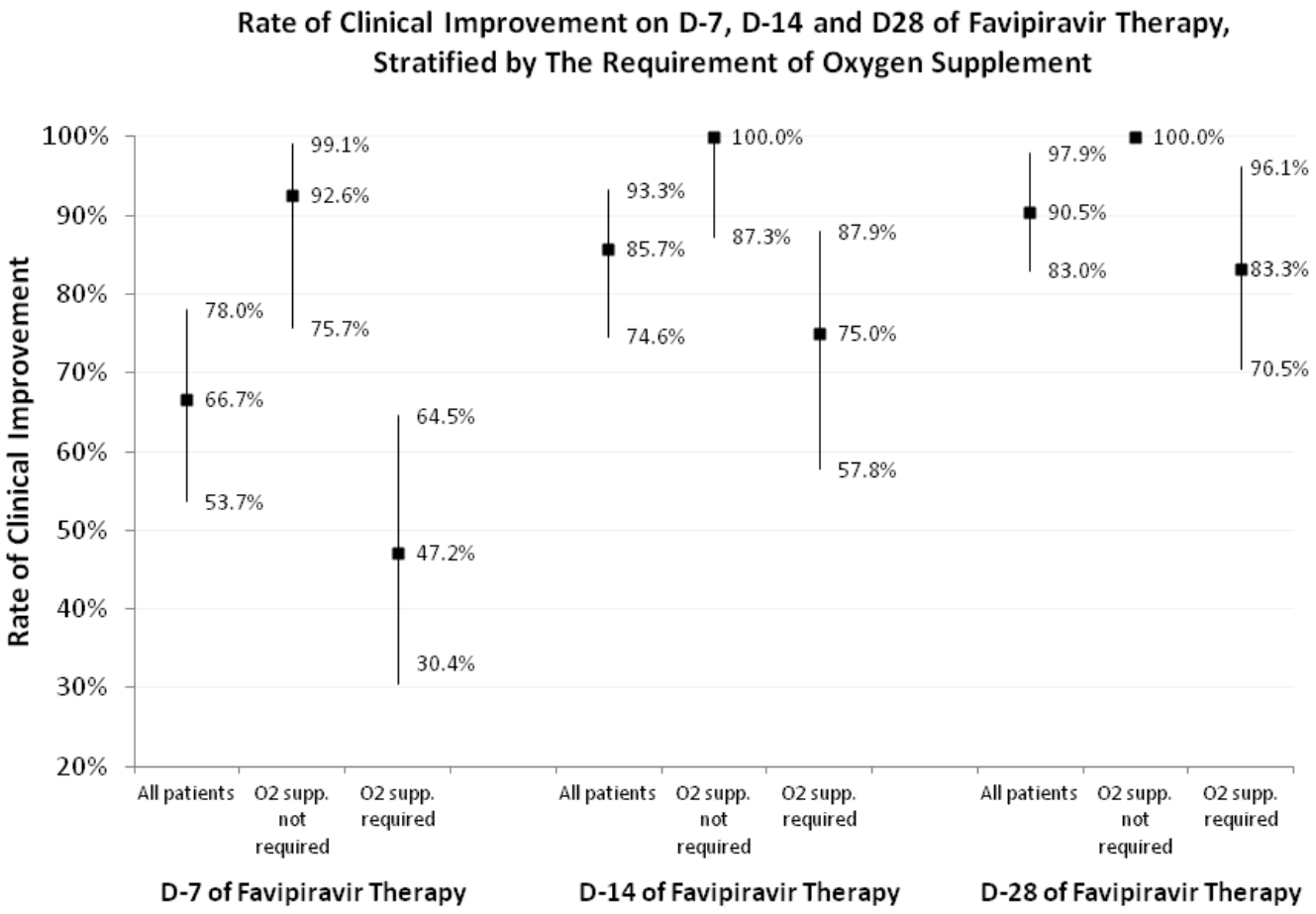

Figure 1

Rate of clinical improvement on Day 7, Day 14, and Day 28 of favipiravir therapy, stratified by the requirement for O2-supplementation.