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Safety and efficacy of Favipiravir in moderate to severe SARS-CoV-2 pneumonia

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ABSTRACT

Background: We examined the safety and efficacy of a treatment protocol containing Favipiravir for the treatment of SARS-CoV-2.

Methods: We did a multicenter randomized open-labeled clinical trial on moderate to severe cases infections of SARS-CoV-2. Patients with typical ground glass appearance on chest computerized tomography scan (CT scan) and oxygen saturation (SpO_2) of less than 93% were enrolled. They were randomly allocated into Favipiravir (1.6 gr loading, 1.8 gr daily) and Lopinavir/Ritonavir (800/200 mg daily) treatment regimens in addition to standard care. In-hospital mortality, ICU admission, intubation, time to clinical recovery, changes in daily SpO_2 after 5 min discontinuation of supplemental oxygen, and length of hospital stay were quantified and compared in the two groups.

Results: 380 patients were randomly allocated into Favipiravir (193) and Lopinavir/Ritonavir (187) groups in 13 centers. The number of deaths, intubations, and ICU admissions were not significantly different (26, 27, 31 and 21, 17, 25 respectively). Mean hospital stay was also not different (7.9 days [SD = 6] in the Favipiravir and 8.1 [SD = 6.5] days in Lopinavir/Ritonavir groups) ($p = 0.61$). Time to clinical recovery in the Favipiravir group was similar to Lopinavir/Ritonavir group (HR = 0.94, 95% CI 0.75 – 1.17) and likewise the changes in the daily SpO_2 after discontinuation of supplemental oxygen ($p = 0.46$)

Conclusion: Adding Favipiravir to the treatment protocol did not reduce the number of ICU admissions or intubations or In-hospital mortality compared to Lopinavir/Ritonavir regimen. It also did not shorten time to clinical recovery and length of hospital stay.

1. Introduction

In the SARS-CoV-2 pandemic, the search for effective antiviral therapy resulted in trying existing antiviral drugs used previously for the treatment of many RNA virus-mediated diseases such as SARS, MERS, AIDS, and Ebola [1–3].

Favipiravir (Avigan) chemically known as 6-fluoro-3-hydroxy-2-pyrazine carboxamide utilized in Japan for the treatment of influenza in 2002 [4], has been used for the treatment of SARS-CoV-2. It selectively inhibits RNA polymerase activity of viruses by binding to RNA-dependent RNA polymerase (RdRp) [5–6]. It has been recognized as a safe and effective drug treatment for influenza and Ebola [7–8] and has been suggested frequently as a treatment modality for SARS-CoV-2 patients [1–2,6–7,9–12]

We therefore explored the safety and efficacy of a treatment protocol containing this drug in moderate to severe cases of SARS-CoV-2 compared to an alternative regimen containing Lopinavir/Ritonavir in a multicenter, randomized, open-labeled study.

2. Methods

2.1. Patients

Patients with the diagnosis of SARS-CoV-2 based on either a positive real-time polymerase chain reaction (RT-PCR) test or typical ground glass appearance on chest CT scan in need of hospital admission due to a SpO_2 reduction of 93% or less were eligible to enter this study. The age of the patients was between 16 and 100 years old from whom an informed and written consent was obtained. Exclusion criteria comprised a history of receiving any antiviral drug such as Ribavirin, Oseltamivir, and Lopinavir/Ritonavir for current illness; a history of chronic renal or liver failure, or gastrointestinal bleeding; being too ill with less than 48 h life expectancy. Also, pregnancy and lactation; known patient of HIV infection/AIDS; and QT interval above 500 ms in Electrocardiogram were excluded.

2.2. Intervention

We compared a treatment protocol that consisted of Favipiravir (made by ZHEJIANG HISUN PHARMACEUTICAL Co., LTD.) and hydroxychloroquine, with Lopinavir/Ritonavir and hydroxychloroquine. At the time hydroxychloroquine was regarded as the standard of care in Iran and skipping it in the treatment protocol was considered unethical. The intervention group received Favipiravir 1600 mg stat and then 600 mg every 8 h plus hydroxychloroquine 200 mg twice a day for 1 week. The control group received a single dose of hydroxychloroquine 400 mg followed by 100 + 400 Lopinavir/Ritonavir twice a day for 1 week. Based on concerns regarding the effect of combination therapy of hydroxychloroquine and Lopinavir/Ritonavir on QT interval, the control group received a single dose of hydroxychloroquine on admission. Later on, during the trial (31 May 2020), in light of emerging evidence, daily hydroxychloroquine in the Favipiravir group was also reduced to a single dose of 400 mg for both treatment and control groups. Both treatment regimens could be continued up to 10 days if needed and physicians could use identical protocols to prescribe other necessary drugs especially for patients in perilous conditions.

2.3. Trial design

We did a multicenter randomized open-labeled clinical trial in 20 centers. Study groups were concurrently registered and patients were randomly allocated into both intervention and control groups. Recruitment started on the first of April and ended on the 3rd of August 2020. (Details of study centers are available in the Iranian Registry of Clinical Trial).

2.4. Randomization

We used stratified block randomization with variable block size of 4 and 6 to create the random sequence for each center, having an equal ratio of distribution of the subjects to both treatment and control groups. A 4-digit special code was allocated to every patient to preserve their identity, and was used to recognize the subjects on the filled CRF forms. Sealed envelopes were used to protect the randomization sequence. We used a central allocation mechanism in which participating centers called a central randomization unit, and registered their eligible patients to receive the 4-digit unique code for assigned group identification.

2.5. Conduct and monitoring

The trial protocol was endorsed by the research committees of the two main universities cooperating in this study. Ethical approval was received from Independent Ethics Committees of the two leading universities (References: IR.IUMS.REC.1399.065 and IR.BMSU.REC.1399.017). Participating centers were approached and invited through national professional bodies and by the chief investigator. Initiation and progress of the study at each participating center were monitored via on-site visits by monitoring teams, including remote central monitoring using specifically designed software intended for this. Discrepancies and errors were detected, recorded, and reported back to the clinical unit for amendments. A five-member Data and Safety Monitoring Board was set up to scrutinize the reported adverse events.

2.6. Outcome definition and measurement

The primary endpoint was the number of admissions to the intensive care unit. We also considered the intubation of patients. Subsidiary endpoints were duration in hospital, In-hospital mortality, time to clinical recovery, and changes in SpO_2 after five minutes interval of supplemental discontinuation of the supplemental oxygen for 5 min. Length of hospital stay was defined as the number of days between admissions and discharge on the physician's advice. Clinical recovery (as an event) was defined as the persistent return of oxygen saturation on ambient air to above 93%, and/or absence of supplemental oxygen requirement and/or medical discharge. This depended on whichever occurred earlier. Treatment side effects were also assessed daily. (Supplemental document-Study protocol)

2.7. Safety and efficacy population

Patients who had been randomly allocated to the Favipiravir and Lopinavir/Ritonavir groups comprised our "intention to treat" (ITT) population. We could not gather any information from the participating centers for 7 patients and therefore did not include them in the modified ITT population. The per-protocol population was defined as those patients who had received their 7 days treatment regimens. Efficacy outcomes were assessed in both modified ITT and per-protocol populations. The safety population was defined as those in the study who had received at least one dose of Favipiravir or Lopinavir/Ritonavir which corresponded to the modified ITT population.

2.8. Data management

A software was developed to manage data collection and transfer. Both the software and paper CRF forms were identical. Clinical units had a local client of the software and locally stored their data. Data were then transferred at will to the main server and stored in a central database as the latest version. An application was also developed to show all the contents of CRF forms in the central database used for remote monitoring.

2.9. Sample size

We calculated our sample size to have 80% power to detect a reduction from 20% to 10% in ICU admissions.

2.10. Statistical analysis

We used Chi-squared to compare proportions of death, ICU admission, and intubation between the two groups. Length of stay in hospital was compared by Man Whitney *U* test. Time to clinical recovery between the two groups was compared using Survival analysis. Cox proportional hazard model was used to estimate hazard ratios and their 95% confidence intervals. Proportional hazard assumption was checked for each model using proportional hazard and Log minus log survival plots including formal testing. Changes (from admission) in SpO_2 after discontinuation of the supplemental oxygen for 5 min were calculated. Their daily values were compared between the treatment groups using the Generalized Estimation Equation (GEE) method considering the time (days), treatment, and their interaction in the model. It was also examined as a binary outcome at beneath and beyond 93% saturation level employing the logit link function. As a sensitivity analysis, multilevel models were built to examine the possible effects of multiple centers. The possible effect of reduction of hydroxychloroquine treatment dose in Favipiravir group following DSMB decision on all analyses was checked. Stata 11 (STATA Corporation) statistical software was used for the analysis.

3. Results

3.1. Study population and baseline comparison

Between 2/4/2020–3/8/2020, 424 eligible SARS-CoV-2 patients were recruited and randomly allocated to the Favipiravir (216) and Lopinavir/Ritonavir (208) groups in 17 centers. Four centers (44 patients) were omitted from the investigation due to inadequate monitoring reports and data for 7 patients could not be retrieved. The flow of participants is outlined in Fig. 1. The remaining 373 patients were used for analysis as a modified ITT population, of which 300 completed the 7-day therapy (per-protocol population) (Fig. 1). Results presented in this paper are based on the modified ITT population unless otherwise specified. Characteristics of the study participants and their baseline comparison in the two study groups are summarized in Table 1. Table 2 displays the additional drugs received during the study period. Fig. 2.

3.2. Outcomes

3.2.1. Death and intubation

Overall, there were 47 deaths in the modified ITT population, 26 in the Favipiravir group, and 21 in the Lopinavir/Ritonavir group ($P = 0.49$). 56 people were transferred to the intensive care unit of whom 44 were intubated. Their corresponding figures were 31 and 26 in the Favipiravir, and 25 and 21 in the Lopinavir/Ritonavir groups respectively. The difference between these groups was not statistically significant (see Table 3). Table 4.

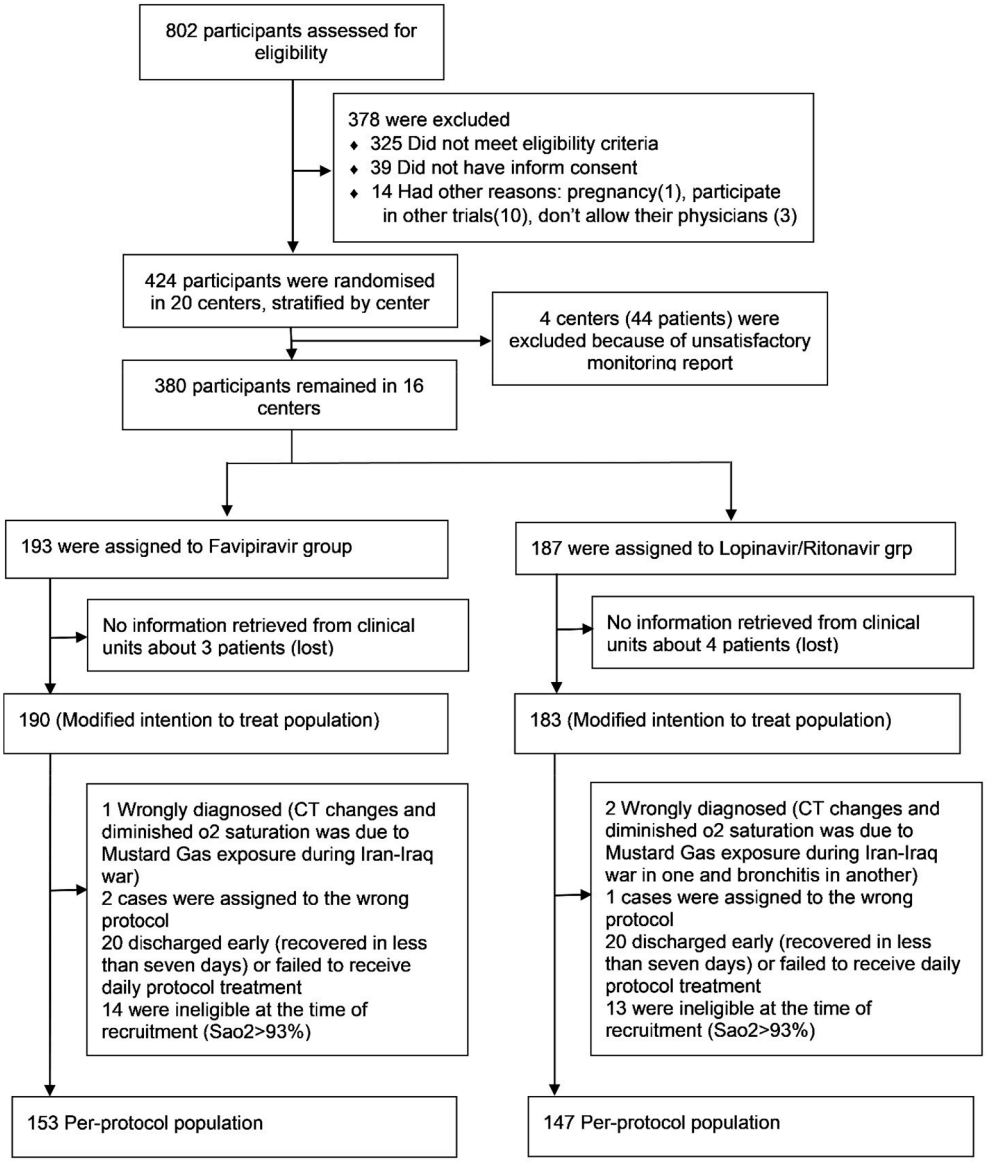

Fig. 1. Participants flow diagram.

3.2.2. Length of stay in hospital

The median length of stay in hospital among those medically discharged (on physician's advice) in the modified ITT population was 7 days (IQR = 4–9) in the Favipiravir, and 6 days (IQR = 4–10) in the Lopinavir/Ritonavir groups (Mann Whitney *U* test, p = 0.85) (see Table 3).

3.2.3. Clinical recovery

Median survival time to clinical recovery was 6 days (IQR = 4–10) in the Favipiravir group and 6 days (IQR = 4–10) in the Lopinavir/Ritonavir group. Also, the difference in the clinical recovery experience was not statistically significant (Log-Rank test: $\chi 2 = 0.38$; p = 0.53) (see Table 3). The hazard ratio for clinical recovery in Favipiravir versus Lopinavir/Ritonavir group was 0.94 (95% CI: 0.75–1.17) using Cox proportional hazard modeling. There were no serious violations of the proportional hazard assumption in all models used.

3.2.4. SpO_2 change over-hospitalization

The results from the GEE model showed that the changes in daily SpO_2 after 5 min discontinuation of supplemental oxygen at the beginning of admission in un-intubated patients had no significant difference between the two study groups during hospitalization (p = 0.46). SpO_2 was also assessed as a binary outcome at beneath and beyond 93% saturation level. SpO2 in patients receiving Favipiravir treatment regimen was equally likely to have a remittance beyond 93% compared with the Lopinavir/Ritonavir treatment group after considering SpO_2 on admission (odds ratio = 1.00 95% CI 0.71–1.42; p = 0.997). Multilevel modeling had no effect the results.

3.2.5. Adverse events

Observed adverse drug reactions have been summarized in Table 5. Overall, more adverse effects were associated with Lopinavir/Ritonavir treatment regimen than with the Favipiravir regimen. Specifically, the adverse effects significantly observed in the Lopinavir/Ritonavir treatment regimen were gastrointestinal, allergic, and respiratory (see Table 5). Reduction of hydroxychloroquine treatment dose in Favipiravir group following DSMB decision did not affect the results.

3.2.6. Discussion

In our observation, the Favipiravir therapy had no influence on ICU admission in comparison with Lopinavir/Ritonavir (31 admissions to ICU versus 25). It also did not reduce the need for intubations (27

Table 1
Participants characteristics and baseline comparison in the modified ITT population by treatment regimens.

	Favipiravir (N = 190)	Lopinavir/ Ritonavir (N = 183)	Total (N = 373)
Age - mean (SD)*	58.6 (17.5)	56.6 (17.1)	57.6 (17.3)
Sex (Male) - no. (%)	115 (60.5)	90 (49.2)	205 (55.0)
BMI - mean (SD)	27.2 (4.8)	27.7 (4.5)	27.4 (4.6)
Education - no. (%)			
Elementary	110 (57.9)	107 (58.5)	217 (58.2)
Diploma	39 (20.5)	36 (19.7)	75 (20.1)
Bachelor	33 (17.4)	26 (14.2)	59 (15.8)
Master	3 (1.6)	5 (2.7)	8 (2.1)
Doctoral and above	5 (2.7)	9 (4.9)	14 (3.8)
Comorbidities - no. (%)			
Hypertension	64 (33.7)	66 (36.1)	130 (34.9)
Diabetes	57 (30.0)	39 (21.3)	96 (25.7)
Chronic heart disease	19 (10.0)	21 (11.5)	40 (10.7)
Chronic lung disease, not asthma	6 (3.2)	7 (3.8)	13 (3.5)
Asthma	7 (3.7)	7 (3.8)	14 (3.8)
Mild liver disease	1 (0.5)	4 (2.2)	5 (1.3)
Kidney disease	3 (1.6)	3 (1.6)	6 (1.6)
Rheumatologic disease	2 (1.1)	4 (2.2)	6 (1.6)
Chronic neurologic disease	6 (3.2)	9 (4.9)	15 (4.0)
Vital signs on admission - no. (%)			
Fever °C - mean (SD)	37.2 (0.7)	37.2 (0.8)	37.2 (0.8)
Heart rate - mean (SD)	90.7 (14.5)	92.0 (14.4)	91.3 (14.4)
Respiratory rate - median (IQR)	20 (8)	22 (8)	21 (8)
SpO_2 % - median (IQR)	89 (5)	89 (7)	89 (6)
Systolic BP mmHg - mean (SD)	122.8 (16.6)	124.6 (14.8)	123.7 (15.8)
Diastolic BP mmHg - mean (SD)	77.3 (10.1)	78.1 (9.8)	77.7 (9.9)
Symptoms - no. (%)			
Respiratory distress	35 (18.9)	40 (22.6)	75 (20.7)
Chill	17 (9.2)	15 (8.5)	32 (8.8)
Cough	52 (28.1)	48 (27.1)	100 (27.6)
Dyspnea	19 (10.3)	24 (13.6)	43 (11.9)
Chest pain	127 (68.7)	133 (75.1)	260 (71.8)
Anorexia	47 (25.4)	47 (26.6)	94 (26.0)
Diarrhea	131 (70.8)	123 (69.5)	254 (70.2)
Vomiting	60 (32.4)	66 (37.3)	126 (34.8)
Abdominal pain	42 (22.7)	58 (32.7)	100 (27.6)
Sore throat	32 (17.3)	35 (19.8)	67 (18.5)
Myalgia	98 (53.0)	88 (49.7)	186 (51.4)
Arthralgia	101 (54.6)	115 (65.0)	216 (59.7)
Fatigue	24 (13.0)	31 (17.5)	55 (15.2)
Headache	41 (22.2)	44 (24.9)	85 (23.5)
Lung CT scan findings – no. (%)			
Ground-glass pattern	163 (85.8)	153 (83.6)	316 (84.7)
Consolidation	29 (15.3)	37 (20.2)	66 (17.7)
Bilateral lesions	172 (90.5)	160 (87.4)	332 (89.0)
Multi-lobar lesions	173 (91.0)	160 (87.4)	333 (89.3)
Lab assessment – no. (median)(IQR)			
WBC (x1000/μl)	184; 6.9 (5.1–8.9)	169; 6.3 (4.9–9.1)	353; 6.5 (5.0–8.9)
Lymphocyte (x1000/μl)	157; 1.1 (0.9–1.6)	143; 1.2 (0.8–1.7)	300; 1.1 (0.9–1.6)
Neutrophil (x1000/μl)	157; 5.3 (3.6–7.1)	142; 4.8 (3.3–7.1)	299; 4.9 (3.4–7.1)
Platelet (x1000/μl)	180; 195.5 (157.0–251.5)	166; 194.5 (150–240)	346; 195 (153.0–249.0)
Hb (g/dl)	183; 13.2 (12.1–14.1)	166; 13.15 (11.6–14.3)	349; 13.2 (11.9–14.2)
HCT (%)	174; 40.0 (37.3–42.7)	161; 39.2 (35.6–43.0)	335; 39.8 (36.3–42.7)
ALT (iu/l)	137; 27 (18.0–39.0)	132; 27 (18.0–48.0)	269; 27 (18.0–42.0)
AST (iu/l)	137; 33 (25.0–45.0)	131; 36 (26.0–51.0)	268; 34 (25.0–48.0)
Alk-Ph (iu/l)	124; 176 (139.5–212.5)	118; 183 (153.0–244.0)	242; 179.5 (146.0–220.0)
PT (sec.)	133; 13 (12.0–15.0)	136; 13 (12.0–14.8)	269; 13 (12.0–14.8)
PTT (sec.)	136; 34 (30.0–40.0)	135; 34 (30.0–38.0)	271; 34 (30.0–39.0)
INR	135; 1.1 (1.0–1.2)	132; 1.0 (1.0–1.2)	267; 1.06 (1.0–1.2)
BUN (mg/dl)	167; 17 (12.0–26.0)	158; 16 (11.0–24.0)	325; 17 (12.0–25.0)
Cr (mg/dl)	173; 1.1 (0.9–1.3)	165; 1 (0.9–1.2)	338; 1.1 (0.9–1.3)
Uric Acid (mg/dl)	29; 6.2 (4.5–7.7)	35; 6.6 (4.6–10.1)	64; 6.35 (4.6–8.9)
BS (mg/dl)	126; 117.0 (98.0–168.0)	117; 122 (97.0–156.0)	243; 118 (98.0–164.0)
Na (mEq/l)	175; 138 (135.0–140.0)	165; 138 (135.0–140.0)	340; 138 (135.0–140.0)
K (mEq/l)	174; 4.1 (3.8–4.5)	163; 4.1 (3.8–4.4)	337; 4.1 (3.8–4.5)
Ca (mg/dl)	128; 8.7 (8.3–9.1)	124; 9 (8.3–9.4)	252; 8.8 (8.3–9.2)
Mg (mEq/l)	121; 2 (1.9–2.2)	117; 2 (1.9–2.2)	238; 2 (1.9–2.2)
Phosphorus (mg/dl)	102; 3.1 (2.5–3.9)	106; 3.3 (2.4–4.0)	208; 3.2 (2.5–4.0)
CRP (mg/l)	111; 22 (3.4–43.0)	92; 24.5 (4.3–45.5)	203; 23 (4.0–44.0)
ESR (sec.)	135; 40 (27.0–63.0)	123; 46 (25.0–62.0)	258; 45.5 (26.0–62.0)
LDH (iu/l)	120; 551.5 (450.0–714.0)	124; 546.5 (427.5–763)	244; 548.5 (441.0–750.5)

* Mean age was calculated in ITT population

Table 2
Additional treatments used in study groups in modified ITT population.

Additional Treatments received during study	Favipiravir (N = 190)	Lopinavir/ Ritonavir (N = 183)	Total (N = 373)
Oral steroid	8 (4.4)	15 (8.5)	23 (6.4)
Intravenous steroid	41 (22.5)	35 (19.8)	76 (21.2)
Interferon	23 (12.6)	23 (12.9)	46 (12.8)
Remdesivir	2 (1.1)	2 (1.1)	4 (1.1)
Other antivirals	9 (5.0)	1 (0.6)	10 (2.8)
Plasmapheresis	1 (0.5)	4 (2.3)	5 (1.4)
Intravenous Immunoglobulin (IVIG)	2 (1.1)	4 (2.3)	6 (1.7)
NSAID[a]	28 (15.4)	25 (14.1)	53 (14.8)
Oral Antibiotics	76 (40.0)	62 (33.9)	138 (37.0)
IV Antibiotics	99 (53.5)	112 (58.1)	211 (58.1)
Oral Anticoagulant	15 (8.1)	18 (10.1)	33 (9.1)
IV Anticoagulant	139 (75.1)	128 (71.9)	267 (73.6)
Proton Pump Inhibitors	129 (69.7)	114 (64.0)	243 (6.9)
ACEI/ARB[b]	26 (14.0)	23 (12.9)	49 (13.5)
Famotidine	16 (8.6)	21 (11.8)	37 (10.2)
Statins	26 (14.0)	21 (11.8)	47 (13.0)

[a] Nonsteroidal anti-inflammatory drugs;
[b] Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker

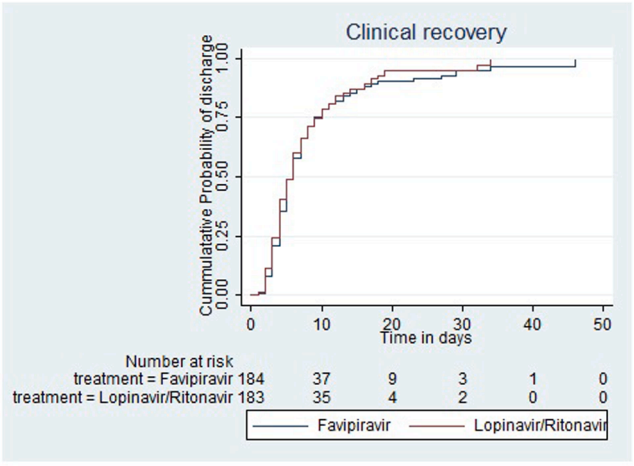

Fig. 2. Kaplan Meier Failure plot showing time to clinical recovery by treatment groups in modified ITT population.

intubations versus 17) or in-hospital mortality (26 deaths versus 21). Length of hospital stay was analogous in the two therapies, respectively 7 and 6 days. The overall clinical recovery of patients receiving Favipiravir was no better than those receiving Lopinavir/Ritonavir regimen (log-rank test: p = 0.53). Besides, the probability of clinical recovery during the study period was not higher in the Favipiravir compared with Lopinavir/Ritonavir group (HR = 0.94; 95% CI: 0.75–1.17). Change in SpO_2 after 5 min discontinuation of supplemental oxygen from SpO_2 on admission also followed similar patterns in the two groups (p = 0.46).

Ethical concerns on treatment efficacy to ensure patients receive the best treatment prevented us from comparing the use of Favipiravir only versus placebo. Hydroxychloroquine and Lopinavir/Ritonavir had been listed as recommended treatment options in Iranian and some foreign guidelines [6,12–15], hence depriving patients of these two treatment modalities was considered unethical at the time. Emerging works of literature [16–18] have raised doubts on the efficacy and safety of these treatments. As a result, we can reasonably claim that the design we used in this study should be capable of showing any potential treatment benefit from Favipiravir if it ever existed. Furthermore, difference in the duration of hydroxychloroquine treatment in early trial (up until 31st of May 2020) in the two regimens due to QT interval prolongation concerns in those who received Lopinavir/Ritonavir [19], is unlikely to change our interpretation of current findings. After that date, DSMB decided to make the doses equal. We also could not avoid using additional treatments and supplements in patients entering our study, particularly when their illness worsened. Instead, we followed equal treatment change rules for all patients regardless of their assigned groups. A comparison of other treatments received by patients is recorded in Table 2. Generally, additional treatment modalities were equally used.

Our centralized allocation system protected the randomization sequence and provided assurances against the introduction of bias, despite the open-labelled design. Patients' national identification and hospital admission reference numbers together with other personal information were registered in the central randomization unit before allocating treatment regimens to the patients. This information was subsequently used in data monitoring. Stratification by center enabled us to exclude data gathered by centers that were regarded as substandard without jeopardizing the random allocation principle.

Patients who received the Favipiravir regimen had poor recovery according to some outcomes. Although this was not statistically significant, it may be an noteworthy. Inferentially, this could result from the compensatory treatment in patients receiving the Lopinavir/Ritonavir treatment regimen, given the open-labelled design. At the time this study was performed, some anecdotal evidence in the social media from clinicians suggested that Favipiravir may be the effective treatment against SARS-CoV-2 disease. This complicated the recruitment process (some patients refused to give consent) and provided additional incentive for extra care by hospital staff in patients not receiving Favipiravir.

One possible explanation for our negative findings regarding the efficacy of Favipiravir in SARS-CoV-2 pneumonia could be the proposed mechanisms for the pathogenicity of this virus. The disease usually has an early infection phase with mild non-specific symptoms, a pulmonary involvement phase with or without hypoxia, and a late phase involving a surge in inflammatory mediators called "cytokine storm" leading to ARDS which is associated with high mortality [20–21]. It seems that those who are hospitalized because of pneumonia and low SpO_2 has already passed the viral replication phase, and therefore are unlikely to benefit from antiviral treatment [21–24]. Accordingly, some studies suggested early prescription of the drug even in the asymptomatic or ambulatory phase of the disease. [25–27]. However, a newly published

Table 4
Hazard ratios and their 95% CI for clinical recovery estimated from Cox proportional Hazard modelling.

	Modified ITT pop		Per protocol pop	
	No. of events	Hazard Ratio (95% CI)	No. of events	Hazard Ratio (95% CI)
Lopinavir/ Ritonavir	152	1.00	124	1.00
Favipiravir Group	156	0.94 (0.75–1.17)	127	0.93 (0.73–1.19)

Table 3
Comparison of the study outcomes in Favipiravir and Lopinavir/Ritonavir treatment regimens.

Modified ITT population				Per-protocol population		
	Favipiravir(N = 190)	Lopinavir/Ritonavir (N = 183)	Total (N = 373)	Favipiravir(N = 153)	Lopinavir/Ritonavir (N = 147)	Total (N = 300)
In-hospital mortality - no. (%)	26 (13.7)	21 (11.5)	47 (12.6) $X^2 = 0.41$; p = 0.52	22 (14.4)	17 (11.6)	39 (13) $X^2 = 0.53$; p = 0.47
Intubation - no. (%)	27 (14.2)	17 (9.3)	44 (11.8) $X^2 = 2.17$; p = 0.14	23 (15.0)	13 (8.8)	36 (12) $X^2 = 2.72$; p = 0.1
ICU admission - no. (%)	31 (16.3)	25 (13.7)	56 (15.0) $X^2 = 0.51$; p = 0.47	26 (17.0)	18 (12.2)	44 (14.7) $X^2 = 1.35$; p = 0.25
Median length of hospital stay - days (IQR)[a]	7 (4–9); n = 153	6 (4–10); n = 150	6 (4–10); n = 303 Mann-Whitney *U* test: p = 0.85	6 (4–9); n = 124	6 (4–9); n = 122	6 (4–9); n = 246 Mann-Whitney *U* test: p = 0.92
Median survival time till clinical recovery - days (IQR[b])	6 (4–10); n = 185	6 (4–10); n = 182	Log-rank $X^2 = 0.38$; p = 0.54	6 (4–9); n = 150	5 (3–9); n = 147	Log-rank $X^2 = 0.38$; p = 0.54

[a] patients discharged against medical advice were excluded
[b] Inter Quartile Range

Table 5
Frequency of Adverse drug effect in Safety population by study groups.

Adverse drug effect	Favipiravir (N = 190)	Lopinavir/ Ritonavir (N = 183)	Total (N = 373)	P-value
Anaphylaxis	1(0.53)	9(4.92)	10(2.68)	0.009
Itching	1(0.53)	4(2.19)	5(1.34)	
Vertigo	0(0.00)	2(1.09)	2(0.54)	
Nausea	0(0.00)	5(2.73)	5(1.34)	
Dyspnea	0(0.00)	3(1.64)	3(0.80)	
Diarrhea	0(0.00)	3(1.64)	3(0.80)	
Abdominal pain	0(0.00)	1(0.55)	1(0.27)	
Gastrointestinal	29(15.26)	54(29.51)	83 (22.25)	0.001
Anorexia	6(3.16)	18(9.84)	24(6.43)	
Nausea	9(4.74)	24(13.11)	33(8.85)	
Vomiting	0(0.00)	6(3.28)	6(1.61)	
Diarrhea	5(2.63)	19(10.38)	24(6.43)	
Abdominal pain	5(2.63)	10(5.46)	15(4.02)	
Dry mouth	9(4.74)	16(8.74)	25(6.70)	
Neurologic	15(7.89)	22(12.02)	37(9.92)	0.2
Fatigue	5(2.63)	10(5.46)	15(4.02)	
Headache	4(2.11)	8(4.37)	12(3.22)	
Lethargy	5(2.63)	11(6.01)	16(4.29)	
Loss of balance	2(1.05)	4(2.19)	6(1.61)	
Low mood	2(1.05)	1(0.55)	3(0.80)	
Paresthesia	1(0.53)	3(1.64)	4(1.07)	
Non-specific pain	0 (0)	2 (2.56)	2 (1.25)	
Stupor	1(0.53)	1(0.55)	2(0.54)	
Ophthalmologic	1(0.53)	4(2.19)	5(1.34)	0.17
Blurred vision	0(0.00)	2(1.09)	2(0.54)	
Lacrimal gland dysfunction	1(0.53)	2(1.09)	3(0.80)	
Endocrine	1(0.53)	2(1.09)	3(0.80)	0.55
Hypothyroidism	1(0.53)	0(0.00)	1(0.27)	
Cardiac	6(3.16)	8(4.37)	14(3.75)	0.55
Cardiomyopathy	3(1.58)	2(1.09)	5(1.34)	
Arrhythmia	1(0.53)	1(0.55)	2(0.54)	
Respiratory	4(2.11)	12(6.56)	16(4.29)	0.04
Dyspnea	3(1.58)	10(5.46)	13(3.49)	
Cough	2(1.05)	9(4.92)	11(2.95)	
Pharyngitis	1(0.53)	0(0.00)	1(0.27)	
Dermatologic	2(1.05)	3(1.64)	5(1.34)	0.63
Skin rash	0(0.00)	2(1.09)	2(0.54)	
Hair loss	1(0.53)	1(0.55)	2(0.54)	
Nephrologic	5(2.63)	3(1.64)	8(2.14)	0.609
Polyuria	2(1.05)	1(0.55)	3(0.80)	
Hematuria	0(0.00)	1(0.55)	1(0.27)	
BUN rises	2(1.05)	0(0.00)	2(0.54)	
Creatinine rise	2(1.05)	0(0.00)	2(0.54)	
Hematologic	1(0.53)	1(0.55)	2(0.54)	0.5
Anemia	1(0.53)	1(0.55)	2(0.54)	

open-labelled randomized trial did not find any benefit from the early prescription of the drug compared with the late prescription, in patients with mild to moderate SARS-CoV-2 [28].

Our patients also included many with moderate cases and the absence of any evidence of rapid clinical recovery in the Favipiravir group may suggest that the severity of the disease is independent of viral replication, even if the findings of reduction in viral load by Favipiravir treatment are true [25,29–30]. This explanation is in line with the existing evidence showing that these patients benefited from the suppression of their exaggerated immune response by steroids [31] rather than by any antiviral treatment.

Our study has the strength of exploring hard outcomes such as mortality, ICU admission, and intubation that are less prone to differences in definitions and interpretation. In summary, we found no clinical benefit from a treatment regimen based on Favipiravir in moderate to severe cases of SARS-CoV-2 over a treatment regimen based on Lopinavir/Ritonavir.

Authors' contributionsRole of the funding source

All authors drafted and drafted the manuscript, revised the manuscript, supervised the treatment and the and wrote the manuscript; and all authors approved the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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