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RESEARCH ARTICLE

Combination Therapy with Favipiravir for Treatment of Hospitalized COVID-19 Adults

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Abstract:

Background:

The optimal treatment for coronavirus disease 2019 (COVID-19) remains unclear. Favipiravir, an RNA polymerase inhibitor, has been used for COVID-19 but its clinical role and safety have not been established.

Methods:

We evaluated the outcomes of hospitalized adults with COVID-19 on favipiravir as part of combination therapy between March 1 and June 1, 2020. Favipiravir was given at a loading dose of 1600 mg orally every 12 hours for 2 doses, followed by a maintenance dose of 600 mg orally every eight hours. We performed a retrospective assessment of virologic clearance, improvement in oxygenation, clinical improvement and possible adverse effects.

Results:

One hundred and nine patients received favipiravir for a mean duration of 5.32 days. Mean time from symptom onset to initiation of favipiravir (day 0) was 4.89 days. Quick Sequential Organ Failure Assessment score was <2 in 83 patients (76.1%), and 17 patients (15.6%) were on invasive mechanical ventilation at day 0. All patients received at least one additional antiviral, 50 patients (45.9%) received tocilizumab and 14 patients (12.8%) received convalescent plasma. Mean clinical and oxygenation improvement at day 28 were 79.8% and 81.6%, respectively, including 10/17 patients (58.8%) who were extubated. There was no statistically significant difference in mean viral RNA clearance time between patients that received >7 days and those receiving <7 days of favipiravir. Mortality was 9.2%. Main adverse events leading to early favipiravir discontinuation were QTc interval prolongation (11%) and hypertriglyceridemia (8.3%).

Conclusion:

Early use of favipiravir as part of combination therapy was associated with improved outcomes, a low mortality rate and a high rate of clinical and oxygenation improvement in patients with mild, moderate, and severe COVID-19. There was no impact on virologic clearance. No severe adverse effects were recorded. The effect of favipiravir as monotherapy and as part of early combination therapy need to be elucidated further in randomized clinical trials.

Keywords: Favipiravir, COVID-19, SARS-CoV-2, Antivirals, RNA, Mortality.

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1. INTRODUCTION

A novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in December 2019 as the cause of a respiratory illness designated coronavirus disease 2019, or COVID-19 and spread rapidly across the globe [1]. As of February 27, 2021, this pandemic has affected close to 113 million people and caused more than 2,500,000 deaths worldwide [2].

Due to the emergent nature of the situation, clinicians and scientists have repurposed several pharmacologic agents with

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potential antiviral activity against SARS-CoV-2. These agents include remdesivir, lopinavir-ritonavir, hydroxychloroquine, interferon gamma, ribavirin, azithromycin, and the newer antiviral agent, favipiravir [3 - 8].

Inhibition of the SARS-CoV-2 RNA polymerase is presumed to be an important drug target in the management of COVID-19 [3, 4]. Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide), formerly known as T-705, is a prodrug of a purine analogue, favipiravir ribofuranosyl-5′-triphosphate [9]. The active agent inhibits the viral RNA polymerase and is incorporated in the growing RNA strand, acting as a guanine and adenine analogue, halting viral replication. Favipiravir has demonstrated activity against influenza and Ebola viruses and has broad activity against other RNA viruses such as West Nile virus, poliovirus, and norovirus [3]. It was shown to have variable activity against SARS-CoV-2 with EC_{50} (half maximal effective concentration) ranging from 62 to >500 μM/L in Vero E6 cells [5, 10, 11]. There are currently no animal model studies demonstrating the activity of favipiravir against SARS-CoV-2. Favipiravir was developed in Japan and approved for clinical use in the treatment of influenza in 2014 [9]. It has remained largely unknown outside of Asia, where it was intended to combat new and pandemic strains of influenza [12].

The initial reports describing the use of favipiravir in the treatment of COVID-19 came from China [13, 14]. Cai *et al.* in an open-label, controlled study enrolled 80 patients with laboratory-confirmed SARS-CoV-2 infection and mild-moderate COVID-19 within 7 days of symptoms onset [13]. Thirty-five patients who received favipiravir plus interferon (IFN)-α 1b by aerosol inhalation were compared with 45 patients who received lopinavir/ritonavir plus IFN-α 1b by aerosol inhalation. A shorter virologic clearance time was found for the favipiravir arm *versus* the control arm (median (IQR), 4 (2.5-9) days *versus* 11 (8-13) days, $p < 0.001$). The favipiravir arm also showed significant improvement at day 14 post-treatment in chest imaging, compared with the control arm, with an improvement rate of 91.43% *versus* 62.22% (p=0.004).

In a non-peer reviewed, randomized clinical trial by Chen *et al.* [14], 120 patients were assigned to the favipiravir group and compared to 120 patients treated with umifenovir. There was no statistically significant difference in the clinical recovery at day 7 between favipiravir and umifenovir treated patients, 71/116 (61.21%) *vs* 62/120 (51.67%) (p=0.1396), respectively. In the post-hoc analysis, study investigators found that for patients with moderate COVID-19, clinical recovery at day 7, defined as continuous (>72 hours) recovery of body temperature, respiratory rate, oxygen saturation, and cough relief after treatment, was 62/111 (55.86%) in the umifenovir group and 70/98 (71.43%) in the favipiravir group (p=0.0199) (DRR: 0.1557, 95% CI: 0.0271~0.2843).

A randomized, open-label trial from Russia showed that the rate of RNA clearance at day 5 was higher with favipiravir compared with standard of care, which included hydroxychloroquine or chloroquine (clearance rates of 62% *versus* 36%) [15].

Favipiravir shows a promising role in the management of COVID-19 and it was introduced in the COVID-19 treatment guidelines at Cleveland Clinic Abu Dhabi from the early stages of the COVID-19 pandemic in the United Arab Emirates.

In this retrospective, single center study, the largest reported so far, we describe our experience with the use of favipiravir in the management of 109 patients with mild, moderate, and severe COVID-19, focusing on their clinical improvement and safety profile of the drug.

2. METHODS

2.1. Study Design and Patients

This is a single-center, retrospective study that included all hospitalized adult patients with laboratory confirmed SARS-CoV-2 infection by Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) assay and treated with favipiravir from March 1 to June 1, 2020 at Cleveland Clinic Abu Dhabi. Due to the lack of proven therapies for COVID-19, the Department of Infectious Diseases developed treatment guidelines based on available data from biologic plausibility, *in-vitro*, and clinical studies. Favipiravir was recommended as a second line therapy in combination with hydroxychloroquine and/or lopinavir-ritonavir, based on the clinical judgment of the primary physician in conjunction with the infectious diseases consultant. The loading dose given was 1600 mg orally every 12 hours for two doses, followed by a maintenance dose of 600 mg orally every eight hours. Intended course duration was 10-14 days during the early stages of the pandemic and decreased to 7 days for the latest versions of our treatment guidelines (Supplement 1). Tocilizumab was recommended for those patients with worsening oxygenation and presumed evolving Cytokine Release Syndrome (CRS) based on the inclusion criteria provided in the guidelines. In several instances, hydroxychloroquine and antivirals were stopped when tocilizumab was given, as the antiviral was deemed ineffective and unnecessary during the presumed CRS.

Due to local public health regulations, all patients with detected SARS-CoV-2 were hospitalized at the time of diagnosis, regardless of the presence or absence of symptoms, until virologic clearance was achieved. Therefore, patients with clinical improvement and normalization of oxygenation were not discharged from isolation and the hospital until viral RNA clearance was documented.

The study was approved by the Research Ethics Committee of Cleveland Clinic Abu Dhabi.

2.2. Data Collection

A standardized chart review included a collection of baseline demographics, clinical variables at admission, laboratory and imaging data, oxygenation and ventilation parameters, concomitant medications, and duration of Intensive Care Unit (ICU) and hospital admission. Potential adverse events related to favipiravir were recorded for all patients.

2.3. Definitions

Completion of favipiravir course was defined as ≥7 days of therapy. Virologic clearance was defined as two consecutive

negative nasopharyngeal swabs by RT-PCR assay done at least 24-hours apart. Clinical improvement was defined by live discharge from the hospital, a decrease of at least 2 points from baseline on a modified six-category ordinal scale (as recommended by the WHO R&D Blueprint Group) [16], or both of these metrics. Clinical improvement was assessed at days 7, 14, and 28 post-therapy with favipiravir. The modified six-category ordinal scale consisted of the following categories: group 1, not hospitalized; group 2, hospitalized, not requiring supplemental oxygen; group 3, hospitalized, requiring supplemental oxygen; group 4, hospitalized, requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation, or both; group 5, hospitalized, requiring Extracorporeal Membrane Oxygenation (ECMO), Invasive Mechanical Ventilation (IMV), or both; and group 6, death. Oxygenation improvement was defined as any decrease in the modified six-category ordinal scale.

2.4. Statistical Analysis

The analysis sample included all patients who received their first dose of favipiravir between March 1 and June 1, 2020, and for whom clinical data for at least 1 subsequent day were available.

Prior to analysis of endpoints, descriptive statistics were calculated from the sample. Numeric variables were described as the mean (SD) or median (IQR). Categorical variables were described by the number of cases (n (%)). Additionally, the distributions of the ordinal scale categories overtime by baseline scale grouping were also tabulated and graphed.

The differences in group means in terms of interleukin-6 (IL-6) were evaluated utilizing one-way ANOVA. To account for heteroscedasticity here, the square root of IL-6 was used in conjunction with a WELCH ANOVA when estimating the F statistic examining mean differences.

We utilized a series of analyses to examine endpoints/outcomes. Endpoint variables included the six-category ordinal scale, dichotomous indicators of clinical improvement and oxygen/ventilation improvement, as well as days to virologic clearance.

Change in the ordinal scale over four time points (days 0, 7, 14, 28) was analyzed using a mixed-effects ordinal regression model, where time points were nested within patients, and a random patient-level intercept was included to account for the repeated-measures nature of the data. Time trends were modelled using a series of dummy variables (with day 0 as the reference group). Additionally, baseline ordinal scale categories were incorporated into the model as dummy variables. Finally, the baseline scale groups by time interactions were included to assess if trends in changes over time vary as a function of baseline ordinal scale values.

The dichotomous endpoints, clinical improvement and oxygenation improvement from day 0 to day 28, were modelled using logistic regression, where baseline ordinal scale groups and baseline lab values (IL-6, C-reactive protein (CRP), ferritin, and procalcitonin) served as the predictors.

Finally, mean days to virologic clearance was calculated and compared across groups that had full and partial favipiravir courses using a simple independent samples t-test.

An alpha criterion of 0.05 was used to determine statistical significance. Microsoft R Open 3.5.3 was used for all statistical analyses. Base R packages were used to calculate all descriptive statistics and logistic regression models. "Ordinal" package version 2019/12-10 was used to estimate the mixed-effects ordinal regression.

3. RESULTS

One hundred and nine hospitalized patients with COVID-19 received at least one dose of favipiravir during the studied period and as recommended by our treatment guidelines. Table **1** shows baseline demographics and clinical characteristics for our patient cohort. The mean age was 50.7 years (SD 15.7), 61 patients (55.9%) were younger than 50 years of age, 87 were men (79.8%). The most common comorbidities were hypertension and diabetes mellitus and, at the time of admission, the most frequent finding was fever (n=58, 53.2%). The most common laboratory abnormality was an elevated CRP seen in 94 patients (86.2%) and the most frequent blood types were O+ (n=30, 27.5%) and B+ (n=25, 22.9%).

Table 1. Baseline patient characteristics.

Characteristic	**-**
Age, years	50.7 (15.7)
Age category	-
<50 years	61 (55.9%)
50-70 years	32 (29.3%)
≥70 years	16 (14.7%)
Sex	-
Men	87 (79.8%)
Women	22 (20.2%)
Region	-
Indian Subcontinent	45 (41%)
United Arab Emirates	22 (20%)
Other Middle East	13 (12%)
South East Asia	13 (12%)

(Table 1) contd.....

Characteristic	**-**
North Africa	6 (6%)
Americas	4 (4%)
Europe	5 (4%)
China	1 (1%)
Comorbidities	-
Obesity	35 (32%)
Chronic obstructive pulmonary disease	6 (5.5%)
Asthma	14 (12.8%)
Hypertension	50 (45.9%)
Diabetes mellitus	44 (40.4%)
Coronary artery disease	18 (16.5%)
Chronic kidney disease	15 (13.7%)
Cancer	4 (3.6%)
Immunosuppressive treatment	1 (0.9%)
Vital signs on hospital admission	-
Body temperature, °C	37.6 (1.0)
Fever	58 (53.2%)
Heart rate, beats/min	98.2 (19.3)
Tachycardia	47 (43%)
Respiratory rate, breaths/min	23.8 (8.4)
Respiratory rate > 22 breaths/min	51 (46.8%)
SpO2, %	95.3 (5.5)
qSOFA score at initiation of favipiravir	-
0	38 (34.8%)
1	45 (41.3%)
2	16 (14.7%)
3	10 (9.1%)
Laboratory data on hospital admission (normal range)	-
Hemoglobin (13.2-17.3 g/dL)	13.1 (2.6)
Hematocrit (0.39-0.49)	0.39 (0.07)
White cell count (4.5-11.0 $x10^9$ per L)	7.38 (4.17)
Lymphocytes (1.5-4.0 $x10^9$ per L)	1.15 (0.55)
Lymphocytes ≤ 1.0 $x10^9$ per L	50 (45.9%)
Neutrophils (1.8-7.7 $x10^9$ per L)	5.59 (3.74)
Platelet count (140-400 $x10^9$ per L)	220.6 (87.8)
C-reactive protein (<5 mg/L)	95.7 (101.2)
C-reactive protein >5 mg/L	94 (86.2%)
Procalcitonin (<0.05 µg/L)	1.9 (6.9)
Ferritin (36-480 µg/L)	1223 (1305.3)
Lactate dehydrogenase (135-225 IU/L)	322.4 (142.6)
D-dimer (<0.5 µg/mL FEU)	1.5 (1.2)
D-dimer > 3.00 µg/mL	14 (18%)
Alkaline phosphatase (40-129 IU/L)	78.3 (41.3)
Alanine aminotransferase (17-63 IU/L)	38.8 (29.2)
Aspartate aminotransferase (<40 IU/L)	46.1 (30.5)
Total bilirubin (5-21 µmol/L)	10.8 (8.3)
Creatinine (0.67-1.18 mg/dL)	1.15 (0.94)
Urea (7.84-22.7 mg/dL)	18.2 (17.1)
Albumin (3.5-5.0 g/dL)	3.64 (0.64)
Hemoglobin A1C (4.8-5.6%)	8.2 (2.9)
Activated partial thromboplastin time (26.3-40.3 sec)	36.5 (17.2)
International Normalized Ratio (0.8-1.2)	1.2 (0.4)
Interleukin-6 (<7.1 pg/mL)	584.9 (1570.5)
Baseline category 2 on six-category ordinal scale (n=16)	108.9 (205.7)

(Table 1) contd.....

Characteristic	-
Baseline category 3 on six-category ordinal scale (n=32)	505.2 (1448.6)
Baseline category 4 on six-category ordinal scale (n=6)	184.3 (165.2)
Baseline category 5 on six-category ordinal scale (n=15)	1451.9 (2470.3)
Blood type	-
A-	4 (4%)
A+	23 (21%)
AB+	3 (3%)
B+	25 (22.9%)
O-	3 (3%)
O+	30 (27.5%)
None	21 (19%)
Chest radiography or computed tomography scan findings	-
Clear	9 (8%)
Unilateral infiltrates	12 (11%)
Bilateral infiltrates	88 (81%)

Data are n (%) or mean (SD)
qSOFA= Quick Sequential Organ Failure Assessment

Imaging studies showed bilateral pneumonia in 88 patients (80.7%). A calculated quick Sequential Organ Failure Assessment score at the time of starting favipiravir was <2 in 83 patients (76.1%).

The mean favipiravir course duration was 5.32 days (SD 3.15). The average time from symptom onset to initiation of favipiravir was 4.89 days (SD 2.85). Favipiravir course was completed in 39 patients (35.8%) and discontinued earlier in the rest due to various reasons (Fig. **1**), including initiation of tocilizumab and interruption due clinical improvement or discharge from the hospital.

For the 67 patients admitted to the ICU, the mean ICU length of stay was 15.4 days (SD 17.7). The overall mean in-hospital length of stay was 21.0 days (SD 17.4), with an overall in-hospital mortality of 9.2% (n=10) (Table **2**).

Table 2. Clinical course of patients.

Intensive care unit admission	**67 (61.5%)**
Duration of stay, days	-
Intensive care unit	15.44 (17.7)
Overall hospital admission	21 (17.4)
In-hospital mortality	10 (9.2%)
Time from illness onset to use of favipiravir, days	4.89 (2.85)
Course of favipiravir, days	5.32 (3.15)
<7 days	70 (64.2%)
≥7 days	39 (35.8%)
Concomitant antivirals and other COVID-19 treatments	-
Lopinavir-ritonavir	86 (78%)
Hydroxychloroquine	61 (55%)
Darunavir-ritonavir	6 (5.5%)
≥3 antivirals	49 (44.9%)
Peginterferon alfa 2a	8 (7%)
Tocilizumab	50 (45.9%)
Convalescent plasma	14 (12.8%)
Time to virologic clearance, days	-
<7 days of favipiravir (n=55)	12.62 (8.5)
≥7 days of favipiravir (n=35)	15.03 (9.2)
Adverse events	-
QTc prolongation	16 (14.6%)
Hypertriglyceridemia	11 (10.1%)
Liver enzyme elevation	7 (6.4%)
Leukopenia	2 (1.8%)

The most used pharmacologic combination for COVID-19 treatment was favipiravir and lopinavir-ritonavir in 86 patients (78%) (Table **2**) with a mean duration of lopinavir-ritonavir therapy of 5.59 days (SD 3.3). Sixty-one patients (55%) concomitantly received hydroxychloroquine for an average of 4.6 days (SD 3.5). Combination therapy with more than two of these drugs was used for 49 patients (44.9%). Additionally, 50 patients (45.9%) received tocilizumab and 14 patients (12.8%) were given convalescent plasma.

Figs. (**2** and **3**) show the distribution of patients in the different categories of the ordinal scale at days 7, 14, and 28. Eighty-seven patients (79.8%) showed improvement in the modified ordinal scale, while 89 patients (81.6%) showed improvement in oxygen support at day 28, including 10/17 patients (58.8%) who were extubated. Clinical and oxygenation improvement at day 14 and 28 (Fig. **2** and Table **3**) were greatest for patients on categories 2-4 in whom favipiravir was given when they were not on IMV (*i.e.* on ambient air, low and high flow oxygen, or non-invasive ventilatory support). This is in contrast to clinical improvement (p=0.003) and oxygenation improvement (p=0.01) that were significantly lower for category 5 patients (those on IMV or ECMO) (Table **4**). For categories 2-4, CRP levels correlated inversely with clinical improvement (p<0.04) and oxygenation improvement (p<0.01). Procalcitonin levels were strongly positively related to clinical improvement (OR=343.8) and oxygenation improvement (OR=2144.8), although they did not reach statistical significance (p<0.11 and p<0.07, respectively). In multivariate analysis, IL-6, ferritin, and completion of a full course of favipiravir were not significant predictors of clinical improvement (p=0.29, p=0.65, and p=0.90, respectively) or oxygenation improvement (p=0.28, p=0.59, and p=0.69, respectively).

Virologic clearance time was absent for 19 patients that were transferred out to continue management at an alternative facility. Thirty-five patients had a complete favipiravir course and had a mean viral RNA clearance time of 15.03 days (SD 9.2) which did not differ statistically from the group that received <7 days of therapy (n=55) and for whom the mean virologic clearance was 12.62 days (SD 8.5) (p of difference=0.21).

Observed adverse events are detailed in Table **2** and Fig. (**1**). These led to discontinuation of favipiravir before completion of a 7 day course in 25 patients. The most frequent occurrences in all 109 patients were prolongation of the QTc interval (n=16, 14.9%) and hypertriglyceridemia (n=11, 10.1%).

Table 3. Patient outcomes: clinical improvement, oxygen improvement and ordinal scale categories.

-	Day 7	Day 14	Day 28
Clinical Improvement	13 (11.9%)	55 (50.5%)	87 (79.8%)
Oxygenation Improvement	27 (24.7%)	67 (61.4%)	89 (81.6%)
Score on modified six-category ordinal scale		-	-
1: discharge (alive)	12 (11%)	45 (41%)	81 (74.3%)
2: hospitalized, not requiring supplemental oxygen	34 (31%)	28 (25.6%)	8 (7.3%)
3: hospitalized, requiring supplemental oxygen	27 (24.7%)	15 (13.8%)	3 (2.8%)
4: hospitalized, requiring nasal high-flow oxygen therapy or noninvasive mechanical ventilation	12 (11%)	1 (0.9%)	1 (0.9%)
5: hospitalized, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation	22 (20%)	17 (15.5%)	8 (7.3%)
6: death	2 (1.8%)	3 (2.8%)	8 (7.3%)

Data are n (%). Clinical improvement (the event) was defined as a decline of two categories on the modified six-category ordinal scale of clinical status, or hospital discharge. Oxygenation improvement was defined as any decrease in the modified six-category ordinal scale.

Table 4. Patient outcomes: Day 0 *vs* Day 28 comparison for clinical and oxygenation improvement.

-		Clinical Improvement (Day 0 *vs* Day 28)		Oxygen Improvement (Day 0 *vs* Day 28)	
Score on modified six-category ordinal scale at Day 0	**Total (n=109)**	**Clinical improvement**	**p (relative to category 2)**	**Oxygen improvement**	**p (relative to category 2)**
2: hospitalized, not requiring supplemental oxygen	41(37.6%)	37 (90.2%)	---	37 (90.2%)	---
3: hospitalized, requiring supplemental oxygen	40 (36.7%)	32 (80%)	0.203	32 (80%)	0.203
4: hospitalized, requiring nasal high-flow oxygen therapy or noninvasive mechanical ventilation	11 (10.1%)	9 (81.8%)	0.445	10 (90.9%)	0.947
5: hospitalized, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation	17 (15.6%)	9 (52.9%)	0.003	10 (58.8%)	0.01

Data are n (%). Clinical improvement (the event) was defined as a decline of two categories on the modified six-category ordinal scale of clinical status, or hospital discharge. Oxygenation improvement was defined as any decrease in the modified six-category ordinal scale.

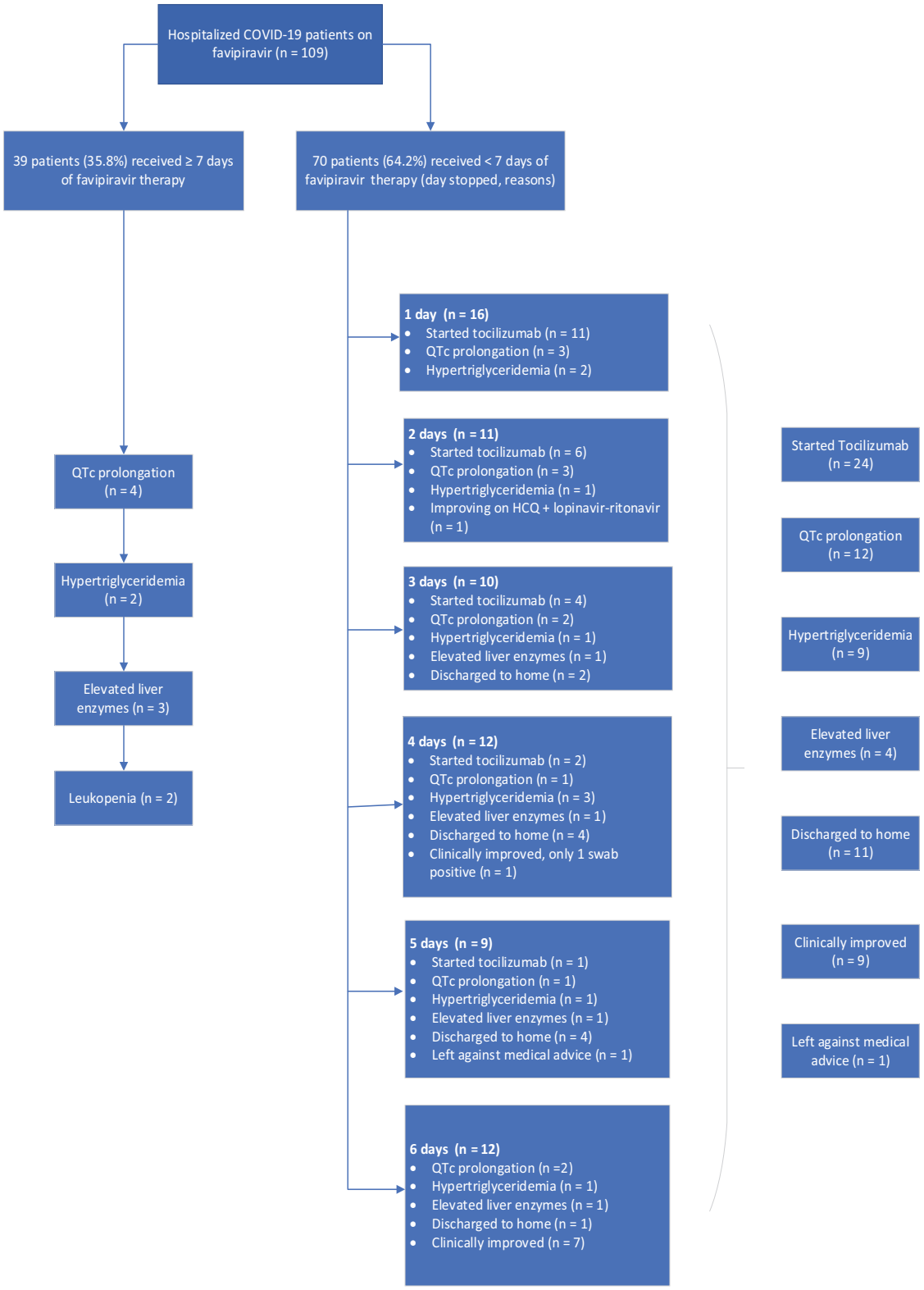

Fig. (1). Favipiravir therapy duration and reasons for early discontinuation.
HCQ= Hydroxychloroquine.

Fig. (2). Distribution of ordinal scale by baseline scale value over time.
The x-axis is the ordinal scale. The y-axis is the percentage of patients (from the base-line scale grouping) that fall into a given ordinal scale value at a given point in time. By looking at this graphic, for each baseline scale group, you can see how the distributions shift left towards better outcomes overtime.

		Invasive (n=17)	High-flow nasal cannula or non-invasive (n=11)	Low – flow oxygen (n=40)	Ambient air (n=41)
	Category on ordinal scale →	5	4	3	2
No. of patients in oxygen-support group at day 28 (%)	Death	6	2 (11·8)	0 (0)	5 (12·5)	1 (2·4)
	Invasive	5	5 (29·4)	1 (9·1)	2 (5)	0 (0)
	High-flow nasal cannula or non-invasive	4	1 (5·9)	0 (0)	0 (0)	0 (0)
	Low-flow	3	1 (5·9)	1 (9·1)	1 (2·5)	0 (0)
	Ambient air	2	3 (17·6)	2 (18·2)	0 (0)	3 (7·3)
	Discharged	1	5 (29·4)	7 (63·6)	32 (80)	37 (90·2)
	Improvement		10 (58·8)	10 (90·9)	32 (80)	37 (90·2)
			Category on ordinal scale ↑			

Fig. (3). Oxygen support status at baseline and after treatment.
For each oxygen-support category, percentages were calculated with the number of patients at baseline as the denominator. Improvement (blue cells), no change (light grey) and worsening (grey cells) in oxygen-support status are shown. Invasive ventilation includes invasive mechanical ventilation or extracorporeal membrane oxygenation. Noninvasive ventilation includes nasal high-flow oxygen therapy or noninvasive positive pressure ventilation.

4. DISCUSSION

In this retrospective analysis of COVID-19 patients treated with favipiravir, the largest so far, we describe our clinical experience and outcomes on 109 patients. Favipiravir was started early in the course of the infection and the majority of patients had mild or no hypoxia. We found a high cumulative incidence of clinical improvement of 79.8%, oxygenation improvement of 81.6%, including 10 of 17 patients (58.8%) in category 5 who were extubated. As a comparison, this percentage of oxygenation improvement is higher than those reported with remdesivir (68% overall and 56% in category 5) [6] and lopinavir-ritonavir (78.8% *vs* standard of care 70%) [7]. Oxygenation improvement was greater for those patients that were still at the early stages of the infection (categories 2-4) and had not progressed to severe respiratory failure with need for IMV or ECMO (category 5). SARS-CoV-2 viral load is believed to peak at around the time of symptom onset and, therefore, patients may benefit from early antiviral therapy [17]. As shown in Table **1**, patients in category 5 had the highest IL-6 levels (mean 1451.9 pg/mL, SD 2470.3 (F=4.005, p=0.011)) suggesting a later stage an evolving CRS where antiviral therapy is likely to be of minimal benefit. Combination antiviral therapy appears to be more effective in the treatment of hospitalized influenza patients with high viral loads [18, 19], and given the paucity of data for SARS-CoV-2, we utilized a similar approach at our hospital since the beginning of this pandemic. The concomitant use of other medications for COVID-19 treatment did not allow us to evaluate the effect of favipiravir as monotherapy. Several clinical trials have shown, however, that hydroxychloroquine and lopinavir-ritonavir appear to have minimal to no role in the treatment of COVID-19 [7, 20, 21] suggesting that favipiravir use may be partially responsible for our outcomes. Concomitant use of tocilizumab and convalescent plasma was also high in our population, in which 50 patients (46%) received tocilizumab for presumed CRS.

The overall mortality rate for our cohort was 9.2% which is significantly lower than that reported in other studies [22, 23].

As for those who were on IMV or ECMO on day 0, the mortality rate was higher (11.8%) but still much lower than in previous reports [24]. It is possible that our overall favorable outcomes were due to our aggressive and early initiation of treatment with combination therapy including favipiravir for mild-moderate COVID-19 patients, early use of convalescent plasma for deteriorating patients and the addition of tocilizumab for evolving CRS.

The virologic clearance time on those who completed a course of favipiravir did not differ statistically from the group that received <7 days of therapy. However, our RT-PCR assay is qualitative (reported as detected or non-detected) and we did not have access to viral cultures, therefore, we were unable to quantify viral copies or determine the viability of the virus detected. A positive result beyond 8 days may indicate presence of genetic material without viable virus [25, 26].

The optimal dose of favipiravir for treatment of SARS-CoV-2 infection has not been established and its attributable benefits may be further overshadowed by its pharmacokinetics which suggests that current dosing schemes may not be adequate to achieve target EC_{50} levels [27].

Few potential adverse effects were observed in our cohort. All patients with QTc interval prolongation were also receiving hydroxychloroquine and/or lopinavir-ritonavir, both known to prolong the QTc interval. Although this could not be firmly attributed to favipiravir, it has been reported in the literature when high doses were used [28]. Liver enzyme elevation was observed in 7 patients (6.4%). This effect had been reported with favipiravir in the past at a rate of 0.9% to 7.8% [29] and can be explained by the fact that favipiravir undergoes metabolism in the liver, through oxidation, resulting in an inactive metabolite (T-705M1) which is excreted by the kidneys [30]. Hypertriglyceridemia is a known adverse effect of propofol which was being used concomitantly in 7/11 patients (63.6%) who developed it in our cohort. Hyperuricemia has been reported previously but this was not observed in our population [3].

CONCLUSION

In conclusion, we found a high rate of clinical and oxygenation improvement at day 28 with the use of favipiravir even for patients with severe COVID-19 and an overall mortality rate of 9.2%, which is significantly lower than in previous publications. Due to the retrospective, non-randomized nature of our study and the concomitant medications used, we are unable to attribute these results to favipiravir alone. However, it is possible that our favorable outcomes are in fact due to this aggressive therapeutic approach. No severe adverse events or drug reactions were noted. The safety and side effect profile and the adequate dosing scheme for favipiravir will be best assessed in placebo-controlled trials. Favipiravir as monotherapy or as part of combination antiviral therapy may have a promising role in the management of COVID-19, but its clinical efficacy needs to be elucidated further by studying it in randomized clinical trials.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Research Ethics Committee of Cleveland Clinic Abu Dhabi, UAE.

HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patients.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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