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ORIGINAL ARTICLE

Effectiveness and safety of favipiravir compared to supportive care in moderately to critically ill COVID-19 patients: a retrospective study with propensity score matching sensitivity analysis

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ABSTRACT

Introduction: Favipiravir is a repurposed drug to treat coronavirus 2019 (COVID-19). Due to a lack of available real-world data, we assessed its effectiveness and safety in moderately to critically ill COVID-19 patients.

Methods: This retrospective study was conducted in two public/specialty hospitals in Saudi Arabia. We included patients ≥18 years) admitted April–August 2020 with confirmed SARS-CoV-2 diagnosed by real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swab. Patients received either favipiravir (1800 mg or 1600 mg twice daily loading dose, followed by 800 mg or 600 mg twice daily) or supportive-care treatment. Patients were excluded if they were outside the study period, classified as having a mild form of the disease per WHO criteria, or had an incomplete patient file. Kaplan–Meier (KM) models were used to estimate median time to discharge. Discharge ratios, progression to mechanical ventilation, and mortality outcomes were estimated across the severity spectrum using Cox proportional-hazards models. As a sensitivity analysis, we performed propensity score-matching (PSM) analysis.

Results: Overall, median time to discharge was 10 days (95%CI = 9–10) in the favipiravir arm versus 15 days (95%CI = 14–16) in the supportive-care arm. The accelerated discharge benefit was seen across the COVID-19 spectrum of severity. The adjusted discharge ratio was 1.96 (95%CI = 1.56–2.46). Progression to mechanical ventilation was slower with favipiravir (HR_{adj} = 0.10, 95%CI = 0.04–0.29). There was no significant effect on mortality (HR_{adj} = 1.56, 95%CI = 0.73–3.36). There was a statistically non-significant trend toward worse outcomes in the critical category (HR_{adj} = 2.80, 95%CI = 0.99–7.89). Age was an independent risk factor for mortality in mechanically ventilated patients. PSM analyses confirmed these findings.

Conclusion: Favipiravir was associated with clinical benefits, including accelerated discharge rate and less progression to mechanical ventilation; however, no overall mortality benefits were seen across the severity spectrum.

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Favipiravir; effectiveness; retrospective; trial; COVID-19; mortality; discharge; supportive care

Introduction

The coronavirus disease 2019 (COVID-19) pandemic is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which belongs to a large family of single-stranded RNA (+ssRNA) implicated in past epidemics over the past two decades[1]. The clinical presentation caused by COVID-19 is very broad and can vary from mild to critical illness. Common symptoms include fever, cough, shortness of breath, muscle aches, dysgeusia, anosmia, gastrointestinal symptoms, cutaneous manifestation, and headache[2,3].

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The clinical course can be fatal in patients with comorbidities and in elderly populations. In just seven days, patients can deteriorate to acute respiratory distress syndrome (ARDS), sepsis, and/or multiple organ failure[4].

Remdesivir (RDV) was synthesized in 2017 to fight the Ebola outbreak and has shown some *in vivo* and *in vitro* activity against SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV)[5]. The Adaptive COVID-19 Treatment Trial (ACTT-1) study group published a preliminary clinical trial report suggesting several clinical benefits in COVID-19 patients. In this double-blind, randomized, placebo-controlled trial (RCT), intravenous (IV) RDV was shown to reduce time to recovery by 11 days (95% confidence interval [CI], 9–12) compared with 15 days (95%CI, 13–19). In the subgroup analysis, recovery-rate ratio was significant in patients on oxygen therapy at 1.47 (95%CI 1.17–1.84). No effect on mortality (14 or 28 days) was seen, with a hazard ratio of 0.70; 95%CI, 0.47–1.04[6]. The US Food and Drug Administration (FDA) recently approved the use of RDV in COVID-19 patients[7].

Favipiravir (FPV), an RNA-dependent RNA polymerase (RdRP) inhibitor with a broad spectrum of activity, is an oral drug synthesized in 2002 and approved in 2004 to treat influenza in Japan[8]. Proposed dosage, though still being formally investigated for coronaviruses, ranges between 1600 and 2000 mg BID (twice daily) followed by a maintenance dosage 300–1800 mg BID[9]. Data on FPV's efficacy and safety are very limited. A recent open-label RCT by Cai et al. found that a 14-day FPV regimen (dosage 1600 mg BID followed by 600 mg) plus interferon-alfa (aerosol inhalation 5 million units) cleared SARS-CoV-2 infection more rapidly than treatment with lopinavir–ritonavir (400 mg/100 mg) with interferon-alfa combination therapy. This was evidenced by significant improvements in chest imaging compared with the control arm (91.43% versus 62.22%; $p = .004$). In this study, fewer side effects were reported in the FPV arm than in the control arm (11.43% versus 55.56%; $p < .001$)[10]. Another open-label, prospective RCT compared FPV (600 mg) to umifenovir (another anti-influenza treatment approved in Russia and China) and found that the clinical-recovery rate at day 7 did not differ significantly in the two arms ($p = .139$). However, FPV has led to shorter latencies of relief for both pyrexia and cough ($p < .001$)[11].

Regarding safety, a systematic review by Pilkington et al. showed that FPV is well-tolerated except for elevation in uric acid levels. Per the systematic review, teratogenicity and QTc prolongation have not yet been adequately studied[12]. With its recent availability in Saudi Arabia, the Ministry of Health (MOH) included FPV as an option for treating moderate to critically ill COVID-19 patients with the following dosage: 1800 mg BID followed by 800 mg BID[13]. Due to the urgent nature of the pandemic and the relative infeasibility of a prospective RCT in the short term, we designed a retrospective trial to evaluate the effectiveness and safety of FPV in moderate-to-severe/critically ill COVID-19 patients when compared to supportive care.

Methods

Study design and setting

This was a retrospective study conducted in two cluster hospitals in Riyadh: King Fahad Medical City (KFMC; 1200 beds) and Prince Mohammed Bin Abdulaziz Hospital (PMAH; 500 beds), both of which are nationally designated hospitals for COVID-19 and to which complicated patients from all over Saudi Arabia are transferred. The study was approved by the Institutional Review Boards at KFMC and PMAH (IRB 20-477E, July 2020). Informed consent was waived as this was considered an exempt study. In our report, we adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement checklist[14].

Participant selection

A list of deceased or discharged patients who had received FPV or supportive care and had been admitted between April and August 2020 to KFMC or PMAH for COVID-19 management was obtained. Through a random-selection process, we screened patients for eligibility. In random selection, each patient's record has an equal opportunity to be selected for coding to minimize sampling bias[15]. The inclusion criteria were as follows: age $\geq$18 years, having received at least two doses of FPV (1800 mg or 1600 mg BID loading dose, followed by 800 mg or 600 mg BID or supportive care with a confirmed diagnosis of SARS-CoV-2 by real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swab. Patients were excluded if they were outside the study period, classified as having a mild form of the disease per WHO criteria, or had an incomplete patient file.

Data collection

Data were manually extracted from electronic health records (EHRs) from a master list and entered into the Research Electronic Data Capture (REDCap) system in a de-identified manner[16]. Data quality during the collection process was ensured to assess consistency and resolve any discrepancies.

Definitions

Disease severity was defined according to WHO classification, which was adopted by the Saudi MOH protocol[17]. Moderate illness was defined as the development of non-severe pneumonia not requiring supplemental oxygen. Severe illness was defined as fever plus $\geq$1 of the following symptoms: respiratory rate $\geq$30/min, dyspnea, respiratory distress, SpO2: $\leq$93% on room air, PaO_2/FiO_2 ratio $<$300 or lung infiltrate $>$50% of lung field within 24–48 hr. Critical illness was defined by one or more of the following presentations: ARDS, septic shock, altered consciousness, multi-organ failure. The criteria for clinical discharge used in our analyses were those prescribed by protocol by the Saudi MOH for symptomatic and confirmed COVID-19 cases. The initial MOH definition for clinical discharge was that a patient must have passed three days beyond recovery (defined as fever resolution without

antipyretic medications and resolution of respiratory symptoms [cough or shortness of breath]), followed by two negative respiratory samples ≥24 h apart[13]. Later, an updated definition by the WHO (May 2020) was adopted by the Saudi MOH and became the standard protocol[18], in which clinical discharge can be after fever resolution without antipyretic medications and resolution of respiratory symptoms for at least 3 days, in addition to at least 10 days having passed since symptoms first appeared[13,18]. Upon review of the discharge dates for patients in our study, we realized that all patients were discharged after 1 June, and therefore that the updated WHO-based definition applied to all discharges.

Study outcomes

The primary endpoint was the time to discharge, which served as a surrogate for clinical recovery. Other endpoints were mechanical ventilation progression and mortality. For the mortality outcome, patients on mechanical ventilation at baseline were analyzed as a subgroup. Safety endpoints included adverse events as defined by the Common Terminology Criteria for Adverse Events (CTCAE)[19].

Sample size calculation

Assuming that 4% of the subjects in the control group and 3% in the FPV group would experience the outcome of death (based on a relative risk of 0.8 between the supportive group and FPV group) and after applying continuity correction, the study was estimated to require a sample size of 234 for each group (i.e. a total sample size of 468, assuming equal groups) to achieve a power of 80% and a level of significance of 5%. In order to declare the test drug to be superior to the supportive care, a −10% margin of superiority was set (assuming that a smaller proportion is desirable).

Statistical analysis

Using R Core Team (2020) software (R Foundation for Statistical Computing, Version 4.0.1, Vienna, Austria), continuous variables in the baseline characteristics were presented as means with standard deviations (±SD) and medians with interquartile ranges (IQRs). Student's *t*-test or Mann–Whitney U test was used for arm comparison. Categorical data were reported as frequencies and percentages and analyzed using either the Chi-square test for nxm tables or Fisher's exact test for 2 × 2-table group comparisons. For modeling purposes, we quantified the correlation between the WHO severity classification and baseline oxygen therapy using Cramér's *V* test. We performed the survival analysis using the "survival package" in R[20]. We fitted Kaplan–Meier (KM) models to estimate median time to discharge for live patients and each WHO severity category. Death was considered as a competing risk with discharge events, and therefore, we analyzed the outcome on the live-patient dataset. Semi-parametric Cox proportional hazard models were fitted with clinically and statistically significant covariates to obtain hazard ratios. We used a rule of 10 events for each covariate considered in the Cox models. Proportional hazard assumption was checked using Schoenfeld residuals plots, and nonlinearity for continuous variables was checked using the Martingale residual. The possibility of time-varying coefficients was rigorously tested using the "timereg" package[21]. There were few missing data for few pertinent variables such as body mass index (BMI), renal function, Acute Physiology and Chronic Health Evaluation II (APACHE II). We determined that these variables were missing at random (MAR); therefore, we performed multivariate imputation with the chained equations (MICE) technique using the "mice" package that included the Nelson–Aalen estimator for hazards in the imputation model, as recommended by the literature[22,23]. We obtained 50 imputations (5 imputed datasets with 10 iterations) and then pooled estimates across datasets. The subgroup analyses for the primary outcomes were performed on the baseline characteristics. In the case of low events, crude odds ratios were estimated with 0.5 correction in the case of zero events in accordance with Deeks and Higgins's recommendations[24]. All statistical inferences were drawn with 95% confidence intervals with $p < .05$.

Propensity score-matching (PSM) sensitivity analysis

The PSM was conducted as a confirmatory analysis. We used the "MatchThem" package on the imputed datasets (50 imputations, 5 datasets with 10 iterations). The use of this package in R was recently illustrated by Pishgar et al.[25]. The matching-procedure specifications followed the nearest-neighbor matching within datasets approach (using Rubin's rules) and 1:1 ratio with a caliper of 0.1 and no replacement. Adequate propensity scores distribution for the matched datasets was evaluated using the standardized mean difference (SMD)[26]. SMD values <0.1 indicated adequate balance and fruitful matching. We produced love plots for the SMD distribution (Figure S1(A–C) and Table S1 in the supplementary material detailing SMD values for the covariates used) and a mirror-diagram distribution to evaluate propensity scores distribution (Figure S2(A–C)). Cox proportional-hazard models were then fitted to the matched datasets to obtain hazards ratios. The variance was estimated using the "Survey" package[27].

Results

A total of 661 patients were identified and through random selection we screened 480 records of patients admitted to the two hospitals (KFMC and PMAH) between April and August 2020. Reasons for exclusion are illustrated in detail in Figure 1. The FPV arm had 234 patients and the supportive-care arm had 223 patients, the latter slightly below the target but sufficient for adequate statistical power. Table 1 presents baseline characteristics for each arm. There were statistical differences for renal function, hypertension, critical-illness category, non-invasive and invasive oxygen therapy, and several of the medications received during the hospital stay, showing a relative imbalance between both treatment arms. The majority of patients (86.7%) received the 1600 mg

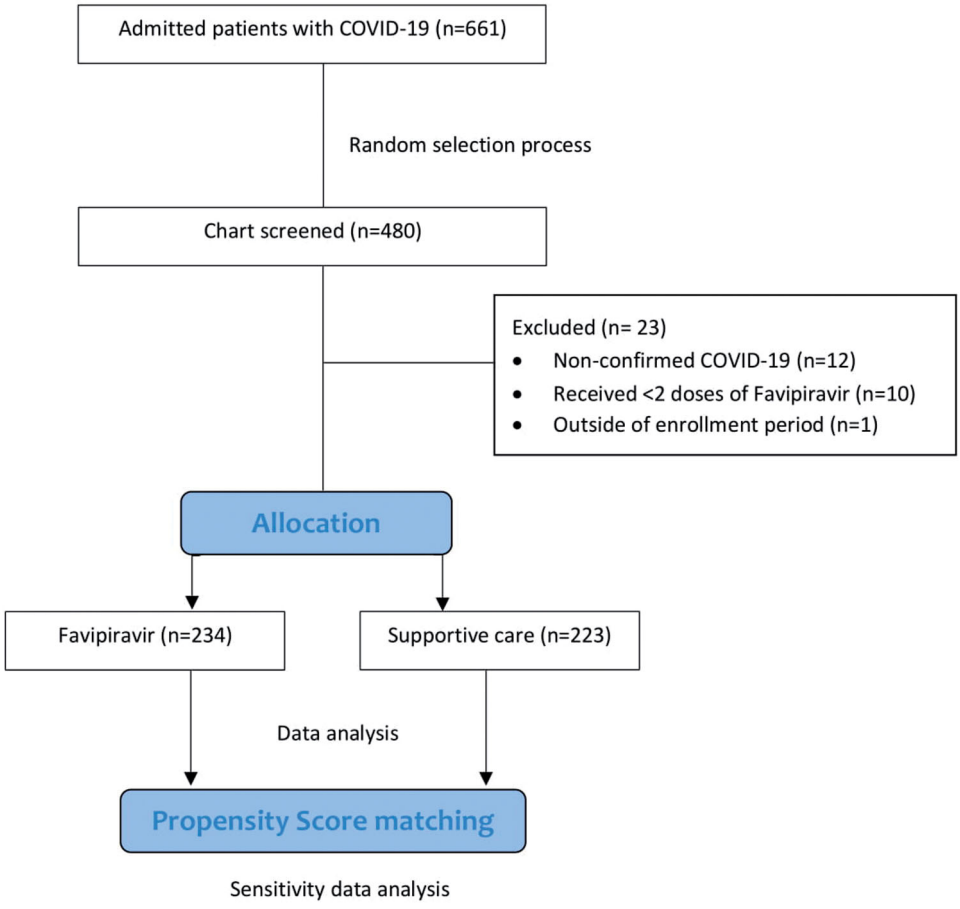

Figure 1. Patients selection flow chart.

BID loading dose with median duration (IQR) of 7 days (6–8 days). The median time (IQR) to start FPV therapy was 2 days (1–3 days) from admission. A moderate association was found between the baseline WHO category and baseline oxygen therapy with a Cramér's V of 0.57.

Clinical outcomes

Live patients on FPV had a median time to discharge of 10 days (95%CI 9–10) compared to 15 days (95%CI 14–16) in the supportive-care arm. The Kaplan–Meier (K–M) curve for discharge events is shown in Figure 2(A). The adjusted discharge ratio was 1.96 (95%CI 1.56–2.46, $p < .001$) favoring the FPV arm. Progression to mechanical ventilation was lower in the FPV arm compared to the supportive-care arm with adjusted HR (HR_{adj}) = 0.10 (95%CI 0.04–0.29, $p < .001$). Clinical outcomes are detailed in Table 2, and Supplemental materials (Figure S3) shows K–M curves for specific categories. FPV was not associated with a decrease in hospital mortality, with adjusted HR_{adj} =1.56 (95%CI 0.73–3.36, $p = .251$). The FPV arm was associated with higher mortality in the critical-illness category, with HR = 2.92 (95%CI 1.04–8.20, $p = .041$); however, when adjusted for age, HR was 2.80 (95%CI 0.99–7.89, $p = .051$). Table 3 shows detailed results for the mortality outcome. The survival K–M curve displayed in Figure 2(B) and Supplemental materials (Figure S4) shows K–M curves for specific categories for mortality outcome.

Subgroup analysis

The subgroup analysis for the discharge outcome (live dataset) (Figure 3) shows greater benefit in male compared to female patients (HR = 1.97, 95%CI 1.51 – 2.56). Fewer Southeast/East Asians were discharged alive compared to other ethnicities (HR = 0.42, 95%CI 0.19 – 0.94). Patients on non-invasive baseline oxygen therapy were more likely to be discharged (HR = 2.45, 95%CI 1.76 – 3.42).

In terms of mortality (Figure 4), patients on mechanical ventilation had a higher risk of death (HR = 4.07, 95%CI 1.32 – 12.56). Considering the baseline characteristics in Supplementary Table S2 and after adjusting for age, APACHE-II score, and BMI, the adjusted HR was statistically non-significant (HR_{adj} = 1.59, 95%CI 0.42–5.95, $p = .487$). Age was an independent risk factor for in-hospital death in the full model (HR = 1.06, 95%CI 1.01–1.12, $p = .013$) (Table S3).

Propensity score-matching

The distribution balance for the covariates is presented in Table S3 in the Supplementary section. Further illustration of the balance of covariates is presented in Figure S1 (Love

Table 1. Baseline characteristics.

Characteristic	Total ($N = 457$)	FPV ($N = 234$)	SC ($N = 223$)	p Value
Age, mean (SD)	51.4 (12.5)	50.3 (12.8)	52.5 (12.1)	.063
Female, *n* (%)	80 (17.5)	40 (17.1)	40 (17.9)	.812
Ethnicity, *n* (%)				.049
Middle Eastern	232 (50.8)	116 (49.6)	116 (52.7)	
East/Southeast Asian	37 (8.1)	24 (10.3)	13 (5.9)	
South Asian	92 (20.1)	39 (16.7)	53 (24.1)	
African	36 (7.9)	17 (7.3)	19 (8.6)	
Unknown/other	60 (13.1)	38 (16.2)	22 (9.9)	
Weight (kg), median (IQR)	78.7 (70.0–92.0)	78.1 (70.0–95.0)	79 (70.0–90.0)	.336
BMI (kg/m^2), median (IQR)	27.5 (24.9–31.8)	27.7 (25.2–33.1)	27.4 (24.6–31.2)	.202
Scr (mg/dl), median (IQR)	0.97 (0.81–1.21)	0.93 (0.78–1.12)	1.00 (0.85–1.30)	<.001
CKD-EPI equation (mL/min/m^2), median (IQR)	87.47 (66.44–100.78)	91.86 (76.19–103.72)	82.86 (61.32–97.56)	<.001
CKD stage				<.001
Normal/Stage1	178 (38.9)	99 (42.4)	79 (35.4)	
Stage 2	133 (29.1)	47 (20.1)	86 (38.6)	
Stage 3A	29 (6.3)	11 (4.7)	18 (8.1)	
Stage 3B	22 (4.8)	8 (3.4)	14 (6.3)	
Stage 4	12 (2.6)	4 (1.7)	8 (3.6)	
Stage 5	17 (3.7)	6 (2.6)	11 (4.9)	
Unknown	66 (14.4)	59 (25.2)	7 (7)	
Respiratory diseases, *n* (%)	38 (8.3)	15 (6.4)	23 (10.3)	.131
Established cardiovascular diseases, *n* (%)	33 (7.2)	13 (5.6)	20 (9)	.159
Atrial fibrillation, *n* (%)	2 (0.4)	0 (0.0)	2 (0.3)	.238
History of VTE, *n* (%)	4 (0.9)	1 (0.4)	3 (1.3)	.292
Type 1 or 2 Diabetes, *n* (%)	217 (47.5)	112 (52.9)	105 (47.1)	.868
Hypertension, *n* (%)	183(40.0)	82 (35.0)	101 (45.3)	.025
Dyslipidemia, *n* (%)	34 (7.4)	18 (7.7)	16 (7.2)	.833
APACHE II score	8.0 (5.0–11.0)	8.0 (5.0–11.0)	9.0 (5.0–12.0)	.691
Severity based on WHO definition, *n* (%)				
Moderate	141(30.9)	72 (30.8)	69 (30.9)	.968
Severe	276 (60.4)	149 (63.7)	127 (57.0)	.149
Critical	40 (8.8)	13 (5.6)	27 (12.1)	.013
Baseline oxygen therapy, *n* (%)				
No oxygen therapy	177 (38.7)	94 (40.2)	83 (37.2)	.517
Non-invasive oxygen therapy	222 (48.6)	133 (56.8)	89 (39.9)	<.001
Mechanical ventilation or ECMO	58 (12.7)	7 (3.0)	51 (22.9)	<.001
Medication use, *n* (%)				
Intravenous steroid	414 (90.6)	223 (95.3)	191 (85.7)	<.001
NSAIDs	30 (6.6)	16 (6.8)	14 (6.3)	.809
Aspirin	43 (9.4)	16 (6.8)	27 (12.1)	.054
Insulin	250 (54.7)	128 (54.7)	122 (54.7)	.999
Statin	78 (17.1)	37 (15.8)	41 (18.4)	.465
ACEI or ARB	107 (23.4)	50 (21.4)	57 (25.6)	.290
Beta blockers	79 (17.2)	26 (11.1)	53 (23.8)	<.001
Calcium channel blockers	113 (24.7)	44 (18.8)	69 (30.9)	.003
LMWH/Heparin	367 (80.3)	182 (77.8)	185 (83.0)	.164
DOAC	10 (2.2)	3 (1.3)	7 (3.1)	.175
Antibiotic use during hospital stay, *n* (%)				
3rd generation cephalosporin	402 (88.0)	216 (92.3)	186 (83.4)	.003
Macrolide	291 (63.8)	152 (64.0)	139 (62.3)	.560
Doxycycline	18 (3.9)	12 (5.1)	6 (2.7)	.181
Vancomycin	74 (16.2)	19 (8.1)	55 (24.7)	<.001
Piperacillin/tazobactam	96 (21.0)	26 (11.1)	70 (31.4)	<.001
Meropenem	68 (14.9)	12 (5.1)	56 (25.1)	<.001
Metronidazole	4 (0.9)	2 (0.9)	2 (0.9)	.956
Other beta lactamase inhibitors	16 (3.5)	12 (5.1)	4 (1.8)	.053
Background COVID-19 therapy, *n* (%)				.621
Supportive care	451 (98.7)	231 (98.7)	220 (99.1)	
Hydroxychloroquine	4 (0.9)	2 (0.9)	2 (0.9)	
Hydroxychloroquine + azithromycin	1 (0.2)	1 (0.4)	0 (0)	

Abbreviations. BMI, body mass index; Scr, serum creatinine; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration. Established cardiovascular disease was defined as a documented history of stable angina, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery, or myocardial infarction (MI). Heart failure and cerebrovascular disease included transient ischemic attack (TIA) or stroke. Respiratory disease: asthma or chronic obstructive pulmonary disease (COPD). VTE, venous thromboembolism; WHO, World Health Organization; ECMO, extracorporeal membrane oxygenation; APACHE II, Acute Physiology and Chronic Health Evaluation II; NSAIDs, nonsteroidal anti-inflammatory drugs; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; LMWH, Low molecular-weight heparin; DOAC, direct oral anticoagulant; COVD-19, coronavirus disease 2019; FPV, favipiravir; SC, supportive care.

plots), and propensity scores distribution is shown in Figure S2 (mirror diagram). As shown in Table 4, PSM matched 221 FPV-treated patients to 194 patients receiving supportive care (live dataset). FPV-treated patients had a greater likelihood of faster discharge (HR = 2.04, 95%CI 1.50–2.76, $p < .001$). Similarly, with 2 FPV-treated patients (1.5%) compared to 14 patients (17.8%) receiving supportive care, progression to mechanical ventilation was lower in the FPV arm (HR = 0.08, 95%CI 0.02–0.32, $p < .001$). In addition, 9 patients (6.1%) in the FPV arm and 7 (4.7%) in the supportive-care

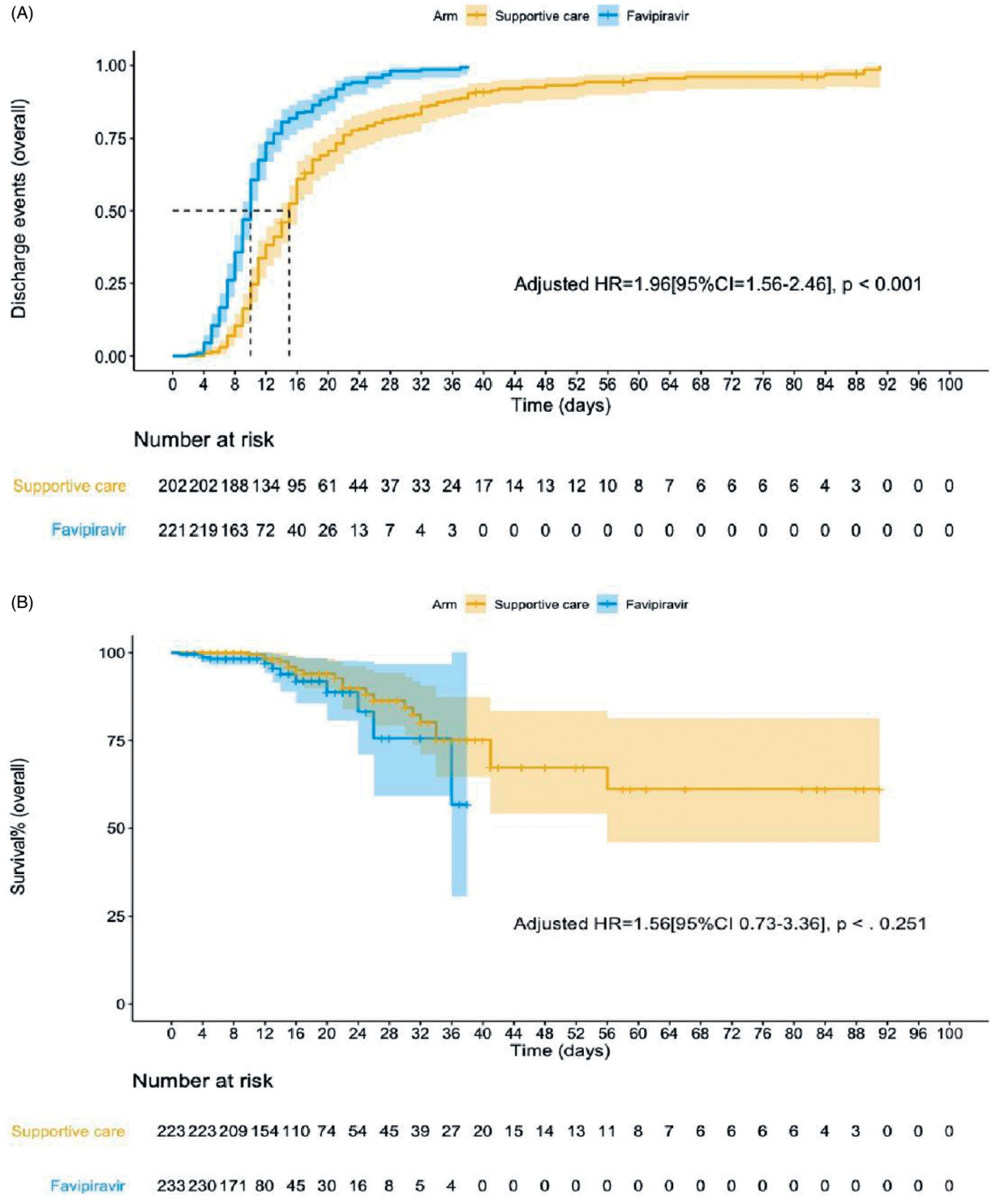

Figure 2. Clinical outcomes: A – Discharge, B – Mortality. Yellow: supportive care. Blue: favipiravir. Shaded area: 95% confidence interval. Dashed line: median time.

arm died, which was statistically non-significant (HR = 2.85, 95%CI 0.92–8.83, $p = .068$). Thus, the PSM analyses confirmed the primary analyses.

Adverse events

There were no statistically significant differences in adverse events between the two study arms, except for hyperuricemia 12 (5.1%) and diarrhea 13 (5.6%) ($p < .001$). See Table 5 for detailed adverse-event results.

Discussion

To date, the US FDA has approved only RDV to treat COVID-19, despite the WHO's large SOLIDARITY clinical trial, which found RDV to be ineffective in reducing hospital mortality

Table 2. Clinical outcomes (discharge, progression to mechanical ventilation) for live patients.

Outcome	Overall		Moderate		Severe		Critical	
Arm	FPV ($N = 221$)	SC ($N = 201$)	FPV ($N = 72$)	Supportive care ($N = 68$)	FPV ($N = 142$)	SC ($N = 114$)	FPV ($N = 7$)	SC ($N = 20$)
Clinical discharge, *n* (%)	221 (100)	194 (96)	72 (100)	67 (98.5)	142 (100)	112 (98.2)	7 (100)	15 (75)
Median time to discharge in days (95% CI)	10 (9–10)	15 (14–16)	9 (9–10)	11 (10–12)	10 (9–11)	16 (15–18)	21 (6–infinity)	32 (18–infinity)
Discharge Ratio (95% CI)[a]	2.32 (1.89–2.84, $p < .001$)		1.65 (1.17–2.31, $p = .004$)		2.51 (1.93–3.27, $p < .001$)		3.01 (1.10–8.62, $p = .031$)	
Adjusted discharge ratio, (95% CI)[b]	1.78 (1.40–2.28, $p < .001$)		1.42 (0.92–2.19, $p = .107$)		2.61 (1.88–3.60, $p < .001$)		3.20 (1.14–8.99, $p = .027$)	
Adjusted discharge ratio (missing data computation), (95% CI)[b]	1.96 (1.56–2.46, $p < .001$)		1.48 (0.97–2.27, $p = .069$)		2.69 (2.00–3.62, $p < .001$)		–	

Outcome	Overall		Moderate		Severe		Critical	
Arm	FPV ($N = 218$)	SC ($N = 165$)	FPV ($N = 72$)	SC ($N = 64$)	FPV ($N = 139$)	SC ($N = 100$)	FPV ($N = 7$)	SC ($N = 7$)
Progression to mechanical ventilation, *n* (%)	4 (1.8)	27 (16.4)	2 (2.8)	6 (9.3)	0 (0)	20 (20)	2 (28.6)	1 (100)
Progression to mechanical ventilation hazard[c]	0.11 (0.04–0.32, $p < .001$)		0.28 (0.05–1.42, $p < .126$)		0.011 (0.0006–0.178, $p = .002$)		0.15 (0.00–5.18, $p = .295$)	
Progression to mechanical ventilation adjusted hazard[c]	0.10 (0.04–0.29, $p < .001$)		–		–		–	

[a]Discharge ratios are analogous for hazard ratios; >1 indicates an association favoring the favipiravir arm; <1 is associated with harm, and 1 has no association. The significance of this association is interpreted by considering the confidence interval. The unadjusted model is a simple Cox model with the arm as a covariate.

[b]Cox proportional hazard model with the following variables: age, sex, BMI (body mass index), ethnicity, baseline oxygen therapy, hypertension, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), diabetes, intravenous steroid, dyslipidemia, established cardiovascular disease, community-acquired pneumonia regimen (azithromycin and ceftriaxone) and angiotensin-converting enzyme inhibitor/receptor blockers (ACEIs/ARBs). In the case of critical cases, due to sample size the adjusted model included only age as a covariate. The missing values were determined to be missing at random (namely CKD-EPI and BMI) and were estimated using a multivariate imputation for the chained equations (MICE) technique that included the Nelson–Aalen estimator for hazards in the imputation model.

[c]In the case of low events in particular categories; crude odds per Deeks and Higgins's recommendations[24]. The adjusted Cox hazard model included age, hypertension, and non-invasive baseline oxygen.

Abbreviations. CI, confidence interval; FPV, favipiravir; SC, supportive care.

Table 3. Mortality outcome.

Outcome	Overall		Moderate		Severe		Critical	
	FPV $N = 233$	SC $N = 223$	FPV $N = 72$	SC $N = 69$	FPV $N = 148$	SC $N = 127$	FPV $N = 13$	SC $N = 27$
Death, *n* (%)	12 (5.2)	21 (9.4)	1 (1.4)	0 (0)	6 (4.1)	13 (10.2)	6 (46.2)	7 (25.9)
Hazard ratio (95% CI)[a]	1.81 (0.85–3.90, $p = .126$)		2.9 (0.11–72.81, $p = .514$)		1.32 (0.46–3.80, $p = .599$)		2.92 (1.04–8.20, $p = .041$)	
Adjusted hazard ratio (95% CI)[b]	1.56 (0.73–3.36, $p = .251$)		–		1.36 (0.47–3.96, $p = .562$)		2.80 (0.99–7.89, $p = .051$)	

[a]Hazard ratios >1 indicate an association of harm in the favipiravir arm; <1 is associated with benefit and 1 has no association. The significance of this association is interpreted by considering the confidence interval. The unadjusted model is a simple Cox model with arm as a covariate. Odds ratios was estimated in the case of low zero events for the moderate category (calculated according to Altman, 1991).
[b]Cox proportional hazard model for baseline oxygen therapy for the overall analysis. For the overall model, we adjusted for age, Acute Physiology and Chronic Health Evaluation (APACHE II) score, and steroid use. The severe category was adjusted for age and APACHE II score only. The critical illness category was adjusted for age only. Age was an independent risk factor for mortality in the overall analysis of severe and critical illness. Missing data computed using the multivariate imputation by chained equations (MICE) technique that included the Nelson–Aalen estimator for hazards in the imputation model. Crude odds ratios were estimated in the case of low zero events for moderate category, per Deeks and Higgins's recommendations[24].
Abbreviations. FPV, favipiravir; SC, supportive care.

and progression to mechanical ventilation[7,28]. Recently, the FDA granted approval for a new monoclonal antibody therapy for COVID-19[29]. Data supporting COVID-19 treatment modalities beyond antivirals, such as tocilizumab and convalescent plasma, remain conflicting[30,31]. However, dexamethasone was found to be associated with lower mortality in specific COVID-19 populations[32]. Novel antiviral drugs with activity against COVID-19 are under investigation, and molecular-docking studies of existing antiviral agents (e.g. protease inhibitors and FPV) have demonstrated that modified antiviral analogues have high drug scores and similarities to parent drugs with improved drug properties[33]. Treatment guidelines published by the National Institutes of Health (NIH) do not include FPV as a treatment option in patients with confirmed COVID-19 infection, possibly due to its lack of availability in the US[34]. By contrast, other institutions and/or country-specific guidelines list FPV as one of the treatment options for patients with confirmed mild-to-severe COVID-19[13,35].

This study examined whether FPV improved COVID-19 patients' clinical outcomes in terms of time to discharge and mortality compared to supportive care. To the best of our knowledge, the present study is the first of its kind to compare FPV to supportive care in patients with COVID-19 across the spectrum of severity definition in a real-world setting. The overall analysis showed that FPV treatment for a median duration of 7 days resulted in a faster discharge rate in the overall analysis (median 10 days versus 15 and discharge ratio: 1.96). Although this statistical significance was not observed, a trend was seen following the adjustment of confounder variables in the moderate subgroup (median 9 days versus 11; discharge ratio: 1.48, 95%CI 0.97–2.27 (Table 2; Supplementary Figure S3(B)). Interestingly, the discharge ratio remained statistically significant in both severe and critical subgroups (Table 2; Figure S3). Chen and colleagues conducted a multicenter, open-label randomized trial that evaluated clinical recovery in the FPV arm compared to umifenovir and found no statistical difference in either the severe or critical subgroups[11]. By contrast, Cai et al. conducted an open-label randomized trial to compare FPV in combination with interferon-alpha to lopinavir/ritonavir in combination with interferon-alpha. The FPV plus interferon-alpha combination was associated with rapid clearance of SARS-CoV-2, evidenced by improvements in chest imaging and rapid viral clearance compared with the control arm[10]. Our results align with those of Cai et al. where FPV was associated with a higher discharge ratio. The benefit of FPV was also evident in regard to reduced progression to mechanical ventilation in the overall analysis and the severe COVID-19 category (Figure S3(E); Table 2). The lack of statistical significance in the moderate group could be explained by the small sample size.

Although not statistically significant, the association with mortality, mainly in the critically ill group, requires further study – considering also that no previous studies have explored the possible effect of FPV on mortality when compared to supportive care or active control[10,11]. The subgroup analysis suggested that mechanically ventilated patients

Subgroup	Level	Discharge events (Favipravir)	Discharge events (Supportive Care)	Interaction	HR (95%CI)
Age category	<65 years	197	168	0.532	0.83 (0.52–1.33)
	>= 65 years	24	26		0.67 (0.39–1.14)
Sex	Female	38	33	0.168	1.31 (0.77–2.26)
	Male	183	161		1.97 (1.51–2.56)
Ethnicity	Middle Eastern	111	103	0.007	2.00 (1.45–2.76)
	African	16	15		2.06 (0.82–5.18)
	South Asian	38	46		2.50 (1.54–4.05)
	Southeast/East Asian	23	13		0.42 (0.19–0.94)
	Other/Unknown	33	17		1.63 (0.83–3.18)
CKD Stage	Normal	97	76	0.43	1.87 (1.34–2.61)
	stage 2	44	75		3.71 (1.17–11.80)
	Stage 3A	10	17		1.51 (1.01–2.25)
	Stage 3B	8	7		1.76 (0.78–3.98)
	Stage 4	4	5		2.17 (0.71–6.61)
	Stage 5	5	9		6.43 (1.43–28.86)
ACEIs/ARBs use	No	174	150	0.026	2.07 (1.59–2.70)
	Yes	47	44		1.13 (0.69–1.86)
CAP regimen	No	11	15	0.558	2.45 (0.93–6.45)
	Yes	210	179		1.82 (1.42–2.34)
Cardiovascular disease	No	211	178	0.548	1.81 (1.40–2.33)
	Yes	10	16		2.40 (0.99–5.79)
BMI category	Normal	53	51	0.876	2.00 (1.29–3.09)
	Obese	75	61		1.72 (1.16–2.55)
	Overweight	91	81		1.85 (1.28–2.68)
Dyslipidemia	No	208	180	0.023	1.96 (1.53–2.53)
	Yes	13	14		0.66 (0.26–1.69)
IV steroid use	No	11	30	0.041	4.38 (1.95–9.81)
	Yes	210	164		1.75 (1.36–2.25)
Diabetes	No	117	105	0.573	1.95 (1.43–2.66)
	Yes	104	89		1.71 (1.19–2.45)
Hypertension	No	145	112	0.783	1.89 (1.40–2.55)
	Yes	76	82		1.77 (1.22–2.58)
Baseline Oxygen Therapy	No oxygen	90	80	0.04	1.36 (0.96–1.92)
	Non–invasive oxygen	128	84		2.45 (1.76–3.42)
	Mechanical ventilation/ECMO	3	30		1.73 (0.49–6.08)

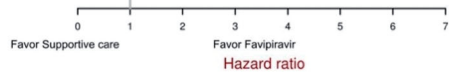

Figure 3. Subgroup analysis for the discharge events outcomes (live patients) based on baseline characteristics. $p < .05$ indicates significant interaction.

Subgroup	Level	Deaths (Favipiravir)	Deaths (Supportive care)	Interaction	HR (95%CI)
Age category	<65 years	4	12	0.384	1.08 (0.33–3.51)
	>= 65 years	8	9		2.08 (0.79–5.51)
Sex	Female	2	5	0.495	1.11 (0.21–5.90)
	Male	10	16		2.06 (0.89–4.77)
Ethnicity	Middle Eastern	5	10	0.945	1.50 (0.50–4.54)
	African	1	2		2.51 (0.22–28.12)
	South Asian	1	4		1.53 (0.17–13.99)
	Other/Unknown	4	5		1.64 (0.42–6.43)
CKD stage	Normal	2	3	0.226	1.99 (0.32–12.38)
	stage 2	3	8		2.63 (0.65–10.59)
	Stage 3A	1	1		3.40 (0.21–55.24)
	Stage 5	1	1		7.22 (0.46–129.68)
ACEIs/ARBs use	No	9	12	0.517	2.16 (0.88–5.35)
	Yes	3	9		1.30 (0.34–4.99)
CAP regimen	No	2	9	0.812	1.59 (0.33–7.65)
	Yes	10	12		1.96 (0.82–4.69)
Cardiovascular disease	No	9	17	0.324	1.55 (0.66–3.66)
	Yes	3	4		3.73 (0.82–17.04)
BMI category	Normal	3	7	0.699	1.34 (0.34–5.30)
	Obese	3	7		1.50 (0.37–6.07)
	Overweight	6	7		2.63 (0.86–8.06)
Dyslipedemia	No	7	19	0.311	1.26 (0.50–3.17)
	Yes	5	2		3.22 (0.61–16.89)
IV steroid use	Yes	12	20		1.68 (0.78–3.60)
Diabetes	No	5	8	0.965	1.86 (0.58–5.92)
	Yes	7	13		1.80 (0.69–4.69)
Hypertension	No	6	6	0.761	2.32 (0.72–7.46)
	Yes	6	15		1.84 (0.67–5.05)
Baseline oxygen	No oxygen	3	3	0.551	1.38 (0.28–6.91)
	Non–invasive oxygen	5	3		3.56 (0.83–15.34)
	Mechanical ventilation/ECMO	4	15		4.07 (1.32–12.56)

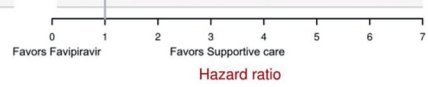

Figure 4. Subgroup analysis for mortality outcomes based on baseline characterstics. p Value $< .05$ indicates significant interaction.

Table 4. Clinical outcomes (discharge, progression to mechanical ventilation, and mortality) using propensity score matching procedure.

Outcome	Hazard ratios
Discharge (FPV vs SC), *n* (%)	221 (100) vs 194 (96)
Discharge ratio (95% CI)[a]	2.04 (1.50–2.76, $p < .001$)
Progression to mechanical ventilation (FPV vs SC), *n* (%)	2 (1.5) vs 24 (17.8)
Progression to mechanical ventilation hazard[a]	0.08 (0.02–0.32, $p < .001$)
Mortality (FPV vs SC), *n* (%)	9 (6.1) vs 7 (4.7)
Mortality hazard ratio (95% CI)[a]	2.85 (0.92–8.83, $p = .068$)

The matching procedure was performed on 5 imputed complete datasets using the multivariate imputation by chained equations (MICE) technique that included the Nelson–Aalen estimator for hazards in the imputation model. Then, using the "MatchThem" package, we performed matching 1:1 ration using 0.1 caliper without replacement, within datasets approach. Matching covariates are explained in detail in the supplementary section.

[a]Cox proportional hazard model was conducted on the matched datasets. For the discharge outcome; 202 were matched in the supportive-care arm vs 221 patients in the FPV arm. For mechanical ventilation progression outcome, 132 patients in each arm were matched. Mortality outcome had 140 patients matched in the supportive-care and 139 patients in the FPV arm.

Abbreviations. CI, confidence interval; FPV, favipiravir; SC, supportive care.

Table 5. Adverse events.

Adverse event	FPV ($N = 234$)	SC ($N = 223$)	*p* Value
Acute kidney injury, *n* (%) (any grade)	10 (4.3)	31 (13.9)	<.001
Grade 1	5 (50)	14 (45.2)	
Grade 2	3 (30)	9 (29.0)	
Grade 3	0 (0)	5 (16.1)	
Grade 4	2 (20)	3 (9.7)	
Increase ALT, *n* (%) (any grade)	101 (43.2)	93 (41.7)	.825
Grade 1	54 (53.5)	41 (44.1)	
Grade 2	34 (33.7)	32 (34.4)	
Grade 3	13 (12.9)	19 (20.4)	
Grade 4	0 (0)	1 (1.1)	
Increased AST, *n* (%) (any grade)	71 (30.3)	85 (38.1)	.098
Grade 1	53 (74.6)	46 (54.1)	
Grade 2	11 (15.5)	24 (28.2)	
Grade 3	5 (7.0)	15 (17.6)	
Grade 4	2 (2.8)	0 (0)	
Increased bilirubin, *n* (%) (any grade)	6 (2.6)	3 (1.3)	.761
Grade 1	3 (50)	2 (66.7)	
Grade 2	2 (33.3)	0 (0)	
Grade 3	0 (0)	1 (33.3)	
Grade 4	1 (16.7)	0 (0)	
Hyperkalemia, *n* (%) (any grade)	70 (29.9)	95 (42.6)	.006
Hypernatremia, *n* (%) (any grade)	8 (3.4)	37 (16.6)	<.001
Hyperuricemia, *n* (%)	12 (5.1)	0 (0)	<.001
Hypoglycemia, *n* (%)	0 (0)	1 (0.4)	.488
Hyperglycemia, *n* (%)	149 (63.7)	148 (66.4)	.613
Hypophosphatemia, *n* (%)	8 (3.4)	7 (3.1)	1.000
Hypermagnesemia, *n* (%)	6 (2.6)	5 (2.2)	1.000
Atrial fibrillation/paroxysmal atrial fibrillation, *n* (%)	0 (0)	1 (0.4)	.488
Ventricular tachycardia, *n* (%)	4 (1.7)	2 (0.9)	.686
QT prolongation, *n* (%)	4 (1.7)	1 (0.4)	.373
Hypotension, *n* (%)	3 (1.3)	15 (6.7)	.003
Constipation, *n* (%)	1 (0.4)	5 (2.2)	.114
Diarrhea, *n* (%)	13 (5.6)	1 (0.4)	.001
Seizure, *n* (%)	1 (0.4)	2 (0.9)	.615

Abbreviations. ALT, Alanine transaminase; AST, Aspartate transaminase; FPV, favipiravir; SC, supportive care.

were at higher risk of dying in the FPV group (Figure 4). This result prompted us to investigate the mortality outcome in this subset of patients. The Cox regression model indicated that age was the only independent risk factor associated with this possible increase in mortality in mechanically ventilated patients. While reassuring, given the retrospective and non-randomized nature of our study, we implemented the PSM procedure to achieve balance in the data and to compensate for the non-randomized study design. This analysis confirmed the benefits seen in the discharge ratio; however, it presented a possible mortality signal, as the 95%CI of the HR was completely outside the (admittedly arbitrary) superiority margin of 0.90, thus signaling a possible association of FPV treatment with mortality.

There could be a number of explanations for the mortality results. Although FPV is well-distributed to the lungs, it is a mild inhibitor of RdRP compared to RDV (a closely related medication in the same class); therefore, its efficacy in the severe/critical subgroups may be limited[36]. Yet RDV efficacy was also examined recently by Beigel and colleagues' RCT in

COVID-19 patients. Similar to our findings, RDV was associated with shorter time to recovery but did not result in any mortality benefits[6]. We believe that the current sample size is sufficient; however, we urge scientific communities to supplement our study with additional data and, possibly, a larger sample size.

Rattanaumpawan and colleagues recently published a retrospective study to determine factors that could predict poor outcomes in FPV recipients. Older age and lower loading dose were associated with poor outcomes in the logistic regression multivariable model[37]. No difference in regard to age was found in our subgroup analysis (Figure 4). Also, since this is a real-world study, it revealed the prescribing pattern in our institutions with a majority of the FPV patients (87%) receiving 1600 mg BID loading dose rather than 1800 mg BID. The initial Saudi MOH treatment protocol (or guidelines) for FPV recommended a loading dose of 1600 mg BID, followed by 600 mg BID; however, the updated protocol recommends a loading dose of 1800 mg BID followed by 800 mg BID. Whether higher doses are associated with better outcomes in COVID-19 patients remains undetermined. Evidence from a recently published pharmacokinetic study indicates that when FPV was dosed at 1600 mg loading dose followed by 600 mg BID, the trough concentration in most samples was lower the limit of quantification (1 μg/mL) and half the maximal effective concentration (9.7 μg/mL) in critically ill patients compared to healthy volunteers[38]. Due to the limited number of patients receiving 1800 mg BID, comparing doses was not possible. Despite this limitation, our study confirmed that FPV was associated with a faster discharge rate and less progression to mechanical ventilation compared to supportive care. In addition, the subgroup analysis provided an insight into which group of patients benefited from FPV therapy. Similar to RDV trials, patients on oxygen therapy benefited more from FPV therapy compared to no-oxygen therapy or mechanical ventilation[6]. This benefit was also independent of steroid use since the Cox proportional hazard models included steroid use as a confounder. Moreover, as we included these covariates (steroid and baseline oxygen therapy) as matching covariates, we eliminated the differences between the two groups in the propensity scores sensitivity analysis.

It can be argued that patients started on FPV treatment were discharged sooner regardless of whether they met the strict clinical criteria for recovery, e.g. chest X-ray clearance or viral clearance. For this study, we were limited by the clinical discharge definition as described in the Saudi MOH guidelines. In the study by Cai et al., viral clearance was the discharge criterion[10]. This was defined as "the presence of two consecutive negative results with quantitative polymerase chain reaction (qPCR) detection over an interval of 24 h." In that study, the median time (IQR) for viral clearance was 4 days (95% CI 2.5–9 days) for FPV treatment versus 10 days (95% CI 9–10) in our study. This could be due to several factors. First, our patients had more severe cases of COVID-19 than those in the study by Cai et al., which excluded patients with severe COVID-19 disease. Second, in that study, FPV was combined with interferon (IFN)-alfa, whereas most of our patients were treated with FPV as the main therapy for COVID-19. Lastly, in cases of a lack of availability of PCR testing, providers had to wait 3 days before a decision could be made, and one may argue that this prolonged discharge rates. However, our understanding of the virus evolved during the pandemic, and the WHO's latest recommendations (updated May 2020) added the criterion that patients could be discharged 3 days after symptom resolution in addition to 10 days having elapsed since initial presentation of symptoms[18]. This is independent of the PCR results, as later evidence showed that some patients may have prolonged shedding of the virus, thus delaying the discharge decision. The delay in discharge can be consequential as it affects access to the healthcare system and the individual's well-being. Moreover, repeated PCR can be challenging due to the unavailability of testing capacity in many parts of the world. We believe that the defined discharge criteria in our case provided an adequate surrogate marker for clinical recovery because patients in Saudi Arabia must meet the discharge criteria based on the Saudi MOH discharge protocol (similar to the WHO's updated recommendation). Moreover, after a review of our data for discharge dates we found out that all the included patients were discharged after June 2020. Therefore, we believe that many providers may have decided based on the second updated criterion as it provides several advantages to the healthcare system as a whole.

Arguably the cellular damage and the fluid accumulation within the lungs induced by the cytokine storm may not be mitigated by FPV when started late during the course of therapy (i.e. >48 h of symptoms onset). In our study, the median time to initiation was 2 days (IQR: 1–3 day) from hospital admission. Given the retrospective nature of our study, lack of evidence from prospective studies, the evolving nature of the disease during the first wave of the pandemic, and inconsistency in the prescriptive pattern, initiating FPV within 48 of symptoms in all patients may not be feasible. In addition, the use of antibiotics differed between the two arms. This may have been due to differences in the change of patients' clinical courses. We have merely described the pattern of usage, as antibiotics are not indicated for COVID-19 disease. We have not attempted to include these variables in the propensity score matching procedure as they can be considered as post-treatment covariates[39]. Moreover, the inclusion of variables as multivariable Cox models may present an unnecessary statistical challenge because it could easily violate the basic assumption of hazards proportionality[40].

Due to the retrospective nature of our study, the pandemic, and the need for a rapid response with effective treatment options, clinicians initially utilized FPV without checking uric acid levels. They began checking levels as their knowledge of this medication expanded with more data being introduced in the literature concerning the safety of this antiviral agent. Furthermore, we have not collected some baseline data, such as C-reactive protein (CRP), procalcitonin, D-dimer, aspartate transaminase (AST), alanine

transaminase (ALT), and lymphocyte count, that may have affected treatment allocation.

Another limitation was the imbalance between the two arms in regards to variables in the baseline characteristics. To address this limitation, we followed two analytical approaches (multivariable Cox models and PSM procedures) to account for clinically important confounders. Lastly, missing data were addressed with the powerful MICE procedure and could have affected the discharge outcome only. However, the outcomes in the complete case analysis and our MICE estimation with missing data showed a negligible numerical difference that did not materially change the outcome.

Conclusion

This independent study suggests that FPV treatment is well-tolerated and is associated with faster discharge compared to supportive care across the COVID-19 severity spectrum. However, FPV treatment is not protective against mortality, and age was the only independent risk factor for mortality in mechanically ventilated patients. To confirm or refute our findings, a large RCT is needed.

Transparency

Declaration of funding

No funding or sponsorship was received for this study or for the publication of this article.

Declaration of financial/other relationships

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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Data availability statement

All data generated or analyzed for this study are included in this published article (and its Supplementary Information files).

Compliance with ethics guidelines

The study was approved by the Institutional Review Boards at KFMC and PMAH (IRB 20-477E, July 2020). Informed consent was waived as this study was considered exempt.

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