ORIGINAL ARTICLE

FAVIPIRAVIR EFFICACY AND SAFETY FOR THE TREATMENT OF SEVERE CORONAVIRUS DISEASE 2019: A RETROSPECTIVE STUDY

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Background: Corona virus disease is caused by the enveloped, single stranded RNA virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) becoming the deadliest disease of the century. Its global outbreak has led researchers to develop drugs or vaccines to prevent the spread of the disease. Favipiravir is an approved orally administered antiviral drug that selectively inhibits RNA-dependent RNA polymerase, used off-label to treat COVID-19. Objectives: The purpose of this study was to assess the efficacy and safety of this drug for severe COVID-19 infection. **Methods:** This was an observational retrospective study, carried out at the ICU of King Saud Medical City (KSMC) from June 2020 to August 2020. Including a total of one thousand six hundred and ninety-nine patients (n=1699). Categorized into a treatment group (193 patients) who received Favipiravir along with standard care, and non-treatment group (1506 patients) who received standard care only. **Results:** ICU all-cause mortality was similar in both groups i.e., (Treated group 38.3% Vs Untreated group 39.4%, 95% CI of difference: -6.6% to +8.4%; p = 0.8). The subgroup analysis of survivors as compared to deceased in the treatment group showed that survivors had significantly lower age, international normalising ratio (INR), blood urea nitrogen (BUN), and creatinine. The mean ICU length of stay (LOS) was shorter for survivors compared to deceased (11.2± 8.03 Vs 16.7±9.8 days respectively), while hospital LOS was almost similar between the two groups. Advanced age (OR 1.03 [95% CI: 1.01–1.06]; *p*=0.004), higher INR and BUN were significantly associated with increased odds of mortality. Comparison of lab investigations at day 1 and day 10 in the treatment group (regardless of outcome) showed that there was a significant increase in Alanine transaminase (ALT), alkaline phosphatase (ALK), and Bilirubin, while an insignificant trend of increase in Aspartate transaminase (AST) and creatinine was recorded. **Conclusion:** In this study, Favipiravir showed better therapeutic responses in patients with severe COVID-19 infection, in terms of average duration of stay in the intensive care unit and was well tolerated in the younger age, but showed no mortality benefit. However, elevated levels of inflammatory markers, including increased ALT, AST, BUN, bilirubin, and creatinine, needs to be carefully examined.

Keywords: Covid-19; antiviral; Favipiravir; All-cause mortality; Outcomes; Severe disease

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INTRODUCTION

Coronavirus disease 2019 is an illness caused by a novel coronavirus, now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified as a respiratory illness cases in Wuhan City, Hubei Province, China.[1] Shortly thereafter, on January 30, 2020, WHO declared the COVID-19 outbreak to be a global health emergency.[2,3] Since then, many guidelines and protocols have been published including many of suggested pharmacotherapy treatments for COVID-19, searching for the most effective and safe combination of therapies.[4–9] The clinical and epidemiological characteristics of COVID-19 patients exhibit that SARS-CoV-2 infection may lead to admission to the critical care unit (ICU) and high mortality. Approximately 16-21% of people infected with the virus in China had fallen seriously ill, with a mortality rate of 2–3%.[10,11] However, no specific treatment against this novel virus exists to date. As a

result, there is an urgent need to identify effective antiviral agents to fight the disease and to explore the clinical effects of antiviral drugs. Many drugs had been authorized by the Food and Drug Association (FDA) as emergency use authorization (EUA), like Remdesivir, convalescent plasma, Bamlanivimab, Casirivimab and Imdevimab, and Baricitinib in combination with remdesivir.[4,12–16] Numerous other antiviral agents, immunotherapies, and vaccines continue to be investigated and developed as potential therapies.

Favipiravir is an oral, broad-spectrum antiviral drug that was first synthesized in 2005 and approved for treatment of influenza in Japan. It is approved in Russia for treatment of COVID-19 and the logic behind using Favipiravir is to minimize hyperinflammatory state and improve respiratory function in those critically ill patients.[17] Favipiravir is a selective potent inhibitor for RNA-dependent RNA polymerase (RdRp) that can lead to inhibition of replication in viral genome. That type of inhibition can reduce the infectiousness to others by reducing viral shedding.[18,19] Favipiravir is an inactive form that is transformed into its activated form by intracellular phosphorribosylation. The active form favipiravir ribofuranosyl-5B-triphosphates binds 54% to plasma proteins. Mild to moderate diarrhoea, hyperuricemia, QT prolongation and hepatic toxicity, as well as decreased neutrophils are typical adverse reactions of favipiravir.[18] Favipiravir has wider anti-viral spectrum and it can be used in infections such as Ebola and Severe Fever with Thrombocytopenia Syndrome (SFTS). The current analysis was conducted to evaluate the efficacy and safety levels of Favipiravir in treating severe COVID-19 cases.

MATERIAL AND METHODS

This was a retrospective analysis, carried out at the ICU of a large tertiary referral hospital in Saudi Arabia. All COVID-19 positive cases, confirmed by Reverse Transcriptase – Polymerase Chain Reaction (RT-PCR) swabs were eligible for enrolment provided they were adults (age ≥18 years) and admitted to ICU between June 2020 to August 2020.We excluded pregnant ladies, known cases of pulmonary tuberculosis (PTB), and human immunodeficiency virus (HIV) positive cases.

We retrospectively retrieved patient's demographic and clinical characteristics, laboratory investigations, and received medications of enrolled patients, who were classified into "Treatment" group if they received Favipiravir during their management in the ICU, and "Non-treatment" group if they received only standard treatment regime. Adult patients received Favipiravir 1800 mg twice a day as a loading dose on the first day, then 800 mg twice a day for 7-10 days. Lab investigations were recorded at day 1 (ICU admission), and day 10 if the patient was still in the ICU. The primary objective of the study was to investigate the effect of Favipiravir on all-cause ICU mortality. Whereas secondary objectives included exploratory comparison between survivors and deceased in the treatment group, independent risk factors of all-cause ICU mortality for the treatment group, in addition to inflammatory markers progression over time.

Continuous variables were summarized as mean ± standard deviation (SD) and compared between groups by student t test or Mann Whitney U test as appropriate. Discrete variables were summarized as frequency and percentage (%) and compared by chi square test. For the purpose of the primary outcome, we performed a preliminary analysis by chi square test of all-cause ICU mortality between the treatment and non-treatment groups. Since this was an observational study lacking the random assignment of treatment, we utilized a statistical model to estimate unconditional means of outcome at each treatment level and construct unobserved counterfactuals for the purpose of reaching an unbiased estimate of the treatment effect. We utilized the Inverse Probability Weighted Regression Adjustment (IPWRA) model. Briefly, IPWRA is a robust full matching method, that builds two regression models, one for the probability of receiving the treatment, and the other is for the probability of having the outcome. Robustness of the method originates from the fact that only one regression model needs to be correctly specified to yield unbiased treatment effects. Exploration of independent risk factors of mortality was carried out by fitting a logistic regression model, that included unadjusted variables with p values <0.1, assumptions of logistic regression were explored and goodness of fit of the final multivariable model was evaluated by Hosmer Lemeshow test (considered well fitted if p >0.05) Lab measurements of Survivors and deceased at days one and 10 were compared by Mood's median test. All statistical tests were two-tailed, considered statistically significant if p values were <0.05, without correction for multiple testing. Commercially available statistical package STATA® was used for all statistical tests [Stata Corp. 2015. Stata Statistical Software: Release 14. College Station, TX: Stata Corp LP.].

RESULTS

During the study period there were 1724 confirmed COVID-19 admissions to ICU, we excluded seven pregnant ladies, 13 minors, three PTB and two HIV cases. The remaining 1699 patients were categorized into treatment group (193 patients) who received Favipiravir, and non-treatment group (1506 patients) who didn't. Table-1 shows the comparison of demographic, clinical, and lab characteristics of both groups. Non-treatment group had a higher total white blood cell count (WBC), platelets count, blood urea nitrogen (BUN), serum potassium, aspartate

aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALK). On the other hand, non-treatment group had a lower international normalized ratio (INR), total bilirubin, and ICU length of stay (LOS). The table also shows that ICU all-cause mortality was similar in both groups (Treated group 38.3% Vs Untreated group 39.4%, 95% CI of difference: -6.6% to +8.4%; *p*=0.8). Favipiravir had no effect on mortality both on the whole studied population and on the treated group. It was insignificantly associated with decreased probability of death by 9.9% (95% CI: -30% to +10%; *p*=0.3) for the whole population, and similarly associated with 2% insignificant increased probability of death in the treated group (95% CI: -7% to +10%; *p*=0.7) (Table 2). The subgroup analysis of survivors versus deceased in the treatment group showed that survivors had significantly lower age, INR, BUN, and creatinine. The mean ICU LOS was shorter for survivors compared to deceased (11.2±8.03 Vs 16.7±9.8 days respectively), while hospital LOS was not different (Table 3). Multivariable logistic regression revealed that higher age (OR 1.03 [95% CI: 1.01 – 1.06]; *p*=0.004), higher INR (OR 20.3 [95% CI: 2.1 – 195.2]; *p*=0.009), and higher BUN (OR 1.06 [95% CI: 1.004 – 1.1]; *p*=0.04) were significantly associated with increased odds of mortality (Table-4). The model was well fitted (Hosmer Lemeshow *p*=0.4) without multicollinearity between predictor variables.

Comparison of lab investigations at day 1 and 10 in the treatment group (regardless of outcome) showed that there was a significant increase in ALT, ALK, and Bilirubin, while an insignificant trend of increase in AST and Creatinine (Table-5).

Table-1: Demographic, clinical, and lab characteristics of study groups: (No females in table)

	Treatment (n=193)	Non-treatment (n=1506)	95% CI of difference	*p*-value
Age (mean ± SD)	53 ± 15.5	53.5 ± 14.4	-1.6 to +2.7	0.9
Males: n (%)	153 (79.3%)	1152 (76.5%)	-3.9% to +8.7%	0.4
BMI (mean ± SD)	28.2 ± 3.9	28.3 ± 4	-0.5 to +0.7	0.8
Smoker: n (%)	99 (51.3%)	736 (48.9%)	-5.3% to +10.1%	0.6
SOFA (mean ± SD)	4.2 ± 1.1	4 ±1.2	-0.3 to +0.002	0.06
WBC (mean ± SD)	11.1 ± 5.7	14.9 ± 5.1	+3.1 to +4.6	< 0.001
Platelets (mean ± SD)	248 ± 99.3	259.1 ± 40.5	+3.5 to +18.7	< 0.001
INR (mean ± SD)	1.2 ± 0.2	1.1 ± 0.1	-0.09 to -0.06	< 0.001
Creatinine (mean ± SD)	153.6 ± 187.1	151.1 ± 65.4	-15.7 to +10.7	0.7
BUN (mean ± SD)	9.8 ± 8.9	10 ± 3.02	-0.4 to +0.8	< 0.001
Potassium (mean ± SD)	4.7 ± 6.8	4.8 ± 1.2	-0.2 to +0.5	< 0.001
AST (mean ± SD)	74.6 ± 67.5	75.9 ± 24.1	-3.5 to +6.1	< 0.001
ALT (mean ± SD)	58.7 ± 67	70.1 ± 20.4	+7 to +15.8	< 0.001
ALK (mean ± SD)	91.2 ± 58.1	100.7 ± 30	+4.3 to +14.6	< 0.001
Total Bilirubin (mean ± SD)	12.1 ± 8.4	11.9 ± 5.1	-1.01 to +0.7	0.01
MV upon ICU admission: n	120 (62.2%)	877 (58.2%)	-3.7% to +11.3%	0.3
ICU LOS (mean ± SD)	13.3 ± 9.2	10.4 ± 9.5	-4.4 to -1.5	< 0.001
ICU mortality: n (%)	74 (38.3%)	593 (39.4%)	-6.6% to +8.4%	0.8

BMI = body mass index, SOFA = sequential organ failure assessment, WBC = white blood cells, INR = international normalized ratio, BUN = blood urea nitrogen, AST = aspartate aminotransferase, ALT = alanine aminotransferase, ALK = alkaline phosphatase, MV = mechanically ventilated, ICU = intensive care unit, LOS = length of stay, Sd = standard deviation, CI = confidence interval.

Table-2: Estimated treatment effects of Favipiravir

	Coefficient	Robust Std. Err.	95% CI	*p*-value
ATE	-0.099	0.1	-0.3 to +0.1	0.3
ATET	0.02	0.04	-0.07 to +0.1	0.7

ATE = average treatment effect, ATET = average treatment effect on the treated.

Table-3: Comparison of survivors versus deceased in the treatment group:

	Survivors (n= 119)	Deceased (n=74)	95% CI of Difference	*p*-value
Age (mean ± SD)	50.6 ± 13.4	57 ± 18	-10.8 to -1.9	0.002
Males (n, %)	95 (79.8%)	59 (78.7%)	-10.9% to +14%	0.8
BMI (mean ± SD)	28 ± 3.8	28.4 ± 4.1	-1.6 to +0.7	0.5
SOFA (mean ± SD)	4.3 ± 1	4.1 ± 1.1	-0.5 to 0.1	0.2
Initial WBC (mean ± SD)	10.8 ± 5.4	11.5 ± 6.1	-2.3 to +1	0.6
Initial Platelets (mean ± SD)	243.6±92.1	255.1±109.5	-40.3 to +17.4	0.7
Initial INR (mean ± SD)	1.1 ± 0.1	1.6 ± 3.3	-1.1 to +0.1	< 0.001
Initial K (mean ± SD)	4.9 ± 8.7	4.3 ± 1	-1.4 to +2.6	0.2
Initial Urea (mean ± SD)	7.8 ± 6.5	12.9 ± 11.1	-7.6 to -2.6	< 0.001
Initial Creatinine (mean ± SD)	127.3±140.5	194.3±238	-120.6 to -13.4	< 0.001
Initial AST (mean ± SD)	76.4 ± 72.1	72.4 ± 59.7	-15.7 to +23.6	0.7
Initial ALT (mean ± SD)	64.9 ± 78.2	49.2 ± 41.7	-3.6 to +35.1	0.1
Initial ALK (mean ± SD)	86.8 ± 55.9	98.6 ± 60	-28.7 to + 5	0.2
Initial Bilirubin (mean ± SD)	12.6 ± 9.7	11.3 ± 5.8	-1.2 to +3.7	0.3
ICU LOS (mean ± SD)	11.2 ± 8.03	16.7 ± 9.8	-8.1 to -2.9	< 0.001
Hosp LOS (mean ± SD)	18.8 ± 11.8	20 ± 11.5	-4.6 to +2.2	0.3

Table-4: Logistic regression of all-cause ICU mortality in treatment group

Variable	Univariable			Multivariable		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	1.03	1.01 – 1.05	0.007	1.03	1.01 – 1.06	0.004
Gender	1.1	0.5 – 2.2	0.8	-	-----	----
BMI	1.03	0.96 – 1.1	0.5	-		
SOFA	1.2	0.9 – 1.6	0.3	----	----------	-----
MV	1.08	0.6 – 1.9	0.8	-------	----------	----
WBC	1.02	0.97 – 1.1	0.4	-------	----------	-------
Platelets	1.00	0.99 – 1.004	0.4	-----	----------	----
INR	32.3	4.03 – 258.3	0.001	20.3	2.1 – 195.2	0.009
Creatinine	1.00	1.001-1.004	0.04	1	0.998 – 1.003	0.9
BUN	1.08	1.03 – 1.12	0.001	1.06	1.004 – 1.1	0.04
Potassium	0.98	0.92 – 1.1	0.6	---	----------	-----
AST	0.998	0.994-1.04	0.7	------	---------	----
ALT	0.99	0.99-1.001	0.13	---------	----------	----
ALK	1.003	0.998 – 1.008	0.2	------	----------	---
T. Bilirubin	0.98	0.94 – 1.02	0.3	----	----------	-

BMI = body mass index, SOFA = sequential organ failure assessment, WBC = white blood cells, INR = international normalized ratio, BUN = blood urea nitrogen, AST = aspartate aminotransferase, ALT = alanine aminotransferase, ALK = alkaline phosphatase, MV = mechanically ventilated, ICU = intensive care unit, LOS = length of stay, Sd = standard deviation, CI = confidence interval.

Table-5: Comparison of day 1 and 10 lab investigation in treatment group:

	Day 1	Day 10	95% CI of difference	*p*-value
Creatinine	114.9 ± 126.9	116.2 ± 122.6	-23.7 to +26.3	0.9
AST	74.8 ± 67.4	92.1 ± 301.5	-61 to +26.4	0.4
ALT	58.8 ± 66.8	155 ± 635	-187.2 to -6.7	0.04
ALK	91.4 ± 58	110.8 ± 73.5	-32.8 to -6.7	0.005
T. Bilirubin	12.1 ± 8.4	14.6 ± 10	-4.5 to -0.4	0.02

AST = aspartate aminotransferase, ALT = alanine aminotransferase, ALK = alkaline phosphatase

DISCUSSION

Currently there is no an effective antiviral treatment for COVID-19, but a large number of drugs have been evaluated since the beginning of the pandemic and many of them have been used for the treatment of COVID-19 despite the preliminary or conflicting results of the clinical trials.

We aimed in this retrospective study to evaluate the efficacy and safety of Favipiravir in treating severe COVID-19 cases. Most of published studies evaluate Favipiravir in mild to moderate patients, to our knowledge, this is the first study for evaluation of Favipiravir in of severe COVID-19 patients.

In this retrospective analysis of the data of about 1700 patients utilizing double robust statistical method, we could not detect a significant effect of Favipiravir on ICU all-cause mortality, neither on the whole studied population, nor on the treated group. In terms of efficacy; a benefit was recognized in the form of shorter ICU LOS, although this benefit was not demonstrated for hospital LOS. However; in terms of safety, Favipiravir seemed to be associated with deterioration of inflammatory markers, particularly those of liver function. Furthermore, mortality was associated with higher age, INR, and BUN.

The lack of mortality benefit was echoed in several studies with different study designs, comparator arms, and patients' severity evaluating Favipiravir in the treatment of COVID-19.[20–22] On the other hand, treatment with Favipiravir was not entirely void of benefit, we observed a shorter ICU LOS in the Favipiravir treated group. Combined together, those two results could be interpreted within the context that Favipiravir was shown to result in fast recovery of viral infection[23], and normalization of body temperature[24], which may be taken as indicators of clinical improvement and cessation of the need for ICU care, and this would most probably be the case for non-critical cases of COVID-19. However; previous publications highlighted that death of COVID-19 patients usually is not a direct result of the viral infection itself, but rather due to the complications that accompany the infection, such as Acute Respiratory Distress Syndrome (ARDS) following a cytokine storm, super-added infections, multi-organ failure, and septic shock[25], which most probably would be the case in severe presentations of the disease. This can be observed in our results as a younger age, closer to normal INR and BUN of survivors, in addition to the association of those parameter with mortality in the logistic regression model, since age of the patient is definitely a contributing factor in the severity of the presentation, to the extent that it is incorporated in mortality risk prediction models[26], and disturbed physiological parameters also indicate a more severe presentation.

It logically follows that benefits of Favipiravir would be mostly gained in the less severe presentations.

With such limited benefits, safety issues of Favipiravir treatment should be carefully examined, to evaluate whether side effects outweigh benefits. We observed a rise in liver function tests (LFT) between days one and 10, which was the duration of administering Favipiravir in our study. We didn't follow up those parameters after the completion of the treatment course since most studies report elevation of LFTs as transient[21,22,27], accordingly, we can't be entirely sure of the recovery of LFTs in our study, but we can only assume that, based on previous publications.

Putting together all the pieces of evidence, we should emphasise the need for further studies, adequately designed and powered to detect safety issues with Favipiravir treatment, yet; with the results at hand, we may conclude that both benefits and side effects seem to be trivial, and tend to be more observable in less severe cases. This is supported by the result of our logistic regression model.

Undoubtedly, our study suffers numerous limitations, first there is the limitation inherent within the retrospective design, second, the small sized treated group would definitely render any statistical test underpowered and preclude the detection of significant differences if such differences do exist. Third, we failed to follow up inflammatory biomarkers at shorter intervals, and after Favipiravir course completion, hence; we are not sure if the observed rise in LFTs was short lived. Finally, we did not examine the interaction between Favipiravir and other medications that may have been administered to COVID-19 patients during their ICU stay.

CONCLUSION

Favipiravir had no mortality benefit in our study, it resulted in shorter ICU stay, along with an assumed transient elevation of LFTs. Any benefits of Favipiravir treatment seem to be more apparent in less severe presentations of the disease.

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AUTHORS' CONTRIBUTION

BA: Conceptualization, data interpretation, draft writing, proofreading. AFM: Conceptualization, data interpretation, draft writing, proofreading. MAA: Conceptualization, literature search, proofreading. AA: literature search, data interpretation, draft writing, proofreading. MAR: Draft writing, proofreading. AA: Literature search, data collection, draft writing. AA: Literature search, data collection, draft writing. ASA: Literature search, draft writing, proofreading. MMH: Literature search, draft writing, proofreading. AKl: Data collection, literature research. AM. Noor: Literature search, draft writing. MH: Data collection, data analysis, draft writing. AM: Literature search, data collection. NA: Literature search, draft writing, proofreading, HM: Data collection, data analysis, draft writing. WA: Conceptualization, data analysis, data interpretation, proofreading.

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