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Original article

Overview of clinical outcome and therapeutic effectiveness of Favipiravir in patients with COVID-19 admitted to intensive care unit, Riyadh, Saudi Arabia



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ABSTRACT

Background: Prior to the availability of the current COVID-19 vaccine, the need to control the pandemic worldwide was focused on management of the disease using previously approved antivirals, including Favipiravir which inhibits viral replication through the RNA dependent RNA polymerase enzyme. Favipiravir's efficacy against different viral infections has made it a potential treatment for COVID-19. We are aiming in this study to assess the therapeutic efficacy and safety of Favipiravir in treating critically ill patients admitted with COVID-19 to Intensive Care Units (ICUs).

Methods: This is a retrospective cohort study was conducted in five tertiary hospitals in Riyadh, Kingdom of Saudi Arabia (KSA). The studied sample was randomized from a huge pool of data collected primarily for critically ill COVID-19 patients admitted to (ICUs) during the period between April 2020 to March 2021. Two groups of patients matched 1: 1 for age and body mass index (BMI) was enrolled in the study; one group received Favipiravir and another comparison group received other antimicrobial medications, not including Favipiravir.

Results: A total data of 538 COVID-19 patients were analyzed, 269 (50%) received Favipiravir and 269 (50%) the control group received different treatments. More than two-thirds 201 (74.7%) were Saudi citizens, the majority 177 (65.8%) were males and the mean age and (BMI) were; (57.23 ± 15.16) years and (31.61 ± 7.33) kg/m² respectively. The most frequent symptoms of presentation were shortness of breath (SOB), fever, and cough, and the most frequent comorbidity was diabetes mellitus, hypertension, and ischemic heart disease.

In the supplemental therapy, corticosteroid, tocilizumab and chloroquine were statistically significant ($P = 0.001$) when combined in the FVP group more than in the comparison group. Severe acute respiratory distress syndrome (ARDS) was more frequent among Favipiravir group, while the overall mortality rate

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among the Favipiravir group was not statistically significant (p-value 0.4).

Conclusion: According to the study's results revealing FVP is not superior to other antivirals, patients who received Favipiravir presented with more severe symptoms, more comorbidities, more complications, and is not effective in controlling the cytokine storm which negatively impact the efficacy of Favipiravir.

FVP therapy had no influence on ICU and hospital length of stay in comparison with the control group as well as in the overall mortality rate among the FVP group was not statistically significant. Further research is needed to understand how FVP along with other treatments can improve the length of stay among COVID-19 patients admitted to the ICU.

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Background

Since the end of 2019, a new type of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) disease, named coronavirus disease 2019 (COVID-19), has spread all over the world and ever since has been designated as a pandemic that originated in Wuhan, China [1,2]. The World Health Organization (WHO) has declared that the coronavirus outbreak has become a global health concern [3]. According to the WHO, the disease has affected over 220 million individuals worldwide and killed 4.5 million of them [4]. Although Covid-19 has been around for a while, there is so little we know about its origins and the way our immune system reacts to it [5]. Understanding the clinical characteristics of COVID-19 assist in identifying high-risk individuals, mapping the disease and directing future management [6] as we are learning to live with this disease, there is a need to discover new therapies or come up with efficient treatment strategies to counteract it. In addition to fever and chills, COVID-19 symptoms usually involve malaise, sore throat, dyspnea, cough, myalgia, and diarrhea which can be mistaken as traditional flu symptoms. However, these mild symptoms can quickly progress to severe respiratory distress leading to COVID associated acute respiratory distress syndrome (CARDS), which in turn can lead to death due to multi-organ failure [7]. The severity of the disease differs amongst groups based on demographic characteristics, comorbidities, and immune system responses [8–10].

Several studies have found that variations in white blood cell count in COVID-19 individuals, such as lymphopenia, leukocytosis and leukopenia, are associated with the severity of the disease [9].

As a result of the unknown nature of the disease and lack of specialized medications, patients received a variety of potential treatments to learn if they are effective against the disease [11]. Corticosteroids especially are highly effective in reducing inflammation and thereby reduce the progression of the disease [12]. Dexamethasone in particular has been proven to reduce mortality especially in patients undergoing invasive mechanical ventilation [13].

Clinical trials have been conducted on various anti-infective; some have been found to be effective, such as hydroxychloroquine [14], while others are still being examined. The goal of the clinical studies on antimalarial medication usage in Covid-19 was to show that hydroxychloroquine and chloroquine are efficacious in pre-exposure and post-exposure prevention and therapy [15].

It was found in meta-analysis study, Hydroxychloroquine alone was not effective for the treatment of COVID-19 patients and the combination of hydroxychloroquine with azithromycin significantly increased mortality [16].

The use of antiviral agents was explored based on the efficacy of Remdesivir on the COVID virus in the in-vitro studies on human lung primary cells and Vero E6 cells [17,18]. Favorable in-vitro studies and clinical trials led to FDA's EUA approval for Remdesivir on May 1, 2020 [19,20]. It was found that antivirals are especially active in the early stages of disease pathogenesis owing to their ability to inhibit active viral replication. Their effectiveness is however limited in later stages of disease progression where a

pro-inflammatory process overtakes necessitating the need for immunomodulatory drugs [21].

lopinavir (LPV), is a potent human immunodeficiency virus type 1 (HIV-1) protease inhibitor, that inhibits SARS-CoV in humans [22]. It is often used in combination with ritonavir (RTV) which increases the plasma half-life of LPV by inhibiting the Cytochrome P450 [23]. Lopinavir/ritonavir combination was shown anti-SARS-CoV-2 activity in patients and in vitro by inhibiting the protease in Vero E6 cells [22] Favipiravir(FVP)is an antiviral agent (Avigan)[®] or (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) that was safe and effective against a wide range of types and subtypes of virus infection like influenza and Ebola [24,25]. FVP directly and selectively blocks the replication of flavi-RNA, alpha-RNA, filo-RNA, bunya-RNA, arena-RNA, noro-RNA, and other RNA viruses [26,27,28,29]. In cells, FVP is transformed to an active phosphoribosylated form (favipiravir-ribofuranosyl-5'-triphosphateRTP), which is recognized as a substrate by viral RNA polymerase and inhibits RNA polymerase activity [25,28], which might theoretically make it effective against SARS-CoV-2 Early clinical experience with FVP in two trials showed favorable therapeutic responses in terms of viral clearance in adult inpatients infected with COVID-19[27,30].

In the Arabian Peninsula, Saudi Arabia is the largest county has a well-developed health-care system that is available free to all citizens. In 2019, There are 494 hospitals in the health-care system, with 22.5 beds / 10,000 people and 113,000 physicians in the country [31,32].

The Ministry of Health developed recommendations for health facilities, case treatment, epidemiological surveillance, and all slices of society. In addition, the Saudi Center for Disease Control issued an infection prevention and control guidebook to assist and guide all sectors throughout the COVID-19 pandemic [33]. The Ministry of Health's national response document, which is available online, has specifics on these instructions [31].

During the pandemic period in Saudi Arabia, Risk assessment, contingency planning, training and other educational initiatives are part of Preparedness. As well as the majority of emergency medical services (EMS) requests were received through a telephone call before and during the pandemic [34,35].

Herein, we present a retrospective analysis of the clinical outcomes, assess the therapeutic efficacy and safety of FVP in treating critically ill patients with COVID-19 admitted to Intensive Care Units (ICUs), and finally compare with those who haven't received FVP treatment.

Design

It is a retrospective cohort multicenter study, conducted in Riyadh hospitals to examine the overall survival outcome and hospital stay as the main predictors for the efficacy of FVP administered in critically ill COVID-19 patients admitted to ICUs between 1st April 2020 and 31st March 2021. The source of our data was a huge pool of data collected primarily from all the tertiary hospitals in Riyadh through the Research Electronic Data Capture (REDCap) registry. The data covered comprehensive information on; socio-demographic profile characteristics of the patients admitted to the ICU with

COVID-19 infection, laboratory parameters, therapeutic interventions, invasive and non-invasive mechanical ventilation settings and modes, complications, and patients' outcomes in terms of overall survival and length of stay in the ICU and hospital. All patients (269) who received FVP were extracted consecutively. A control group with the same number was randomly selected in a 1:1 match for age and BMI. An ethical clearance to conduct the study was obtained from Institutional Review Board "REDACTED". Since it is a retrospective study, the data was identified for publication purpose and no consent was required. The study has adhered to the ethical guidelines of the Declaration of Helsinki and good clinical practice through all stages of the study design.

Statistical analysis

We applied the Statistical Package for Social Sciences (SPSS, version 25) as standard statistical procedure for the analysis. The collected data was first validated for accuracy and completeness before any statistical analysis was conducted on it. We have performed both descriptive and inferential statistical tests on these two groups of people to analyze our results further. In the descriptive analysis, the socio-demographic and clinical variables were analyzed and reported as frequencies and means \pm standard deviation (SD). In inferential statistics, we have applied the chi-square test, t-test, survival analysis Kaplan Meier test, and binary logistics tests. Total number of patients who received FVP were made categorical (yes/ no) variables. A binary logistic regression was used to evaluate whether there is a significant difference in overall survival between these two groups of patients; patients who received FVP versus the group of patients treated with other medications. In this model, treatment with FVP was the dependent variable; survival status, length of hospital stays, and acute respiratory distress syndrome (ARDS) were the main independent categorical variables. Differences between treatment groups were considered statistically significant when the two-sided p-value was ≤ 0.05 .

Results

Data on 538 COVID-19 patients were analyzed using IBM-SPSS Version 25, half of them, 269 (50.0%) received FVP and the second half control group received other different treatments. More than two-thirds 201 (74.7%) were Saudi citizens, the majority 177 (65.8%) were males and the mean age and (BMI) were; (57.23 \pm 15.16) years and (31.61 \pm 7.33) kg/m² respectively. Out of the 538 patients, 69 (12.8%) were smokers, as shown in Table 1. Shortness of breath (SOB), fever, and cough were the most common presenting symptoms, while diabetes and hypertension were the most common co-existing morbidities as shown in Table 2.

Table 3-A represents the laboratory findings of the patients on ICU admission. Inflammatory markers D-dimer and C-reactive protein (CRP) were significantly lower in the FVP group (2.97 \pm 5.70 vs. 5.21 \pm 9.59, $P = 0.011$) compared with the control group (106.03 \pm 85.58 vs. 170.55 \pm 282.69, $P = 0.016$).

In the supplemental therapy, corticosteroid, tocilizumab and chloroquine were applied combined in the FVP group more than in the comparison group (84% vs. 57%, 56%vs.19%, 7% vs. 25%) respectively, Table 3-B. The difference was statistically significant ($P = 0.001$). Severe acute respiratory distress syndrome (ARDS) was more frequent among the FVP group. However, the overall mortality rate among the FVP group was lower [119 (44.2%) vs. 128 (47.6%)], the difference was not significant (P -value 0.4), Table 4.

The Kaplan–Meier survival curves for ICU- length of stay for both kinds of therapy were presented in Fig. 1.

The median time of ICU LOS for the patients treated with FVP was estimated to be 12.5 days (IQR: 14), which was significantly longer than the time for patients in the other arm, which was 9 days (IQR: 9) ($P < 0.001$).

Table 1
Baseline characteristics (n = 538).

Characteristics	Received favipiravir N = 269 (50.0%)	Didn't receive favipiravir N = 269 (50.0%)	P-value
Hospitals	168 (62.5%)	079 (29.4%)	0.0001
Hospital A	060 (22.3%)	133 (49.5%)	
Hospital B	026 (09.7%)	035 (13.0%)	
Hospital C	013 (04.8%)	013 (04.8%)	
Hospital D	002 (00.7%)	009 (03.3%)	
Hospital E			
Nationality	201 (74.7%)	120 (44.6%)	0.0001
Saudi	068 (25.3%)	149 (55.4%)	
Non-Saudi			
Gender	177 (65.8%)	198 (73.6%)	0.049
Males	092 (34.2%)	71 (26.4%)	
Female			
Smoker	033 (12.3%)	036 (13.4%)	0.69
Yes	236 (87.7%)	233 (86.6%)	
No			
Age	57.23 \pm 15.16 years	57.65 \pm 12.35 years	0.72
BMI	31.61 \pm 7.33	30.93 \pm 4.95	0.21

Table 2
Presenting signs and comorbidities (n = 538).

Symptoms and laboratory findings	Received favipiravir N = 269 (50.0%)	Didn't receive favipiravir N = 269 (50.0%)	p-value
Signs and Symptoms of presentation	231 (85.9%)	228 (84.8%)	0.715
SOB	013 (04.8%)	009 (03.3%)	0.384
Rhinorrhea	181 (67.3%)	191 (71.0%)	0.351
Fever	020 (07.4%)	014 (05.2%)	0.288
Abdominal pain	162 (60.2%)	171 (64.3%)	0.016
Cough	045 (16.7%)	026 (09.7%)	0.328
Chest pain	053 (19.7%)	019 (07.1%)	0.001
Headache	047 (17.5%)	013 (04.8%)	0.001
Joint pain	054 (20.1%)	022 (08.2%)	0.001
Muscle ache	067 (24.9%)	039 (14.5%)	0.002
Fatigue	051 (19.0%)	019 (07.1%)	0.001
Sore throat			
Comorbidities	179 (66.5%)	152 (56.5%)	0.017
Diabetes mellitus (DM)	152 (56.5%)	139 (51.7%)	0.143
Hypertension (HTN)	040 (14.9%)	032 (11.9%)	0.194
Ischemic heart disease (IHD)	019 (07.1%)	010 (03.7%)	0.110
Heart failure (HF)	039 (14.5%)	021 (07.8%)	0.012
Bronchial asthma (BA)	027 (05.0%)	016 (03.0%)	0.026
Chronic kidney disease (CKD)			

Discussion

FVP is an antiviral drug that has been used to treat COVID-19 infections in several countries throughout the world. This retrospective study described the clinical outcome and therapeutic effectiveness of FVP between hospitalized patients with COVID-19 who received antiviral treatment and those without it in Saudi Arabia. Out of 538 patients included in this study, 70% were male, 60% were from Saudi Arabia and 13% were smokers, which is in accordance with the previous study where the majority of admitted ICU patients with COVID-19 were males (87.2%) and the most common symptoms were cough (96%) and shortness of breath (90%) [36]. The mean BMI for patients in our study in both groups was closer to 30 kg/m² which correspond with the data presented in other studies reported in New York [37,38]. Obesity is associated with poor outcomes in COVID-19 patients [39]. Since the patients in our study were not obese, it might not have influenced the outcomes on the patients on FVP and the control group. Our data also showed that there was no significant difference in the history of smoking

Table 3-A
Laboratory findings between the two groups (n = 538).

Laboratory findings	Received favipiravir n = 269 (50.0%)	Didn't receive favipiravir n = 269 (50.0%)	P - value
Leukocytes	8.87 ± 4.88	9.97 ± 5.59	0.020
Erythrocyte sedimentation rate (ESR)	52.86 ± 32.69	56.80 ± 47.55	0.464
D-Dimer	2.97 ± 5.70	5.21 ± 9.59	0.011
Ferritin	932.52 ± 1260.64	1123.19 ± 2098.46	0.352
C reactive protein (CRP)	106.03 ± 85.58	170.55 ± 282.69	0.016
Hemoglobin	11.87 ± 2.15	12.50 ± 7.14	0.170
Lactic acid dehydrogenase (LDH)	518.99 ± 509.79	614.90 ± 606.73	0.113
Alanine aminotransferase (ALT)	56.63 ± 102.36	62.83 ± 109.79	0.539
Aspartate aminotransferase (AST)	74.64 ± 134.93	103.41 ± 160.73	0.153
Creatinine	130.6 ± 160.86	140.61 ± 149.93	0.475

Table 3-B
Supplemental therapies between the two groups (n = 538).

Supplemental therapy	Received favipiravir n = 269 (50.0%)	Didn't receive favipiravir n = 269 (50.0%)	P - value
Corticosteroids	227 (84.4%)	153 (56.9%)	0.001
Tocilizumab	151 (56.1%)	050 (18.6%)	0.001
Remdesivir	002 (0.07%)	001 (0.04%)	0.467
Chloroquine	020 (7.4%)	068 (25.3%)	0.001
Azithromycin	164 (61.0%)	172 (63.9%)	0.448

age, and body mass index (BMI) between the two groups that is consistent with the result of the study conducted in Wuhan, China [40].

According to the medical records of our data, common symptoms of the patients with severe pneumonia COVID-19 were shortness of breath (86%), fever (67%) and dry cough (60%), but the difference was not statistically significant except for cough. The results on fever and shortness of breath are in line with the study conducted by (Wang et al.) [40–42]. The improvement in the cough symptoms is in tune with another clinical study where FVP did not show any significant improvement in the patient's clinical condition but reduced the latency period for relief from cough symptoms [43]. However, in the clinical study, the patients' febrile condition improved but it didn't show any improvement in our FVP group's febrile condition.

Most of the poor prognostic indicators in COVID-19 hospitalized patients happen to be the presence of comorbidities and old age [42,44,45]. A retrospective study from Saudi Arabia in 352 hospitalized patients with COVID-19 showed that the most usual comorbidities were hypertension (51.1%) and diabetes mellitus (27.6%) [36]. In our study, the majority of the comorbidities were diabetes mellitus (66.5%), hypertension (56%), and ischemic heart disease (15%).

Due to the SARS-CoV-2 infection, the host exhibits an exaggerated immune response which is often identified by lymphopenia and cytokine storm [46,47]. Studies have shown that Covid-19 patients have higher levels of cytokines which are linked to

Table 4
Intervention and overall clinical outcome (n = 538).

Characteristics	Received favipiravir 269 (50.0%)	Didn't receive favipiravir 269 (50.0%)	P-value
Length of hospital stay	24.98 ± 20.76 days MDN 18.00 days IQR 17	18.29 ± 19.14 days MDN 14.00 days IQR 14	0.001
Length of ICU stay	16.31 ± 14.09 days MDN 12.5 days, IQR 14	12.20 ± 13.56 days MDN 9.00 days, IQR 9	0.001
ARDS	076 (28.3%)	070 (26.9%)	0.270
Severe ARDS	193 (71.7%)	199 (73.1%)	
Mild and no ARDS			
Overall survival	119 (44.2%)	128 (47.6%)	0.440
Death	150 (55.8%)	141 (52.4%)	
Alive			

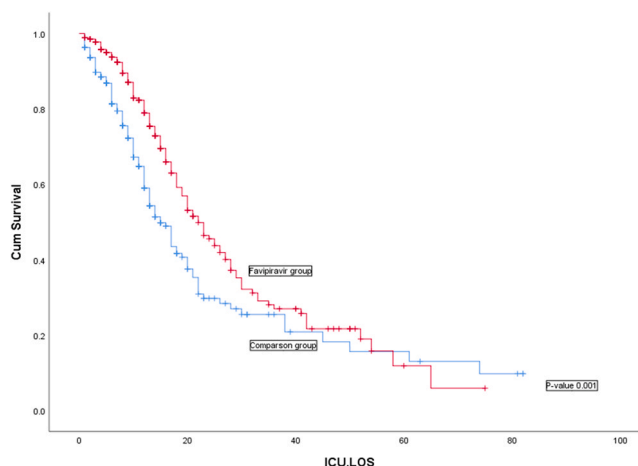


Fig. 1. Kaplan meier curve survival of critically ill patients with COVID - 19 pneumonia.

pulmonary inflammation, lung and multi-organ failure, often leading to death [47,48]. The cytokine storm can be predicted by some laboratory values including lymphocyte count, CRP, D-dimer, and ferritin levels. The association between D-dimer and C-reactive protein is well established in COVID-19 patients [49]. Moreover, Vidali et al. reported in a systematic review the correlation between the degree of elevation of D-dimer, the severity of disease, rate of complications, and prognosis of COVID-19 infection [50].

Early literature reported by Wu et al. that D-dimer values in ARDS patients were significantly higher compared with non-ARDS patients (difference between the two groups 0.52 µg·mL⁻¹, 95% CI 0.21–0.94 µg·mL⁻¹; p < 0.001) [51]. Our findings showed that D-dimer values in COVID - 19 patients receiving FVP therapy (2.97 ± 5.70) was lower than the other group (5.21 ± 9.59); P = 0.011.

The inflammatory response and cytokine storms caused by SARS-CoV-2 in the blood vessels lead to an increased level of CRP[52]. This is in accordance with previous studies, which showed that the CRP

level was positively correlated with the pneumonia severity[53]. Our data showed CRP values in COVID – 19 patients in the FVP therapy arm (106.03 ± 85.58) is much less than the control arm without FVP treatment (170.55 ± 282.69); $P=0.016$. However, a study by Mortaz et al.[54], on the effect of antiviral therapy (FVP or Kaletra) for 7 days on COVID-19 infected individuals showed a significant elevation in serum levels of IL-8 in non-ICU patients and TNF α , IL-1 β , and IL-6 in ICU patients. TNF α , IL-1 β , and IL-6 are some of the main factors that contribute to the cytokine storm [55]. Thus, FVP is not effective in controlling the cytokine storm.

In our observation, it was seen that the FVP therapy had no influence on ICU and hospital length of stay in comparison with the control group who received other treatments. Severe acute respiratory distress syndrome (ARDS) was more frequent among the FVP group (28% versus 26%) probably due to its inability in controlling the cytokine storm. Hospital length of stay was higher in the FVP group compare with others (24.98 ± 20.76 vs. 18.29 ± 19.14) that is consistent with the study conducted in Iran where the length of hospital stay was analogous in the two therapies (FVP, and Lopinavir), respectively 7 and 6 days [56].

The median time of ICU LOS for the patients treated with FVP was estimated to be 12.5 days (IQR: 14), which was significantly longer than the time for patients in the other arm, which was 9 days (IQR: 9) ($P < 0.001$). In line with the results seen in another controlled study where a group of 35 patients treated with FPV was compared with 45 patients who had received LPV/RTV. The median time of viral clearance for the patients treated with FPV was estimated to be 4 days (IQR: 2.5–9), which was significantly shorter than the time for patients in the control arm, which was 11 d (IQR: 8–13) ($P < 0.001$) [22].

However, the overall mortality rate among the FVP group was lower [119 (44.2%) vs. 128 (47.6%)], the difference was not significant (P -value= 0.4), in contrast to the previous report, Kocayigit et al. a high mortality of 66.2% in patients with severe COVID-19 infections who received FVP versus 54.3% in the comparator drug [57] Khamisa et al. reported in another study, where the use of hydroxychloroquine was compared to FVP plus inhaled interferon beta-1b in patients with moderate to severe COVID-19 infection, FVP therapy were reported to have no significant effect in regards to overall mortality (11.4% vs 13.3%; $p=0.778$) and ICU admission (18.2% vs 17.8%; $p=0.960$) [58]. The data from the study by Mortaz et al.[54] suggests that treating COVID-19 patients with antiviral therapy can improve the clinical features of the lungs which were determined by blood markers (CRP, LDH, ESR, and CPK) and CT scans. However, this effect was not seen on the cytokine levels in the blood as their levels were increased significantly. Thus, it looks like the antivirals had no inhibitory effect on the upregulation of cytokines, and therefore even though the mortality rate is low, the antivirals could not prevent the development of the cytokine storm.

The negative results from this study regarding the effectiveness of FVP in COVID-19 pneumonia may be attributed to the pathogenicity mechanism of the coronavirus. COVID associated acute respiratory distress syndrome (ARDS) has three phases: an early infection phase with mild and non-specific symptoms, a pulmonary involvement phase with or without hypoxia, and a late phase which include the rise in inflammatory mediators known as a "cytokine storm" that leads to ARDS, which is associated with a high mortality rate. This was partly due to delay in starting FVP therapy in the course of illness of these patients; this may have contributed to the lack of a meaningful favorable clinical benefit of FVP. Nonetheless, this result is not unique to our study, but was reported in other multiple studies; Chen et al.[59] and Shrestha et al. [60] said that FVP therapy showed no effect on viral clearance or the need for assisted ventilation when compared to other therapies or the standard of care.

Conclusion

The COVID – 19 infections is rapidly spreading throughout the world, and the lack of medical cure is seen as the most serious problem. According to the study's results revealing FVP is not superior to other antivirals, patients who received Favipiravir presented with more severe symptoms, more comorbidities, more complications, and is not effective in controlling the cytokine storm which negatively impact the efficacy of Favipiravir.

FVP therapy had no influence on ICU and hospital length of stay in comparison with the control group as well as in the overall mortality rate among the FVP group was not statistically significant.

Although our study with FVP did not show any promising benefit among COVID-19 patients, there is a lot of upside for this antiviral. In short, further research is needed to understand how FVP along with other treatments can improve the length of stay among COVID-19 patients admitted to the ICU.

Limitations

This study collected data from 5 tertiary hospitals in Riyadh, but has some limitations include relatively small sample size and retrospective nature of the study is not possible to rule out all confounders.

Strengths

This study has several strengths. First, the data being collected from multicenter tertiary hospitals using a, MOH electronic health record of patients with COVID-19 associated critical illness reported in the Saudi Arabia. Second, our findings mirror the ongoing outbreak of COVID-19 in Saudi Arabia, in addition, the study includes a comparator arm (control group), and lastly data analyses were done with near-complete data.

CRedit authorship contribution statement

AA- conception, proposal development, ethical approval, data recruitment, formal analysis and manuscript preparation, **JS-** proposal development, **SA-** manuscript preparation, **LL-** manuscript refinement, **GA-** formal analysis, **KT-** manuscript refinement, **MA-** data recruitment, **SA-** manuscript preparation, **MB-** formal analysis, **AK-** manuscript refinement, **KD-** manuscript refinement, **LA-** manuscript refinement, **AW-** manuscript refinement, **AR-** manuscript preparation.

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