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Original Article

Favipiravir versus standard of care in patients with severe COVID-19 infections: A retrospective comparative study

Zainab Almoosa[a,*], Mustafa Saad[b], Samer Qara[c], Mahmoud Mustafa[d], Ali Mansour[d], Duaa Alshab[e], Jehad Alhashem[d], Sajida ALKhawajah[e], Saleh Alkhalifah[d], Mokhtar ALmarzooq[e], Mohammed ALzain[e], Neda'a Anshasi[d], Gasmelseed Ahmed[f], Abbas Al Mutair[f,g,h]

[a] Pediatric Infectious Diseases, Almoosa Specialist Hospital, Alahsa, Saudi Arabia
[b] Adult Infectious Diseases, Almoosa Specialist Hospital, Alahsa, Saudi Arabia
[c] Intensive Care Unit, Almoosa Specialist Hospital, Alahsa, Saudi Arabia
[d] Internal Medicine Department, Almoosa Specialist Hospital, Alahsa, Saudi Arabia
[e] Pediatric Department, Almoosa Specialist Hospital, Alahsa, Saudi Arabia
[f] Research Center Almoosa Specialist Hospital, Alahsa, Saudi Arabia
[g] School of Nursing, Princess Nourah Bint Abul Rahman University, Riyadh, Saudi Arabia
[h] School of Nursing, Wollongong University, Australia

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ABSTRACT

Objective: To assess the efficacy of Favipiravir compared to the standard therapy in treating patients with severe COVID-19 infection.
Methods: This is a retrospective cohort of patients with COVID-19 pneumonia who were treated with favipiravir, versus comparison group that received the standard of care.
Results: A total of 226 patients were included; 110 patients received favipiravir and 116 patients received standard of care. Patients who received favipiravir had longer time to recovery (14.2 ± 8.8 versus 12.8 ± 5.2, p = *0.17*). Favipiravir was associated with an improved early day 14 mortality (4 [3.6%] versus 11 [9.5%]), p = 0.008), but was associated with a higher day 28 mortality (26 [23.6%] versus 11 [9.5%], p = 0.02). The overall mortality was higher in the favipiravir versus the standard of care group but difference was not statistically significant (33 [30.0%] versus 24 [20.7%], p = 0.10).
Conclusion: The addition of favipiravir to standard of care was not associated with any improvement in clinical outcomes or mortality. Larger randomized controlled clinical trials are needed to further assess the efficacy of favipiravir.

Introduction

Background information

Coronavirus infectious disease 2019 (COVID-19) is caused by the newly emerging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was first identified in 2019 in the city of Wuhan, China, and has since spread globally [1–3]. SARS-CoV-2 has presented unprecedented challenges to healthcare systems in almost every country around the world. The disease is a highly disseminating global pandemic. Currently there is no specific antiviral agents with established activity against the virus, and therefore efforts are directed towards infection prevention and control measures, vaccination, and supportive care for those who get infected.

Clinical and laboratory characteristics of different subtypes of COVID-19 illness severity helps in early identification and prompt treatment. Efficient viral subtyping enables visualization and modeling of the geographic distribution and temporal dynamics of disease spread. Subtyping thereby advances the development of effective containment strategies and, potentially, therapeutic and vaccine strategies [4,5]. Since the global outbreak of the severe acute respiratory syndrome, human coronaviruses (HCoVs) two decades ago, several studies have compared it to the currently

* Corresponding author at: Almoosa Specialist Hospital, Dharan St. Alfaisal District Al-Ahsa, P.O. Box 5098 Eastern Province, Saudi Arabia.
E-mail address: z.almoosa@almoosahospital.com.sa (Z. Almoosa).

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emerged acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Some similarities and differences in the epidemiology and clinical features between SARS-CoV and SARS-CoV-2 in the context of their virus incubation, originations, diagnosis and treatment methods, genomic and proteomic sequences, and pathogenic mechanisms and clinical prognostic outcomes were reported. Through these comparative studies seven types of CoVs cause human disease have identified. The two highly pathogenic viruses, SARS-CoV and MERS-CoV. It has been reported that SARS-CoV-2 shared almost 80% of the genome with SARS-CoV. In addition to the well-known SARS-CoV, MERS-CoV, as one Merbecovirus subgenus of β-CoVs, is also extremely invasive. MERS-CoV is the pathogen of the Middle East Respiratory Syndrome, which can infect both humans and animals. Studies had demonstrated that the clinical course of SARS and MERS was highly similar, and SARS and MERS may have similar pathogenesis. The genome sequence of SARS-CoV-2 also shows some similarities to that of MERS-CoV [6].

Due to the unknown nature of the disease and lack of specific drugs, several potential treatments were used for patients [7]. None of the therapeutic modalities have been shown to be efficacious. However, dexamethasone has been shown to decrease mortality especially among patients receiving invasive mechanical ventilation [8]. Several antimicrobials have been under investigation; some have already been shown to be in-effective such as the antimalarial drug, hydroxychloroquine, others are still undergoing clinical trials. Remdesivir, is the only antiviral drug that has been issued by an FDA as Emergency Use Authorization on May 1, 2020. Remdesivir has been shown in clinical trials to be superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 pneumonia but without significant effect on mortality [9].

Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazineca rboxamide) is an anti-viral agent that selectively and potently inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses. Favipiravir is safe and effective against a wide range of types and subtypes of influenza viruses, including strains resistant to existing anti-influenza drugs. It has been suggested as a treatment for SARS-CoV-2 patients [10].

In the current global COVID-19 pandemic, there is a compelling need to explore an effective pharmacological therapy. We therefore carried out this study to assess the efficacy of Favipiravir compared to standard of care in the treatment of patients who were diagnosed to have severe COVID-19 infections in a retrospective cohort design.

Materials and methods

Study design

This is a retrospective cohort of patients with COVID-19 pneumonia whose infections were confirmed with a positive polymerase chain reaction (PCR) test and were treated with favipiravir, compared to a group that received the standard of care only. Favipiravir was given as a loading of 1600 mg or 1800 mg for two doses on day 1, followed by a maintenance dose of 600 mg or 800 mg twice daily for 7–10 days. The two groups; case series and comparison group were matched based on age, gender, initial oxygen requirement, initial admission to ward versus ICU, and comorbid conditions. Medical records of all patients were reviewed as the source of the data for this study. Patients were included in the study if they full filled all of the following criteria: 1) age was 18 years or more, 2) had a PCR-confirmed COVID-19 infection, 3) had pneumonia on chest imaging (chest X-ray or CT scan), 4) were admitted to the hospital, 5) had oxygen saturation less than 94% on room air, and, 6) required supplemental oxygen of 3 L/minute or higher. Patients who received favipiravir constituted the study group and those who did not (i.e. received only the standard of care) constituted the comparison group. Furthermore, patients were excluded from the study group if they received favipiravir more than 14 days after obtaining the swab for COVID-19 diagnosis, and if they received 2 days or less of the study drug. Pregnant females were not offered favipiravir due to its known teratogenic effect and therefore were also excluded. In the Favipiravir arm, all patients who met the inclusion criteria were enrolled in the study consecutively from May 29, 2020 until October 27, 2020. On the other hand patients in the comparison group were diagnosed between April 18, 2020 to August 4, 2020 and enrolled between May and October.

The study was conducted in a single tertiary care center in Al-Ahsa, Eastern Province, Saudi Arabia. Almoosa Specialist Hospital is a 220-bed tertiary care center and the largest healthcare facility in Alahsa, Saudi Arabia, serving a local catchment population of over 1.4 million people with all medical specialties available. A national treatment guideline developed by the Saudi Ministry of Health was followed in the management of all patients; favipiravir was chosen as one of the treatment modalities for moderate to severe COVID-19 infections. Initially, favipiravir was not always available and therefore it was sporadically offered to patients who presented with COVID-19 infection early in the pandemic; therefore the majority of the comparison group were enrolled early in the pandemic, after stable supplies were secured, favipiravir was given to all patients who met the inclusion criteria.

The primary outcome of the study was crude mortality in both groups at days 14 and 28, in addition to the overall mortality. Secondary outcome measures included time to resolution of fever, the need for assisted ventilation, and the time to recovery.

The study was approved by the ethics committee of Almoosa Specialist Hospital, with IRB log number (ARC-20.10.6).

Definitions

Cytokine storm was diagnosed when patients had rapidly worsening respiratory signs and symptoms in the absence of systemic bacterial or fungal co-infections plus two or more of the following criteria: (1) Ferritin >300 ng/mL with doubling within 24 h, (2) Ferritin > 600 ng/mL at presentation with LDH > 250 U/L, (3) D-Dimer >1 mcg/mL, (4) CRP > 70 mg/L.

Data collection and management

The study team developed a data collection form composed of 6 sections and 74 items covering demographic profile, comorbid conditions, clinical presentations, laboratory and radiological findings, therapies received, and outcomes. The content, construct and validation of the data collection form was done by a team of infectious diseases' specialists, an epidemiologist and a biostatistician. A follow up phone call was made to all patients who were discharged earlier from the hospital to assess the day-14, day-28 outcomes, and the overall mortality. Data was collected by a group of eight resident doctors. The research team conducted all data management steps and statistical analysis, implemented and maintained research and data quality; generated, documented, and reported in compliance with the protocol and in accordance with the standards of Good Clinical Practice (GCP). The research team revised and verified the collected data for accuracy and completion. The statistical software, statistical package for social science (SPSS) V25, was used for data analysis. Both descriptive and inferential statistics were conducted. Categorical data was presented as numbers and percentages, while continuous data was presented as means with standard deviations. Chi-square test was used to compare categorical data, while the Student's t-test was used to compare continuous variables. A multivariate regression analysis was used to assess for

Table 1
Comparison of baseline characteristics of Favipiravir and control group (n = 226).

Characteristics	Favipiravir group (n = 110)	Standard of care (n = 116)	*p*-value
Age, years (mean ± SD)	56.8 ± 15.6	56.5 ± 16.0	0.88
Gender, number (%)			
Male	68 (61.8%)	70 (60.3%)	
Female	42 (38.2%)	46 (39.7%)	0.82
Nationality, number (%)			
Saudi	95 (86.4%)	90 (77.6%)	
Non-Saudi	15 (13.6%)	26 (22.4%)	0.08
Swab to admission, days (mean ± SD)	5.5 ± 4.1	4.8 ± 3.4	0.35
Swab to favipiravir therapy, days (mean ± SD)	6.3 ± 4.1	Not applicable	
Initial Admission, number (%)			
To ward	104 (94.5%)	113 (97.4%)	
To ICU	6 (5.5%)	3 (2.6%)	0.27
BMI, kg/m^2 (mean ± SD)	32.9 ± 8.6	31.2 ± 6.9	0.12
Cigarette Smoking, number (%)			
Smoker	11 (10.0%)	18(14.5%)	
Non-smoker	99 (90.0%)	98 (84.5%)	0.27
Charlson Comorbidity Index, mean ± SD	3.0 ± 2.5	3.1 ± 2.6	0.70
Hypertension, number (%)	69 (62.7%)	65 (56.0%)	0.30
DM, number (%)	58 (52.7%)	62 (52.6%)	0.91
CAD, number (%)	12 (10.9%)	16 (13.8%)	0.51
Bronchial asthma, number (%)	8 (7.3%)	6 (5.2%)	0.49
Sickle Cell Anemia, number (%)	4 (3.6%)	3 (2.6%)	0.65
COPD, number (%)	2 (1.8%)	2 (1.7%)	0.96
CKD, number (%)	9 (8.2%)	9 (7.8%)	0.92
CKD on Hemodialysis, number (%)	6 (5.5%)	5 (4.3%)	0.70

Abbreviations: SD: standard deviation, ICU: intensive care unit, BMI: body mass index, CAD: coronary artery disease, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, DM: Diabetes mellitus.

the independent risk factors of mortality. P-value of ≤ 0.05 was considered significant for all statistical tests.

Results

A total of 226 patients were included in this study; 110 patients received favipiravir and 116 patients received standard of care only. In the favipiravir group, 10 patients were excluded from the study; five patients received 2 days or less of favipiravir therapy, and five received their first favipiravir dose more than fifteen days after the diagnosis.

The majority of patients had severe COVID-19 infections with bilateral pneumonias (211/226 [93%]), were Saudi (185, [81.9%]) and males (138, [61.1%]). Patients in both groups did not have any significant difference regarding age (56.8 ± 15.6 versus 56.5 ± 16.0 years, p = 0.88), male gender (68 [61.8%] versus 70 [60.3%], p = 0.82), and Saudi nationality (95 [86.4%] versus 90 (77.6%), p = 0.08). The two groups had similar duration of time from swab to admission (5.5 ± 4.1 versus 4.8 ± 3.4 days, p = 0.35), but the favipiravir group had more patients, although not significant, who were initially admitted to the ICU (6 [5.5%] versus 3 [2.6%], p = 0.27). In the favipiravir group, the mean time from getting the swab for diagnosis of COVID-19 infection to receiving favipiravir was 6.3 (± 4.1) days (Table 1). Comorbid conditions were assessed in both groups. Overall, hypertension was the most prevalent comorbidity (134, [59.3%]), followed by diabetes mellitus (120, [53.1%]), and coronary artery disease (28, [12.4%]). Patients in the two study groups had similar Charlson comorbidity index (mean, 3.0 ± 2.5 versus 3.1 ± 2.6, p = 0.70), body mass index (BMI) (mean, 32.9 ± 8.6 versus 31.2 ± 6.9, p = 0.12), and smoking habits (11 [10.0%] versus 18 [14.5%], p = 0.27). Both the favipiravir and the standard of care group had comparable baseline comorbid conditions that included hypertension, diabetes mellitus, coronary artery disease, bronchial asthma, chronic obstructive pulmonary disease (COPD), sickle cell anemia, and chronic kidney disease (CKD) including patients on hemodialysis. Table 1 compares baseline characteristics of patients in both groups.

Overall, fever and loss of taste were the commonest presenting symptoms (each was documented in 210/226 patients [92.9%]) among all studied patients, followed by cough (195/226, [86.3%]) and shortness of breath (178/226, [78.8%]). The two study groups had similar symptoms on presentation that included fever, cough, shortness of breath, loss of taste, nausea, vomiting and diarrhea, Table 2. On the other hand, patients in the favipiravir group were more likely to present with tachycardia (44 [40.0%] versus 23 [19.8%], p = 0.001), and tachypnea (54 [49.1%] versus 24 [20.7%], p = 0.0005), and were more likely to develop the cytokine storm (70 [63.6%] versus 35 [30.2], p = 0.0005). Laboratory findings are also shown in Table 2. Absolute lymphocyte count was significantly lower in patients who received favipiravir (mean ± SD, 690 ± 430 versus 970 ± 610 cells/μl, p = 0.0005), while other hematological findings (leukocyte count, hemoglobin, platelets, and met-hemoglobin) were comparable in the two study groups. Markers of inflammation, namely C-reactive protein (CRP), ferritin and lactate dehydrogenase (LDH) tended to be higher in patients in the favipiravir group than the standard of care group (mean ± SD; 179.9 ± 100.8 versus 145.9 ± 93.5, p = 0.02, 1220 versus 778, p = 0.005, and 563.1 ± 316.3 versus 456.2 ± 337.7, p = 0.02, respectively). Other laboratory variables that included D-dimer, creatinine, blood urea nitrogen (BUN), liver enzymes (ALT and AST), and troponin I were all comparable in the two groups. The rates of hematological, renal and liver function test abnormalities were not significantly different between patients in the favipiravir and the control groups throughout the study. Uric acid was not tested in our cohort of patients. Patients in the favipiravir group were more likely to have laboratory-confirmed bacteremia than the control group (12 [10.9%] versus 5 [4.3%], p value = 0.01), while laboratory-confirmed secondary bacterial pneumonia was comparable in the two groups (9 [8.2%] versus 7 (6.0%), p = 0.52). Blood pathogens isolated included *Coagulase negative Staphylococcus* (CoNS) in 3 patients and *Candida albicans* in 2 patients in the control group, while the pathogens in the favipiravir group were CoNS in 4 patients and *Stenotrophomonas maltophilia* in 2 patients, while *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, *Candida krusei*, *Enterococcus*

Table 2
Comparison of clinical and laboratory findings (n = 226).

Findings: Signs and symptoms	Favipiravir group (n = 110)	Control group (n = 116)	*p*-value
Fever, number (%)	105 (95.5%)	105 (90.5%)	0.14
Cough, number (%)	94 (85.5%)	101 (87.1%)	0.72
Dyspnea, number (%)	90 (81.8%)	88 (75.9%)	0.27
Loss of taste, number (%)	105 (95.5%)	105 (90.5%)	0.14
Nausea, number (%)	12 (10.9%)	7 (6.03%)	0.18
Vomiting, number (%)	12 (10.9%)	7 (6.03%)	0.27
Diarrhea, number (%)	12 (10.9%)	8 (6.9%)	0.28
Tachypnea, number (%)	54 (49.1%)	24 (20.7%)	0.0005
Tachycardia, number (%)	44 (40.0%)	23 (19.8%)	0.001
Cytokine storm, number (%)	70 (63.6%)	35 (30.2%)	0.0005
Laboratory findings			
Leukocytes, $\times 10^9$ cells/L (mean ± SD)	6.4 ± 4.1	5.7 ± 2.2	0.13
Hemoglobin, g/dl (mean ± SD)	10.9 ± 2.9	11.1 ± 2.5	0.60
Platelets, $\times 10^9$ cells/L (mean ± SD)	189.1 ± 114.1	216.9 ± 110.2	0.06
ALC, cells/μL (mean ± SD)	690 ± 430	970 ± 610	0.0005
CRP mg/L (mean ± SD)	179.9 ± 100.8	145.9 ± 93.5	0.02
Ferritin, ng/mL (mean ± SD)	1220 ± 2604	778 ± 1250	0.005
LDH U/L (mean ± SD)	563.1 ± 316.3	456.2 ± 337.7	0.02
D-Dimer mcg/mL (mean ± SD)	2.7 ± 2.9	2.5 ± 2.3	0.68
Methemoglobin g/dL (mean ± SD)	1.3 ± 0.5	1.3 ± 0.97	0.88
ALT, IU/L (mean ± SD)	51.0 ± 48.5	51.1 ± 50.9	0.98
AST, IU/L (mean ± SD)	57.1 ± 50.7	47.4 ± 41.9	0.17
Creatinine umol/L (mean ± SD)	183.8 ± 165.5	155.3 ± 148.4	0.22
BUN mg/dL (mean ± SD)	21.8 ± 15.0	21.9 ± 13.6	0.98
Troponin ng/mL (mean ± SD)	3.3 ± 2.2	4.2 ± 2.4	0.10
Sputum culture growing a bacterial pathogen, number (%)	9 (8.2%)	7 (6.0%)	0.52
Blood culture growing a bacterial pathogen, number (%)	12 (10.9%)	5 (4.3%)	0.01
Chest X ray findings, number (%)			
Unilateral infiltrate	3 (2.7%)	12 (10.3%)	
Bilateral infiltrate	107 (97.3%)	104 (89.7%)	0.001

Abbreviations: SD: standard deviation, ALC: Absolute lymphocyte count, ALT: alanine transaminase, AST, aspartate transaminase, BUN: blood urea nitrogen, CRP: C-reactive protein, Hgb: hemoglobin, LDH: lactate dehydrogenase.

faecalis, *Corynebacterium jekium*, *Klebseilla pneumoniae*, and *Streptococcus agalactiae* were isolated in one patient each. All patients had lung infiltrates on chest X rays with the majority of patients showing bilateral pulmonary infiltrates but this was more commonly seen in the favipiravir group (107 [97.3%] versus 104 [89.7%], p = 0.001). Table 2 outlines clinical, laboratory and radiological findings in patients in both groups.

All patients (100%) in both groups who were included in the study received supplemental oxygen. More patients in the favipiravir group than the standard of care group received corticosteroids (109 [99.1%] versus 88 [75.9%], p = 0.005), therapeutic doses of clexane (87 [79.1%] versus 74 [63.8%], p = 0.01),and tocilizumab (36 [32.7%] versus 8 [6.9%], p = 0.001). On the other hand, patients in the standard of care group were more commonly prescribed vitamin C (84 [72.4%] versus 60 [54.5%], p = 0.005) and prophylactic doses of clexane (42 [36.2%] versus 23 [20.9%], p = 0.01). Otherwise, patients in both groups were treated with comparable rates of narrow and broad-spectrum antimicrobials in addition to other supplemental therapies as summarized in Table 3. Clinical outcomes were compared in the two study groups. Patients who received favipiravir had longer (but not significant) time to recovery (14.2 ± 8.8 versus 12.8 ± 5.2, p = *0.17*), had significantly longer duration of fever (4.9 ± 4.1 versus 3.9 ± 2.9 days, p = 0.05), were more likely to require assisted ventilation (57 [51.8%] versus 34 [29.3%], p = 0.001), and developed adult respiratory distress syndrome (ARDS) more commonly than the standard of care group (18 [16.4%] versus 5 [4.3%], p = 0.001). On the other hand, patients in the favipiravir group had longer time to mortality (20.8 ± 10.4 versus 17.5 ± 13.4) but the difference was not statistically significant (p = 0.29). Favipiravir was associated with an improved early day 14 mortality (4 [3.6%] versus 11 [9.5%]), p = 0.008), but was associated with a higher day 28 mortality (26 [23.6%] versus 11 [9.5%], p = 0.02). The overall mortality was higher in the favipiravir versus the standard of care group but difference was not statistically significant (33 [30.0%] versus 24 [20.7%], p = 0.10). Table 4 summarizes all clinical outcomes in both study groups. In a multivariate analysis for the independent risk factors, binary logistic regression was applied for; mortality, admission to ICU, signs and symptoms of presentation (tachycardia and tachypnea), cytokine release storm and lab results (lymphocytes). They were modeled comparing the two study groups. They all revealed significant difference between the two groups except in the death rate. Odds ratio (OR) and p-values were [(1.6, p-value 0.1), (1.9, p-value 0.02), (2.7, p-value 0.001), (3.7, p-value 0.0005), (4, p-value 0.0005) and 0.33, p-value 0.005] respectively.

Discussion

Favipiravir has been used in many countries in the world as part of the regimens to treat COVID-19 infections. Yet data from large prospective, blinded, and placebo-controlled studies on the use of favipiravir to treat severe COVID-19 infection is lacking. Here, we report the results of our study assessing the efficacy of favipiravir in 110 patients compared to a matched control group of 116 patients who did not receive favipiravir; all patients were treated during the peak of the pandemic in a single center from Saudi Arabia, and all had severe COVID-19 infections with 93% having bilateral pneumonias. The study, despite its limitations, has multiple points of strength that include the treatment of all patients according to a standardized approach in a single-center following one protocol, comprising patients who were severely ill with COVID-19 infections, and provides data that represents real-world experience of COVID-19 treatment challenges.

There are few important findings in our study that should be highlighted. First, the use of favipiravir in this cohort of patients with severe COVID-19 infections did not show any significant improvement in the assessed clinical outcomes; patients who

Table 3
Comparison of supplemental therapies given to favipiravir and control groups, (n = 226).

Therapy	Favipiravir group (n = 110)	Control group (n = 116)	P-value
Oxygen Therapy	110 (100%)	116 (100%)	031
Aspirin	23 (20.9%)	18 (15.5%)	0.29
Azithromycin	100 (90.9%)	108 (93.1%)	0.54
Ceftriaxone	89 (80.9%)	95 (81.9%)	0.84
Clexane, prophylactic dose	23 (20.9%)	42 (36.2%)	0.001
Clexane, therapeutic dose	87 (79.1%)	74 (63.8%)	0.01
Corticosteroids	109 (99.1%)	88 (75.9%)	0.0005
Glycopeptide	18 (16.4%)	16 (13.8%)	0.59
Levofloxacin	63 (57.3%)	56 (48.3%)	0.17
Meropenem	20 (18.2%)	21 (18.1%)	0.98
Pentoxyfylline	8 (7.3%)	1 (0.86%)	0.01
Piperacillin/tazobactam	56 (50.9%)	55 (47.4%)	0.59
Tocilizumab	36 (32.7%)	8 (6.9%)	0.001
Vitamin C	60 (54.5%)	84 (72.4%)	0.005
Zinc	63 (57.3%)	62 (53.4%)	0.56

Table 4
Comparison of clinical outcomes between Favipiravir group and control group (226).

Outcome	Favipiravir group (n = 110)	Control group (n = 116)	*p*-value
Days from admission to recovery – patients who recovered, (mean ± SD)	14.2 ± 8.8	12.8 ± 5.2	0.17
Duration of fever, days (mean ± SD)	4.9 ± 4.1	3.9 ± 2.9	0.05
Need for assisted ventilation, number (%)	57 (51.8%)	34 (29.3%)	0.001
Duration of assisted ventilation, days (mean ± SD)	11.4 ± 8.1	10.4 ± 10.1	0.65
Duration of non-assisted oxygen supplementation, days (mean ± SD)	6.3 ± 5.7	6.2 ± 3.9	0.87
Development of ARDS	18 (16.4%)	5 (4.3%)	0.001
Days from swab to mortality, (mean ± SD)	20.8 ± 10.4	17.5 ± 13.4	0.29
Day 14 mortality, number (%)	4 (3.6%)	11 (9.5%)	0.008
Day 28 mortality, number (%)	26 (23.6%)	11 (9.5%)	0.02
Overall mortality, number (%)	33 (30.0%)	24 (20.7%)	0.10

Abbreviations: SD: standard deviation, ARDS: adult respiratory distress syndrome.

received favipiravir had longer duration of fever, were more likely to require assisted ventilation, and developed ARDS at a higher rate than the control group. In the current study, favipiravir was given to patients after a mean of 6.3 days; this was partly due to the delay in getting the results of the PCR test, and partly due to the preset requirement to have the patient on oxygen to be eligible for favipiravir therapy. Therefore, favipiravir therapy was commonly started late in the course of illness of these patients; this may have contributed to the lack of a meaningful favorable clinical impact for favipiravir; early anti-viral therapy (within 48 h) has been suggested to improve outcomes of mild-moderate COVID-19 infection as reported by Doi et al. [11], Wu et al. [12], and Oruc et al. [13]. Nonetheless, lack of a clinical benefit of favipiravir in comparison to other therapies or standard of care is not unique to our study, but was reported in other multiple studies; Guner et al. [14] reported increased ICU admission when favipiravir was compared to hydroxychloroquine, while Chen et al. [15] and Shrestha et al. [16], in 2 separate meta-analyses, reported that favipiravir therapy showed no effect on viral clearance or the need for assisted ventilation when compared to other therapies or to standard of care. Similar findings were reported by Chen [17] who, in a randomized study, compared favipiravir to Arbidol and reported no added benefit of favipiravir therapy concerning ICU admission, the need for assisted ventilation or all-cause mortality. Contrary to our findings, improved clinical outcomes and/or viral load reductions were reported in multiple underpowered small studies that mostly examined patients with mild-moderate COVID-19 infections Cai [18] Dabbous [19], Udwadia [20], Manosuthi et al. [21], Dabbous [22].

Second, recipients of favipiravir had significantly lower mortality at day 14 of follow up. Yet this effect was not sustained, and indeed was reversed on day 28 of follow up when the mortality was significantly higher in the favipiravir group. The final overall mortality, albeit higher in the favipiravir group, was not statistically different in the two groups. This dramatic change in mortality between the 2 groups from day 14 to day 28 cannot be simply explained by one factor (i.e. favipiravir) but this is likely to represent multiple confounding factors affecting this cohort of patients. Furthermore, although patients in the two groups were matched for age, gender, oxygen requirement, initial admission to ICU, and comorbid conditions, yet patients who received favipiravir were more likely to have worse clinical findings (tachypnea, tachycardia, and cytokine storm), lymphopenia, and elevated inflammatory markers; all of these constitute criteria of a more severe illness and may likely have contributed to the mortality recorded in the favipiravir group. In addition, bacteremia was more commonly encountered in patients in the favipiravir group, many of these pathogens are difficult to treat, carry additional risks, and probably represent additional risk for the mortality seen in the favipiravir group. Our data are comparable to the findings reported in two other studies that addressed the outcomes of antiviral treatment of severe COVID-19 infections with favipiravir versus lopinavir/ritonavir; Solaymani-Dodaran et al. [23] reported no significant effect of favipiravir in terms of mortality (26 [13%] versus 17 [11%]), ICU admission, or mechanical ventilation in comparison to lopinavir/ritonavir, while Kocayigit et al. [24] reported a high mortality in patients with severe COVID-19 infections who received favipiravir with a mortality rate of 66.2% versus 54.3% in the comparator drug. In another study by Khamisa et al. [25] where the use of favipiravir plus inhaled interferon beta-1b was compared to hydroxychloroquine in patients with moderate to severe COVID-19 infection, favipiravir therapy was reported to have no significant advantage in regards to ICU admission (18.2% vs 17.8%; p = 0.960), and overall mortality (11.4% vs 13.3%; p

= 0.778). Finally, in a study on a group of critically ill patients with severe COVID-19 infections who were mechanically ventilated, Irie et al. [26] evaluated favipiravir serum concentrations after the usual 1600 mg dose, and found much lower concentrations in this group compared to healthy subjects. This finding, if confirmed in other studies, would represent additional therapeutic challenges and may provide another explanation for the lack of clinical benefit of favipiravir in critically ill COVID-19 patients.

Third, although favipiravir use in our study with severe COVID-19 infections was not associated with any clinical benefit or improved mortality, yet in the multivariate regression analysis, favipiravir was not found to be a risk factor of mortality. Furthermore, in our study, we did not find any specific safety concerns regarding the use of favipiravir in this group of severely infected patients versus the comparison group. Despite the findings by Pramod Kumar recent study that reported drug-induced liver injury (DILI) in patients treated with favipiravir for COVID-19 [27], our latter finding is important to pave the way to further investigate this drug in additional studies.

Besides favipiravir, other group of drugs tried and revealed variant level of effect were; remdesivir, nonstructural proteins (eg, 3-chymotrypsin-like protease, papain-like protease, RNA-dependent RNA polymerase), which share homology with other novel coronaviruses (nCoVs). Moreover, Hydroxychloroquine or chloroquine, often in combination with a second-generation macrolide, are being widely used for treatment of COVID-19 [28–31].

Our study has several limitations inherent to its design; its retrospective approach, the non-randomized nature with the potential risk of selection bias, the potential for unmeasured confounders that cannot be completely excluded especially in relation to lack of matching between the two study groups in relation to the disease severity, being a single-center study, and the relatively small sample size.

In conclusion, in our cohort of patients with severe COVDI-19 infections, the addition of favipiravir to standard of care was not associated with any meaningful improvement in clinical outcomes or mortality. Larger randomized controlled clinical trials with early initiation of favipiravir within 48 h of presentation are needed to further assess the efficacy of favipiravir in the treatment of patients with severe COVID-19 infections.

Competing interests

None declared.

Ethical approval

Not required.

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None.

Authors' contributions

ZA, MS and GA were involved in writing the proposal, design of the data collection form, and implementation of the study, data analysis, and manuscript preparation. The eight resident doctors were involved in data collection. AA conducted the statistical analysis. ZA, MS GA, and SQ contributed to the manuscript writing. All the team was involved the final revision and edit of the final version of the manuscript.

References

[1] Naming the coronavirus disease (COVID-19) and the virus that causes it. World Health Organization (WHO). Archived from the original on 28 February 2020. Retrieved 28 February 2020.
[2] Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health – the latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis 2020;91(February):264–6, http://dx.doi.org/10.1016/j.ijid.2020.01.009. PMID31953166.
[3] World Health Organization (WHO) (Press release). 11 March 2020. Retrieved 12 March 2020.
[4] Zhang Shan-Yan, et al. Clinical characteristics of different subtypes and risk factors for the severity of illness in patients with COVID-19 in Zhejiang, China. Infect Dis Poverty 2020;9:85.
[5] Zhao Zhengqiao, Sokhansanj Bahrad A, Malhotra Charvi, Zheng Kitty, Rosen Gail L. Genetic grouping of SARS-CoV-2 coronavirus sequences using informative subtype markers for pandemic spread visualization. PLOS Comp Biol 2020;(September), http://dx.doi.org/10.1371/journal.pcbi.1008269.
[6] Xu Jiabao, Zhao Shizhe, Teng Tieshan, Abdalla Abualgasim Elgaili, Zhu Wan, Xie Longxiang, et al. Systematic comparison of two animal-to-human transmitted human coronaviruses: SARS-CoV-2 and SARS-CoV. Viruses 2020;12(February (2)):244, http://dx.doi.org/10.3390/v12020244.
[7] Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020;382:1787–99.
[8] The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. N Engl J Med 2021;384(8):693–704, http://dx.doi.org/10.1056/NEJMoa2021436.
[9] Beigel JH, et al. Remdesivir for the treatment of Covid-19-preliminary report. N Engl J Med 2020;383(19):1813–26, http://dx.doi.org/10.1056/NEJMoa2007764.
[10] Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci 2017;93(7):449–63.
[11] Doi Yohei, Hibino Masaya, Hase Ryota, Yamamoto Michiko, et al. A prospective, randomized, open-label trial of early versus late favipiravir therapy in hospitalized patients with COVID-19. Antimicrob Agents Chemother 2020;(November).
[12] Wu, et al. Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19. J Intern Med 2020;(July).
[13] Oruc MUhammet Ali, Oz Hatice, Ozturk Onut. Investigation of the disease process and drug combinations in patients with suspected/confirmed COVID-19 using Favipiravir. J Clin Pract 2021;20(March).
[14] Guner Rahmet, Hasanoglu Imran, Kayaaslan Bircan, Aypak Adalet, Akinci Esragul, Bodur Hurrem, et al. Comparing ICU admission rates of mild/moderate COVID-19 patients treated with hydroxychloroquine, favipiravir, and hydroxychloroquine plus favipiravir. J Infect Public Health 2021;14(March (3)):365–70.
[15] Chen Ping-Jen, Chao Chien-Ming, Lai Chih-Cheng. Clinical efficacy and safety of favipiravir in the treatment of COVID-19 patients. J Infect 2020;(December).
[16] Shrestha Dhan Bahadur, Budhathoki Pravash, Khadka Sitaram, Shah Prajwol Bikram, Pokharel Nisheem, Rashmi Prama. Favipiravir versus other antiviral or standard of care for COVID-19 treatment: a rapid systematic review and meta-analysis. Virol J 2020;17:141.
[17] Chen Chang, Yi Zhang, Huang Jianying, Yin Ping, Cheng Zhenshun, Wu Jianyuan, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. medRxiv 2021;383(13):1199–207, http://dx.doi.org/10.1101/2020.03.17.20037432.
[18] Dabbous Hany M, Abd-Elsalam Sherief, El-Sayed Manal H, Sherief Ahmed F, Ebeid FatmaFS, Ghafar Mohamed SamirAbdEl, et al. Efficacy of favipiravir in COVID-19 treatment: a multi-center randomized study. Arch Virol 2021;166:949–54.
[19] Cai Qingxian, Yang Minghui, Liu Dongjing, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering 2020;6(October (10)):1192–8.
[20] Udwadia Zarir F, Singh Pawan, Barkate Hanmant, Patil Saiprasad, Rangwala Shabbir, Pendse Amol, et al. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: a randomized, comparative, open-label, multicenter, phase 3 clinical trial. Int J Infect Dis 2021;103(February):62–71.
[21] Manosuthi Weerawat, Jeungsmarn Somlerk, Okada Pilailuk, Suwanvattana Pawita. Nasopharyngeal SARS-CoV-2 viral load response among COVID-19 patients receiving favipiravir. Jpn J Infect Dis 2021;(103):62–71, http://dx.doi.org/10.7883/yoken.JJID.2020.827.
[22] Dabbous Hany M, El-Sayed Manal H, Assal GihanEl, Elghazaly Hesham, Ebeid Fatma FS, Sherief Ahmed F, et al. Safety and efficacy of favipiravir versus hydroxychloroquine in management of COVID-19: a randomised controlled trial. Sci Rep 2021;11:7282.
[23] Solaymani-Dodaran Masoud, Ghanei Mostafa, Moazen Javad. Safety and efficacy of Favipiravir in moderate to severe SARS-CoV-2 pneumonia. Int Immunopharmacother 2021;(March). Elsevier.
[24] Kocayigit H, Suner Kezban Ozmen, Tomak Yakut, Demir Gurkan. Observational study of the effects of Favipiravir vs Lopinavir/Ritonavir on clinical outcomes in critically Ill patients with COVID-19. J Clin Pharm Ther 2020;46(2):454–9.
[25] Khamis Faryal, Naabi Hanan Al, Lawati Adil Al, Ambusaidi Zaiyana, Sharji Mariam Al, Barwani Umkulthum Al, et al. Randomized controlled open label trial on the use of favipiravir combined with inhaled interferon beta-1b in hos-

pitalized patients with moderate to severe COVID-19 pneumonia. Int J Infect Dis 2021;102(January):538–43, http://dx.doi.org/10.1016/j.ijid.2020.11.008.
[26] Irie Kei, Nakagawa Atsushi, Fujita Hirotoshi, Tamura Ryo, Eto Masaaki, Ikesue Hiroaki, et al. Pharmacokinetics of Favipiravir in Critically Ill Patients with COVID-19. Clin Transl Sci 2020;13(September (5)):880–5, http://dx.doi.org/10.1111/cts.12827. Epub 2020 Jun 29.
[27] Kumar Pramod, Kulkarni Anand, Sharma Mithun, Rao Padaki Nagaraja, Reddy Duvvuru Nageshwar. Favipiravir-induced liver injury in patients with coronavirus disease 2019. J Clin Transl Hepatol 2021;9(2):276–8, http://dx.doi.org/10.14218/JCTH.2021.00011.
[28] Sanders James M, Monogue Marguerite L, Jodlowski Tomasz Z, et al. Pharmacologic treatments for coronavirus disease 2019 (COVID-19). April 13, 2020. JAMA 2020;323(18):1824–36, http://dx.doi.org/10.1001/jama.2020.6019.
[29] Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis 2003;3(11):722–7, http://dx.doi.org/10.1016/S1473-3099(03)00806-5.
[30] Al-Bari MAA. Targeting endosomal acidification by chloroquine analogs as a promising strategy for the treatment of emerging viral diseases. Pharmacol Res Perspect 2017;5(1):e00293.
[31] Mehra Mandeep R, Desai Sapan S, Ruschitzka Frank. Hydroxychloroqquine or chroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet 2020;(May), http://dx.doi.org/10.1016/S0140-6736(20)31180-6.