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HYDROXYCHLOROQUINE, FAVIPIRAVIR OR STANDARD CARE IN MANAGEMENT OF SARS-COV-2: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Background: Despite the tremendous efforts to offer safe and effective treatment guides for patients with SARS-CoV-2 infection, no clear answers exist. Here we are studying two relatively safe medications that were previously recommended for SARS-CoV-2 treatment and comparing them with standard of care. **Methods:** This is a retrospective electronic chart review study on SARS-CoV-2 infected patients between June and August 2020. Patients were eligible if they fulfilled the following criteria: (1) Age more than 14 years old, (2) Have confirmed SARS-CoV-2 infection and (3) Symptomatic, regardless of severity. **Results:** A total of 361 patients were included in the study. The mean age was 53 years ±16.8, with 204 (56.4%) males. Patients were selected to be distributed between the hydroxychloroquine/zinc (HCQ/Z), favipiravir and standard of care group at 1:1:2 ratio. Most patients become asymptomatic at day 14 (n=139, 39%). There was no statistically significant difference between the three groups in terms of symptom resolution. Favipiravir showed earlier virologic clearance (as early as day 5) as compared to HCQ/Z and standard of care groups, even though this difference was not statistically significant (36%, 28% and 30% respectively, P-value 0.866). More patients in the favipiravir group required ICU admission (7% for favipiravir, 3% for HCQ/Z and 5% for the standard of care group (P-value 0.343). Similarly, out of 12 deaths, 4 were in the favipiravir group, 8 in the standard of care group and none in the HCQ/Z group (P-value= 0.137). No sever side effect was reported in any of the treatment groups. **Conclusions:** Standard of care alone was shown to be as effective as HCQ/Z and favipiravir in terms of symptom control. Similarly, no difference could be appreciated in terms of number of ICU admission and mortality. Implementation of clear therapeutic guidelines are needed to better define the components and goals of the best supportive care.

KEYWORDS: COVID-19, *SARS*-CoV-2, hydroxychloroquine, favipiravir.

INTRODUCTION

Despite the tremendous efforts to provide safe and effective treatment to SARS-CoV-2, physicians are still faced with too many controversies and uncertainties when it comes to selecting the best therapeutic options for their patients.[1] Guidelines and recommendations have been rapidly changing as new therapeutic strategies evolved and a previously known medications had their indication modified to adopt for SARS-CoV-2 therapy.[2][3][4][5][6]

Almost a year since the start of SARS-CoV-2 pandemic, preventive strategies such as social distancing, early case identification with isolation and the innovation of

vaccines were shown to be the most effective in the face of SARS-CoV-2 pandemic with increasing certainty.[7][8][9][10] When it comes to a patient who had actually contracted SARS-CoV-2 infection, science still didn't give us the best answer.

Here we are conducting this study comparing three therapeutic approaches: 1) the use of hydroxychloroquine plus zinc (HCQ/Z) together with the best supportive care, 2) favipiravir with the best supportive care and 3) standard of care offering the best supportive care alone. We examined the difference in symptom improvement, documented viral clearance as well as mortality across the three groups.

MATERIAL AND METHODS

We conducted a retrospective cohort study on patients with symptomatic PCR-confirmed SARS-CoV-2 infection, both in inpatient and outpatient setting. The study took place in King Fahd Armed Forces Hospital in Jeddah- Saudi Arabia between June and August 2020.

All patients with confirmed SARS-CoV-2 who were seen during the study period were assessed for eligibility. We included all patients who fulfilled the following criteria: (1) Age more than 14 years old, (2) Have confirmed SARS-CoV-2 infection. (defined as detection of the viral RNA by RT-PCR from various respiratory specimens, including nasal or nasopharyngeal swab, sputum, saliva or BAL), (3) Symptomatic, regardless of severity. Exclusion criteria were (1) Patients with suspected cases of SARS-CoV-2 who never had a positive RT-PCR, (2) Asymptomatic SARS-CoV-2 patients, (3) Pregnant or breast-feeding women, (4) known allergy/ hypersensitivity to hydroxychloroquine or favipiravir, (5) patients who received the trial medications for indications other than SARS-CoV-2 treatment (e.g. SLE patient on hydroxychloroquine already) or (6) patient with baseline LFT >3x normal or advanced cirrhosis (child C).

Patients' medical chart were retrospectively reviewed and data extracted into a pre-coded data collection sheet. We collected information on baseline patient characteristics including age, sex, comorbidities, presenting signs and symptoms, basic laboratory values: serum electrolytes, complete blood count (CBC), ferritin, **C-reactive protein (CRP)**, **Lactate dehydrogenase (LDH)**, glucose-**6-phosphate dehydrogenase** (G6PD) level and pregnancy test, baseline corrected QT interval and chest x-ray (CXR). Patients were classified into hydroxychloroquine/zinc group (HCQ/Z) or favipiravir group if at least they received one dose of the medication within 72 hours of diagnosis. This time frame will help us minimize the risk of bias as almost all patients eligible for the study started the medication at roughly the same time rather than because they were performing clinically worse. Other eligible patients who didn't receive neither hydroxychloroquine/zinc nor favipiravir were considered in "standard of care alone" group. All three groups received the needed supportive measures according to the treating physician discretion as the use of steroid, antibiotics, intravenous fluids and venous thromboembolism (VTE) prophylaxis.

Primary outcome was time until resolution of symptoms as determined by the number of days required for the symptom severity category to drop by to category (1), which means the patient become asymptomatic. Secondary outcomes were the time to swab negativity, calculated as days-difference between the first positive and the first negative COVID-19 swab, and the 30-day mortality rate.

Continuous variables were reported as mean and standard deviation. Categorical variables were reported as frequency and proportions. Bivariate association between the treatment group and baseline characteristics were measured using chi-square test for categorical variables. T-test was used for continuous variables. Survival probability at 30-days was estimated using Kaplan-Meier curve and the difference between the three treatment groups tested by log-rank test. Statistical analysis was performed using SPSS 27.0 package.

RESULTS

A total of 361 patients were found eligible and included in the study. Baseline characteristics are found in table 1. The mean age was 53 years (with standard deviation ±16.8 years) with 204 (56.4%) males. The majority of patients had at least one comorbidity (n= 241, 66.57%). Among the study groups, 87 (24%) received hydroxychloroquine with zinc, 87 (24%) received favipiravir, both with standard of care, while the third group 187 (52%) received standard of care alone. Mild upper respiratory symptoms were seen in 102 (28%), 110 (30.5%) required low-flow oxygen, 7 (2%) started on non-invasive ventilation and 1 (0.3%) required ICU admission and mechanical ventilation.

Patients who experienced symptom resolution were more likely to do so at day 14 (139, 39%). When we examined the time needed across different treatment groups to drop the symptom score by 1 or more, no statistically significant difference was seen between the both treatment groups and the standard of care only group (table 2) and (figure 1).

A total of 122 (34%) patients had their SARS-CoV2 swab repeated. Of them, 36 (32%) had documented swab conversion from positive to negative. Divided by study group, 12 (39%) patients of those tested in the HCQ/Z group become negative, 14 (29%) on the favipiravir group and 10 (24%) on the standard of care group. Nearly one-third of patients on favipiravir group become negative at day 5 (36%), compared with 28% for the HCQ/Z group and 30% for the standard of care group (P-value 0.866) (table 3).

Collectively, 18 (5%) patients required ICU admission. Two were in the HCQ/Z group (2, 11.1%), six in the favipiravir group (6, 33%) and ten in the standard of care group (10, 55.6%, P-value 0.343). When we looked at the proportion relative to the number of patients in each arm, we found that among those on the HCQ/Z group 3% required ICU admission, 7% in the favipiravir group and 5% in the standard of care group.

Death occurred in 12 patients (3.33 %). Eight were males and four females (67% and 33% respectively). All twelve patients had underlying chronic comorbidities (100%). Diabetes was found in 9 patients (75%) and hypertension in all but one patient (n=11, 92%). Four patients (33%) also had underlying cardiovascular disease, two (17%) had underlying chronic lung disease and one was kidney transplant recipient (8%). At presentation, 3 (25%) patients came with mild to moderate symptoms (upper respiratory tract symptoms or shortness of breath not requiring oxygen supply) and seven (58%) were requiring oxygen from the start. Two patients (17%) were on non-invasive ventilation at admission.

Among the hydroxychloroquine/zinc arm, no deaths occurred, 4 (33%) were in the favipiravir group and 8 (67%) in the standard of care group (P-value=0.137). Taking HCQ/Z as baseline since no deaths occur, the odds ratio (OR) 0.048, 95% CI 0.018-0.131 for the favipiravir group and OR 0.45, 95% CI 0.022-0.091 for the standard of care group (P-value= 0.095). Estimation of survival probability at 30-days can be seen in Kaplan-Meier curve (figure 2).

HCQ/Z was discontinued in 7 (4.6 %) patients, all because of QTc prolongation on follow up ECG. Favipiravir was discontinued in 2 (2.3%) patients, both because of elevated liver enzymes more than three times the upper limit of normal. One patient on favipiravir developed self-limited urticarial rash that responded well to antihistamine and was able to complete the treatment course.

Table 1: Baseline characteristics and clinical presentation of enrolled patients (n=361).

Variable	n (%) or mean (standard deviation SD)
Age	54 years [±16.8]
Sex	
Male	204 (55.4)
Female	158 (43)
Missing	6 (1.6)
Baseline symptoms	
Mild URT symptoms	187 (52)
SOB requiring oxygen	138 (38)
Advanced ventilation required	8 (2.2)
Missing	35 (10)
Comorbidities	
Diabetes	196 (54)
Hypertension	152 (42)
Cardiovascular disease	77 (21)
Lung disease	34 (9)
Chronic renal disease	50 (14)
Chronic liver disease	2 (0.6)
Neurological disorders	16 (4)
Immunocompromised patients	26 (7)
Obesity (BMI >30)	34 (9)
Smoker	26 (7)
Study Group	
HCQ/Z	87 (24)
Favipiravir	87 (24)
Standard of care	187 (51)
Laboratory Data	
Serum sodium	136 (122-151) mmol/L
Serum potassium	4 (2.5- 6) mEq/L
Absolute lymphocyte count	1.38 (0.14-25) 10^9 cells/**liter**
Platelets count	203 (24- 573) 10^9 cells/**liter**
Ferritin	405 (105-7860) ng/mL
LDH	263 (10-1687) **units** per liter (U/L)

URT= upper respiratory tract; SOB= shortness of breath; BMI = body mass index; HCQ/Z= hydroxychloroquine and zinc; LDH= lactate dehydrogenase.

Table 2: Study outcomes across different study groups.

	HCQ/Z (n=87)	Favipiravir (n=87)	Standard of care (n=187)	total
Symptomatic resolution				
By day 2	4 (5)	1(1.15)	5 (2.3)	10 (3)
By day 5	10 (11.5)	8 (9.2)	15 (8)	33 (9)
By day 10	6 (7)	14 (16)	9 (5)	29 (8)
By day 14	29 (33)	34 (39)	76 (41)	139 (38.5)
By day 21	2 (2.3)	3 (3.45)	9 (5)	14 (4)
By day 30	18 (21)	8 (9.2)	26 (14)	52 (14)
Medication discontinuation	7 (8)	2 (2.3)	NA	9 (2.5)
ICU admissions	2 (3)	6 (7)	10 (5)	18 (5)
Withdrawal from the study	1 (1.14)	0 (0)	2 (1.1)	3

HCQ/Z= hydroxychloroquine and zinc; NA= not applicable; ICU= intensive care unit.

Table 3: SARS-Cov-2 clearance across different study groups (n=122).

Days until documented clearance Negative swab/total tested (%)	**HCQ/Z**	**Favipiravir**	**Standard of care**	**P-value**
By day 5	3/31 (10)	5/49 (10)	3/42 (7)	0.866
By day 10	6/31 (19)	6/49 (12)	4/42 (10)	
By day 21	3/31 (10)	3/49 (6)	3/42 (7)	
Total negative (%)	12 (39)	14 (29)	10 (24)	

HCQ/Z= hydroxychloroquine and zinc.

Figure 1. A: Outcome at day 2

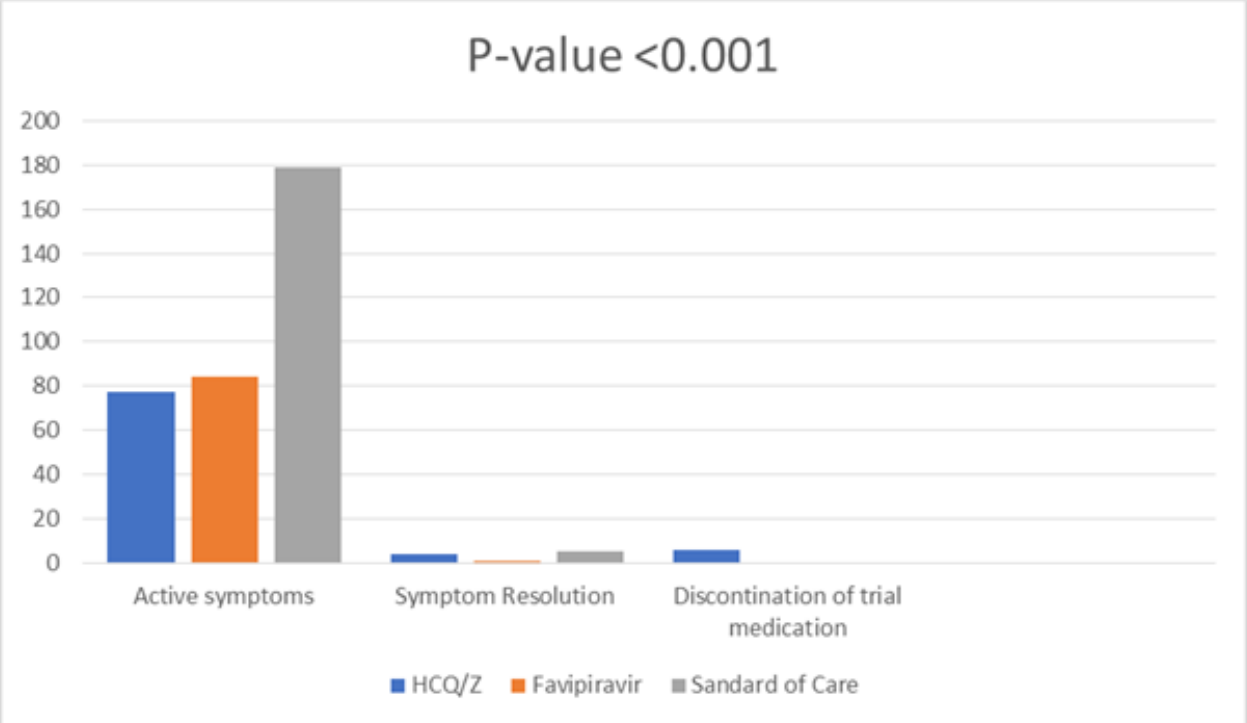

Figure 1: Symptomatic improvement and clinical outcome across different study groups.

Figure 1. B: Outcome at day 5

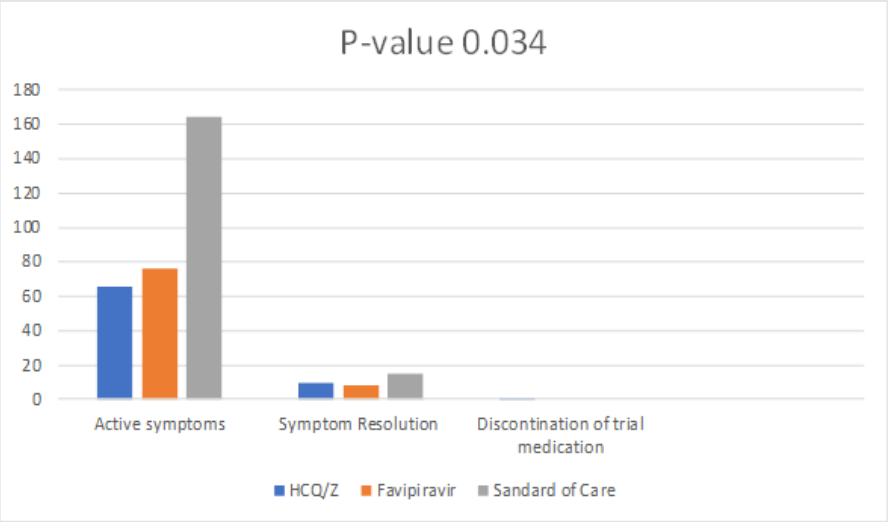

Figure 1. C: Outcome at day 10

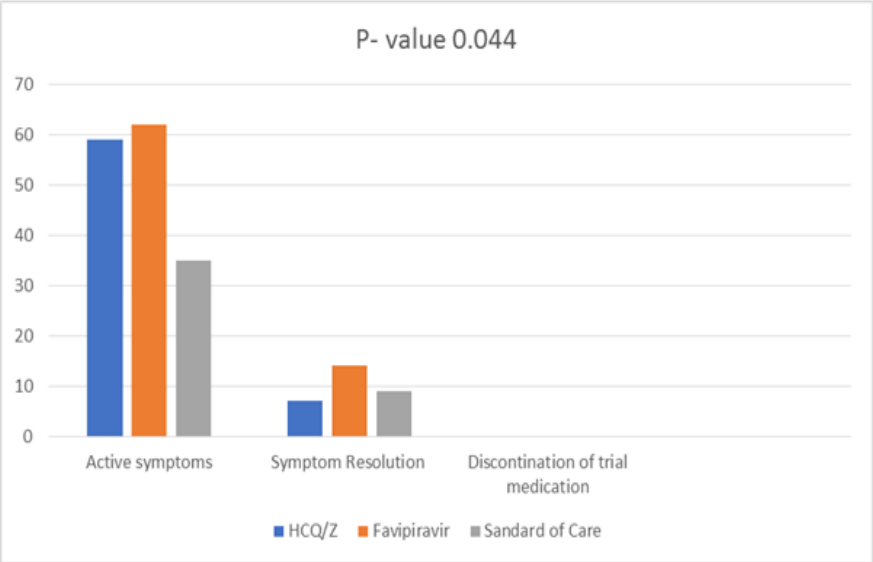

Figure 1. D: Outcome at day 14

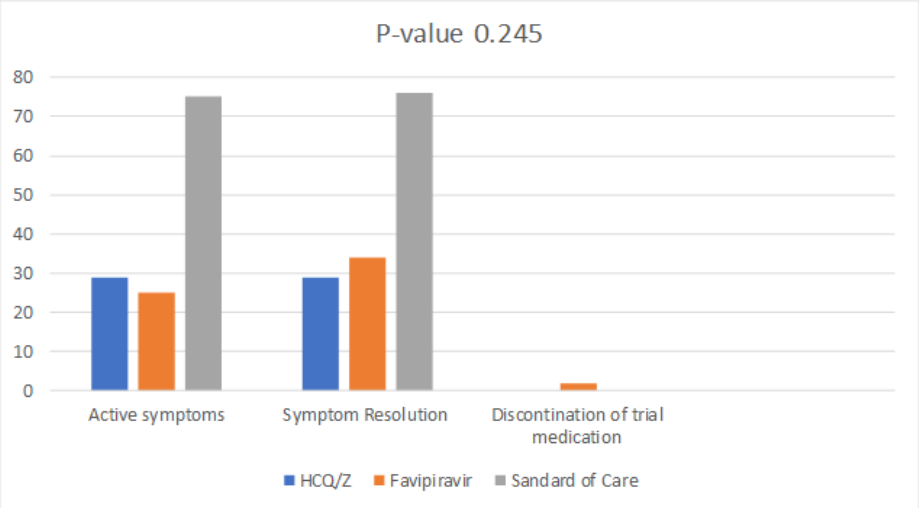

Figure 1. E: Outcome at day 21

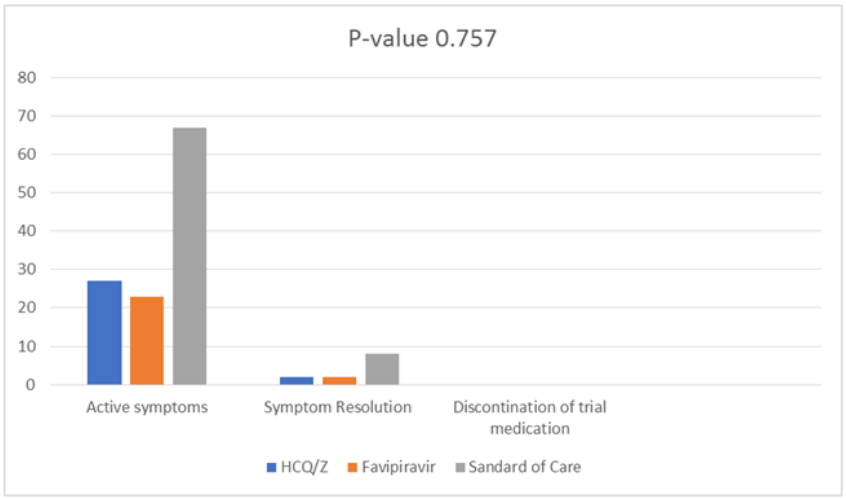

Figure 1. F: Outcome at day 30

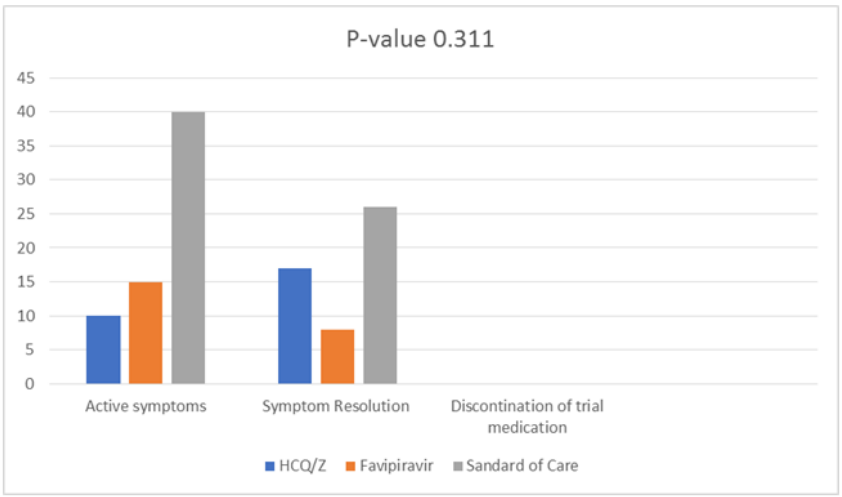

Figure 1: Graphic representation of symptoms resolution, patients with ongoing infection and medication discontinuation across different study group A) at day 2; B) at day 5; C) at day 10; D) at day 14; E) at day 21 and F) at day 30.

HCQ/Z= hydroxychloroquine and zinc.

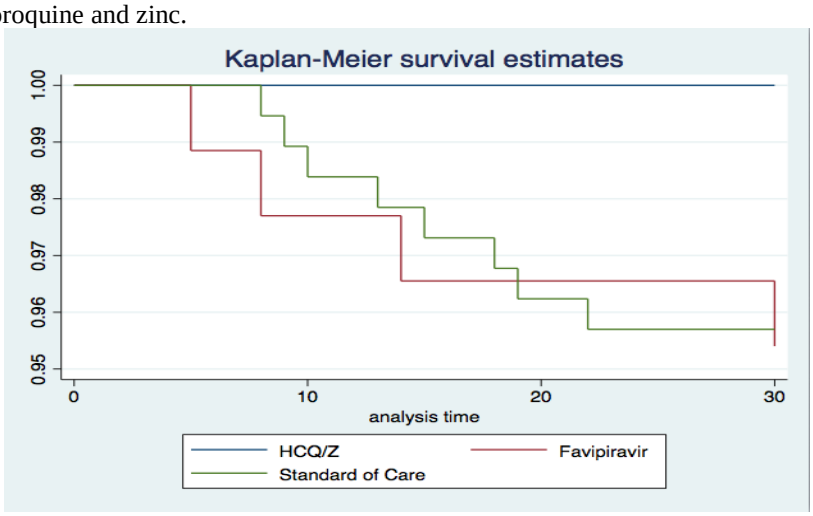

Figure 2: Kaplan-Meier survival estimate by treatment group.

Log-rank test for equality of survivor among treatment groups (P-value= 0.14)
HCQ/Z= hydroxychloroquine and zinc.

DISCUSSION

Our study clearly demonstrates that in terms of symptom resolution there is no advantage for neither hydroxychloroquine/zinc nor favipiravir over standard of care alone at day 14 (57.5% for hydroxychloroquine/zinc, 65% for favipiravir, 56% for standard of care alone, p-value 0.24). The lack of effect was seen consistently until the end of the 30-day follow-up period (table 2). Even though *in vitro* activity was demonstrated for HCQ against SARS-CoV2[11], results from clinical trials are conflicting.[12][13][14][15][16]

Keeping the lack of clinical benefit in mind, it's worthwhile to note that 4.6% of the patients who received hydroxychloroquine/zinc and 2.3% on favipiravir had their medications discontinued. The reason for those on HCQ/Z was prolonged QTc on follow up ECG, mostly detected in the first 48 hours of drug administration. Clinically significant arrhythmia however didn't happen in any of our study population. Surprisingly not a single case of mortality was reported in the HCQ/Z group. This contradicts previous studies that show patients on HCQ were less likely to be discharged alive.[17] In the favipiravir group, elevation of liver enzymes- albeit significant- was transient and both patients showed full recovery.

Previous studies showed that favipiravir shortens the median time needed for viral clearance compared to control.[18][19][20][21][22][23] Hydroxychloroquine on the other hand has been shown to delay viral clearance in patients with mild to moderate SARS-CoV-2 illness.[24][25][26] The number of patients who came back for repeated SARS-CoV-2 swab was relatively low (122, 34%). In our study, more patients on the HCQ/Z group had documented viral clearance as compared to the favipiravir and standard of care groups, even though this finding was not statistically significant (39%, 29% and 24% respectively, P-value 0.866). Regarding the time needed for viral clearance however, favipiravir showed more patients becoming negative as early as day 5 as compared to HCQ/Z and standard of care (36%, 28% and 30% respectively). This was consistent with findings from previous studies as discussed previously.

Relatively more patients in the favipiravir group were admitted to the ICU compared to HCQ/Z and standard of care group (7%, 3% and 5% respectively, P-value 0.343). This finding even though wasn't shown to be statistically significant should alert the physicians when using favipiravir. Despite the fact that favipiravir was associated with rapid virologic clearance, it showed a relative increase in ICU admissions and more deaths compared to HCQ/Z.

The overall mortality rate was low in our cohort (3.33%) and all has underlying comorbidities. Internationally, the reported mortality rate ranges from 0.1 – 25%.[16][27][28] While no mortality reported in the hydroxychloroquine group, four patients died in the favipiravir group. Eight patients in the standard of care group died. No significant difference can be appreciated between the different treatment groups however.

Our study has the advantage of comparing the effect of hydroxychloroquine with zinc and favipiravir against standard of care alone in the same hospital setting. This gave us the opportunity to examine any difference in response among treatment groups while unifying the supportive care provided under the same hospital protocol and treating physicians. The retrospective nature of the study and the relatively small number of patients are some limitations. Further analysis of the mortality cases and significance test also was not possible given the small number of events.

In conclusion, offering your patient the best supportive care with anti-inflammatory agents, steroids, paying close attention to fluid balance together with venous thromboembolism (VTE) prophylaxis still constitutes the cornerstone of management for COVID-19 patients. Further studies need to be conducted on novel antiviral agents with reasonable safety profile. Our study is a reminder that other than preventive measures, physicians caring for patients who actually contract and develop COVID-19 illness are still facing many unanswered questions and uncertain treatment recommendations.

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