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ORIGINAL ARTICLE

Comparison of Favipiravir to Hydroxychloroquine Plus Azithromycin in the Treatment of Patients with Non-critical COVID-19: A Single-center, Retrospective, Propensity Score-matched Study

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ABSTRACT

Objectives: In this study, we compared the clinical outcomes and effects of the treatments on laboratory parameters between patients who were treated with favipiravir (FAV) or hydroxychloroquine plus azithromycin (HCQ/AZ) for COVID-19 pneumonia in non-Intensive Care Unit (non-ICU) patients.

Methods: We collected data of 260 moderate or severe COVID-19 patients hospitalized in COVID-19 wards between March 20, 2020, and September 30, 2020 retrospectively. We used propensity score matching to evaluate treatment effect on laboratory parameters of COVID-19 infection.

Results: We compared 42 patients using FAV and 42 HCQ/AZ after propensity score matching. While there were statistical differences between the therapy groups in terms of transfer to ICU and/or exitus before matching (p=0.031), this was not significant after propensity analysis (p=0.250). Patients treated with FAV stayed in the hospital nearly one more day than HCQ/AZ group but the difference was not statistically significant (9.02 days vs 8.14 days, p=0.903). The levels of AST,ALT, and LDH increased at discharge in both groups, especially in the FAV group.

Conclusions: FAV is not superior to HCQ/AZ in the treatment of COVID-19 infection in hospitalized patients with pneumonia.

Keywords: COVID-19, hydroxychloroquine, azithromycin, favipiravir, propensity-matched analysis

INTRODUCTION

After more than a year of the COVID-19 (Coronavirus Disease 2019) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with over 185,000,000 infected individuals and 4 million deaths worldwide [1], there is still insufficient evidence about the optimal treatment. Although vaccination programs have been launched in many countries, the rate of vaccination is far from taking the pandemic under control soon, and the number of cases is still increasing with a new challenge by variant strains [2]. Therefore, the necessity of defining an optimal treatment modality is essential than ever.

Since the beginning of the pandemic, several therapeutic agents have been administered in different countries. Despite in vitro effects of interferons, lopinavir/ritonavir, ribavirin, chloroquine (CQ), hydroxychloroquine (HCQ), remdesivir, favipiravir (FAV), and ivermectin, there is still no approved treatment with proven efficacy [3].

HCQ, alone or in combination with azithromycin (AZ), has being used for treatment of COVID-19 during the initial months of the pandemic worldwide when it was enlisted as an option for treatment due to its anti-inflammatory and antiviral effects [4-7]. After initial controversial reports on efficacy, the Solidarity Trial and Recovery Trial both revealed that HCQ did not reduce the mortality and duration of hospitalization of COVID-19 patients [8,9]. On the other hand, increased concerns for cardiovascular adverse events have precluded the widespread use of HCQ alone or combined with AZ [10].

FAV, an RNA-dependent RNA polymerase inhibitor, has been shown to inhibit SARS-CoV-2 infection in Vero E6 cells (EC50 value 61.88 μM) [11-13]. Although several observational studies have suggested that FAV is beneficial for improvement in thoracic computerized tomography (CT) and viral clearance, control inflammatory responses in patients undergoing mechanical ventilation, and shortening the length of stay in the intensive care unit (ICU) [14-18], others failed to show any beneficial effect of FAV [19-22].

In spite of scarcity of convincing and evidence-based data, our COVID-19 treatment strategy followed the in-hospital guidelines developed by a multi-disciplinary team based on updated guidelines issued by the Turkish Ministry of Health [23].

In this study, we compared the clinical outcomes and effects of the treatments on laboratory parameters between patients who were treated with FAV or HCQ/AZ.

MATERIALS AND METHODS

Study Design and Population

This single-center, retrospective study was conducted in Hacettepe University Hospital, a tertiary care hospital with 1200 beds for adult patients. We collected data of confirmed COVID-19 patients (older than 18 years old) hospitalized in COVID-19 wards between March 20, 2020, and September 30, 2020 retrospectively. Approval of the local ethical committee (Approval number: GO 20/353, date: 31.03.2020), and permission of the Ministry of Health of the Republic of Turkey were obtained.

The study enrolled all consecutive patients who met the following inclusion criteria: (a) patients 18 years or older age; (b) SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) test (c) hospitalized between March 20-September 30, 2020; (d) hospitalized at least five days in COVID-19 wards; (e) patients with pneumonia detected via CT ; (f) patients who did not require non-invasive/invasive mechanical ventilation (g) patients with "moderate" or "severe" disease according to according to the World Health Organization (WHO) classification (24) (h) patients who completed treatment as per protocol without early discontinuation due to any adverse reaction.

Critically-ill patients with sepsis and/or acute respiratory distress syndrome (ARDS) who required ICU care those with "mild disease" (without pneumonia) and "critical disease" according to the WHO classification (24) at the time of admission were excluded.

Clinical and laboratory data were retrieved from patient medical records until discharge, transfer

to the ICU or death in the ward. Decisions for hospitalization, treatment, transfer to the ICU and discharge were made by the Infectious Diseases consulting physicians and the primary consultants of the wards according to the hospital guidelines composed and regularly updated by a multi-disciplinary team of physicians based on the guidelines issued by the Scientific Board of the Ministry of Health of the Republic of Turkey [23].

Initially, patients with pneumonia received HCQ plus AZ (HCQ/AZ). FAV was not available in large quantities, and its use was restricted to critically ill patients who required intensive care unit (ICU) in the early days of the pandemic. Later, FAV became available widely and was preferred to treat patients with pneumonia regardless of the severity of the disease. Patients treated with HCQ/AZ received HCQ 400 mg twice on the first day, then 400 mg/day for 4 days plus AZ 500 mg on the first day, then 250 mg/day for 4 days. The standard protocol of FAV was 1600 mg of FAV b.i.d. on the first day, then 1200 mg/day (2x600 mg) for 4 days.

The discharge criteria in our center were absence of fever in the last 48 hours and clinical recovery, regardless of laboratory values.

Outcomes / Endpoints

The primary outcome of this study was to compare the changes in laboratory parameters in SARS Cov-2 infected patients treated with HCQ/AZ or FAV at admission and at discharge.

The secondary outcome was to evaluate the effect of the treatment in terms of transfer to the ICU, length of hospital stay, and/or exitus.

Propensity Score Matching

Since this was not a randomized trial, we used propensity score matching to estimate average treatment effect on laboratory parameters of COVID-19 infection in order to minimize the bias due to confounding factors, assuming that an imbalance in the patient background between the FAV and HCQ/AZ groups may exist.

The propensity score for each patient was calculated as a probability from a logistic regression model, including all important clinical and laboratory covariates that were shown to be of prognostic value [24]; a. gender, b. age, c. time from symptom onset to admission, d. symptoms such as sore throat, cough, myalgia - arthralgia, nausea - vomiting, diarrhea, loss of smell and/or taste, e. fever (body temperature ≥ 38° Celcius on admission), f. tachypnea (respirations ≥ 22/min), dyspnea, oxygen saturation (SpO2 ≥ 93% or lower) at admission g. comorbidities such as hypertension, diabetes mellitus, coronary heart disease, congestive heart failure, and/or chronic obstructive pulmonary disease, h. lymphocyte count, serum levels of ferritin, c-reactive protein (CRP), D-dimer and lactate dehydrogenase (LDH) on admission. In the propensity-score matching analysis, the nearest-neighbor method was applied to create a matched sample.

Statistical Analysis

Statistical analysis was performed with IBM SPSS for Windows version 23 package. The normality of numerical data was assessed with Shapiro Wilks test. Normally distributed continuous data were summarized by mean ± standard deviation, while non-normally distributed continuous data were summarized by median [25-75th percentiles]. The categorical variables were shown with the numbers and the percentages. The Chi-square test or Fisher exact test were applied to detect the relation between categorical variables. Independent sample t test or Mann Whitney U test was used to compare independent two groups in terms of numerical data. Within group differences were shown by Wilcoxon test. A 2-tailed p value of 0.05 was considered significant.

RESULTS

A total of 741 adult patients with laboratory confirmed COVID-19 were hospitalized in COVID-19 wards between March 20-September 30, 2020. Four hundred and eighty-one patients were excluded because of absence of pneumonia, hospital stay less than 5 days, early discontinuation of treatment due to adverse events or invasive/non-invasive mechanical ventilation (Figure 1). After propensity score matching, there were 42 patients who received FAV and 42 patients who received HCQ/AZ.

215 (82.7%) of 260 unmatched patients were treated with FAV and the rest 45 (17.3%) with HCQ/AZ. In this unmatched sample, there was a statistically significant difference in terms of age, hypertension,

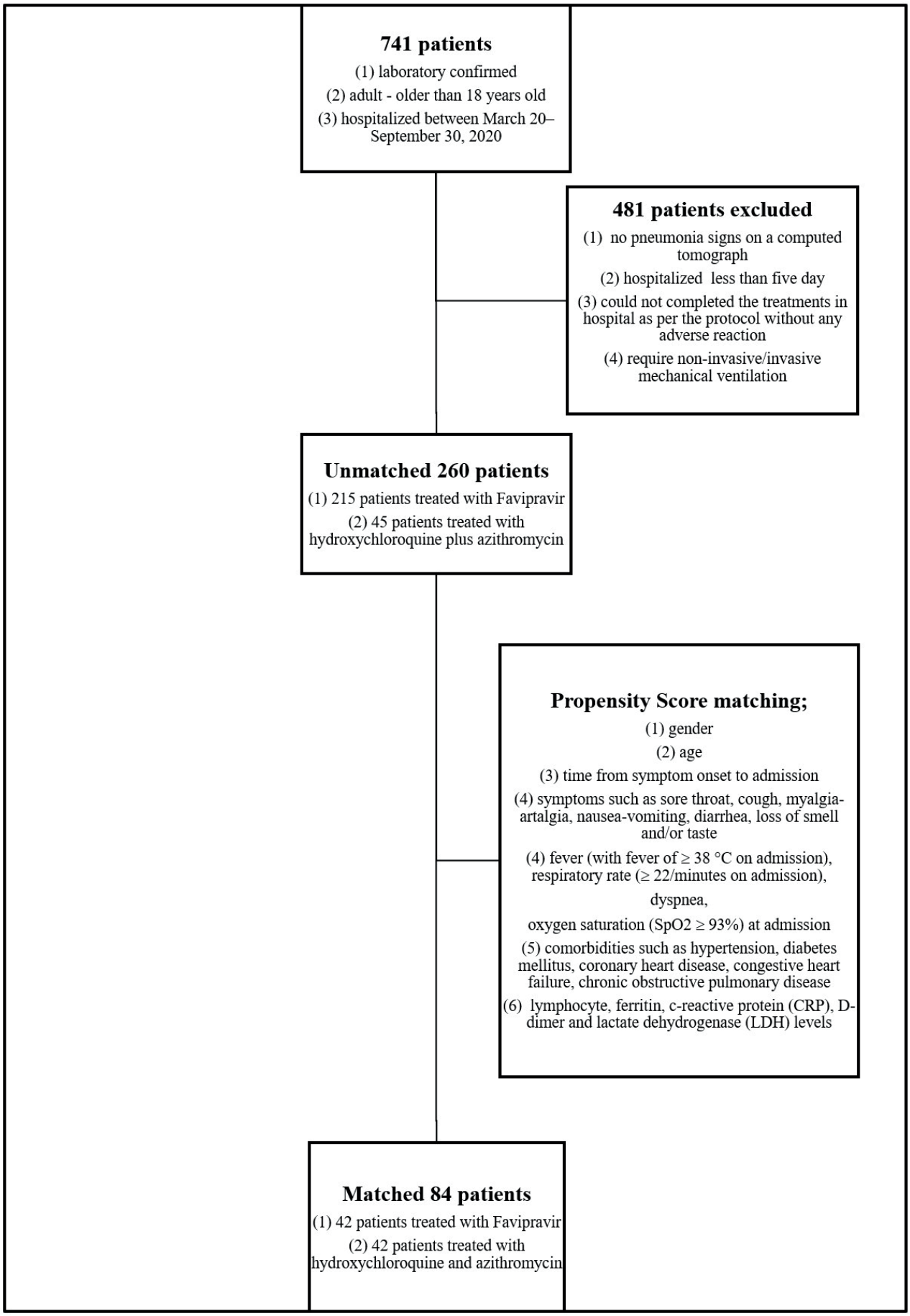

Figure 1. Case selection flowchart.

fever, respiratory rate, and oxygen saturation between treatment groups. The distribution of the baseline characteristics both in the unmatched and propensity-score matching analytic samples is shown in Table 1.

Propensity scores ranged from 0.00682 to 0.54438 in the FAV group, and from 0.01593 to 0.56627 in the HCQ/AZ group. While there were statistical differences between the patient groups in terms of transfer to ICU and/or exitus before matching (p=0.031), none of the treatment group was superior to the other in terms of discharge after propensity analysis (p=0.250). There were no statistically significant difference in terms of length of hospital stay between patients treated with FAV [9.02 days, SD: 6.4] and HCQ/AZ [8.14 days, SD:3.4] (p=0.903).

Total leukocyte counts increased at discharge in both treatment arms, but it was not significant. There was no difference between the two treatment groups in the measurements of leukocyte and neutrophil counts at admission and at discharge. On the other hand, the increase in lymphocyte and thrombocyte counts at discharge were statistically significant compared to admission values in both treatment arms. However, neither the increase in lymphocyte counts (p=0.956) nor platelet counts (p=0.280) were different between the two groups (See Table 2).

The levels of aspartate aminotransferase (AST), alanine transaminase (ALT), and LDH increased at discharge in both groups. The increases in AST (100.3% vs %39.4, p=0.043) and LDH (24.6% vs 9%, p=0.004) levels were observed more frequently in the FAV group compared to HCQ/AZ.

The levels of CK decreased significantly in the FAV group at discharge [167.6 (SD; 212) vs 110.12 (SD; 162.8), p=0.003]. Although there was a decrease in the HCQ group, it was not significant [118.2 (SD; 136) vs 87.7 (SD; 138.3), p=0.105]. Overall, there was no significant difference between the groups in terms of changes in CK levels at admission and discharge [34.3% vs 25.8%, p=0.071].

The changes in levels of CRP (p=0.167 at admission and p= 0.957 at discharge), procalcitonin (p=0.015 at admission and p= 0.121 at discharge),, and D-dimer (p=0.513 at admission and p= 0.383 at discharge), at admission and discharge were similar in any of the treatment arms. Both treatment groups were also comparable (See Table 2).

Finally, serum levels of ferritin and fibrinogen increased significantly during hospital stay in both groups whereas that of albumin decreased. The changes were similar in both treatment arms (See Table 2).

Although uric acid levels were mildly low in HCQ/AZ group at admission (5.13 vs 5.74 mg/dL), there were no statistical differences between the two treatment groups in terms of both uric acid levels at discharge (5.56 vs 5.01, p=0.164) and elevation of uric acid levels after treatments (p=0.399 for FAV group and p=0.427 for HCQ plus AZ group).

Only one (2.4%) patient in the HCQ/AZ group had nausea / vomiting whereas none who received FAV had any gastrointestinal discomfort. On the other hand, 9 (21.4%) patients in the FAV group and 4 (9.5%) patients in the HCQ/AZ group had more than 3-fold (but less than 5-fold) elevation in hepatic transaminases. There was no statistical difference between the groups (p = 0.227).

DISCUSSION

In this study, we showed that FAV was not superior to HCQ/AZ in terms of reducing transfer to ICU or exitus or the length of hospital stay, and although the levels of AST and LDH increased more frequently in the FAV group, both treatment regimens had similar effects in the values of laboratory tests at admission and discharge.

The efficacy of FAV in the treatment of COVID-19 is controversial. Early clinical studies with FAV from China showed reduction in viral load as well as improvement in clinical and radiological outcomes [15,25,26]. Two randomized trials failed to show that FAV was superior to CQ or HCQ. The efficacy of FAV was found to be similar to that of CQ for treatment of mild to moderate COVID-19 [27]. In the mentioned study, there were 48 patients in the CQ arm and 48 in the FAV arm. The length of hospital stay was shorter, and the need for mechanical ventilation was less among FAV-treated patients, but this did not reach a statistical significance. Our study also supports the similar efficacy of FAV to HCQ plus AZ for treatment or reducing transfer to ICU or exitus or the length of hospital stay in mild

Table 1. The distribution of the patients' baseline characteristics according to treatments both in the unmatched and propensity-score matching analytic samples.

	Unmatched, n=260			Matched, n=82		
	Favipravir n= 215	HCQ plus AZ n= 45	*P*	Favipravir n= 42	HCQ plus AZ n= 42	*P*
Age, mean (SD), year	59.32	46.69	**<0.001**	51.38 (17.152)	47.31 (15.203)	0.253
Sex, n (%)			0.820			1.0
Female	112 (52.1)	22 (48.9)		21 (50)	20 (47.6)	
Male	103 (47.9)	23 (51.1)		21 (50)	22 (52.4)	
Symptoms, n (%)						
Fever	131 (60.9)	27 (60)	1.0	25 (59.5)	25 (59.5)	1.0
Cough	115 (53.5)	30 (66.7)	0.146	23 (54.8)	29 (69)	0,261
Dyspnea	57 (26.5)	8 (17.8)	0.298	10 (23.8)	7 (16.7)	0.587
Myalgia	137 (63.7)	35 (77.8)	0.101	27 (64.3)	33 (78.6)	0,227
Nausea/Vomiting	23 (10.7)	9 (20)	0.139	5 (11.9)	7 (16.7)	0.755
Diarrhea	31 (14.4)	4 (8.9)	0.454	4 (9.5)	3 (7.1)	1.0
Headache	47 (21.9)	16 (35.6)	0.079	5 (11.9)	15 (35.7)	0.021
Sore Throat	31 (14.4)	15 (33.3)	**0.005**	6 (14,3)	14 (33.3)	0.073
Loss of Smell	14 (6.5)	5 (11.1)	0.340	1 (2.4)	4 (9.5)	0.360
Loss of Taste	12 (5.6)	2 (4.4)	1.0	1 (2.4)	2 (4.8)	1.0
Co-mobordities, n (%)				20 (47.6)	15 (35.7)	0.376
Diabetes mellitus	58 (27)	6 (13.3)	0.082	7 (16.7)	6 (14.3)	1.0
Hypertension	103 (47.9)	12 (26.7)	**0.015**	14 (33.3)	12 (28.6)	0.813
CAD	57 (26.5)	7 (15.6)	0.173	11 (26.2)	7 (16.7)	0.425
CHF	16 (7.4)	2 (4.4)	0.747	1 (2.4)	2 (4.8)	1.0
COPD	30 (14)	2 (4.4)	0.129	2 (4.8)	2 (4.8)	1.0
Malignancy	25 (11.6)	2 (4.4)	0.187	2 (4.8)	2 (4.8)	1.0
CKD	15 (7.0)	2 (4.4)	0.745	2 (4.8)	2 (4.8)	1.0
Immunsupressive treatment, n (%)	26 (12.1)	2 (4.4)	0.186	3 (7.1)	2 (4.8)	1.0
Admission						
Fever, mean (SD), °C	37.76 (1.02)	37.45 (0.96)	**0.047**	37.5 (1.07)	37.47 (0.93)	0.817
Fever, n (%) *						
< 38 C	90 (46.9)	29 (65.9)	**0.022**	17 (40.5)	17 (40.5)	1.0
> 38 C	102 (53.1)	15 (34.1)		25 (59.5)	25 (59.5)	
Respiratory rate, mean (SD)	20.8 (4.3)	19.48 (3.3)	**0.016**	20.61 (3.41)	19.6 (3.34)	0.098
Respiratory rate, n (%)						
< 22/min	131 (60.9)	38 (84.4)	**0.005**	33 (78.6)	35 (83.3)	0.781
> 22/min	84 (39.1)	7 (15.6)		9 (21.4)	7 (16.7)	
Saturation, mean (S.D)	93.8 (3.81)	95.81 (2.93)	**<0.001**	94.45 (3.26)	95.75 (2.98)	0.009
Oxygen Support, n (%)						
Not required	170 (79.1)	41 (91.1)	0.095	36 (85.7)	38 (90.5)	0.736
Nasal oxygen	45 (20.9)	4 (8.9)		6 (14.3)	4 (9.5)	
Disease Severity						
Moderate, n (%)	192 (89.3)	42 (93.3)	**0.587**	40 (95.2)	39 (92.9)	1.0
Severe, n (%)	23 (10.7)	3 (6.7)		2 (4.8)	3 (7.1)	
Outcome						
Length of Stay, mean (SD), days	9.93 (5.49)	7.96 (3.35)	**0.027**	9.02 (6.403)	8.14 (3.397)	0.903
ICU transfer, n (%)	17 (7.9)	0 (0.0)	**0.031**	1 (2.4)	0 (0.0)	0.250
Exitus	7 (3.3)	1 (2.2)		0 (0.0)	1 (2.4)	
Discharged	191 (88.8)	44 (97.8)		41 (97.6)	41 (97.6)	

HCQ; Hydoxychloroquine, AZ; Azithromycin, CAD: Coronary Artery Disease, CHF: Chronic Heart Failure, COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease, °C: degree Celcius; *missing variables

Table 2. The comparison of Favipiravir with hydroxychloroquine + azithromycin therapies in terms of laboratory values alterations between the first (at admission) and the last day of hospitalization (discharge).

	Admission	*P*[1]	Discharge	*P*[2]	*Δ P*
Leukocyte (/mm^3), mean (SD)					
Favipiravir, n=42	5192.5 (2097)	0,830	5727.5 (2723)	0.593	0.361
HCQ plus AZ, n=42	5121 (1595.5)		5734.2 (1914)		0.112
Neutrophil (/mm^3), mean (SD)					
Favipiravir, n=42	3402.2 (1792.8)	0.731	3417.3 (2399.5)	0.217	0.397
HCQ plus AZ, n=42	3441.3 (1256.8)		3455.5 (1341.8)		0.766
Lymphocyte (/mm^3), mean (SD)					*P**= 0.956
Favipiravir, n=42	1202.3 (581)	0.564	1518.3 (794.2)	0.715	0.001
HCQ plus AZ, n=42	1193.7 (409.2)		2031.8 (2980.8)		0.001
Platelet (/mm^3), mean (SD)					*P**= 0.280
Favipiravir, n=42	195.5 (62.8)	0.132	241.8 (105.4)	0.497	0.002
HCQ plus AZ, n=42	172.5 (51.2)		254.6 (118.7)		0.000
Aspartate aminotransferase (AST) (U/L), mean (SD)					*P**= 0.043
Favipiravir, n=42	26.3 (9.3)	0.272	52.7 (47.5)	0. 454	0.000
HCQ plus AZ, n=42	30.7 (11.5)		42.8 (36.6)		0.009
Alanine aminotransferase (ALT) (U/L), mean (SD)					*P**= 0.070
Favipiravir, n=42	24.5 (19.7)	0.420	63.9 (60.3)	0.338	0.000
HCQ plus AZ, n=42	29.3 (16.8)		46.9 (42.1)		0.003
Lactate dehydrogenase (LDH) (U/L), mean (SD)					*P**= 0.004
Favipiravir, n=42	235.8 (106)	0.532	293,9 (104.1)	0.003	0.002
HCQ plus AZ, n=42	221.8 (103.5)		223.8 (96.9)		0.876
Creatin Kinaz (U/L), mean (SD)					*P**= 0.071
Favipiravir, n=42	167.6 (212)	0.613	110.12 (162.8)	0.992	0.003
HCQ plus AZ, n=42	118.2 (136)		87.7 (138.3)		0.105
C-reactive protein (mg/dL), mean (SD)					
Favipiravir, n=42	2.3 (2.1)	0.167	2.7 (2.9)	0.957	0.857
HCQ plus AZ, n=42	2.0 (2.3)		3.8 (5.9)		0.106
Procalcitonin (ng/mL), mean (SD)					*P**= 0.382
Favipiravir, n=42	0.63 (2.9)	0.015	0.13 (0.36)	0.121	0.400
HCQ plus AZ, n=42	0.06 (0.1)		0.05 (0.05)		0.932
D-dimer (mg/L), mean (SD)					
Favipiravir, n=42	0.77 (1.5)	0.513	0.71 (1.0)	0.383	0.851
HCQ plus AZ, n=42	0,75 (1.1)		0,75 (1.1)		0.681
Fibrinogen (mg/dL), mean (SD)					P*= 0.849
Favipiravir, n=42	380.2 (83.4)	0.934	448.8 (134.3)	0.860	0.006
HCQ plus AZ, n=42	351.3 (80.7)		435,4 (176,8)		0.021
Ferritin (µg/L) , mean (SD)					*P**= 0.096
Favipiravir, n=42	269.4 (554.3)	0.858	567.9 (992.1)	0.417	0.000
HCQ plus AZ, n=42	258.4 (628,8)		411.2 (903.6)		0.000
Creatinin (mg/dL), mean (SD)					*P**= 0.222
Favipiravir, n=42	0.95 (0.3)	0.141	0.84 (0.25)	0.264	0.002
HCQ plus AZ, n=42	0.83 (0.3)		0.78 (0.26)		0.024
Albumin (g/dL) , mean (SD)					*P**= 0.721
Favipiravir, n=42	3.97 (0.42)	0.323	3.60 (0.45)	0.400	0.000
HCQ plus AZ, n=42	3.94 (0.52)		3.59 (0.67)		0.000
Uric acid (mg/dL), mean (SD)					
Favipiravir, n=42	5.74 (1.61)	0.048	5.56 (2.03)	0.164	0.399
HCQ plus AZ, n=42	5.13 (1.90)		5.01 (1.62)		0.427

P[1] ; differences between parameters on admission, P[2]; differences between parameters at discharge, ΔP; differences between parameters (discharge - admission), P*; differences of alterations between groups

to moderate COVID-19 patients. Another recent study from Egypt compared FAV (50 patients) and HCQ plus oseltamivir (50 patients) in the treatment of mild and moderate COVID-19 cases [28], They concluded FAV was a safe effective alternative for HCQ in these patients. The average onset of SARS-CoV-2 PCR negativity was 8.1 and 8.3 days in HCQ-arm and FAV-arm, respectively; 55.1% of the patients on HCQ-arm became PCR-negative on/or before 7th day from diagnosis compared to 48% in FAV-arm (p=0.7). Four patients in FAV arm developed transient transaminitis whereas heartburn and nausea were reported in about 20 patients in HCQ-arm. Only one patient in HCQ-arm died after developing acute myocarditis that resulted in acute cardiac failure [28].

A recent meta-analysis did not reveal any significant difference between the intervention and the comparator on fatality rate (OR 1.11, 95% CI 0.64-1.94) and mechanical ventilation requirement (OR 0.50, 95% CI 0.13-1.95). There is no significant difference in fatality rate and mechanical ventilation requirement between FAV treatment and the standard of care in moderate and severe COVID-19 patients [29]. The results of our study support this meta-analysis and are valuable because of propensity matching.

The safety of FAV was evaluated in a review of 29 studies with a total of 4,299 participants and an estimated 175 person-years-of-follow-up [30]. There were significantly fewer gastrointestinal adverse events on FAV arm versus the comparators. The patients who received FAV showed significantly more uric acid elevations than those treated with comparators [5.8% vs 1.3%; P<0.0001]. Elevation in liver function tests were not observed. In our study, we could not detect any difference in terms of adverse effects (nausea/vomiting, liver enzymes elevation) between the two treatment groups. Only one (2.4%) patient in the HCQ/AZ group had nausea/vomiting.Doi et al. reported a total of 144 adverse events among 82 patients who received FAV; the most common was hyperuricemia (84%), followed by increases in serum triglyceride (11.0%) and serum ALT levels (8.5%) (20). In a prospective, observational study that included 174 hospitalized patients in COVID-19 wards, nausea, vomiting, and increase in transaminase levels were found to be higher in FAV group than those HCQ and AZ group [31]. In a study, pretreatment serum uric acid level has not found as a surrogate marker for the outcome of favipiravir treatment in COVID-19 patients, however, post-treatment uric acid levels were not observed in this study [32]. In our study, the pre-treatment levels were similar to mentioned study [32]; in addition, we did not observe a significant increase in uric acid levels after both FAV and HCQ/AZ treatments. In contrast, a study from Tokyo showed a high incidence of uric acid elevation, with regard to the established standards, in COVID-19 patients who received FAV therapy. The typical signs and symptoms such as gout and urinary stones were not observed in this study; however, uric acid levels increased more than 2.0-fold in 50% of these patients, and uricemia of moderate to severe intensity was recorded. In addition, the median onset time of uric acid elevation was 4.5 days [33]. The dosage of favipiravir and younger patient age were two potential risk factors for uric acid elevation. The dose of FAV in this study were higher than our study. Although the mentioned study [33] showed that uric acid levels may increase in high-dose FAV, it should be recommended to monitor uric acid levels closely in high risk patients who treated with FAV.

Inconsistent with Doi's study [20], there was no significant increase in ALT in the group using FAV, but a significant increase was observed in both AST and LDH with FAV than the HCQ/AZ treatment. However, it must be noted that patients who developed an adverse event that necessitated discontinuation of treatment were excluded in this study.

The primary outcome in the present study was the influence of FAV on some laboratory tests. During the course of COVID-19 infection, lymphopenia develops, the levels of some inflammatory parameters such as procalcitonin, CRP, ferritin and fibrinogen levels as well as hematological parameters such as D-dimer may increase [24] and these alterations have been reported to be of prognostic significance [24]. Even though improvement in these parameters could be expected with an effective drug such as FAV treatment, we could find no difference. On the contrary, a more significant decrease in d-dimer and CRP values in the group that received Favipiravir after HCQ before discharge compared to the group that received Favipiravir alone or HCQ alone was found in a study. However, the authors interpreted

the situation by the relationship between CRP and d-dimer reduction and disease recovery [34]. In our study the comparison between FAV and HCQ/AZ is insignificant in this regard. In the mentioned study [34], an evaluation was made on the 5th day independent of recovery and/or discharge. The comparison made when the patients met the discharge criteria could be more significant as in our study.

Our study has some limitations. As this was a retrospective study, we were unable to evaluate control imaging or time to PCR negativity as well as time to improvement in clinical parameters. The length of hospital stay was similar for both treatment arms (9.02 days vs 8.14 days, P=0.903), and all patients were afebrile for at least 48 hours and did not require supplemental oxygen at the time of discharge as per local guidelines. Although the number of patients seems to be low due to the study method, our study is valuable in that it presents real-life data.

In conclusion, FAV was not superior to HCQ/AZ in terms of reducing transfer to ICU or exitus or length of hospital stay. In addition, there were no differences in the change of laboratory parameters with a prognostic value in the course of COVID-19 infection between these two treatment modalities.

Author contribution

Study conception and design: ÖU, OAU, and NÇB; data collection: OAU, MÇS, and GTD; analysis and interpretation of results: OAU, MÇS, GTD, NÇB, SK, ÖU; draft manuscript preparation OAU, and ÖU. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Non-interventional Clinical Research Ethics Board (Protocol no. GO 20/353/31/03/2020).

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Conflict of interest

The authors declare that there is no conflict of interest.

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