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

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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 been 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 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 multidisciplinary 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 | \( P \) | Unmatched, n=260 | Matched, n=82 | \( P \) |
|------------------------|------------------|--------------|---------|------------------|--------------|---------|
| Age, mean (SD), year   | 59.32            | 46.69        | <0.001  | 51.38 (17.152)   | 47.31 (15.203) | 0.253   |
| Sex, n (%)             |                  |              | 0.820   |                  |              |         |
| 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)         | 4 (4.4)      | 1.0     | 1 (2.4)          | 2 (4.8)      | 1.0     |
| Symptom co-morbordities, n (%) | | | | | | |
| 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 (11.5)        | 3 (6.5)      | 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     |
| Immunosuppressive treatment, n (%) | | | | | | |
| 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)    | 0.173   | 25 (59.5)        | 25 (59.5)    | 1.0     |
| 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)     | 0.187   | 9 (21.4)         | 7 (16.7)     | 1.0     |
| Saturation, mean (SD)  | 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: Hydroxychloroquine, AZ: Azithromycin, CAD: Coronary Artery Disease, CHF: Chronic Heart Failure, COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease, °C: degree Celsius; *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         | \( P^2 \) | \( \Delta P \) |
|------------------|--------------------|-----------|-------------------|-----------|--------------|
| 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) | 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) | 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) | 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) | 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) | 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) | 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) | 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) | 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) | 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) | 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) | 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, \( \Delta P \): differences between parameters (discharge - admission), \( P^* \): differences of alterations between groups
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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.

REFERENCES
[1] World Health Organization. WHO Coronavirus (COVID-19) Dashboard. Available from: https://covid19.who.int
[2] World Health Organization (WHO). New updates. Latest news from WHO on COVID-19 and other breaking health stories. Updated on 21 January 2021. Available from: https://www.who.int/news-room/news-updates
[3] World Health Organization (WHO). Therapeutics and COVID-19: living guideline. Updated on 31 March 2021.
[4] Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International journal of antimicrobial agents. 2020;56(1):105949.
[5] Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. bmj. 2020;369.
[6] Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. New England Journal of Medicine. 2020;382(25):2411-8.
[7] Piszczałowski, Christopher R, and Jason Powell. “Emergency authorization of chloroquine and hydroxychloroquine for treatment of COVID-19.” Annals of Pharmacotherapy 54.8 (2020): 827-831.
[8] World Health Organization. “Solidarity” clinical trial for COVID-19 treatments. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments.
[9] RECOVERY Collaborative Group. “Effect of hydroxychloroquine in hospitalized patients with Covid-19.” New England Journal of Medicine 383.21 (2020): 2030-2040.
[10] Simmering JE, Polgreen LA, Polgreen PM, Teske RE, Comellas AP, Carter BL. The Cardiovascular Effects of Treatment with Hydroxychloroquine and Azithromycin. Pharmacotherapy. 2020;40(9):978-983. doi:10.1002/phar.2445
[11] Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research 2020;30(3):269-71.
[12] Joshi S, Parkar J, Ansari A, et al. Role of favipiravir in the treatment of COVID-19. International Journal of Infectious Diseases. 2020.
[13] Furuta Y, Gowen BB, Takahashi K, et al. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Antiviral Research 2013;100(2):446-54.
[14] Bouazza N, Treluyer J-M, Foissac F, et al. Favipiravir for children with Ebola. Lancet 2015;385(9968):603-4.
[15] Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: An open-label control study. Engineering (Beijing) 2020;6(10):1192-8.
[16] Yamamura H, Matsuura H, Nakagawa J, et al. Effect of favipiravir and an anti-inflammatory strategy for COVID-19. Critical Care 2020;24(1):413.
[17] Ivashchenko AA, Dmitriev KA, Vostokova NV, et al. AVIFAVIR for treatment of patients with moderate COVID-19: Interim results of a phase II/III multicenter randomized clinical trial. Clinical Infectious Disease 2020 Aug 9;ciaa1176.
[18] Fu D, Cao R, Zhao L, et al. Oral favipiravir for patients with delayed SARS-CoV-2 viral RNA clearance: a case series. Crital Care 2020;24(1):578.
[19] Doi K, Ikeda M, Hayase N, et al. Nafa mostat mesylate treatment in combination with favipiravir for critically ill patients with Covid-19: a case series. Crital Care 2020;24(1):392.
[20] Doi Y, Hibino M, Hase R, et al. “A prospective, randomized, open-label trial of early versus late favipiravir therapy in hospitalized patients with COVID-19.” Antimicrobial agents and chemotherapy 64.12 (2020).
[21] Kocayiğit H, Özmen Süner K, Tomak Y, et al. Observational study of the effects of Favipiravir vs Lopinavir/Ritonavir on clinical outcomes in critically ill patients with COVID-19. Journal of Clinical Pharmacy and Therapeutics 2020 Oct 31.
[22] Lou Y, Liu L, Yao H, et al. Clinical outcomes and plasma concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 patients: An exploratory randomized, controlled trial. European Journal of Pharmaceutical Sciences 2020:105631.
[23] Republic of Turkey Ministry of Health Directorate General of Public Health (2020). COVID-19 (SARS-CoV-2 Infection) Guide (in Turkish). Available from: https://covid19.saglik.gov.tr/Eklenti/39061/0/covid-19rehberieriskinhastatedavisi.pdf
[24] World Health Organization (WHO). COVID-19 Clinical management: living guidance. Updated on 11 January 2021.
[25] Chen C, Zhang Y, Huang J, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. MedRxiv (2020).
[26] Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nature Reviews Drug Discovery 2020;19:149-50.
[27] Dabbous HM, Abd-Elsalam S, El-Sayed MH, et al. Efficacy of favipiravir in COVID-19 treatment: a multi-center randomized study. Archives of Virology 2021;166(3):949-954.
[28] Dabbous HM, El-Sayed MH, El Assal G, et al. Safety and efficacy of favipiravir versus hydroxychloroquine in management of COVID-19: A randomised controlled trial. Scientific Reports. 2021;11(1):7282.
[29] Özlüşen B, Kozan Ş, Akcan RE, et al. Effectiveness of favipiravir in COVID-19: a live systematic review. Eur J Clin Microbiol Infect Dis. 2021;40(12):2575-2583.
[30] Victoria P, Pepperrell T, Hill A. A review of the safety of favipiravir-a potential treatment in the COVID-19 pandemic?. Journal of virus eradication 2020; 6 (2): 45-51.
[31] Çalık Başaran N, Uyaroğlu OA, Telli Dizman G, et al. Outcome of noncritical COVID-19 patients with early hospitalization and early antiviral treatment outside the ICU. Turk J Med Sci. 2021; 30;51(2): 411-420.
[32] Inkaya AÇ, Kara E, Çalik Başaran N, et al. Pretreatment serum uric acid level is not a surrogate marker for the outcome of favipiravir treatment in COVID-19 patients. Turk J Med Sci. 2021; 51: 2786-2788.
[33] Yuki H, Sadako Y, Kazuhiro M, et al. Evaluation of risk factors for uric acid elevation in COVID-19 patients treated with favipiravir. Diagn. Microbiol. Infect. Dis. 2022; 115640.
[34] Çilingir BM, Sunnetcioglu A, Yildiz H, et al. What Is The Case of More Accessible Treatment Options in COVID 19: Comparison of Hydroxychloroquine and Favipiravir Based on Laboratory Values. Eastern Journal of Medicine, 2021; 26(3): 426-432.