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Comparing ICU admission rates of mild/moderate COVID-19 patients treated with hydroxychloroquine, favipiravir, and hydroxychloroquine plus favipiravir

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ABSTRACT

Background: In this study, we aimed to compare the intensive care unit (ICU) admission rate of hospitalized mild/moderate COVID-19 patients treated with hydroxychloroquine (HCQ), favipiravir, and HCQ plus favipiravir.

Methods: Single center retrospective designed observational study conducted in Ankara City Hospital. Patients who were hospitalized between March 15, 2020 and June 1, 2020 in COVID-19 inpatient clinics with laboratory confirmed diagnosis of COVID-19 were included in the study. An inverse probability of treatment weighting (IPTW) for multiple treatment groups approach was used to balance the differences in several variables on admission.

Results: Among 2441 patients hospitalized with diagnosis of COVID-19 during the study period, 824 were eligible for the analysis. Median age of patients was 42 (18–93 years). Among all, 347 (43.2%) of the patients had mild disease, 470 (56.8%) had pneumonia. Propensity scores ranged from 0.1841 to 0.9381 in the HCQ group, from 0.03643 to 0.29885 in the favipiravir group, and from 0.03542 to 0.56184 in the HCQ plus favipiravir group. After IPTW for multiple treatment groups was applied, all the covariates in the planned propensity score had weighted standardized effect sizes below 10% which were ranged from 0.005 to 0.092. Multivariate analysis of treatment effect (adjusted effect of treatment) was indicated that there is no statistically significant difference between HCQ, favipiravir, and HCQ plus favipiravir treatment. After using combination of SMOTE and Bootstrap resampling approach, we found no statistically significant difference between HCQ and HCQ plus favipiravir groups in terms of ICU admission. However, compared with the HCQ group, ICU admission rate was statistically significantly higher in the favipiravir group. We obtained the similar results after the sensitivity analysis.

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Conclusions: HCQ with or without favipiravir treatment is associated with reduced risk of ICU admission compared to favipiravir alone in mild to moderate COVID-19 adult patients.

Introduction

It is evident now that the world was not prepared for such a pandemic that rapidly spread to hundreds of countries causing more than a million deaths even though two former coronavirus outbreaks: severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) were recently experienced. The COVID-19 pandemic, which turned 2020 into a nightmare, is a challenging disease that appeared to be just an upper respiratory tract infection at first but showed its dark side later. Eventually, it was understood that it was a complicated disease which could cause systemic inflammation and even thrombosis.

Prevention is simple (or not *complicated*). If you play with the rules, you win. However, it is not possible to say the same for the treatment since we neither know the rules nor the real target. Is it the virus, the host, or both? There is no approved treatment with proven efficacy. While the doctors were dealing with a large number of COVID-19 patients on one hand, they tried to carry out studies to reveal the virus characteristics and find an effective treatment on the other. Although we have left more than half of the year behind and encountered millions of patients, some points of the SARS-CoV-2 virus have still not been elucidated. Virus dynamics in different hosts remains unclear. Scientists all over the world are working in a race to find both vaccine and effective treatment. Although hopes are high, more time is needed for the vaccine to become commonly applicable and development of a new drug generally requires more than 10 years. At this point, repurposing existing drugs which are effective for viruses that have similar genome with SARS-CoV-2 lend a helping hand to physicians. Currently, several drugs have been shown to have some in-vitro activity against betacoronaviruses including, interferons, lopinavir/ritonavir, ribavirin, chloroquine (CQ), hydroxychloroquine (HCQ), remdesivir, and favipiravir. Some of these drugs found their place in different guidelines, while some appeared only in studies. World Health Organization (WHO) launched "Solidarity" trial for finding the effective treatment of COVID-19 and compared four treatment regimens (remdesivir, lopinavir/ritonavir, lopinavir/ritonavir plus interferon beta-1a, and CQ/HCQ) with standard of care. Now, thousands of patients have been recruited in 35 countries [1]. On June 17th, 2020, WHO announced that HCQ arm of the Solidarity Trial was being stopped based on evidence from the Solidarity trial and UK's Recovery trial which both revealed that HCQ does not reduce the mortality of hospitalized COVID-19 patients. WHO guideline for clinical management of COVID-19 recommends that these drugs not be administered as treatment outside of the context of clinical trial [2]. On June 15, The Food and Drug Administration (FDA) revoked the emergency use authorization (EUA) that permitted the use of CQ and HCQ for treatment of COVID-19. After this announcement, Centers for Disease Control (CDC) updated the COVID-19 treatment guideline and made a recommendation which is rated as AI against the use of CQ or HCQ [3].

Favipiravir is not included in neither the WHO guideline nor the CDC guideline. Chinese guideline's last version (7th) recommends alpha-interferon, lopinavir/ritonavir, ribavirin, and chloroquine phosphate [4]. In Turkey, COVID-19 Scientific Board of the Ministry of Health prepared and regularly updated the treatment guideline [5]. Both favipiravir and HCQ are recommended for mild, moderate, and severe patients diagnosed or suspected with COVID-19 [5].

Randomized double-blind clinical trials are the ideal studies since they do not contain bias and they provide reliable data. Most of the randomized controlled studies compare the antivirals with standard of care which includes no treatment rather than supportive treatment. The ethical aspect of leaving a moderate or severe COVID-19 patient without treatment is highly controversial. However, observational studies in a real-world setting can also provide important results if they are designed well. In this study, we aimed to compare the intensive care unit (ICU) admission rate of hospitalized mild to moderate COVID-19 patients treated with HCQ, favipiravir, and HCQ plus. As of the time this paper is submitted, no studies existed comparing these three treatment regimens.

Materials and methods

Study design

Single center retrospective designed observational study conducted in Ankara City Hospital which is the largest hospital in Europe with a total of 3811 beds (723 of which are intensive care unit beds) and the major pandemic response center in the capital of Turkey. Patients who were hospitalized between March 15, 2020 and June 1, 2020 in COVID-19 inpatient clinics with laboratory confirmed diagnosis of COVID-19 were included in the study.

Inclusion criteria:

- Patients with a positive SARS-CoV-2 PCR test for nasopharyngeal/oropharyngeal, sputum, or lower respiratory tract samples
- Patients 18 years or older age
- Patients with signs and symptoms consistent with COVID- 19
- Patients who completed treatment duration in hospital

Exclusion criteria:

- Pregnancy
- Patients with severe COVID-19 on admission and/or those died within the 72 h after admission
- Patients who have been involved in any interventional studies
- Patients with severe hepatic impairment on admission (Child Pugh grade C or alanine aminotransferase higher than fivefold the upper limit)
- Patients already receiving HCQ for treatment of diseases other than COVID-19

We classified COVID-19 patients according to the WHO guideline [2]. Mild disease group consisted of symptomatic patients without evidence of pneumonia or hypoxia. Moderate disease group consisted of patients with pneumonia without signs of severe pneumonia like <90% oxygen saturation (spO2) on room air.

We implemented a central database for data collection. Demographic features such as age, gender, symptoms and onset time, comorbidities, medications, physical examination, fever, and vital signs were recorded. Laboratory tests such as complete blood count, blood chemical analysis (including renal and liver function), coagulation parameters, acute phase reactants (ferritin, C-reactive protein (CRP), procalcitonin (PCT) were obtained. Laboratory analysis for PCR were carried out at Public Health Institute of Turkey

Table 1
Characteristics of the patients.

	All patients (n, %)	HCQ based (n = 604) (n, %)	Favi based (n = 100) (n, %)	Favi+ HCQ (n = 120) (n, %)
Demographic characteristics				
Age, years (median, min–max)	42 (18–93)	39 (18–93)	51 (18–81)	51 (20–89)
18–30	189 (22.9)	176 (29.0)	8 (8.0)	5 (4.2)
31–45	279 (33.7)	211 (34.8)	28 (28.0)	40 (33.3)
46–65	273 (33.0)	173 (28.5)	48 (48.0)	52 (43.3)
>65	86 (10.4)	47 (7.7)	16 (16.0)	23 (19.2)
Sex, male (n, %)	436 (52.7)	305 (50.2)	56 (56.0)	75 (62.5)
Preexisting conditions				
Smoking status (n = 490)				
Never	358 (73.1)	254 (72.0)	50 (72.5)	54 (79.4)
Current or former	132 (26.9)	99 (28.0)	19 (27.5)	14 (20.6)
Any comorbidity (var)	290 (35.1)	174 (28.7)	52 (52.0)	64 (53.3)
Number of comorbidities				
≤1	676 (81.7)	521 (85.8)	71 (71.0)	84 (70.0)
≥2	151 (18.3)	86 (14.2)	29 (29.0)	36 (30.0)
Diabetes	91 (11.0)	53 (8.7)	17 (17.0)	21 (17.5)
Chronic cardiac disease				
Hypertension	153 (18.5)	89 (14.7)	25 (25.0)	39 (32.5)
Coronary artery disease	45 (5.4)	25 (4.1)	8 (8.0)	12 (10.0)
Chronic pulmonary disease	63 (7.6)	38 (6.3)	14 (14.0)	11 (9.2)
Neurological diseases	9 (1.2)	6 (1.2)	1 (1.0)	2 (1.7)
Chronic renal disease	9 (1.1)	6 (1.0)	1 (1.0)	2 (1.7)
Malignancy	18 (2.2)	9 (1.5)	2 (2.0)	7 (5.8)
Regular drug usage for comorbidity	242 (29.4)	145 (24.0)	40 (40.0)	57 (47.5)
ACEI	44 (5.3)	29 (4.8)	7 (7.0)	8 (6.7)
ARB	36 (4.4)	21 (3.5)	6 (6.0)	9 (7.5)
ACEI or ARB	78 (9.4)	49 (8.1)	13 (13.0)	16 (13.3)
Oral anticoagulant	36 (4.4)	18 (3.0)	10 (10.0)	8 (6.7)
Clinical features				
Time between onset of symptoms to admission (median, min–max, IQR)	3 (0–30, 2–6)	3 (0–30, 2–5)	3 (1–15, 2.5–7)	4 (1–30, 3–7)
Fever	281 (34.0)	192 (31.9)	36 (37.6)	53 (42.9)
Cough	414 (50.1)	296 (48.8)	50 (50.0)	68 (56.7)
Dyspnea	163 (19.7)	94 (15.5)	30 (30.0)	39 (32.5)
Sore throat	156 (18.9)	118 (19.4)	21 (21.0)	17 (14.2)
Disease severity				
Quick SOFA (n = 703)				
≤1	697 (99.3)	517 (98.9)	88 (92.9)	92 (95.3)
≥2	5 (0.7)	6 (1.1)	7 (7.1)	5 (4.7)
Body temperature, >37.8 °C	112 (13.5)	65 (10.7)	15 (15.0)	32 (26.7)
Respiratory rate (n = 716)	20 (14–40, 18–22)	20 (14–28, 18–22)	20(16–40,18–22)	20(14–30,18–22)
Heart rate > 100/min	14 (1.7)	4 (0.7)	2 (2.0)	8 (6.7)
Oxygen saturation level % (n = 738)	96 (85–99, 95–98)	97 (87–99, 96–98)	96 (86–99, 94–98)	95 (85–99, 93–97)
Laboratory findings (median, IQR)				
White blood cell count - ×109/L	5220 (4245–6530)	5140 (4230–6430)	5600 (4500–7030)	5100 (3980–6450)
Neutrophil count- $\times 10^9$/L	3200 (2400–4220)	3120 (2260–4100)	3430 (2740–4530)	3470 (2520–4850)
Lymphocyte count- $\times 10^9$/L	1300 (960–1820)	1365 (1000–1900)	1330 (1040–1800)	1060 (760–1402.5)
Neutrophil to lymphocyte ratio	2.2982 (1.5389–3.8191)	2.1862 (1.4476–3.6513)	2.4118 (1.7632–3.4206)	3.1154 (1.9423–4.8774)
C-reactive protein (CRP)- mg/L	0.007 (0.003–0.2035)	0.005 (0.002–0.014)	0.012 (0.004–0.04)	0.02 (0.007–0.063)
Procalcitonin (PCT) μg/L	0.03 (0.03–0.05)	0.03 (0.03–0.04)	0.03 (0.03–0.07)	0.05 (0.03–0.09)
Lactate dehydrogenase (LDH)- U/L	212.0 (185.0–265.0)	204.0 (180.0–247.5)	244 (199.75–299.5)	240 (203.0–303.0)
Aspartate transaminase (AST)- U/L	23.0 (17.0–33.0)	21 (15–30)	26 (20.75–36.25)	26.5 (20–41.75)
Alanine transaminase (ALT)- U/L	27.0 (18.5–40.0)	26 (17–39)	31.5 (23.75–42.25)	27.5 (20.25–43)
Creatinine - μmol/L	0.8 (0.67–0.94)	0.79 (067–0.91)	0.825 (0.67–0.965)	0.91 (0.71–1.035)
eGFR- ml/min/1.73 m^2	102.0 (87.0–115.0)	105 (92–117)	98.5 (81.5–109)	95 (74–107)
Creatinine kinase (CK) - μ/L	88.0 (59.0–139.0)	88 (60–131)	80 (53.5–152)	109 (65.75–166.25)
D-dimer	0.39 (0.24–0.62)	0.35 (0.22–0.58)	0.45 (0.325–0.865)	0.45 (0.3–0.84)
Ferritin, μg/L	102.0 (43.0–220.0)	91.5 (35.5–172.5)	134 (50–318)	173 (76.5–428.5)
Prothrombin time (PT)	12.0 (11.6–12.6)	12 (11.6–12.5)	12 (11.7–12.8)	12.3 (11.9–13.0)
Activated partial thromboplastin time (aPTT)	25.0 (23.5–26.5)	25.2 (23.7–26.5)	25.0 (23–26.6)	24.6 (23.35–26)
INR	1.02 (0.99–1.08)	1.02 (0.98–1.07)	1.03 (1.0–1.1)	1,045 (1.0–1.115)
Fibrinogen - g/L	3.03 (2.53–3.88)	2.9 (2.5–3.5)	3.5 (2.9–4.32)	3.64 (2.71–5.03)
Interleukin 6, pg/mL	15.0 (7.0–35.0)	12 (5.5–24.75)	35 (12–74)	22.5 (8.5–86)
Troponin, μg/L	2.5 (2.5–5.0)	2,5 (2.5–4.0)	2.5 (2.5–6.0)	4.0 (2.5–7.0)
Myoglobin, μg/L	39.0 (26.0–61.0)	34 (23–56)	46 (33–66)	54 (36.5–91)
CT (n = 793)				
Normal	189 (22.9)	172 (28.3)	9 (9.0)	8 (6.7)
Consolidation	78 (9.4)	46 (7.6)	14 (14.0)	18 (15.0)
Unilateral ground-glass opacity	160 (19.3)	127 (20.9)	11 (11.0)	22 (18.3)
Bilateral ground-glass opacity	362 (43.8)	220 (36.2)	65 (65)	77 (64.2)
Patchy infiltration	44 (5.3)	30 (4.9)	8 (8)	6 (5)
Crazy paving	18 (2.2)	9 (1.5)	3 (3.0)	6 (5.0)
Air bronchogram	8 (1.0)	6 (1.0)	1 (1.0)	1 (0.8)

Virology Reference and Research Laboratory and Ankara City Hospital Virology Laboratory. Both X-ray and computed tomography (CT) of the chest were used for radiological assessment.

The decision of treatment regimen was based on Turkish Ministry of Health COVID-19 Treatment Guideline. Standard care consisted of oxygen support, noninvasive and invasive mechanical ventilation, antibiotic treatment, vasopressor support, renal replacement therapy, and extracorporeal membrane oxygenation (ECMO) when needed. Patients who developed severe or critical disease according to the WHO definitions were evaluated by an intensive care unit (ICU) physician for ICU admission according to the Turkish Ministry of Health COVID-19 patient management guideline [5].

Treatment groups

HCQ: Patients received HCQ 2 × 400 mg tb on Day 1, 2 × 200 mg tb on Day 2–5

Favipiravir: Patients received favipiravir 2 × 1600 mg tb on Day 1, 2 × 600 mg tb on Day 2–5.

Favipiravir + HCQ: Patients received HCQ 2 × 400 mg tb + 2 × 1600 mg favipiravir tb on Day 1, 2 × 200 mg HCQ tb + 2 × 600 mg favipiravir tb on Day 2–5

Study outcome

Study outcome was need for ICU transfer during the follow up.

Statistical analysis

Descriptive statistics were presented as median (minimum - maximum value) for numerical data and frequency and percentage for categorical data. Independence between treatment groups and categorical variables were assessed using Pearson Chi-square test.

An inverse probability of treatment weighting (IPTW) for multiple treatment groups approach [6] was used to balance the differences in several variables including age, gender, existence of comorbidity, disease severity (mild disease or pneumonia), CT findings, oxygen saturation on admission. Variables of the propensity score model were planned and pre-specified before constructing outcome model. Multinomial logistic regression model was constructed to estimate each patient's propensity scores using R VGAM package [7]. Standardized differences were examined to assess balance, with a threshold of 10% designated to indicate clinically meaningful imbalance in addition to graphical evaluation using R twang package [8].

Outcome model process

The standardized baseline measurements and several other covariates including additional drug treatment (azithromycin, doxycycline, oseltamivir, Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB)), and fever were evaluated by univariate analysis to select candidate variables which could affect the outcome. A p value <0.05 was considered as significant candidate to construct multivariate quasi-binomial logistic regression model using R survey package [9].

Validation process

To validate our results and overcome the class imbalance problem combination of Synthetic Minority Oversampling Technique (SMOTE) and Bootstrap resampling approach was used, and Bootstrap Confidence Interval of the Odds ratios were reported. 1000 Bootstrap samples were drawn randomly to estimate mean Odds ratios of the treatment groups.

Table 2
Analysis of treatment effect to ICU admission after adjusting covariates by IPTW.

	Odds ratio	2.5% CI	97.5% CI
Univariate analysis			
Favipiravir (vs HCQ)	4.47	0.718	27.847
HCQ plus favipiravir (vs HCQ)	5.54	0.951	32.339
Multivariate analysis			
Favipiravir (vs HCQ)	4.41	0.569	34.159
HCQ plus favipiravir (vs HCQ)	2.44	0.248	23.970

Sensitivity analysis process

Sensitivity analysis was carried out by trimming the propensity scores above 99th percentile and estimate the average treatment effect by using the same procedure mentioned above.

Results

Among 2441 patients hospitalized with diagnosis of COVID-19 during the study period, 824 were eligible for the analysis. HCQ, favipiravir, and HCQ plus favipiravir groups consisted of 604, 100, and 120 patients, respectively. Characteristics of the patients are given in Table 1. Median age of patients was 42 years (range 18–93 years). Among all, 347 (43.2%) of the patients had mild disease, 470 (56.8%) had pneumonia. The need for ICU follow-up were observed in 3 (0.5%) patients in HCQ group, 7 (7%) in favipiravir group, and 13 (10.8%) in HCQ plus favipiravir group. None of the patients received anti-cytokine/anti-inflammatory treatments including steroids before admission to the ICU.

Propensity scores ranged from 0.1841 to 0.9381 in the HCQ group, from 0.03643 to 0.29885 in the favipiravir group, and from 0.03542 to 0.56184 in the HCQ plus favipiravir group. After IPTW for multiple treatment groups was applied, all the covariates in the planned propensity score had weighted standardized effect sizes below 10% which were ranged from 0.005 to 0.092.

Outcome model results

Analysis of treatment effect to ICU admission after adjusting covariates by IPTW is given in Table 2. Univariate analysis of treatment effect after adjusting covariates (age, gender, existence of comorbidity, disease severity, CT findings, oxygen saturation on admission) by IPTW revealed no statistically significant difference between treatment groups in terms of ICU requirement. We evaluated baseline values of white blood cell, neutrophil lymphocyte ratio, ferritin, hemoglobin, platelet, glomerular filtration rate, albumin, creatine kinase, CRP, procalcitonin, troponin, coagulation parameters, presence of fever and additional drug treatment (azithromycin, doxycycline, oseltamivir, ACE inhibitors, and ARB) variables in univariate analysis to determine the candidate variables which could effect the ICU admission. In univariate analysis, neutrophil lymphocyte ratio, glomerular filtration rate, albumin, CRP, ferritin, and presence of fever were statistically significant ($p < 0.05$). Therefore, in addition to treatment effect those variables were included the multivariate model. Multivariate analysis of treatment effect (adjusted effect of treatment) was indicated that there is no statistically significant difference between HCQ, favipiravir, and HCQ plus favipiravir treatment.

Validation results

ICU admission probability after validation of results using combination of SMOTE and Bootstrap resampling approach is given in Table 3. After using combination of SMOTE and Bootstrap resampling approach, we found no statistically significant difference between HCQ and HCQ plus favipiravir groups in terms of ICU admission (Bootstrap estimates of Odds ratio and 95% Confidence

Table 3
ICU admission rates after validation of results using combination of SMOTE and Bootstrap resampling approach.

	Odds ratio[a]	2.5% CI[a]	97.5% CI[a]
Favipiravir (vs HCQ)	9.72	2.063	38.378
HCQ plus favipiravir (vs HCQ)	4.47	0.692	19.171

[a] Bootstrap estimates.

Table 4
ICU admission rates after sensitivity analysis.

	Odds ratio[a]	2.5% CI[a]	97.5% CI[a]
Favipiravir (vs HCQ)	10.06	1.912	40.882
HCQ plus favipiravir (vs HCQ)	4.32	0.652	18.726

[a] Bootstrap estimates.

Interval: 4.4, 95% CI: 0.7–19.2). However, compared with the HCQ group, ICU admission rate was statistically significantly higher in the favipiravir group (Bootstrap estimates of Odds ratio and 95% Confidence Interval: 9.7, 95% CI: 2–38.4). We obtained the similar results after the sensitivity analysis (Table 4).

Discussion

In this single center retrospective observational study on laboratory confirmed mild to moderate COVID-19 adult patients, HCQ with or without favipiravir treatment is found to be associated with reduced risk of ICU admission compared to favipiravir alone. It is difficult to make a head to head comparison of our results since there is no study in the literature which is similar to ours. However, there are studies listed in the ClinicalTrials.gov database that encompass treatment regimens researched in this study. Unfortunately, none of these studies are published yet.

There are conflicting articles regarding both HCQ and favipiravir [10–17]. However, studies conducted in different countries, with patients from differing ethnicities, with different endpoints/outcomes, and different designs should be interpreted with caution. In our study, 73.3% of patients received HCQ. These patients were more likely to be younger; have lower CRP and ferritin; and have higher lymphocyte count on admission when compared to patients receiving favipiravir or favipiravir plus HCQ treatment. They less likely had bilateral ground-glass opacity and had a lower rate of comorbidities such as diabetes, chronic cardiac disease as well. However, these differences were balanced for potential confounders as explained in "statistical analysis" section. It must be noted that the observational nature of this study makes it is impossible to be sure that no residual confounding factors remain. Therefore, conclusions drawn should be interpreted with caution.

Use of chloroquine in COVID-19 patients became a part of clinical practices after it was shown to reduce infection in human cells [18] and was noted to have a significant positive effect on both clinical outcome and viral clearance in a clinical trial by Gao et al. [19]. In light of these results, a team of experts from government and regulatory institutions concluded that chloroquine had potent activity against COVID-19 and included the drug in the guidelines for the prevention, diagnosis, and treatment of pneumonia caused by COVID-19 under the National Health Commission of the People's Republic of China [4]. Since then, HCQ has been a part of standard treatment in hospitals in China, New York, Spain, Iran, and Turkey despite the fact that recommendations of WHO and several other medical associations are against its usage (outside clinical trials). In an observational study from New York, it is reported that HCQ has no effect in lowering or increasing the risk of intubation or death compared to standard of care (hazard ratio, 1.04, 95% confidence interval, 0.82–1.32) [14]. CloroCovid-19 study, which is a randomized, phase IIb clinical trial, compared high-dosage (600 mg twice daily for 10 days) vs low-dosage CQ (450 mg twice daily on day 1 and once daily for 4 days) and concluded that higher CQ dosage is not safe for critically ill patients with COVID-19 and CQ has no benefit regarding mortality [20]. An RCT including 150 patients from 16 government COVID-19 centers in China evaluated the efficacy and safety of HCQ + standard of care vs standard of care alone in adults with mild to moderate COVID-19. Results of this study indicate that adding HCQ to standard of care did not provide viral clearance and had higher risk for adverse events [21]. A retrospective observational study from France compared HCQ (600 mg/day) vs standard care without HCQ in 181 adult patients with severe COVID-19 who required oxygen. Researchers evaluated the survival without transfer to the ICU, overall survival, survival without acute respiratory distress syndrome (ARDS), and discharge on day 21 and concluded that HCQ treatment has no positive effect [22]. Rosenberg et al. reported the in-hospital mortality rate among inpatients diagnosed with COVID-19 who received HCQ with or without azithromycin. This retrospective cohort study included 1438 patients and no statistically significant difference in mortality rates was found [17]. In an RCT from China HCQ was found to be statistically significantly better than lopinavir/ritonavir in terms of viral clearance, improvement of CT findings, and hospital discharge rate [23]. In a large multi-center retrospective observational study from United States, Arshad et al. reported that HCQ with or without azithromycin provided reduction in COVID-19 associated mortality [10]. In a large retrospective observational study conducted in France, Lagier et al. reported that treatment with HCQ and azithromycin reduced length of stay in hospital, risk of ICU transfer, and mortality in COVID-19 [24]. Similarly, retrospective observational multicenter study from Belgium among 8910 hospitalized patients with COVID-19 demonstrated that HCQ treatment is independently associated with lower in hospital mortality compared with standard care [11]. Recently completed and published CORIST Project includes 3971 laboratory confirmed COVID-19 patients from 33 centers in Italy. According to this large observational study, HCQ treatment reduces overall in-hospital mortality 30% (adjusted hazard ratio = 0.684, 95% CI: 0.617–0.758) [12]. Most of the studies regarding HCQ treatment on COVID-19 compares HCQ with standard care. To the best of our knowledge, there are no studies in the literature comparing HCQ treatment with favipiravir or combined favipiravir and HCQ treatments. Mortality was not evaluated as an outcome in our study since mild/moderate severity patients were included and number of deaths was not sufficient for reliable analysis. In addition, since no patient received standard of care alone, results were presented as comparisons of treatment regimens with each other.

Favipiravir (FPV, T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is a purine nucleic acid analog that inhibits the RNA-dependent RNA polymerase enzyme and is approved in Japan (with brand name Avigan) for the treatment of influenza. On March 2020, it was approved for the treatment of COVID-19 in China. There are far less studies related with favipiravir in the literature when compared with HCQ and none exists comparing it with HCQ or combination therapy. First clinical study of favipiravir, which was an observational study comparing favipiravir and lopinavir/ritonavir concluded that viral clearance and rate of improvement in CT were higher in favipiravir group than lopinavir/ritonavir group [25]. In a randomized controlled study conducted in Russia which included 60 laboratory confirmed COVID-19 patients with moderate severity, two different doses of favipiravir (1600 mg BID on Day 1 followed by 600 mg BID on Days 2–14 and 1800 mg BID on Day 1 followed by 800 mg BID on Days 2–14) and standard treatment were compared [15]. In the standard treatment group HCQ or CQ was used in 15 patients (75%). One patient received lopinavir/ritonavir and 4 patients received no antivirals. Although some concerns related with this study are

reported by WHO [26], in this pilot phase II/III clinical trial, viral clearance on the fifth day, time to resolution of fever, and recovery rate in CT on the 15th day were found to be significantly better in patients using favipiravir [15]. A recent randomized, open-label study including 89 asymptomatic or mildly ill COVID-19 patients from 25 hospitals across Japan evaluated early vs late favipiravir treatment (starting day 1 vs day 6). They reported no significant difference between early and late favipiravir groups in terms of viral clearance and time to resolution of fever [13].

This study has limitations that are common to all retrospective studies. Most important of all, the treatments are not randomized. However, as explained in the "statistical analysis" section, significant confounders including age, sex, comorbidities, CT, and laboratory findings were adjusted for. As mentioned before, despite the applied adjustments, the possibility of residual confounding cannot be ruled out. There is no doubt that RCTs are the optimum studies in evaluating the effectiveness of treatment. However, observational studies can also provide results in similar quality after balancing bias and patient differences in real world setting. Secondly, in this study a patient group that only received standard of care does not exist. Therefore, analysis are made through comparison of included treatment regimens. Thirdly, only mild/moderate patients were included in the study. It is not possible to generalize these results to include severe patients. Fourthly, adverse event related to the treatments have not been evaluated. It is also worth mentioning that the retrospective design of the study renders some parameters unavailable.

In conclusion, according to results obtained in this single center retrospective observational study on laboratory confirmed mild to moderate COVID-19 adult patients, both HCQ and HCQ plus favipiravir treatments are associated with reduced risk of ICU admission compared with the treatment regimen of favipiravir alone. However, these results need confirmation through randomized controlled studies with larger patient groups comprised of diverse ethnicities.

Author contributions

Concept and design of the study: RG, IH, BK, EA, AKK, FE. Data collection: IH, BK, AA, AKK, FE, OK, YTT, ZB, FMG, HNA. Data analysis: RG, IH, IA, AB, BC, Sİ, DE, SA, MC, HB. Interpretation of the data: RG, IH, BK, EA, HH, HK, OK, FE. Drafting the manuscript: RG, IH, TB, BK. Critical revision of the manuscript: IH, BK, AA, EA, SI, DE. All authors approved the final version of the manuscript.

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Ethical approval

The study was approved by the Turkish Ministry of Health and ethics board of Ankara City Hospital (No: E1-20-764).

Conflict of interest

None to declare.

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