RESEARCH

COMPARING THE EFFECTS OF HYDROXYCHLOROQUINE, FAVIPIRAVIR, AND HYDROXYCHLOROQUINE PLUS FAVIPIRAVIR ON SURVIVAL OF GERIATRIC POPULATION WITH COVID-19-RELATED PNEUMONIA: A PROPENSITY SCORE-MATCHED ANALYSIS

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Abstract

Introduction: Elderly patients are among the most vulnerable populations during the COVID-19 pandemic. Although hydroxychloroquine and favipiravir, separately and in combination, have been used in the general population, their benefits are unclear, especially in the geriatric population. This study aims to compare the effects of different drug regimens on the clinical outcomes of elderly patients with COVID-19-related pneumonia.

Materials and methods: This retrospective cohort study, conducted in a tertiary healthcare center between April 2020 and October 2020, included all patients over 65 years of age admitted to the emergency department with confirmed COVID-19-related pneumonia. Patient characteristics and clinical outcomes were recorded. The patients were classified into hydroxychloroquine, favipiravir, and hydroxychloroquine plus favipiravir treatment groups. Propensity score matching was performed to balance the differences between the groups. The primary outcome was 30-day survival. The secondary outcomes were length of hospital stay and the need for mechanical ventilation.

Results: A total of 335 patients were included in the study; 144 were matched according to the propensity scores and divided into groups of 48 each. There was no significant difference between the treatment groups' survival curves. The length of hospital stay was significantly longer in the favipiravir group. No significant difference was detected in mortality or the need for noninvasive or invasive mechanical ventilation.

Conclusion: The hydroxychloroquine, favipiravir, and hydroxychloroquine plus favipiravir treatments had similar effects on 30-day survival, mortality, and the need for mechanical ventilation. The length of hospital stay was longer in the patients treated with favipiravir.

Keywords: COVID-19; Geriatrics; Hydroxychloroquine; Favipiravir.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) affects people of all ages (1). However, elderly patients are among the populations most vulnerable to more severe illness and mortality, because aging itself and multiple accompanying comorbidities can increase the risk of poor outcomes in this population (2). A large epidemiologic study reported that the case fatality rate (CFR) was 2.3% in all populations compared to a CFR of 8% in patients between 70 and 80 years and 14.8% in patients older than 80 years (1). Another study reported that the pneumonia in elderly patients was significantly more severe compared to young and middle-aged patients with COVID-19 related pneumonia (3).

Comorbidities and polypharmacy lead to more challenging management of COVID-19 in the geriatric population (4). Since a specific pharmacotherapy is still not approved for COVID-19, an individualized approach while carefully assessing the adverse effects and interactions of suggested treatments should be practiced for elderly patients (4). To date, many treatment alternatives have been recommended for patients with COVID-19, including antiretroviral drugs (mostly lopinavir/ritonavir), interferons, remdesivir, ribavirin, chloroquine, hydroxychloroquine (HCQ), and favipiravir (FVP) (5). However, treatment guidelines vary between countries (5). In Turkey, the use of HCQ and FVP for COVID-19 was recommended by the COVID-19 Scientific Board of the Ministry of Health (6). Although the use of HCQ has been discontinued in Turkey, many resource-limited countries continue to use HCQ to treat COVID-19 (7). A nationwide epidemiologic study from Turkey showed that FVP was given to 34.5% of patients over 60 years old and 41% of patients over 80 years old. Conversely, HCQ was used for 79% of patients over 60 years old (8). The use of the combination of HCQ and FVP was also reported in elderly patients with COVID-19 (5).

Although many studies have evaluated the safety and efficacy of FVP and HCQ for COVID-19, inconsistent results have led to a debate about their confident utilization (9). FVP is a selective RNA polymerase inhibitor that has been shown to be effective in preventing viral replication in human cells (10). Preliminary results from a systematic review and meta-analysis indicate that FVP is safe; however, its effectiveness is limited in the treatment of COVID-19 (11critically impacting public health systems. A number of already approved and marketed drugs are being tested for repurposing, including Favipiravir. We aim to investigate the efficacy and safety of Favipiravir in treatment of COVID-19 patients through a systematic review and meta-analysis. This systematic review and meta-analysis were reported in accordance with the PRISMA statement. We registered the protocol in the PROSPERO (CRD42020180032). Some adverse effects related to FVP have been reported in the literature; however, they are mostly manageable (12,13). HCQ is also among the most controversial treatments for COVID-19. Despite the lack of strong evidence, the antiviral and anti-inflammatory activities of HCQ have been suggested as effective in treating COVID-19 (14hydroxychloroquine (HCQ). Conversely, several systematic reviews and meta-analyses showed no tangible benefits of HCQ treatment in mild COVID-19; moreover, significant adverse effects were reported (15). Conjecturally, the combination of HCQ and FVP is also suggested through their synergistic effects on different target sites (16).

For COVID-19, the use of treatments with limited effectiveness and potential adverse effects raises concerns, particularly in a more vulnerable elderly population. Data on the effects of HCQ and FVP treatments in the geriatric population are scarce in the literature. This study aims to compare the effects of HCQ, FVP, and HCQ plus FVP on the clinical outcomes in elderly patients with COVID-19-related pneumonia.

MATERIALS AND METHODS

Study Design and Settings

This was a retrospective cohort study conducted in a tertiary healthcare center between April 1, 2020, and October 1, 2020. Institutional review board (No: 15/21, 17.09.2020) and the Ministry of Health of Turkey, COVID-19 Scientific Research Platform approval (No: 2020-10-07T14_14_00) was obtained before the study began.

Study Protocol

All patients admitted to the emergency department (ED) between April 1, 2020 and October 1, 2020 with COVID-19 were screened from the hospital's electronic medical records (EMR).

Inclusion criteria were as follows: the

1. Patients above 65 years of age who had a positive PCR test for SARS-CoV-2
2. Patients who had confirmed pneumonia on a chest CT,
3. Patients who had been treated with HCQ, FVP, or HCQ combined with FVP for COVID-19.

The exclusion criteria were as follows:

1. Patients younger than 65 years
2. Patients who needed mechanical ventilation in the ED
3. Patients who died within 72 hours of admission
4. Patients whose clinical outcomes could not be determined from the EMR or by phone call.
5. Patients who were not treated in adherence to the guidelines of the COVID-19 Scientific Board of the Ministry of Health of Turkey
6. Patients whose treatment regimens changed during the first five days of hospitalization.

Patient demographics, initial symptoms, vital signs, laboratory test results, severity of illness, comorbidities, administered treatment, length of hospital stay, and patient outcomes were obtained from the EMR. Patients discharged from the hospital were phone called by an investigator to determine the clinical outcome. All included patients were classified into three groups according to treatment with HCQ, FVP, or HCQ plus FVP. Characteristics related to the patients' demographics, clinical features, and outcomes were compared between the treatment groups.

Treatment Groups

HCQ: 200 milligrams (mg) orally twice per day for 5 days.

FVP: 1600 mg twice per day orally on the first day as a loading dose and 600 mg twice per day orally for 4 more days as a maintenance dose.

HCQ plus FVP: 200 mg HCQ plus 1600 mg FVP orally twice on the first day and 200 mg HCQ plus 600 mg FVP twice per day orally for 4 more days.

Outcome measures

The outcomes of this study were the effects of HCQ, FVP, and HCQ plus FVP on patients' 30-day survival and length of hospital stay. Thirty-day follow-up was determined as the study endpoint to evaluate the short-term effects of HCQ, FVP, and HCQ plus FVP treatments on patient outcomes.

Data Analysis

MedCalc version 20 (MedCalc Software Ltd. Ostend, Belgium) was used for the statistical analysis. The categorical variables are presented as numbers and percentages. The continuous variables are presented as means and standard deviations or medians and interquartile ranges according to the normality of the distribution. The Kolmogorov–Smirnov

test was used to assess the normality of the distribution. Propensity score (PS) matching was performed between the cohorts to balance the covariates, including age, sex, the Carlson comorbidity index, the pneumonia severity index, adjuvant antibiotic treatments, and use of low-molecular-weight heparin, to prevent possible biases caused by the study's retrospective nature. One-way ANOVA or Kruskal-Wallis tests were used to compare the continuous variables according to the normality of the distribution. Pairwise comparisons with Tukey's or Dunn's posthoc tests were carried out if 3 groups comparison was statistically significant. The chi-square test was used to compare the categorical variables. The Kaplan–Meier method was used to construct 30-day survival curves. The log-rank test was used to compare the survival curves.

RESULTS

During the study period, 2772 patients were screened for eligibility, of whom 355 were eligible. After excluding 20 patients due to missed information or loss of contact, 335 patients were included in the study. The mean age of the patients was 75 ± 8 years, and 188 (56%) were male. Among the patients, 84 (25%) were discharged from the ED, 188 (56%) were admitted to hospital wards, and 63 (19%) were admitted to intensive care units. Mortality occurred in 78 patients (27%). HCQ was used in 64 (19%) patients, FVP was used in 193 (58%) patients, and HCQ plus FVP was used in 78 (23%) patients.

A total of 144 patients were matched according to the PS, which resulted in 48 patients for each treatment group. There were no significant differences between the demographic features and initial vital signs between the groups (Table 1).

Mortality occurred in 32 patients (22%) within 30 days of ED admission, including 12 (25%) in the HCQ group, 11 (23%) in the FVP group, and 9 (19%) in the HCQ plus FVP group. The PS-matched Kaplan–Meier survival curves of the treatment groups are shown in the Figure 1. The mean survival time were 24.9 ± 8.9 days (95% CI: 22.4–27.5) in the HCQ group, 25.8 ± 8.1 days (95% CI: 23.6–28.1) in the FVP group, and 27.1 ± 6.9 days (95% CI: 25.2–29) in the HCQ plus FVP group. There was no statistically significant difference between the survival curves of the treatment groups (p=0.7).

The length of hospital stay was significantly longer in the FVP group (p=0.007). In the post hoc comparisons, this difference was detected between the FVP and the HCQ groups (mean difference [md]=3.7 days, p<0.05) and between the FVP and the HCQ plus FVP groups (md=3.5 days, p<0.05). No significant difference was detected for mortality or the need for noninvasive and invasive mechanical ventilation between the treatment groups (p=0.8, p=0.9, and p=0.7, respectively) (Table 2).

DISCUSSION

This study's results showed that HCQ, FVP, and HCQ plus FVP had similar effects on the 30-day survival of geriatric patients with COVID-19-related pneumonia. However, HCQ-containing regimens provided a shorter length of hospital stay. To date, no studies have focused on the survival of elderly patients with COVID-19 treated with HCQ and FVP or the combined treatment of HCQ and FVP.

Figure 1. Kaplan Meier Survival Curve of the patients for 30 days survival

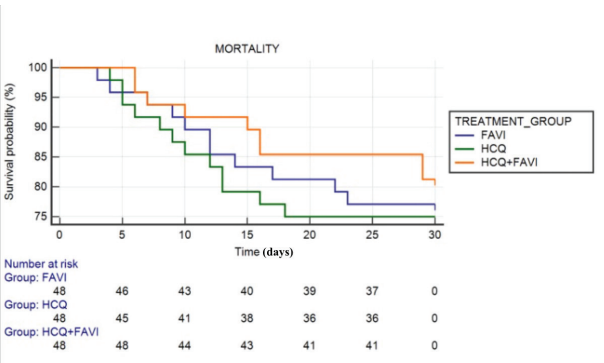

Table 1. Demographic features of the patients

	Total (n=144)	HCQ (n=48)	FVP (n=48)	HCQ + FVP (n=48)	p value
Age (mean±SD)	73,4±8,1	73,6±8,6	73,4±7,9	73,1±8,1	0,94
Male sex (n, %)	75(52,1)	22(45,8)	24(50)	29(60,4)	0,34
DM (n, %)	51(35,4)	11(22,9)	18(37,5)	22(45,8)	0,08
HTN (n, %)	111(77,1)	39(81,3)	33(68,8)	39(81,3)	0,24
COPD (n, %)	27(18,8)	9(18,8)	8(16,7)	10(20,8)	0,87
CAD (n, %)	34(23,6)	14(29,2)	8(16,7)	12(25)	0,34
Cancer (n, %)	8(5,6)	3(6,3)	4(8,3)	1(2,1)	0,4
CVD (n, %)	25(17,4)	10(20,8)	10(20,8)	5(10,4)	0,3
CKD (n, %)	11(7,6)	3(6,3)	6(12,5)	2(4,2)	0,28
Heart failure (n, %)	2(1,4)	-	2(4,2)	-	-
Charlson CI (n, %)	6,43±2,39	6,15±2,13	6,56±2,3	6,58±2,71	0.6
Vital Signs					
Temperature, °C, (mean±SD)	37,5±0,7	37,4±0,5	37,6±0,7	37,5±0,8	0,14
SBP, mmHg, (mean±SD)	118,1±18,1	115,67±22,71	119,83±19,13	118,15±18,1	0,59
DBP, mmHg, (mean±SD)	67,88±10,92	68,54±9,05	68,54±13,06	66,56±10,37	0,6
HR, bpm, (mean±SD)	94,51±16,58	91,38±14,19	96±17,99	96,15±17,2	0,28
RR, breath/m, (mean±SD)	23,31±3,65	23,04±4,36	23,33±3,01	23,56±3,52	0,78
SaO2, (mean+SD)	93,13±5,78	94,35±4,49	91,73±7	93,31±5,38	0,08
GCS, (mean±SD)	14,77±0,56	14,81±0,39	14,65±0,78	14,85±0,41	0,16

HCQ: hydroxychloroquine, FVP: favipiravir, SD: standard deviation DM: diabetes mellitus, HTN: hypertension, COPD: chronic obstructive pulmonary disease, CAD: coronary artery disease, CVD: cerebrovascular disease, CKD: chronic kidney disease, CI: comorbidity index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, RR: respiratory rate, SaO2: oxygen saturation, GCS: Glasgow coma scale

Optimal management for COVID-19 has continuously evolved since the beginning of the pandemic. Since there is no specific therapy for COVID-19, several alternative treatment options have been suggested. HCQ is one of the most controversial drugs among the alternative treatment options. Most systematic reviews and meta-analyses have revealed that HCQ treatment has no tangible benefit in treating or preventing COVID-19 (17). In addition, possible adverse events have been reported to be associated with its use (17). Although many countries have abolished or limited the use of HCQ, there is still usage of HCQ, especially in resource-limited countries (7). Uncontrolled use of HCQ for COVID-19, particularly in a more vulnerable geriatric population, could pose a higher risk due to comorbidities or concomitant drug use (18). Conversely, FVP has been suggested as a safe alternative for

Table 2. Clinical outcomes of the patients

	Total (n=144)	HCQ (n=48)	FVP (n=48)	HCQ + FVP (n=48)	p value
Survived days (mean±SD)	26,2±8,5	25,15±9,2	25,9±8,2	27,6±7,9	0,33
Mortality (n, %)	34(23,6)	13(27,1)	11(22,9)	10(20,8)	0,76
Antibiotics (n, %)	118(81,9)	40(83,8)	39(81,3)	39(81,3)	0,95
NIMV (n, %)	34(23,6)	11(22,9)	11(22,9)	12(25)	0,96
IMV (n, %)	23(16)	6(12,5)	8(16,7)	9(18,8)	0,7
Wards LOS (mean±SD)	7,65±4,9	6,13±4,14	9,8±5,81	6,34±3,5	**0,007**
ICU LOS (mean±SD)	11,18±8,84	9,07±7,54	9,5±6,35	14,71±11,04	0,18

HCQ: hydroxychloroquine, FVP: favipiravir, SD: standard deviation, NIMV: non-invasive mechanicalventilation, IMV: invasive mechanical ventilation, LOS: length of stay, ICU: intensive care unit

treating patients with COVID-19 (19). However, contradictory results regarding the treatment effectiveness of FVP from previous studies limit the usability of this agent for the elderly population (202021, we searched PubMed, bioRxiv, medRxiv, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL).

FVP is an RNA-dependent RNA polymerase inhibitor that acts as a purine analog and therefore inhibits DNA replication (19). FVP has been shown to be effective in treating infections caused by RNA viruses, including influenza, Ebola, rabies, norovirus, and SARS-CoV-2 (21). Many studies have compared the efficacy and safety of FVP with the standard care in COVID-19. Manabe et al. conducted a systematic review and meta-analysis to measure viral clearance and clinical improvement in patients with COVID-19 treated with FVP (19). They reported that the FVP treatment favors viral clearance by 7 days and contributes to clinical improvement in 14 days compared to a placebo, remdesivir, HCQ, other available antivirals, and the standard care (19). It has been suggested that FVP treatment could be an effective treatment, especially in patients with mild to moderate COVID-19. In another systematic review and meta-analysis, Hassanipour et al. evaluated clinical improvement, viral clearance, ICU admission, adverse events, and mortality rates in patients with COVID-19 treated with FVP compared to the standard of care or other antiviral treatments (11critically impacting public health systems. A number of already approved and marketed drugs are being tested for repurposing, including Favipiravir. We aim to investigate the efficacy and safety of Favipiravir in treatment of COVID-19 patients through a systematic review and meta-analysis. This systematic review and meta-analysis were reported in accordance with the PRISMA statement. We registered the protocol in the PROSPERO (CRD42020180032). Better clinical improvement was reported in the patients treated with FVP during 7 days of hospital admission (risk ratio =1.24, 95% CI: 1.09–1.41, p=0.001). However, no significant difference has been shown regarding viral clearance, intensive care unit (ICU) admission, adverse events, and mortality in the general group of patients with mild to moderate COVID-19 (11critically impacting public health systems. A number of already approved and marketed drugs are being tested for repurposing, including Favipiravir. We aim to investigate the efficacy and safety of Favip-

iravir in treatment of COVID-19 patients through a systematic review and meta-analysis. This systematic review and meta-analysis were reported in accordance with the PRISMA statement. We registered the protocol in the PROSPERO (CRD42020180032). Özlüşen et al. performed a systematic review and meta-analysis on the effectiveness of FVP on mortality and the need for mechanical ventilation in patients with moderate to severe COVID-19 (202021, we searched PubMed, bioRxiv, medRxiv, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL). They reported that FVP treatment had no superiority over the standard of care or other antivirals for up to 14 days after COVID-19 diagnosis (202021, we searched PubMed, bioRxiv, medRxiv, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL). However, systematic reviews and meta-analyses are mostly limited due to the low number of randomized controlled trials (RCTs), the higher number of retrospective studies, and the heterogeneity of the included studies. More recently, the preliminary results of the PRESCO study (Preventing Severe COVID-19 Disease) which is a double-blind, placebo controlled, randomized, multi-center phase 3 trial, showed that FVP did not achieve statistical significance for the sustained clinical recovery in 1231 patients. (22). Because of the PRESCO study was only included adult outpatients with mild-to-moderate COVID-19, more randomized-controlled trials that also include a broader population such as elderly patients, children and hospitalized patients are needed.

Many studies have compared the safety and efficacy of HCQ and FVP in patients with COVID-19 in general populations. The safety and efficacy of FVP were compared to HCQ plus oseltamivir in an RCT in patients with mild and moderate COVID-19 (9). Both drug regimens provided similar efficacy for viral clearance and length of hospital stay. Moreover, no serious adverse events were seen in either group except for one patient who died of myocarditis on the eighth day of infection in the HCQ group. Another RCT by the same investigators comparing the efficacy of FVP and chloroquine revealed no significant difference between the groups regarding the length of hospital stay, the need for mechanical ventilation, and adverse effects (23). Guner et al. compared the effects of HCQ, FVP, and HCQ plus FVP on the need for ICU transfer in hospitalized patients with mild to moderate COVID-19 (5). Both HCQ and HCQ plus FVP provided a lower need for ICU transfer compared to FVP alone. Among the patients, 10.4% were over 65 years old. However, no subgroup analysis was performed for elderly patients in this study. In addition, 73.3% of the study patients were younger and had lower C-reactive protein and ferritin levels in the HCQ group compared to the patients receiving FVP-containing regimens (5). Başaran et al. compared the effects of HCQ, HCQ plus azithromycin, and FVP-containing regimens in non-critical COVID-19 patients on symptoms and clinical improvement (24). Longer symptom resolution, clinical improvement, and length of hospital stay were reported in the patients treated with the FVP-containing regimens. However, it is important to note that FVP was initiated as a second-line treatment in patients who deteriorated under the HCQ or HCQ plus azithromycin treatments (24). In our study, the length of hospital stay was also significantly longer in the FVP group. Conversely, FVP treatment was one of the first-line treatments like the HCQ and the HCQ plus FVP groups. The possible reason for a longer hospital stays in FVP group despite its being first-line treatment in our study could be that the geriatric population in our study is more sensitive to be clinically deteriorated compared to the Basaran et al.'s non-critical general population. In another study, Ömeroğlu et al. compared the effects of HCQ, FVP, and HCQ plus FVP on symptom improvement, PCR negativity, and the need for hospitalization in patients with COVID-19 (25). HCQ was significantly better for symptom im-

provement and PCR negativity than FVP or HCQ plus FVP. However, no significant difference was reported for the need for hospitalization between the treatment groups (25). In an RCT by Bosaeed et al., the FVP and HCQ combination was also compared to the HCQ or FVP monotherapies in patients with moderate to severe COVID-19 (16). Time to clinical improvement and the mortality rate were not significantly different between the treatment groups (16). In our study, mortality and the need for invasive or noninvasive mechanical ventilation rates were also similar between the treatment groups. The negative results of FVP were mostly attributed to the late initiation of therapy or its use as a second-line therapy (24-26). Although FVP was initiated in the early period as a first-line therapy in this study, the outcome did not change. This difference could be because previous studies were conducted with a younger population with mild to moderate COVID-19. However, in this study, like Bosaeed et al.'s study, the patients were critically ill and required hospitalization at the time of diagnosis (16). From the point of our study results view, FVP alone or the combination with HCQ did not provide additional benefit than HCQ treatment. Moreover, resulted in longer hospital stays. Although our study is very limited for suggesting that FVP had no better than HCQ, we believe that the new results from high-quality RCTs would direct clinicians to alternative anti-viral treatments for COVID-19.

LIMITATIONS

This study has several limitations. First, this was a single-center retrospective study, which limits the generalizability of the study results. Second, although PS matching was performed to minimize potential biases caused by this study's retrospective nature, a significant amount of data was lost during the matching process. This resulted in a lower number of patients being included in the final analysis. Third, this study only included a geriatric population with COVID-19-related pneumonia. Therefore, including a general population could lead to different results. Fourth, although the COVID-19 treatment guidelines recommended by the Ministry of Health of Turkey were strictly adhered to in our study center, some adjunct treatments, such as steroids or antibiotics, varied between the patients. This might have led to some differences in patient outcomes. Fifth, the adverse effects associated with treatment regimens were not evaluated in this study. Especially in a vulnerable population, including elderly patients, the adverse effects of treatments would influence treatment selection.

CONCLUSION

In this study, we found that HCQ, FVP, and the combination of HCQ plus FVP had similar effects on 30-day survival. Although no differences were detected in mortality or the need for noninvasive or invasive mechanical ventilation, the length of hospital stay was longer in the patients treated with FVP-containing regimens.

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