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ARAŞTIRMA / RESEARCH

Comparison of biventricular myocardial strain according to treatment regimens in patients discharged after COVID-19 recovery

COVID-19'dan iyileşme sonrası tedavi rejimlerine göre biventriküler miyokard geriliminin karşılaştırılması

Pelin Karaca Özer[1], Elif Ayduk Gövdeli[1], Mustafa Altınkaynak[2], Derya Baykız[1], Huzeyfe Arıcı[2], Yunus Catma[2], Alpay Medetalibeyoğlu[2], Ekrem Bilal Karaayvaz[1]

[1]Istanbul University, Istanbul Medical Faculty, Department of Cardiology, [2]Department of Internal Medicine, Istanbul, Turkey

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Abstract

Purpose: The effects of different COVID-19 therapeutic strategies on cardiac function are uncertain. Therefore, this study aimed to evaluate the effects of different medical treatments on biventricular function in patients who had recovered from COVID-19.

Materials and Methods: Speckle-tracking echocardiography was performed to examine the biventricular myocardial function of patients at follow-up visits after recovery from COVID-19. The patients were divided into two groups based on the medication they used during the active disease: favipiravir (FAV; n = 60) or hydroxychloroquine (HCQ; n = 60). A comparison was made with risk factor–matched controls (n = 41).

Results: A total of 161 patients were included in the study. The left ventricular end-diastolic volume, end-systolic volume, end-diastolic diameter, and end-systolic diameter were higher in the HCQ and FAV groups compared to the controls, while the left ventricular ejection fraction was similar between all the groups. The right ventricular diameter was increased, and the systolic pulmonary artery pressure was higher in the HCQ and FAV groups compared to the controls. The left ventricular global longitudinal strain (-18±6.6 vs. -19.7±4.4 vs. -20.4±5, respectively), the right ventricular global longitudinal strain (-19.8±7.5 vs. -22.2±6 vs. -23.4±6.2, respectively), and the right ventricular free wall strain (-16.9±3.6 vs. -18.2±2.4 vs. -19.6±4.7, respectively) were worse in the HCQ group compared to the FAV and control groups.

Conclusion: This study found echocardiographic evidence of subclinical cardiac involvement in both the HCQ and FAV groups compared to the controls.

Öz

Amaç: COVID-19' da farklı terapötik stratejiler uygulanmıştır ve bu stratejilerin kardiyak fonksiyon üzerindeki etkisi belirsizdir. Çalışmanın amacı, COVID-19' dan iyileşen hastalarda farklı tıbbi tedavilerin biventriküler fonksiyon üzerindeki etkilerini değerlendirmektir.

Gereç ve Yöntem: COVID-19'dan iyileştikten sonra takip ziyaretlerinde hastaların biventriküler miyokardiyal işlevini incelemek için benek izleme ekokardiyografisi yapıldı. Hastaların aktif hastalık sırasında kullandığı medikasyonlar retrospektif olarak öğrenildi ve favipiravir (FAV, n=60) ve hidroksiklorokin (HCQ, n=60) alanlar olmak üzere iki gruba ayrıldı. Risk faktörü uyumlu kontroller (n=41) ile bir karşılaştırma yapıldı.

Bulgular: Toplam 161 hasta çalışmaya dahil edildi. Sol ventrikül diyastol sonu hacmi, sistol sonu hacmi, diyastol sonu çapı ve sistol sonu çapı HCQ ve FAV gruplarında kontrollere göre daha yüksekti, ancak gruplar arasında sol ventrikül ejeksiyon fraksiyonu benzerdi. Kontrollere göre HCQ ve FAV gruplarında sağ ventrikül çapı artmış ve sistolik pulmoner arter basıncı daha yüksekti. HCQ grubunda, FAV ve kontrol grupları ile karşılaştırıldığında, sol ventrikül global uzunlamasına gerilim (%-18±6,6; %-19,7±4,4; %-20,4±5; sırasıyla), sağ ventrikül global uzunlamasına gerilim (%-19,8±7,5; %-22,2±6; %-23,4±6,2; sırasıyla) ve sağ ventrikül serbest duvar gerilimi (%-16,9±3,6; %-18,2±2,4; %-19,6±4,7; sırasıyla) daha kötüydü.

Sonuç: Çalışmamızdaki mevcut sonuçlara dayanarak, hem HCQ hem de FAV gruplarında kontrollere kıyasla subklinik kardiyak etkilenmenin ekokardiyografik kanıtları vardır. Bununla birlikte, HCQ tedavisi, FAV ile

Yazışma Adresi/Address for Correspondence: Dr. Pelin Karaca Özer, Istanbul University, Faculty of Medicine, Department of Cardiology, Istanbul, Turkey. E-mail: pkaracaozer@gmail.com
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However, HCQ treatment was associated with an increased risk of biventricular subclinical systolic dysfunction in COVID-19 survivors compared with FAV treatment.
Keywords:. COVID-19, recovery, favipiravir, hydroxychloroquine, speckle-tracking echocardiography

karşılaştırıldığında COVID-19'dan kurtulanlarda biventriküler subklinik sistolik disfonksiyon riskinde artış ile ilişkilendirilmiştir.

Anahtar kelimeler: COVID-19, iyileşme, favipiravir, hidroksiklorokin, benek izleme ekokardiyografi

INTRODUCTION

The viral genome of severe acute respiratory syndrome coronavirus 2, which causes novel coronavirus disease 2019 (COVID-19), has been rapidly identified to allow the development of preventive and therapeutic strategies[1]. However, there is no evidence from randomized clinical trials of any potential therapy that can improve outcomes in patients with COVID-19[2,3]. The Food and Drug Administration (FDA) gave emergency approval for the use of hydroxychloroquine (HCQ) to treat COVID-19, and it has since been used as standard therapy in some countries. However, in June 2020, the World Health Organization announced that HCQ does not reduce the mortality rate of hospitalized COVID-19 patients. Accordingly, the FDA revoked its emergency approval for the use of HCQ[4]. Since then, no specific antiviral drugs have been approved for the treatment of COVID-19. Favipiravir (FAV), a viral RNA-dependent RNA polymerase inhibitor and purine nucleic acid analog used for the treatment of influenza A virus infection, was approved for the treatment of COVID-19 in China in March 2020. However, there is very little data on the efficacy of FAV for the treatment of COVID-19[5,6,7]. In addition, both these medications have potential adverse cardiac effects. This is important because patients with COVID-19 may have cardiac injuries, which can further increase the risk of cardiomyopathy and arrhythmias[8]. The American Heart Association lists HCQ as an agent that can cause direct myocardial toxicity and exacerbate underlying myocardial dysfunction[9]. Again, HCQ has been shown to have proarrhythmic effects[10]. Similarly, FAV can prolong the QT interval and cause Torsade de Pointes[11]. Thus, HCQ and FAV may be associated with adverse cardiovascular system effects. The evaluation of myocardial function in recovered patients may also be predictive of both the efficacy and possible adverse cardiac effects of these drugs.

Speckle-tracking echocardiography (STE) has been demonstrated to be an accurate and sensitive tool for detecting subclinical impairment of ventricular function[12]. Studies have attempted to demonstrate myocardial involvement with STE in hospitalized patients with COVID-19[13,14].

Comparative data on the effects of HCQ and FAV, the agents most commonly used in the treatment of this infection, are still limited. The hypothesis of this study was to reveal whether there was a possible cardiotoxic effect on the myocardium associated with HCQ or FAV treatment, or whether there was a difference between them.

No previously published study has aimed to investigate the possible adverse effects of HCQ or FAV therapy on the myocardium. Therefore, this study aimed to evaluate the biventricular function of patients who had recovered from COVID-19 according to the HCQ or FAV treatment regimens used during the disease.

MATERIALS AND METHODS

Study design and population

This single-center observational study was conducted at Istanbul University, Istanbul Faculty of Medicine, between September 30, 2020, and March 15, 2021. The study included consecutive adult patients who had recovered from COVID-19 and attended follow-up visits at the COVID-19 Outpatient Clinic and were referred to the echocardiography laboratory. Patients with preexisting cardiovascular disease (e.g., heart failure, coronary artery disease, and valvular heart disease), atrial fibrillation, ≥stage 2 hypertension (HTN), uncontrolled diabetes mellitus (DM) (HbA1c ≥ 8), cerebrovascular disease, chronic liver or kidney disease (GFR < 30 ml/min), asthma, chronic obstructive pulmonary disease, prior history of pulmonary hypertension or pulmonary embolism, and malignancy were excluded from the study.

Patients who did not use FAV or HCQ during the active disease, those who used the two drugs together, and those with poor echogenicity for strain measurement were also excluded from the study.

Although approximately 1300 patients were referred for echocardiography, only 120 patients were included in the study due to the exclusion criteria and poor echogenicity.

Two groups were defined according to the use of FAV (n = 60) or HCQ (n = 60) during the active phase of COVID-19. These two groups of COVID-19 survivors were compared to controls without a history of respiratory infection matched for age, sex, and risk factor (n = 41). Two-dimensional (2D) transthoracic echocardiography (TTE) and 2D STE were performed on all subjects.

This study complied with the Declaration of Helsinki. The study was approved by the Ministry of Health COVID-19 Research Registry and Istanbul University Faculty of Medicine Ethics Committee (Date: 25/09/2020, Number: 23). All the patients gave their informed consent.

Data collection

Clinical demographic characteristics and echocardiographic measurements were obtained during the patient's follow-up visits. The medications the patients had received for COVID-19 were collected retrospectively identified from medical records and detailed anamnesis. The results of blood tests undertaken during the active disease and requested at follow-up visits were obtained retrospectively from the medical records, if available. For all COVID-19 patients, thorax computed tomography (CT) images obtained on admission to the hospital were retrieved from the picture archiving and communication system. In our hospital, care is taken to ensure the confidentiality of patient data, and medical records are accessible only to physicians. Approval was obtained from the COVID-19 Scientific Research Board of the Istanbul Faculty of Medicine to collect the patients' laboratory and clinical data.

Two-dimensional transthoracic echocardiography

The echocardiography was performed by echocardiographers (P.K.Ö. and E.A.G.) who were blinded to the clinical and laboratory data. The examinations were performed using the Vivid 7 echocardiography device (GE, Milwaukee, WI) with a middle-range frequency (3-8 MHz) broadband transducer.

Conventional echocardiographic analysis

LV end-systolic volume (LVESV), end-diastolic volume (LVEDV), and ejection fraction (LVEF) were measured using the biplane Simpson method. LV dimensions were measured from the apical long axis view, using M-mode, included LV end diastolic (LVEDD) and end systolic diameter (LVESD). LV diastolic function was estimated using the early transmitral flow velocity (E), late transmitral flow velocity (A), and the early diastolic medial septal tissue velocity (e'). Left atrial (LA) volume was calculated using the biplane method in 4- and 2-chamber views and indexed to body surface area for LA volume index (LAVI). Right atrial (RA) and RV size were determined from the apical 4-chamber view. Tricuspid annular plane systolic excursion (TAPSE) of the tricuspid lateral annulus was measured on M-mode imaging. RV fractional area change (FAC) was calculated as (RV enddiastolic area-endsystolic area/enddiastolic area) x 100%. Tricuspid lateral annular systolic velocity (TDI S') was assessed using tissue Doppler imaging. Pulmonary artery systolic pressure (SPAP) was assessed from the peak velocity of the tricuspid regurgitation jet[15,16].

Two-dimensional speckle tracking strain analysis

STE was utilized to characterize systolic longitudinal strain (LS)[17]. Peak systolic LS with muscle contraction, expressed as a percentage, reflected as a negative strain. The images were analyzed using a dedicated software package (Automatic Function Imaging (AFI), EchoPac.; GE, USA) in the apical 3-, 2-, and 4-chamber views at 70–100 frames/s. For each view, the operator placed three points (two points at the base of the LV and one point at the apex) by using AFI at the end of diastole. The endocardial border of the LV was then automatically traced by the software. Seventeen segmental strain curves were obtained to give the so-called bull's-eye plots, and LV global LS (LV-GLS) was calculated by averaging the values of all segments at aortic valve closure time (Figure 1).

RV LS was calculated from the apical 4-chamber view. After marking with AFI, the software automatically tracked the endocardial border of the RV. The RV was divided into six segments (basal free wall, mid-free wall, apical free wall, basal septum, mid septum, and apical septum). RV-GLS was defined as the average of all six segments. RV free wall strain

(RV-FWS) was calculated as the mean of three segments of the free wall (Figure 2). Manual adjustment was performed to ensure adequate tracking. If it was not feasible to track one or more segments, the case was excluded.

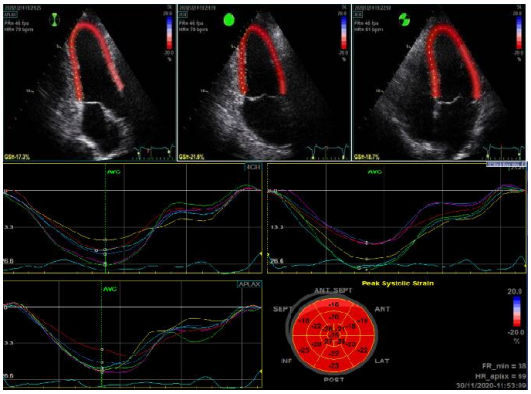

Figure 1. Apical 3-, 2-, and 4-chamber view and bull's eye image of left ventricular global longitudinal strain with speckle-tracking imaging

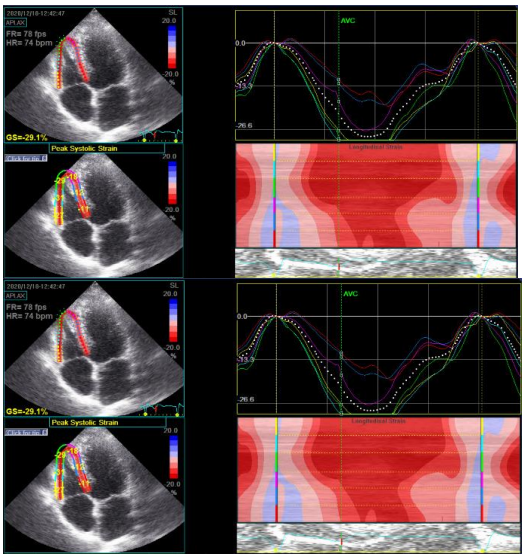

Figure 2. Apical four-chamber view of right ventricular longitudinal strain with speckle-tracking imaging

Definitions

The COVID-19 patients were considered as recovered if they had resolution of symptoms and negative results on a swab test at the end of the isolation period or when they were discharged from hospital.

Mild to moderate pneumonia was defined as patients with laboratory and thorax CT-confirmed interstitial pneumonia in the absence of clinical signs of severe pneumonia. Patients without pneumonia were defined as patients without signs of pneumonia with laboratory or thorax CT scans. Severe pneumonia was defined with any of the following in patients with laboratory and thorax CT-confirmed interstitial pneumonia: (1) respiratory distress (respiratory rate ≥ 30 breaths/min); (2) oxygen (O_2) saturation at rest ≤ 93%; (3) ratio of the partial pressure of arterial O_2 to the fractional concentration of O_2-inspired air (≤ 300); or (4) a critical complication [need for mechanical ventilation, septic shock, multiple organ dysfunction or failure and intensive care unit (ICU) admission][18].

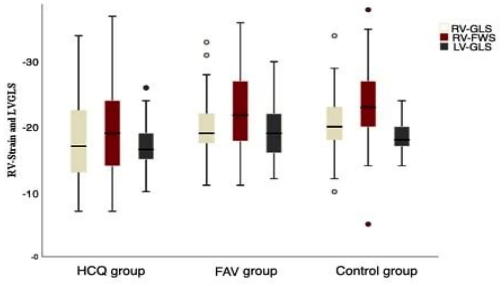

Figure 3. Comparison of LV-GLS, RV-GLS and RV-FWS between HCQ, FAV, and control groups

LV-GLS: left ventricular global longitudinal strain, RV-GLS: right ventricular global longitudinal strain, RV-FWS: right ventricular free wall strain, HCQ: hydroxychloroquine, FAV: favipiravir.

Treatment groups

HCQ: Patients received HCQ 2 × 400 mg tb on Days 1 and 2 × 200 mg tb on Days 2–5.

FAV: Patients received FAV 2 × 1600 mg tb on Days 1 and 2 × 600 mg tb on Days 2–5.

Statistical analysis

During the study period, the daily number of COVID-19 cases was between 5000-10000 and approximately 1500 recovered patients per month were served in the COVID-19 follow-up outpatient clinic in our hospital. Among those referred for echocardiography from this outpatient clinic, 9% met the inclusion criteria. Therefore, this study had to recruit 117 individuals with a 95% confidence interval, 5% type I error level, and 80% power for the

group recovered from COVID-19. All statistical tests were conducted using the Statistical Package for the Social Sciences 26.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to analyze the normality of the data. Continuous data are expressed as mean ± standard deviation (SD), and categorical data are expressed as percentages. A Chi-square was used to assess the differences in categorical variables. The primary analysis used ANOVA to compare all reported data for parametric variables, whereas the Kruskal–Wallis test was performed for comparison among non-parametric variables between groups. For the continuous parameters which are only present for COVID-19 patients, a student's t-test or the Mann–Whitney U test was used to compare unpaired samples as needed. The posthoc power analysis of ANOVA using G power (version 3.1.9.4) assuming an alpha level of 0,05 revealed a power of 82%. Significance was assumed at a two-sided $p < 0.05$.

RESULTS

Of the 120 recovered COVID-19 patients, 60 were treated with HCQ and 60 were treated with FAV. We also included 41 patients in a risk factor-matched control group for a total of 161 cases in the present study. The median follow-up duration was 2.8 ± 1.5 months for COVID-19 survivors and was similar between the HCQ and FAV groups (2.9 ± 1.5 vs. 2.6 ± 1.5 months, $p = 0.198$). There were no statistical differences between the HCQ, FAV, and control groups in terms of age, gender, body mass index (BMI), and pre-existing cardiovascular conditions, including stage 1 HTN, controlled DM, and smoking. Women were the dominant gender in all the groups.

According to laboratory findings at follow-up, the levels of fibrinogen and LDH were significantly higher in the HCQ and FAV groups than in the control group ($p = 0.004$ and $p = 0.005$, respectively). In addition, the pro-brain natriuretic peptide (pro-BNP) level was significantly higher in the HCQ group than in the FAV and control groups ($p = 0.007$).

The medical records were reviewed retrospectively, and cardiac injury and inflammatory parameters at hospital admission were compared between the two groups. As a result of comparison, there was no difference between the two groups in terms of peak hs-troponin T and pro-BNP levels and inflammatory parameters during the disease.

Typical pneumonia was observed on CT images in 48 patients (80%) in the HCQ group, six of whom were severe, and in 45 patients (75%) in the FAV group, eight of whom were severe ($p = 0.672$). Twenty patients (33%) in the HCQ group and 22 patients (36%) in the FAV group required hospitalization ($p = 0.902$). Although the FAV group had a shorter hospital discharge time than the HCQ group, it did not reach statistical significance (7.2 ± 5.5 vs. 9.2 ± 6.9 days, $p = 0.073$).

The HCQ group received azithromycin (AZM) (33%, n = 20), antibiotics (other than AZM) (42%, n = 25), immune modulators (anakinra or tocilizumab) (13%, n = 8), low molecular weight heparin (LMWH) (30%, n = 18), acetylsalicylic acid (ASA) (23%, n = 14), dipyridamole (20%, n = 14), and steroid therapy for COVID-19 (2%, n = 1). None of the patients in the HCQ group received FAV. Of the twenty (33%) hospitalized patients in the HCQ group, five patients (8%) required high-flow nasal cannula (HFNC) or noninvasive ventilation (NIV) with continuous positive airway pressure (CPAP), and three patients (5%) required orotracheal intubation (OTI). Six patients (10%) were admitted to the ICU.

The FAV group received AZM (15%, n = 9), antibiotics (other than AZM) (15%, n = 9), immune modulators (anakinra or tocilizumab) (12%, n = 7), LMWH (28%, n = 17), ASA (13%, n = 8), dipyridamole (13%, n = 8), and steroid (6%, n = 4) therapy. None of the patients in the FAV group received HCQ. Of the twenty-two (36%) hospitalized patients in the FAV group, six patients (10%) required HFNC or NIV with CPAP, and two patients (3%) required OTI. Four patients (7%) were admitted to the ICU. The rate of use of AZM and other antibiotics in the HCQ group was higher than that in the FAV group ($p = 0.019$, $p = 0.001$, respectively).

The clinical and demographic features and laboratory findings of the HCQ, FAV, and control groups are presented in Table 1.

Table 1. Clinical, demographic features and laboratory findings of HCQ, FAV, and control groups.

	Total patients (n=161)	HCQ group (n=60)	FAV group (n=60)	Control (n=41)	p-value
Clinical Characteristics and Comorbidities					
Age (year)	47.4 ± 12.8	48.1 ± 12.7	48.8 ± 12.4	44.5 ± 13.5	0.224

Gender, Male, n(%) Female, n(%)	62 (39%) 99 (61%)	26 (43%) 34 (57%)	22 (37%) 38 (63%)	14 (34%) 27 (66%)	0.605
BMI (kg/m^2)	27.7 ± 4.7	28.1 ± 4.7	27.9 ± 4	26.7 ± 5.4	0.321
SBP (mmHg)	131.8 ± 14.9	132.2 ± 14.6	131.2 ± 15.2	132 ± 15.3	0.945
DBP (mmHg)	80.5 ± 9.8	80.9 ± 9.5	80.3 ± 10	80.4 ± 10.2	0.984
HT, n(%)	43 (27%)	16 (27%)	20 (33%)	8 (20%)	0.193
DM, n(%)	19 (12%)	5 (8%)	8 (13%)	6 (15%)	0.564
Smoking, n(%)	43 (27%)	14 (25%)	13 (22%)	16 (39%)	0.134
Hospitalization for COVID-19	42 (26%)	20 (33%)	22 (36%)	-	0.902
Hospital stay (days)	8.2 ± 6.3	9.2 ± 6.9	7.2 ± 5.5	-	0.073
Follow-up duration, (months)	2.8 ± 1.5	2.9 ± 1.5	2.6 ± 1.5	-	0.198
Laboratory Findings at Follow-up Visit					
Hgb (gr/dl)	13.3 ± 1.5	13.3 ± 1.5	13.1 ± 1.6	13.7 ± 1.4	0.198
WBC (10^3/µl)	6.7 ± 1.5	6.8 ± 1.6	6.6 ± 1.5	6.9 ± 1.4	0.383
Neutrophil (10^3/µl)	3.7 ± 1.2	3.5 ± 1.2	3.6 ± 1.2	3.9 ± 1.3	0.319
Lymphocyte (10^3/µl)	2.4 ± 0.6	2.6 ± 0.8	2.3 ± 0.6	2.3 ± 0.7	0.502
Neutrophil/Lymphocyte Ratio	1.9 ± 0.9	1.8 ± 0.9	2 ± 1	1.8 ± 0.8	0.684
Creatinine (mg/dl)	0.76 ± 0.4	0.8 ± 0.2	0.8 ± 0.5	0.8 ± 0.4	0.086
D-dimer (µg/L)	330 (170-4810)	340 (190-4810)	315 (170-1910)	350 (210-840)	0.436
Fibrinogen (mg/dl)	334 (211-517)	345 (224-517)[b]	323 (218-513)[c]	305 (211-346)[b,c]	0.004*
CRP (mg/l)	2.1 (0-39)	2.1 (0-24)	2.1 (0-39)	1.95 (0-17)	0.676
Ferritin (ng/ml)	54.7 (5-486)	66.8 (5-426)	49.8 (7-486)	46.6 (10-212)	0.151
LDH (U/l)	187.5 (96-364)	196 (134-364)[b]	191.5 (139-248)[c]	165 (96-357)[b,c]	0.005*
Hs-troponin T (pg/ml)	3 (3-26)	3 (3-26)	3 (3-5)	3 (3-9)	0.385
Pro-BNP (pg/ml)	39.61 (4-255)	83.5 (10-195)[a,b]	10 (5-255)[a]	33.9 (4-119)[b]	0.007*
Laboratory Findings at Hospital Admission					
Hgb (gr/dl)	12.84 ± 1.9	13.43 ± 1.7	12.74 ± 2	-	0.083
WBC (10^3/µl)	5.5 ± 2.4	5.62 ± 2.4	5.4 ± 2.1	-	0.218
Neutrophil (10^3/µl)	3.86 ± 1.8	3.71 ± 1.8	3.88 ± 1.9	-	0.557
Lymphocyte (10^3/µl)	1.53 ± 0.9	1.69 ± 0.9[a]	1.3 ± 0.9[a]	-	0.013*
D-dimer (µg/L)	620 (210-7340)	465 (210-5200)[a]	790 (270-7340)[a]	-	0.044*
Fibrinogen (mg/dl)	463 (204-747)	447 (293-619)	465 (204-747)	-	0.392
CRP (mg/l)	22.42 (1-230)	16.85 (5-127)	30.5 (1-230)	-	0.119
Ferritin (ng/ml)	208.1 (15-1718)	189.7 (15-1654)	290.7 (16-1718)	-	0.364
Hs-troponin T (pg/ml) (peak)	5 (3-86.9)	4 (3-86.9)	5 (3-67.4)	-	0.629
Pro-BNP (pg/ml) (peak)	77.85 (5-1821)	80.98 (5-1821)	68.16 (7-1093)	-	0.610
Pneumonia Severity					
Without pneumonia, n(%)	27 (23%)	12 (20%)	15 (25%)	-	0.672
Mild-moderate, n(%)	79 (66%)	42 (70%)	37 (62%)	-	
Severe, n(%)	14 (12%)	6 (10%)	8 (13%)	-	
Treatment					
Azithromycin, n (%)	29 (24%)	20 (33%)[a]	9 (15%)[a]	-	0.019*
Steroid, n (%)	5 (4%)	1 (2%)	4 (6%)	-	0.171
Immune modulator, n (%)	15 (13%)	8 (13%)	7 (12%)	-	0.783
Antibiotics, n (%)	34 (42%)	25 (42%)[a]	9 (15%)[a]	-	0.001*
ASA, n (%)	22 (18%)	14 (23%)	8 (13%)	-	0.157
LMWH, n (%)	35 (29%)	18 (30%)	17 (28%)	-	0.841
Dipyridamole, n (%)	20 (17%)	12 (20%)	8 (13%)	-	0.327
RAS blocker, n (%)	34 (21%)	13 (22%)	15 (25%)	6 (15%)	0.452
Beta-blocker, n (%)	26 (16%)	12 (20%)	5 (8%)	9 (22%)	0.112
OAD, n (%)	14 (23%)	4 (7%)	6 (10%)	4 (10%)	0.448
ICU admission	10 (6%)	6 (10%)	4 (7%)	-	0.531
HFNC/NIMV, n(%)	11 (7%)	5 (8%)	6 (10%)	-	0.544
Orotracheal intubation, n (%)	5 (3%)	3 (5%)	2 (3%)	-	0.665

[a]: p <0.05 between HCQ and FAV groups; [b]: p <0.05 between HCQ and control groups; [c]: p <0.05 between FAV and control groups
BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HT: hypertension, DM: diabetes mellitus, HR: heart rate, Pro-BNP: pro-brain natriuretic peptid, Hs-troponin-T: high sensitive troponin-T, Hgb: haemoglobin, WBC: white blood cell, LDH: lactate dehydrogenase, CRP: C-reactive protein, HCQ: hydroxychloroquine, ASA: acetylsalicylic acid, LMWH: low molecular weight heparin, RAS: renin angiotensin system, OAD: oral antidiabetics, HFNC: high flow nasal cannula, NIMV: non-invasive mechanic ventilation, ICU: intensive care unit.

The LVEDV, LVESV, LVEDD, and LVESD were higher in the HCQ and FAV groups than in the controls (p = 0.019, p = 0.030, and p = 0.019 and p = 0.030, respectively), while the LVEF was similar between the groups (p = 0.764). The LA diameter was higher in the HCQ and FAV groups than in the controls, while the LAVI and E/e' ratios were similar between the groups (p < 0.001; p = 0.112; p = 0.628, respectively). The RV diameter was increased and the SPAP was higher in the HCQ and FAV groups than in the controls (p = 0.013 and p < 0.001, respectively). In addition, the TDI S' was lower in the HCQ group than in the FAV and control groups (p < 0.001 for each). The RV FAC, RA, and TAPSE were similar between the groups (p = 0.633, p = 0.422, and p = 0.647, respectively).

LV-GLS was impaired in the HCQ group compared with the FAV and control groups (-18 ± 6.6%, -19.7 ± 4.4%, -20.4 ± 5%, respectively, p = 0.015). RV-GLS was impaired in the HCQ group compared with the FAV and control groups (-19.8 ± 7.5%, -22.2 ± 6 %, -23.4% ± 6.2%, p = 0.008). Moreover, RV-FWS was impaired in the HCQ group compared with the FAV and control groups (-16.9 ± 3.6%, -18.2 ± 2.4%, and -19.6 ± 4.7%, respectively, p = 0.005).

The echocardiographic parameters of the HCQ, FAV, and control groups are presented in Table 2.

Table 2. The echocardiographic parameters of HCQ, FAV, and risk factor-matched control groups

	Total patients (n=161)	**HCQ group (n=60)**	**FAV group (n=60)**	**Control (n=41)**	**p-value**
LVEDV (ml)	96.2 ± 22.9	98.5 ± 27.3b	99.2 ± 19c	88.2 ± 19.4b,c	0.019*
LVESV (ml)	32.9 ± 11.3	34.9 ± 15.2b	33.1 ± 7.5c	29.8 ± 8.4b,c	0.030*
EF (%)	64.6 ± 5.4	63.7 ± 7.1	65.1 ± 4.2	65 ± 3.9	0.764
LVEDD (mm)	45.5 ± 4.4	45.9 ± 4.9b	46.2 ± 3.8c	43.9 ± 4.1b,c	0.019*
LVESD (mm)	29 ± 3.5	29.5 ± 4.3b	29.2 ± 2.7c	27.9 ± 3.1b,c	0.030*
LA (mm)	34.9 ± 4.6	36 ± 4.4b	36 ± 4.7c	32.4 ± 4b,c	<0.001*
RV (mm)	26.8 ± 2.7	27.3 ± 2.3b	27.1 ± 2.9c	25.9 ± 2.7b,c	0.013*
RA (mm)	31.3 ± 3.1	31.8 ± 3.4	31.2 ± 3	30.8 ± 2,8	0.422
E/e' ratio	8.5 ± 3.3	9 ± 3.5	8.8 ± 2.6	7.8 ± 3.5	0.628
LAVI (ml/m2)	19.9 ± 6.6	20.6 ± 7.2	19.3 ± 6.9	18.7 ± 5.7	0.112
TAPSE (mm)	22 ± 3.5	21.6 ± 3.8	22.5 ± 3.8	22.1 ± 3.1	0.647
sPAP (mmHg)	22.9 ± 6.7	25.8 ± 5.4a,b	25.3 ± 6.6a,c	17.7 ± 4.8b,c	<0.001*
TDI S' (cm/s)	14 ± 2.6	12.9 ± 2.1a,b	14.7 ± 2.8a	15.2 ± 2.5b	<0.001*
RV FAC (%)	56.7 ± 12.3	55 ± 13.2	56.8 ± 13.2	57.8 ± 11.4	0.633
LVGLS (%)	-19.4 ± 5.6	-18 ± 6.6a,b	-19.7 ± 4.4a	-20.4 ± 5b	0.015*
RVGLS (%)	-21.6 ± 6.8	-19.8 ± 7.5a,b	-22.2 ± 6a	-23.4 ± 6.2b	0.008*
RVFWS (%)	-18.2 ± 3.9	-16.9 ± 3.6a,b	-18.2 ± 2.4a	-19.6 ± 4.7b	0.005*

[a]: p <0.05 between HCQ and FAV groups; [b]: p <0.05 between HCQ and control groups; [c]: p <0.05 between FAV and control groups
LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; EF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LA: left atrial; LAVI: left atrial volume index; E: early diastolic transmitral flow; e': early diastolic tissue velocity; RV: right ventricular; RA: right atrial; RVFAC: right ventricular fractional area change; LVGLS: left ventricular global longitudinal strain; RVGLS: right ventricular global longitudinal strain; RVFWS: right ventricular free wall strain; TAPSE: tricuspid annular plane systolic excursion; sPAP: pulmonary artery systolic pressure; TDI *S'*: tissue Doppler velocity of the basal free lateral wall of the right ventricle. LVGLS, RVGLS and RVFWS values are absolute values.

DISCUSSION

This study involved consecutively recruited patients who had recovered from COVID-19 after HCQ or FAV treatment. LV-GLS, RV-GLS, and RV-FWS were reduced in the HCQ group compared to the FAV and control groups. Although there was no difference in peak hs-troponin T and pro-BNP levels during hospitalization between the FAV and HCQ groups, the pro-BNP level was found to be higher in the HCQ group after discharge compared to the FAV and control groups in relation to subclinical biventricular systolic dysfunction. It is difficult to assess our study because no studies have compared patients treated with HCQ or FAV in terms of cardiac function using TTE; however, some studies have examined the efficacy of these drugs for COVID-19 treatment.

Systematic reviews and meta-analyses show that HCQ did not significantly decrease mortality in hospitalized patients, and concomitant use with AZM was associated with increased mortality[19,20]. In the Netherlands, the use of HCQ was associated with increased 21-day mortality in hospitals that routinely treated patients with HCQ compared to those that did not when stratified by treatment received by individual patients[21].

There are fewer studies on FAV compared to HCQ in the literature. A retrospective cohort study on patients with COVID-19 administered with either FAV or HCQ concluded that FAV and HCQ showed comparable efficacy in decreasing mortality and oxygen requirements. A prolonged QT interval was reported only in the HCQ group, and the FAV group likely had a more favorable safety profile regarding cardiac toxicity[22].

In randomized controlled trials, the median time to a negative PCR was shorter for FAV plus standard supportive care compared to supportive care alone[23], and viral clearance, time to fever resolution, and CT recovery at day 15 were significantly earlier[7]. Better fever resolution and viral clearance time, and hence a reduction in inflammation in patients using FAV, may predict better outcomes for cardiac function than HCQ after recovery.

However, no echocardiographic cardiac evaluation of the patients was performed in any of the randomized clinical drug studies discussed here.

Cardiac involvement due to COVID-19 in hospitalized patients has been demonstrated by STE in previous studies. Moreover, impairment of LV-GLS and RV-GLS were predictors of in-hospital mortality in these studies[13,14].

Mechanisms related to possible cardiac damage observed in COVID-19 patients can be summarized as follows: an imbalance between oxygen supply and the oxygen demand of the myocardium secondary to hypoxia caused by respiratory failure, cytokine storm and acute systemic inflammatory response, embolic complications caused by thrombosis, cardiotoxicity that may develop depending on the agents used in treatment, and possible direct entry of the virus into the cell[24,25]. Given these mechanisms, the myocardium at the tissue level can be affected, especially in relation to the severity of the disease. Therefore, LV-GLS and RV-GLS have a more pronounced effect than conventional parameters in the assessment of cardiac impairment.

In patients who recovered from COVID-19, whether cardiac involvement persisted after discharge and its echocardiographic characteristics continue to be investigated[26,27]. The results of STE studies support the possibility of continued myocardial involvement after recovery. However, no comparison was made according to treatment protocols in any of the studies.

In our study, echocardiographic evidence of subclinical cardiac involvement in both the HCQ and FAV groups was compared to the controls. However, patients treated with HCQ therapy had higher pro-BNP levels and worse LV-GLS, RV-GLS, and RV-GLS at follow-up compared to the FAV treatment group. While it is reasonable to have subclinical myocardial involvement in those recovering from COVID-19, this effect was more pronounced in the HCQ group compared to the FAV group, which may support its cardiotoxic effect. Because these agents have wide indications for use and their potential effects on the myocardium have not been thoroughly investigated, it is appropriate to support these findings with further clinical trials.

Our study has several limitations. Most importantly, the treatments were not randomized: information about the drugs used during the disease was collected retrospectively. The sample size was relatively small because the data were derived from a single center, and the follow-up duration was relatively short. Moreover, there were no echocardiographic data on whether patients with myocardial impairment had any impairment prior to COVID-19. Another

limitation of the study was that intra- and inter-observer variability was not evaluated.

In conclusion, based on the results of this single-center observational study of adult COVID-19 survivors, FAV was associated with a lower risk of biventricular subclinical systolic dysfunction compared to the HCQ treatment regimen. These findings may refer to the cardiotoxic effect of HCQ on the myocardium. These implications may be useful and predictive for other indications and clinical uses of these agents; however, randomized clinical trials with larger patient groups and longer follow-up periods are required to confirm this.

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