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# Distribution of arrhythmic events in COVID-19 patients receiving favipiravir and hydroxychloroquine

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## Abstract

**Aim:** Favipiravir, first used for novel influenza strains, is used today in coronavirus disease 2019 (COVID-19). While many studies have been reported in the literature on hydroxychloroquine's (HQ) arrhythmogenic adverse effects, data on favipiravir are limited. The authors purposed to demonstrate that the arrhythmic effects of favipiravir are not negligible.

**Materials and Methods:** The researchers conducted a retrospective observational study on 194 COVID-19 patients. The study population was classified into two groups based on the treatment regimen: favipiravir (n=101) and HQ (n=93). Pre/post-medication electrocardiograms were evaluated for arrhythmic events.

**Results:** Twenty of 101 (19.8%) subjects in the favipiravir group and 13 of 93 (13.9%) subjects in the HQ group had arrhythmogenic events (p=0.42). The most frequent arrhythmic events in the favipiravir group were sinus bradycardia (13 of 20, 65%) and third-degree atrioventricular block (4 of 20, 20%). Corrected QT (QTc) prolongation was the most seen arrhythmogenic adverse effect (9 of 13, 69%) in the HQ group. The proportion of patients with prolonged QTc were higher in the HQ group than the favipiravir group (9 vs. 3, p=0.04). However, the difference between final and baseline QTc did not differ between the HQ and the favipiravir group (11 [IQR:-9—57] vs. 12 [IQR:-7—103], p=0.59, respectively). The change between pre and post-treatment heart rate was more remarkable in the favipiravir group than the HQ group (12 [IQR:-6—70] vs. 5 [IQR:-8—41], $p < 0.001$, respectively).

**Conclusions:** Favipiravir was significantly associated with sinus bradycardia requiring drug withdrawal. Clinicians should more routinely implement arrhythmia monitoring for patients receiving favipiravir.



## Introduction

Since the first case was reported, coronavirus disease 2019 (COVID-19) has led to a significant increase in morbidity and mortality worldwide. The researchers are conducting several pharmacological studies against COVID-19 [1]. Among these research drugs, hydroxychloroquine (HQ), an antimalarial and anti-rheumatic drug, received wide attention at first. However, its usage has recently remained in the background due to its side effect profile. We included the HQ in the study to prove that favipiravir's arrhythmogenic effects were not inferior to HQ. The point to be considered is the relationship between QT prolongation with HQ [2]. Excessive QT interval prolongation may trigger Torsade de Pointes (TdP) [3].

Favipiravir, an RNA-dependent RNA polymerase inhibitor, was approved for drug-resistant influenza treatment in 2014 in Japan [4, 5]. A previous study demonstrated that favipiravir was associated with a shorter time to viral clearance and a higher recovery rate than lopinavir and ritonavir on chest scanning in COVID-19 patients [6]. Chen et al. reported that favipiravir had a faster recovery period than umifenovir in COVID-19 patients [7]. Studies have reported that favipiravir is well tolerated and has a good safety profile [8, 9]. Diarrhea, hyperuricemia, and elevated liver enzymes were the most frequent adverse effects reported in clinical trials [6,10]. Besides, Ghasemiyeh et al. revealed that favipiravir was infrequently associated with drug-induced psychotic symptoms [8]. Contrary to studies reporting that favipiravir has a well-established safety profile, we observed frequent conduction disorders in our patients. This study investigates the arrhythmogenic adverse effects of favipiravir in COVID-19 patients

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by comparing it with HQ, the best-known culprit in this regard.

## Materials and Methods

A total of 969 patients hospitalized between April 2020 and January 2021 were screened in this retrospective study. Two hundred ninety-three participants with polymerase chain reaction confirmed COVID-19 were divided into the favipiravir group (n=159) and the HQ group (n=135). The exclusion criteria were: the presence of atrial fibrillation or conduction disorders (sinus bradycardia, AV blocks), previously prolonged QT, use of negative chronotropic and antiarrhythmic medication, development of electrolyte disturbance, myocarditis, or myocardial infarction during follow-up, impaired clinical situation (renal and hepatic dysfunction, invasive/noninvasive mechanical ventilation requirement, septic shock, acidosis). Finally, 101 participants in the favipiravir group and 93 in the HQ group were included in the study (Figure 1).

Healthcare system algorithms have been applied to the treatment of patients. HQ, azithromycin, and oseltamivir triple therapy were given to patients hospitalized until July 2, 2020. Afterward, algorithms switched to favipiravir and levofloxacin. The authors compared the arrhythmic adverse effects between the two groups. HQ group treatment regimens were; HQ 200 mg orally twice a day for five days, azithromycin 500 mg orally once daily for five days, and subcutaneous enoxaparin 1 mg/kg. Favipiravir group protocol was as follows; favipiravir 1600mg loading dose, 600mg twice daily for four days, levofloxacin 500 once a day for five days, and subcutaneous enoxaparin 1 mg/kg. Symptom-based medications such as ceftriaxone, paracetamol, pantoprazole, dexamethasone were given in both groups.

The patient data registry obtained demographic, clinical characteristics, laboratory data, medications, outcomes, and basal and predischarge electrocardiography (ECG). Electrolyte levels that could trigger arrhythmia, troponin, D-dimer, and C-reactive protein were examined in all participants. Inpatient medications and hemodynamic parameters such as heart rate, blood pressure, and oxygen saturation were reconsidered daily. The present study was approved by the local ethics committee (466) and the Ministry of Health Scientific Research Platform (2021-02-15T01_58_28). Written and signed informed consent was obtained from the participants.

A standard 12-lead ECG (Cardiofax m, NIHON KOHDEN Corp. Tokyo, Japan) was performed at admission and discharge. Baseline and final ECGs of the participants were compared. The following data were analyzed in the admission and predischarge ECG or ECG during the arrhythmia; rhythm, heart rate (HR), QRS duration, PR and QT interval, extrasystole, and conduction disturbance. All parameters were manually measured from an ECG by the same cardiologist. The physician employed Lead-II to analyze rhythm, QRS duration, PR, and QT interval on ECG. If lead-II was not applicable, lead-I was assessed. Bazett formula was utilized to calculate the corrected QT (QTc) interval. The QTc prolongation was defined as $>$ 440 ms in males $>$ 460 ms in females.

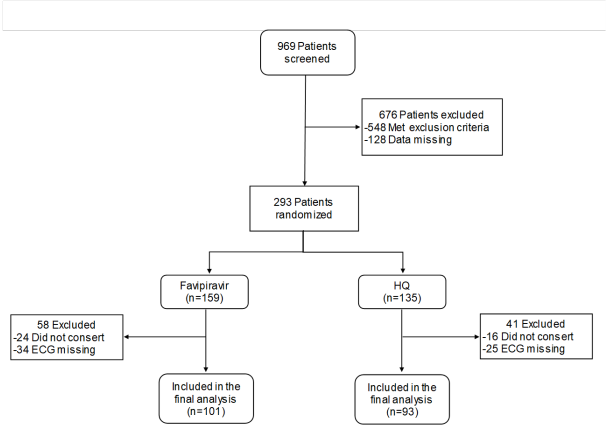


**Figure 1.** Patient enrollment. Based on this, a total of 969 COVID-19 patients were evaluated for eligibility. Of those, 194 participants were included in the study and were divided into two groups, favipiravir (n=101) and HQ (n=93). HQ, hydroxychloroquine; ECG, electrocardiography.

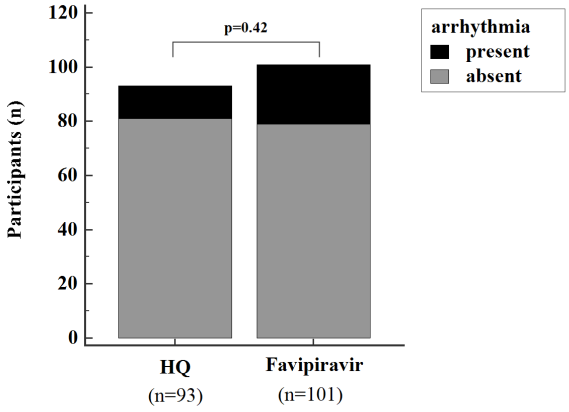


**Figure 2.** Depicts the post-treatment proportion of arrhythmic events of the two groups. HQ, hydroxychloroquine

The primary analysis was an evaluation of the arrhythmogenic adverse effects of the favipiravir and HQ groups. The Shapiro-Wilk test evaluated the normal distribution of variables. Continuous and categorical variables were given as mean±SD or median (IQR) and percentage. According to the data's distribution, the groups' variables were compared using the student t-test or Mann-Whitney U test and the chi-square test or Fisher's exact test. Paired samples t-test was applied to evaluate initial and final ECG measurements within groups. Statistical analyses were undertaken using the SPSS version 22.0 software package (IBM SPSS, New York, USA) and MedCalc version 15.8 statistical software (Ostend Belgium). The statistical significance threshold was adjusted as $p < 0.05$.

## Results

Of the 969 screened patients, adequate data, baseline, and final ECG were available in 194 patients for analy-

**Table 1.** Clinical characteristics of the study population grouped according to treatment

| | Total n=194 | Favipiravir n(%)=101(52.1) | HQ n(%)=93(47.9) | p-value* |
|---|---|---|---|---|
| Age, year | 55.4±13.8 | 59.0±13.2 | 51.5±13.4 | < 0.001 |
| Sex | | | | |
| Male, n (%) | 98 (50.5) | 52 (51.5) | 46 (49.5) | 0.77 |
| Female, n (%) | 96 (49.5) | 49 (48.5) | 47 (50.5) | 0.77 |
| History, n (%) | | | | |
| CAD | 17 (8.8) | 13 (12.9) | 4 (4.3) | 0.03 |
| Hypertension | 71 (36.6) | 44 (43.6) | 27 (29.0) | 0.03 |
| Diabetes Mellitus | 43 (22.2) | 26 (25.7) | 17 (18.3) | 0.21 |
| Laboratory data | | | | |
| Haemoglobin, g/dL | 13.0±1.6 | 13.4±1.7 | 13.1±1.5 | 0.14 |
| WBC, 10^+3/µL | 7.2±3.8 | 6.4±2.9 | 8.0±4.4 | 0.004 |
| Creatine, mg/dL | 0.8±0.2 | 0.8±0.2 | 0.7±0.1 | 0.10 |
| ALT, mg/dL | 21 (5-155) | 22 (5-155) | 19 (7-83) | 0.01 |
| Glucose, mg/dL | 106 (63-472) | 107 (74-472) | 105 (63-411) | 0.14 |
| Na, mmol/L | 130.0±3.7 | 138.0±3.8 | 140.0±3.3 | < 0.001 |
| K, mmol/L | 4.2±0.4 | 4.2±0.4 | 4.2±0.3 | 0.90 |
| Ca, mg/dL | 8.6±0.5 | 8.5±0.5 | 8.8±0.4 | < 0.001 |
| Troponin I, pg/mL | 3.9 (0-133) | 3.3 (0-133) | 6.4 (0-57) | 0.003 |
| D-dimer, ng/mL | 379 (50-26100) | 269 (50-8076) | 461 (74-26100) | < 0.001 |
| CRP, mg/dL | 17 (1-231) | 31 (1-231) | 7.5 (2-104) | < 0.001 |
| Discharge duration, day | 6.5±2.7 | 6.0±2.4 | 7.0±3.0 | 0.01 |

HQ: hydroxychloroquine; CAD: coronary artery disease; WBC: wight blood cell; ALT: alanine aminotransferase; Na: sodium; K: potassium; Ca: calcium; CRP: C-reactive protein.*p-value is the comparison between favipiravir and HQ group. Values are presented as the mean ± SD, median (IQR), or n (%).

**Table 2.** Electrocardiographic evaluation and arrhythmic events of the groups

| | Total n=194 | Favipiravir n(%)=101(52.1) | HQ n(%)=93(47.9) | p-value* |
|---|---|---|---|---|
| Baseline HR, bpm | 89±12 | 89±12 | 90±11 | 0.64 |
| Baseline PR, ms | 151±15 | 151±14 | 150±15 | 0.63 |
| Baseline QTc, ms | 402±20 | 400±21 | 404±20 | 0.14 |
| Final HR, bpm | 78±14 | 73±16 | 82±12 | < 0.001 |
| Final PR, ms | 161±20 | 162±19 | 159±20 | 0.21 |
| Final QTc, ms | 417±27 | 413±23 | 421±31 | 0.04 |
| ΔHR, bpm | 8 (-8—70) | 12 (-6—70) | 5 (-8—41) | < 0.001 |
| ΔPR, ms | 8 (-11—77) | 9 (-11—77) | 7 (-8—50) | 0.08 |
| ΔQTc, ms | 12 (-9—103) | 11 (-9—57) | 12 (-7—103) | 0.59 |
| Arrhythmias, n (%) | 32 (16.4) | 20 (19.8) | 13 (13.9) | 0.42 |
| Sinus bradycardia | 16 (8.2) | 13 (12.9) | 3 (3.2) | 0.01 |
| First-degree AV block | 3 (1.5) | 1 (1) | 2 (2.2) | |
| Third-degree AV block | 5 (2.6) | 4 (4) | 1 (1.1) | |
| Nonsustained VT | 2 (1) | 0 (0) | 2 (2) | |
| QTc prolongation | 12 (6.2) | 3 (3) | 9 (9.7) | 0.04 |

HQ: hydroxychloroquine; HR: heart rate; bpm: beat per minute; ms: milliseconds; PR: PR interval on the electrocardiogram; QTc: corrected QT interval on the electrocardiogram; ΔHR: baseline-final HR; ΔPR: final-baseline PR; ΔQTc: Final-Baseline QTc; AV: atrioventricular; VT: ventricular tachycardia.*p-value is the comparison between favipiravir and hydroxychloroquine group. Values are presented as the mean ± SD, median (IQR), or n (%).

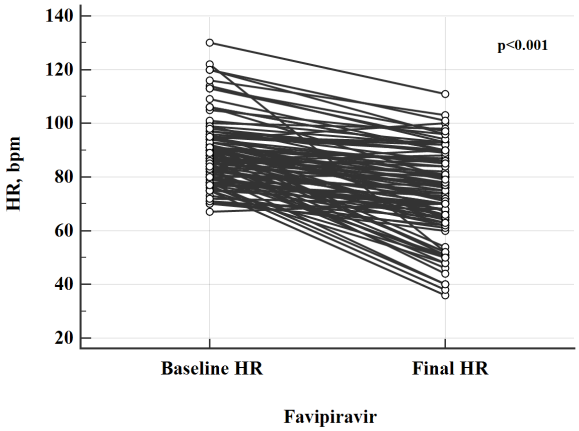


**Figure 3.** Pre/post-treatment HR interval changes in patients receiving favipiravir. HR, heart rate.

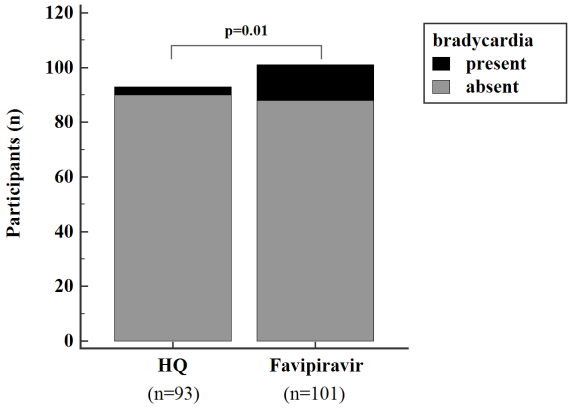


**Figure 4.** Pre/post-treatment HR interval changes in patients receiving HQ. HQ, hydroxychloroquin

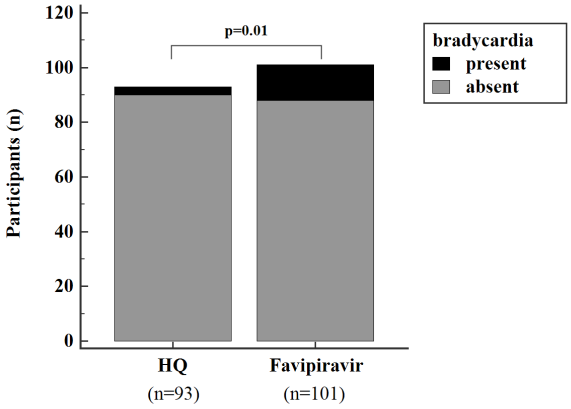


**Figure 5.** The rates of the sinus bradycardia cases of the groups after treatment. HQ, hydroxychloroquine

sis, and this group constitutes the study population. Table 1 depicts the clinical characteristics and laboratory data of the participants. The entire group's mean age was 55.4±13.8. The male participants' proportion was slightly higher (50.5%). The favipiravir group was older than the HQ group (59.0±13.2 vs. 51.5±13.4, $p < 0.001$, respectively). There was no significant difference in the gender distribution of the two groups (p=0.77). History of coronary artery disease and hypertension were more frequent in the favipiravir group than in the HQ group (13 [12.9%] vs 4 [4.3%], p=0.03; 44 [43.6%] vs 27 [29.0%], p=0.03, respectively). The diabetes mellitus rates of the two groups were similar (26 [25.7%] vs. 17 [18.3%], p=0.21). The HQ group's white blood cell count was significantly higher than in the favipiravir group (8.0±4.4 vs. 6.4±2.9, p=0.004, respectively). A significantly higher level of alanine aminotransferase was found in the favipiravir group as compared to the HQ group (22 [IQR:5-155]vs. 19 [IQR:7-83], p= 0.01.) Sodium and calcium levels were significantly higher in the HQ group than the favipiravir group (140.0±3.3 vs. 138.0±3.8, $p < 0.001$; 8.8±0.4 vs. 8.5±0.5, $p < 0.001$, respectively). The value of troponin and D-dimer in the HQ group was significantly higher than those in the favipiravir group (6.4 [IQR: 0-57] vs 3.3 [IQR:0-133], p=0.003; 461 [IQR:74-26100] vs 269 [IQR:50-8076], $p < 0.001$, respectively). Conversely, C-reactive protein levels were significantly higher in the favipiravir group as compared to the HQ group (31 [IQR:1-231] vs. 7.5 [IQR:2-104], $p < 0.001$, respectively). The favipiravir group's hospitalization day was shorter than the HQ group (6.0±2.4 vs. 7.0±3.0, p=0.01, respectively). There was no significant difference in hemoglobin, creatinine, and potassium levels between the two groups.

Table 2 describes the ECG evaluation results. The primary outcome involving the arrhythmogenic adverse effects was non significantly higher in the favipiravir group as compared to the HQ group (20 [19.8%] vs. 13 [13.9%], p=0.42, respectively) (Figure 2). The patients' baseline HR, PR, and QTc intervals were 89±12 bpm, 151±15 ms, and 402±20 ms, respectively. No significant difference was found in the baseline HR, PR, and QTc interval among the groups (p=0.64; p=0.63; p=0.14, respectively). The subjects' final HR, PR, and QTc intervals were 78 ± 14 bpm, 161 ± 20 ms, 417 ± 27 ms, respectively. The predischarge HR was significantly lower in the favipiravir group than the HQ group (73±16 vs. 82±12, $p < 0.001$, respectively). The difference in the pretreatment and the post-treatment heart rate (ΔHR) was significantly higher in the favipiravir group than the HQ group (12 [IQR:-6—70] vs. 5 [IQR:-8—41)], $p < 0.001$, respectively) (Figure 3-4). Also, patients with sinus bradycardia were significantly higher in the favipiravir group than in the HQ group (13 [12.9%] vs. 3 [3.2%], p=0.01, respectively) (Figure 5). Favipiravir was terminated in five symptomatic sinus bradycardia patients in the favipiravir group. Subsequently, the subjects' heart rates were raised without intervention in the follow-up. Considering that patients with sinus bradycardia in the HQ group were asymptomatic, the treatment regimen was continued. No significance was found in the PR interval difference (ΔPR) among the groups (9 [IQR:-11—77] vs. 7 [IQR:-8—50], p=0.08, respectively). The most ex-

tended PR interval was 240 ms, and treatment protocols were completed without intervention in this patient. The prolongation from baseline in QTc (ΔQTc) was similar between the groups (11 [IQR:-9—57] vs. 12 [IQR:-7—103], p=0.59, respectively). The number of patients with prolonged QTc was higher in the HQ group when compared with the favipiravir group ( 9 [9.7%] vs. 3 [3%], p=0.04, respectively). Four of the patients had a QTc > 500 ms during the medication in the HQ group, and the most prolonged QTc interval was 534 ms. Of those, two patients' QTc interval shortened to < 500 ms after HQ withdrawal. The other twos' QTc regressed to < 500 ms with both HQ and azithromycin discontinuation. The other subjects with extended QTc intervals completed the 5-day HQ cure without QTc prolongation > 500 ms. In contrast, none of the participants had a QTc > 500 ms in the favipiravir group. Furthermore, three patients had first-degree, and five had a third-degree atrioventricular (AV) block in the entire study (Table 2). A temporary pacemaker was implanted in whole patients with complete AV block. In one, the pacemaker was converted into a permanent one. Additionally, monomorphic non-sustained ventricular tachycardia that was not progressing in the follow-up was recorded in two patients in the HQ group. TdP induced by QT prolongation, atrial fibrillation, and arrhythmogenic death was not observed in the entire cohort.

## Discussion

In this retrospective cohort study, the researchers compared the arrhythmogenic adverse effects of favipiravir and HQ in COVID-19 patients. The key findings of this cohort were [1] the favipiravir group's arrhythmic events were numerically superior to the HQ group; however, there was no statistically significant difference between them, [2] favipiravir revealed arrhythmic events, the majority of which were sinus bradycardia, [3] both favipiravir and HQ groups had an increase in the QTc interval; nevertheless, no significant difference occurred among the groups.

The arrhythmogenic adverse effects of HQ have been reported in several previous studies [11–13]. These studies remarkably emphasize QT prolongation and its consequence, TdP. Chorin et al. documented that QTc interval prolonged > 500 ms in 23% of patients treated with HQ [11]. Furthermore, previous studies recommended that QT-prolonging agents not be used in individuals with a QTc > 500 ms due to increased risk for TdP [14,15]. In this cohort, 4 of 93 (4.3%) HQs' patients had a QT prolongation > 500 ms. Jankelson et al. stated that HQ lengthened QTc up to 35 ms on day 3, and the combination of azithromycin and HQ prolonged the QTc by an average of 5 ms in addition to HQ alone [3]. This study calculated a median of 12 ms of QTc prolongation between the terminal and initial ECG in the HQ group on day 7±3 (p < 0.001). A previous case reported a prolonged QT interval, resulting in TdP in lupus erythematosus patients treated with HQ [16]. Likewise, another research of 90 COVID-19 inpatients revealed that the QT prolongation incidence was 20%, and a case of TdP was recorded in a patient treated with HQ and azithromycin [2]. Other published rare arrhythmic events of HQ were as follows: nonsustained and sustained monomorphic ventricular tachycardia, atrial fibrillation, sinus bradycardia, first degree AV block, left bundle branch block, widened QRS complex, and sudden death [3, 12, 17]. The present study found that 9 of 93 (9.7%) patients treated with the HQ prolonged the QTc interval on day 4.2±1.7 of therapy. None of those induced TdP. The QTc prolongation was the HQ's most frequent arrhythmogenic adverse effect in this study, consistent with previous studies. We also discovered sinus bradycardia (n=3), first-degree AV block (n=1), third-degree AV block (n=1) and nonsustained monomorphic ventricular tachycardia (n=2) in the HQ group.

Contrary to the findings of previously published research of favipiravir [6,18], we found a high rate of arrhythmic events in the subjects treated with favipiravir. Twenty patients (19.8%) prescribed favipiravir had an arrhythmogenic adverse effect. Arrhythmic events included thirteen patients (65%] with sinus bradycardia, four patients (20%] with complete AV block, three patients (15%] with prolonged QTc, and one patient (5%] with first-degree AV block in the favipiravir group. A recent study computed that favipiravir yielded high-risk parameters regarding QT prolongation [19]. Chinello et al. reported that an Ebola virus-infected patients' QT interval had prolonged 98 ms on day seven of favipiravir therapy [20]. In this cohort, 3 of 101(3%) had a QT prolongation among the patients with the favipiravir-treated. Additionally, the QTc interval of patients treated with favipiravir increased by a median of 11 ms (p < 0.001) on day 6. Since the patients' QTc interval treated with favipiravir did not exceed 500 ms, the treatment protocol continued.

A review conducted with 93 favipiravir patients reported that sinus tachycardia (9%), QT prolongation (5%), and bradycardia (3%) were the most frequent arrhythmic events. Naksuk et al. reviewed that favipiravir was associated with QT prolongation but was safe for conduction disturbances. In this study, the researchers documented sinus bradycardia as the most observed arrhythmogenic adverse effect in the favipiravir group. We found a median of 12 and 5 bpm (p < 0.001) decreases in post-treatment HR in the favipiravir and HQ groups. Five of the favipiravir patients with sinus bradycardia were symptomatic. An improvement in the heart rate was observed two or three days after the favipiravir withdrawal in these subjects.

Another notable finding indicated that a complete AV block was developed in the four patients using favipiravir. The entirety of these patients had required a temporary pacemaker; consequently, a permanent pacemaker was implanted in one of these. We also found that the favipiravir group's PR interval extended more than the HQ group's, although it was not statistically significant (p=0.08). However, they did not develop PR prolongation to the degree that led to drug withdrawal.

According to these findings, the inquiry arises about whether the arrhythmic events are only due to favipiravir and HQ. Tsikouris et al. reported that a 7-day levofloxacin course did not prolong QT interval [21]. In a controlled clinical trial, moxifloxacin patients had a significant QT prolongation than levofloxacin patients (17.8 vs. 3.5, p < 0.001, respectively) [22]. Therefore, the role of levofloxacin in QT prolongation is weak or uncertain. A prospective

study manifested a mild but not significant QT interval prolongation on day 7 of azithromycin therapy (406 ms to 412 ms) [23]. A case documented that a QT prolongation leading to TdP developed on day 7 of azithromycin treatment [24]. A retrospective study on 89 cystic fibrosis patients revealed no significant difference in the QT prolongation between patients receiving and not receiving azithromycin [25]. Given these confusing findings, it should keep in mind that azithromycin may extend the QT interval.

The difference in troponin and D-dimer levels between the groups might affect developing arrhythmic events, even under the upper reference limit. Also, fever, inflammation, hypoxia, myocarditis, myocardial ischemia, electrolyte imbalance, and usage of other drugs can trigger arrhythmic events in COVID-19 patients. However, the two groups' clinical conditions were similar, and critically ill patients were not included in the study. Eventually, after existing drug withdrawal in both groups, the improvement in arrhythmic events suggested that favipiravir and HQ should be the primary culprit.

This study has several limitations. The researchers evaluated the participants' baseline and final ECGs; however, arrhythmic events could have been followed more closely by daily ECG recordings. Second, as a retrospective study, valuable information such as echocardiography and Holter monitoring were not presented in the study, as data were lacking due to limited conditions associated with isolation. Third, the arrhythmic events may involve multiple causes, and it is not easy to discriminate the favipiravir or HQ as the direct trigger. Further work with a larger group of patients is needed to confirm these findings.

In conclusion, this research fortifies previous studies regarding the arrhythmic events of HQ. Although the proportion of patients with QT prolongation in the HQ group was significantly higher than that of the favipiravir group, there was no significant difference in $\Delta$QTc. In addition, conduction disorders such as sinus bradycardia and complete AV block, most of which improved with favipiravir withdrawal, were identified. Therefore, patients using favipiravir should be focused on in arrhythmic events, such as HQ.

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