DR MAJID HAGHJOO (Orcid ID : 0000-0002-9963-6628)

Article type : Original Paper

# Effect of COVID-19 Medications on Corrected QT Interval and Induction of Torsade de Pointes: Results of a Multicenter National Survey

**Running title: QT prolongation and COVID-19 medications**

**Authors:**

Majid Haghjoo, MD[1]; Reza Golipra, MD[2]; Jalal Kheirkhah, MD[3]; Allahyar Golabchi, MD[4]; Javad Shahabi, MD[5]; Saeed Oni-Heris, MD[4]; Ramin Sami, MD[6]; Marzieh Tajmirriahi, MD[7]; Mehrdad Saravi, MD[8]; Mozhdeh Khatami, MD[9]; Mehran Varnasseri, MD[10]; Mohammadreza Kiarsi, MD[11]; Seyed Fakhreddin Hejazi, MD[12]; Mojtaba Yousefzadeh Rahaghi, MD[12]; Maryam Taherkhani, MD[13]; Haleh Ashraf, MD[14]; Mohammad Sadegh Keshmiri, MD[15]; Mohammad Ali Akbarzadeh, MD[16]; Ali Bozorgi, MD[17]; Fateme Mottaghizadeh, MD[16]; Behnam Hedayat, MD[17]; Mona Heidarali, MD[2]; Azita Hajhossein Talasaz, Pharm D[17]

**Affiliations:**

1. Cardiac Electrophysiology Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran
2. Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran
3. Department of Cardiology, School of Medicine, Heshmat Hospital, Guilan University of Medical Sciences
4. Shahid Beheshti Hospital, Kashan University of Medical Sciences, Kashan, Iran

5. Heart Failure Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
6. Department of Internal Medicine, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
7. Hypertension Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Science, Isfahan, Iran
8. Clinical Research Development Unit, School of Medicine, Babol University of Medical Science, Babol, Iran
9. Imam Sajad Hospital, Iran University of Medical Sciences, Shahryar, Iran
10. Infectious and Tropical Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
11. Atherosclerosis Research Center, Ahvaz University of Medical Sciences, Ahvaz, Iran
12. Shahid Beheshti Hospital, Qom University of Medical Sciences, Qom, Iran
13. Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
14. Research Development Center, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran
15. Lung Transplantation Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
16. Cardiovascular Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
17. Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran

**"All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation"**

**Corresponding author:** Majid Haghjoo, MD, FACC, FESC, Rajaie Cardiovascular Medical and Research Center, Vali-Asr St, Hashemi-Rafsanjani Blvd, Tehran, Iran
**Zip code:** 1995614331
**Phone**: (+98) 21-2392 3830**; Fax**: (+98) 21- 2392 3430**; Email**: majid.haghjoo@gmail.com
**Disclosures**: Authors contributing to this project have no conflict to disclose.

**Source of funding**: This study was sponsored by Rajaie Cardiovascular Medical and Research Center (grant no. 9962).

**Abstract**

**Background:** There are some data showing that repurposed drugs used for the Coronavirus disease-19 (COVID-19) have potential to increase the risk of QTc prolongation and torsade de pointes (TdP), these arrhythmic side effects have not been adequately addressed in COVID-19 patients treated with these repurposed medications.

**Methods:** This is the prospective study of 2,403 patients hospitalized at 13 hospitals within the COVID-19 epicenters of the Iran. These patients were treated with chloroquine, hydroxychloroquine, lopinavir/ritonavir, atazanavir/ritonavir, oseltamivir, favipiravir, and remdesivir alone or in combination with azithromycin. The primary outcome of the study was incidence of critical QTc prolongation and secondary outcomes were incidences of TdP and death.

**Results**: Of the 2403 patients, 2365 met inclusion criteria. The primary outcome of QTc≥500 ms and ΔQTc≥60 ms was observed in 11.2% and 17.6% of the patients, respectively. The secondary outcomes of TdP and death were reported in in 0.38% and 9.8% of the patients, respectively. The risk of critical QT prolongation increased in the presence of female gender, history of heart failure, treatment with hydroxychloroquine, azithromycin combination therapy, simultaneous furosemide or betablocker therapy and acute renal or hepatic dysfunction. However, the risk of TdP predicted by treatment with lopinavir-ritonavir, simultaneous amiodarone or furosemide administration and hypokalemia during treatment.

**Conclusion:** This cohort showed significant QTc prolongation with all COVID-19 medications studied, however, life-threatening arrhythmia of TdP occurred rarely. Among the repurposed drugs studied, hydroxychloroquine or lopinavir-ritonavir alone or in combination with azithromycin clearly demonstrated to increase the risk of critical QT prolongation and/or TdP.

**Keywords:** QT prolongation; COVID-19; torsades de pointes; repurposed drugs

## Introduction

As the coronavirus disease 2019 (COVID-19) global pandemic spreads across the world, the use of off-label repurposed drugs such as chloroquine/hydroxychloroquine with and without azithromycin, have gained attraction, appearing in international and domestic therapeutic guidelines. The presumed efficacies of these drugs mainly originated from in vitro investigations[1-3] and small nonrandomized studies.[4,5] However, subsequent randomized studies have failed to confirm these findings.[6-9] Simultaneously, a group of antiviral agents including lopinavir/ritonavir, atazanavir/ritonavir, oseltamivir, favipiravir, and remdesivir have been tested in prospective observational and randomized clinical trials in different countries.[10-12]

Although these repurposed drugs are generally well-tolerated in clinical practice, some of these drugs such as chloroquine, hydroxychloroquine, azithromycin, and lopinavir/ritonavir have been clearly shown to increase the risk of QT interval prolongation and torsade de pointes (TdP).[13] There are no adequate clinical data on QT prolonging effect and torsadogenic potentials of other drugs such as atazanavir/ritonavir, oseltamivir, favipiravir, and remdesivir. This risk of arrhythmic death could be further amplified if multiple medications are used in combination. Although there are some studies evaluating QT prolongation and TdP risk in those treated with chloroquine, hydroxychloroquine with and without azithromycin in COVID-19 patients,[14-16] the present study evaluated eight repurposed drugs in a large of number of the patients with COVID-19.

Our country is seriously involved with the covid-19 outbreak and many patients received these drugs or are going to receive in the future. Therefore, we designed this study to evaluate the risk of QT interval prolongation, TdP, and death among the hospitalized COVID-19 patients treated with chloroquine, hydroxychloroquine, lopinavir/ritonavir, atazanavir/ritonavir, oseltamivir, favipiravir, and remdesivir alone or in combination with azithromycin.

## Methods

*Study Population*: In this multicenter national survey, we prospectively collected data on pharmacotherapy of patients with COVID-19. Between June 2020 and October 2020, a total of

consecutive 2,403 patients were enrolled from 13 Hospitals within the COVID-19 epicenters of the Iran. For the purpose of this study, we included all patients who are 18 years of age and older, have positive polymerase chain reaction (PCR) for SARS-CoV-2 in nasopharyngeal swab and/or typical chest-CT findings and treated with chloroquine, hydroxychloroquine, lopinavir/ritonavir, atazanavir/ritonavir, tocilizumab, oseltamivir, favipiravir, and remdesivir as monotherapy or in combination with azithromycin. In addition, patients should have an interpretable baseline ECG and at least one ECG recorded on second day of therapy or later. Baseline ECGs otherwise unsuitable for accurate QT interval measurement were excluded. Patients without 12-lead ECG or rhythm strip recordings on day 2 of drug therapy or later were also excluded. This study was approved by the Research Ethics Committee of National Institute for Medical Research Development (Approval ID: IR.NIMAD.REC.1399.055) and all patients gave written informed consent for participation in the study.

*Data collection*: Data were collected by patient interview and review of medical records. Collected data were entered into web-based electronic database (Regitory, Tehran, Iran: https://regitory5.rhc.ac.ir). All information was kept confidential and password protected. We gathered all data related to patient demographics, associated comorbidities (i.e. heart disease, heart failure, renal failure, liver disease), laboratory data (i.e. electrolyte levels, renal function test, and liver function tests), drug history (including COVID-19 drugs and other QT prolonging drugs), electrocardiographic findings at baseline ECG and after drug intake, and all important events during admission or follow-up (TdP, sudden death, and mortality).

*Drug therapy protocols*: The decision to treat with above-mentioned drugs was based on the clinical decision of the treating physician and national guidelines. The treatment regimens were as follows: (1) Chloroquine 500 mg by mouth twice daily for 1 day followed by 250 mg by mouth twice daily for 5-7 days; (2) Hydroxychloroquine 400 mg by mouth twice daily for 1 day followed by 200 mg by mouth twice daily for 5-7 days; (3) Azithromycin 500 mg by mouth daily for 1 day and followed by 250 mg daily for 5 days; (4) Lopinavir/ritonavir 200/50 mg twice daily for 5 days; (5) Atazanavir/ritonavir 300/100 mg daily for 5 days; (6) Oseltamivir 75 mg twice daily for 5 days; (7)

Favipiravir 1600 mg twice daily for 1 day and then 600-800 mg twice daily for 5 days; (8) Remdesivir 200 mg daily for first day and then 100 mg daily for 5-7 days.

All decisions on patient care were taken by the hospital clinicians, and no attempt was made by research team to influence their decisions. Furthermore, decisions regarding situations such as critical QT prolongation and or TdP were at the sole discretion of the physicians responsible for patient care.

*QT measurements*: A baseline QTc was measured from a 12-lead ECG before treatment. If no baseline ECGs were available, ECGs recorded within 30 days of drug initiation were used for the baseline measures. On-treatment QT measurements were done using 12-lead ECGs or single-lead rhythm strip of lead II.

QT measurements were independently reviewed and validated by 13 expert cardiologists who were blinded to other patient data. The QT intervals were calculated manually from either lead II or V5 using the tangent method[17] and QT corrections were done using Bazett's formula. For patients with intraventricular conduction delays (paced rhythms or bundle branch block), a modified QTc was calculated using the formula: modified QTc = (QT-(QRS-120))/√RR.[18] Using ECGs recorded before and during treatment, we also assessed the change from baseline in QTc (ΔQTc).

*Study outcomes*: The primary outcome of the study was incidence of critical QTc prolongation, defined as maximum on-therapy QTc ≥500 ms (if QRS <120 ms) or QTc ≥550 ms (if QRS ≥120 ms) and ΔQTc of ≥60 ms. Secondary outcomes were incidences of documented TdP and all-cause mortality. Cause of death was adjudicated by review of the resuscitation records from all patients with attempted resuscitation, and the reviewers of these data were blinded to the QTc data. TdP should be clearly documented by a single-lead ECG tracing.

*Statistical analysis*: Fitness of interval variables with normal distribution was assessed by one-sample Kolmogorov-Smirnov test. Data are presented as mean±SD for continuous and frequency (percentage) for categorical variables. Comparisons of characteristics were made using Pearson's chi-square or Fisher's exact test for categorical variables and unpaired Student t test for continuous variables. The ECG characteristics before vs during drug therapy were compared using paired t test.

Independent predictors for prolonged QTc were identified by logistic regression models. P value <0.05 was considered as statistically significant. Statistical analyses were performed using IBM SPSS Statistics 22 for Windows (IBM Corp, Armonk, NY).

## Results

*Patient characteristics*: Clinical characteristics of the study population were presented in Table 1. Of the 2,403 patients initially enrolled in the study, 2,365 met inclusion criteria and 38 were excluded because of non-interpretable baseline ECG or incomplete clinical data. Out of 2,365 patients, 1311 (54.6%) were male and the mean age was 59.6±16.4 years (range, 18-99 years). The most common comorbidities were hypertension (35.8%), diabetes mellitus (31%), non-ischemic structural heart disease (14.9%), and coronary artery disease (12.9%).

Hydroxychloroquine was prescribed to treat COVID-19 infection in 1430 (60.5%) of the patients. A minority of the patients (n=9,0.4%) received chloroquine. Azithromycin was added to 1080 (75.5%) patients in hydroxychloroquine group and 3 (33%) in chloroquine group. Lopinavir/ritonavir and atazanavir/ritonavir were administered to 689 (29%) and 16 (0.7%) of the patients, respectively. Azithromycin was added to 206 (30%) patients in lopinavir/ritonavir group and 4 (25%) in atazanavir/ritonavir group. One-hundred twenty-one patients (5%) were treated with oseltamivir, including 103 monotherapy and 18 combination therapy with azithromycin. Other antiviral agents favipiravir, and remdesivir were also employed in 33 (1.4%) and 67 (2.8%) patients, respectively.

*Electrocardiographic characteristics*: A 12-lead ECG was obtained from all patients before treatment. ECG characteristics were summarized in Table 2. The mean baseline QTc interval was 399.5±42.5 ms and 48 patients (2.0%) had a baseline QTc ≥500 ms. On-treatment measurements showed significant increase in QTc interval (432.5±53.8 ms, p<0.001). All COVID-19 drug regimens were associated with significant increase in on-treatment QTc (all p <0.05). Maximal increases in on-treatment QTc were observed following combination of azithromycin with either chloroquine, lopinavir/ritonavir, or hydroxychloroquine (Table 3). Compared with monotherapy, combination therapy led to significantly

more increase in on-treatment QTc (ΔQTc: 26.4 ms vs. 37.6 ms, p<0.001) and higher number of the patients with QTc ≥500 ms (8.0% vs. 13.5%, p<0.001) and ΔQTc ≥ 60 ms (12% vs. 212.6%, p<0.001).

*Outcome analysis*: Primary and secondary outcome for different drug regimens were summarized in Table 4. After receiving COVDI-19 medications, QTc ≥500 ms and ΔQTc ≥ 60 ms were detected in 11.2% (n=266), and 17.6% (n=417) of the patients, respectively.

Compared to the those with QTc<500 ms, the patients with QTc≥500 ms were more likely to have history of heart failure and chronic kidney disease (CKD), more likely to receive hydroxychloroquine, lopinavir-ritonavir, azithromycin, diuretics, beta-blockers, and calcium antagonists, and more likely to develop acute renal or hepatic dysfunction during treatment. However, female gender, history of heart failure, acute hepatic dysfunction, treatment with hydroxychloroquine, azithromycin combination therapy, and simultaneous furosemide therapy remained as independent predictors of QTc≥500 ms in multivariate analysis (Table 5).

In comparison to those who had ΔQTc <60 ms, patients with ΔQTc≥60 ms were more likely to have history of CKD, more likely to develop acute renal or hepatic dysfunction during treatment, and more likely to receive hydroxychloroquine, lopinavir-ritonavir, oseltamivir, azithromycin combination therapy, furosemide, and betablockers. In multivariate analysis, simultaneous betablocker therapy and acute renal failure remained as independent predictors for ΔQTc≥60 ms (Table 6).

During the study period, a total of 9 patients (0.38%) experienced TdP and required emergent defibrillation. Of the 9 patients who had TdP, 4 were treated with combination of hydroxychloroquine and azithromycin and 5 with combination of lopinavir/ritonavir and azithromycin. Patients who developed TdP were more likely to have history of non-ischemic structural heart disease, history of heart failure, history of CKD, history of chronic liver disease, more likely to receive lopinavir-ritonavir, azithromycin combination therapy, furosemide, metolazone, amiodarone, and other QT prolonging drugs, more likely to have QTc≥500 ms, and ΔQTc≥60 ms during treatment, and more likely to develop electrolyte abnormalities (hypokalemia, hypocalcemia), and acute renal dysfunction.

However, treatment with lopinavir-ritonavir, simultaneous amiodarone or furosemide administration and hypokalemia during treatment remained as independent predictors of TdP (Table 7).

Of the 2365 patients in the whole study cohort, 231 (9.8%) died during the study period. In comparison to those who survived, the patients who died were older, more likely to be men, more likely to have coronary artery disease, heart failure, CKD, diabetes, hypertension, and more likely to receive hydroxychloroquine, lopinavir-ritonavir, combination therapy, furosemide, amiodarone, betablockers, and digoxin, and more likely to experience hypokalemia, acute renal or liver dysfunction, QTc≥ 500 ms, ΔQTc≥60 ms during treatment. However, age, azithromycin combination therapy, greater amiodarone exposure, furosemide therapy, and acute renal dysfunction remained as independent predictors of mortality in multivariate analysis (Table 8). Survival analysis of the eight drug regimens showed clear increase in mortality among the patients who received hydroxychloroquine or lopinavir-ritonavir with and without azithromycin combination therapy (Figure 1).

## Discussion

In present cohort of 2365 patients with COVID-19, primary outcome of critical QT prolongation defined as QTc≥500 ms or ΔQTc≥60 ms was observed in 11.2% and 17.6% of the patients, respectively. There were 9 cases (0.38%) of the secondary outcome of TdP in entire cohort.

To the best of our knowledge, this is the largest multicenter study reporting on QT prolongation and arrhythmic complications of treatment with multiple repurposed drugs in patients with COVID-19. Although there is some information on cardiac safety of chloroquine and hydroxychloroquine with and without azithromycin in patients with COVID-19,[14-16] our current knowledge on cardiac safety of other repurposed medications for the COVID-19 treatment is limited. Present cohort included a large dataset on cardiac safety of hydroxychloroquine, lopinavir-ritonavir, and oseltamivir with and without azithromycin. This study, for the first time, systematically investigated the QT prolongation and arrhythmogenicity in patients with COVID-19 who were treated with atazanavir-ritonavir, favipiravir, and remdesivir. We showed that all eight COVID-19 medications were associated with some degree of QTc prolongation. Maximal QTc interval prolongation was observed in chloroquine combination

with azithromycin and favipiravir monotherapy was associated with minimum QT prolongation. Combination therapy with azithromycin led to a significantly greater increase in the QTc interval when compared to monotherapy. Hydroxychloroquine use and combination therapy with azithromycin were predictors for having critical QT prolongation during treatment. All cases of the TdP occurred in combination therapy group. Although critical QT prolongation was associated with higher risk of TdP, only treatment with lopinavir-ritonavir, simultaneous administration of amiodarone or furosemide and hypokalemia could predict the occurrence of TdP during therapy. Of the COVID-19 medications evaluated in this study, azithromycin combination therapy also predicted a higher risk of mortality.

Effect of chloroquine/hydroxychloroquine with and without azithromycin on QTc interval and TdP has been studied in several cohorts of COVID-19 patients.[14-16] In the present study, 1430 patients who were treated with hydroxychloroquine with or without azithromycin developed QTc ≥500 ms in 14%, ΔQTc ≥ 60 ms in 21%, and TdP in 0.3% of the patients. Female gender, history of heart failure, acute hepatic dysfunction, treatment with hydroxychloroquine, azithromycin combination therapy, and simultaneous furosemide therapy were significant predictors of QTc ≥ 500 ms. In largest published study, 415 patients with COVID-19 from 3 hospitals who treated with hydroxychloroquine/azithromycin were prospectively included.[15] Critical QTc prolongation ≥500 ms was detected in 21% of patients and no instance of TdP was reported. Age, body mass index <30kg/m$^2$, heart failure, elevated creatinine, and peak troponin > 0.04 mg/ml were significant predictors of QTc≥ 500 ms. Second important study reported the retrospective analysis of 251 patients with COVID-19 from 2 centers who were treated with combination of hydroxychloroquine and azithromycin.[16] On-treatment QTc ≥500 ms had developed in 23% of the patients, ΔQTc ≥ 60 ms in 22% was seen in 20% of the patients and one patient experienced TdP (0.4%). Baseline QTc interval and simultaneous amiodarone therapy were predictors for QTc ≥500 ms and baseline creatinine level and simultaneous amiodarone therapy were predictors of simultaneous amiodarone therapy.

In addition to chloroquine/hydroxychloroquine with and without azithromycin, we studied the effect of five other antiviral repurposed drugs on QT interval prolongation and arrhythmic events. Lopinavir-ritonavir and atazanavir-ritonavir, two fixed-dose combination antiretroviral medications,

repurposed for COVID-19 treatment in the light of some efficacy in the SARS-CoV and the Middle-East Respiratory Syndrome Coronavirus (MERS-CoV).[19] Lopinavir/ritonavir and atazanavir/ritonavir were used 29% and 0.7% of our patients, respectively. Azithromycin was added to 30% of the patients in lopinavir/ritonavir group and 25% in atazanavir/ritonavir group. Treatment with lopinavir-ritonavir increased the risk of TdP by more than 8 times; five cases of TdP occurred in patients who are receiving lopinavir-ritonavir and azithromycin combination, however, there was no report of TdP in atazanavir-ritonavir group. Latter finding may be related to small number (n=19) of the patients who were treated with atazanavir-ritonavir.

Oseltamivir, an antiviral to treat influenza, was used in the early days of the COVID-19 pandemic because there was some evidence that the active site of the spike protein of SARS-COV2 virus is similar to that of influenza virus neuraminidase, suggesting that neuraminidase inhibitors (e.g. oseltamivir) may be useful to treat COVID-19. In the present study, it was used in 5% of the patients mainly as combination therapy with azithromycin. Oseltamivir use significantly increased baseline QT and led to critical QT prolongation as QTc ≥500 ms in 6.6% and ΔQTc ≥ 60 ms in 11% of the patients. However, there were no instances of oseltamivir-related TdP in entire cohort. In a small study, Celik et al.[20] critical QTc prolongation (QTc ≥500 ms or ΔQTc ≥ 60 ms) was detected in 12% of the population. The use of oseltamivir in combination with hydroxychloroquine and azithromycin was found to cause critical QTc prolongation more than five times. Both studies indicate that we should be more careful when prescribing the combination of oseltamivir with COVI-19 medications during influenza season.

Favipiravir is an oral drug that was approved for influenza and Ebola-virus infection. In our study, favipiravir monotherapy was safer than other COVID-19 mediations in terms of QTc prolongation. Of the 33 patients on favipiravir therapy, there were one case (3%) of QTc ≥500 ms and 3 cases (9%) of ΔQTc ≥ 60 ms, however, no TdP was observed. In a case report, QTc prolongation was observed on the 9th day of treatment in a patient who was using favipiravir for Ebolavirus infection.[21] However, small study by Cap et al. in COVID-19 patients showed no significant increase in QTc interval.[22] Together, available data indicate that favipiravir is better tolerated in terms of cardiac arrhythmia in COVID-19 patients.

Remdesivir originally tested in patients with Ebola, now the FDA approved an Emergency Use Authorization to allow treatment of COVID-19 patients hospitalized with severe disease.[11] Currently, there is little data on QT prolonging effect of this drug. In our series of 67 patients on remdesivir, there was significant increase in QTc interval. In addition, we observed 6 cases (9%) of QTc ≥500 ms and 6 cases (9%) of ΔQTc ≥ 60 ms, however, no instance of TdP was reported. There is only one case report of critical QT prolongation (555 ms) in COVID-19 patient following third dose of a five-day treatment with remdesivir.[23] It is important to note that this patient was on azithromycin while receiving remdesivir which is well known to prolong the QT interval. It is possible that it contributed to the prolongation of the QT interval in this patient. However, in our study, all patients received remdesivir monotherapy. It appears that remdesivir monotherapy, among the COVID-19 medications studied, has a low risk profile in terms of QT prolongation and TdP induction.

Repurposed drugs used in COVID-19 treatment cause QT prolongation by blocking the voltage-gated ion channel that mediates the rapid component of the delayed rectifier potassium current, IKr, resulting in lengthening of the ventricular action potential.[24] A timely early Afterdepolarization, in the presence of a prolonged QT interval, may result in TdP. This risk increases in the presence of concomitant use of QT prolonging agents, loop diuretic, female sex, elderly, structural heart disease, heart failure, myocardial infarction, electrolyte disturbances, bradycardia, renal disease, and hepatic disease.[25] In addition, concomitant cardiac injury from SARS-CoV-2 infection may increase the risk of adverse events from generally safe drugs.[26] We similarly showed that female sex, history of heart failure, treatment with hydroxychloroquine, azithromycin combination therapy, simultaneous furosemide or betablocker therapy, and acute renal or hepatic dysfunction were independently increased risk of the critical QT prolongation, however, the risk of TdP increased with lopinavir-ritonavir use, amiodarone or loop diuretic coadministration and hypokalemia during treatment. Drug-induced bradycardia is the common mechanism for the QT prolongation following amiodarone, betablocker, and digoxin use,[25] however, amiodarone has also a known risk of prolonging QTc secondary to action potential prolongation.[27] We also observed that the risk of mortality increased independently by azithromycin combination therapy, simultaneous amiodarone or loop diuretic therapy, and acute renal dysfunction.

Importance of ECG monitoring has been studied in a recent multicenter study in 6476 hospitalized patients with COVID-19 who were treated with hydroxychloroquine with or without azithromycin.[28] Using a simplified approach to monitoring for QT prolongation and arrhythmia, TdP was observed in 1 (0.015%) patient and sixty-seven (1.03%) patients had hydroxychloroquine with and without azithromycin held or discontinued due to excessive QT prolongation.

Practical recommendations for healthcare providers: 1) Considering the limited efficacy and important safety concerns, we think that chloroquine/hydroxychloroquine, fixed-dose combination antiretroviral medications with and without azithromycin should be avoided in COVID-19 treatment. 2) Although monotherapy with oseltamivir, favipiravir, and remdesivir are better tolerated in terms of the critical QT prolongation and TdP, treatment with these drugs still needs close ECG monitoring for QT prolongation. 3) Optimization of renal/hepatic functions and electrolyte status is highly recommended.4) Simultaneous use of antiarrhythmic drugs such as amiodarone, betablockers, etc. is discouraged.

**Limitations**: Results of the present study should be interpreted in the light of certain limitations: first, patients without a baseline or post-medication ECGs were excluded from the analysis, which can represent a bias. We tried to minimize this bias by the consecutive inclusion of patients meeting study criteria. Second, the present cohort was consisted of hospitalized patients, and the results may not apply to outpatient setting or prophylactic treatments. Third, although a specific dosing schedule was recommended by national COVID-19 guidelines for all physicians, the decisions when and how to prescribe these drugs were deferred to the prescribing physicians.

**Conclusions**: Hospitalized COVID-19 patients treated with chloroquine, hydroxychloroquine, lopinavir/ritonavir, atazanavir/ritonavir, oseltamivir, favipiravir, and remdesivir alone or in combination with azithromycin had a significant increase in QTc during drug therapy. Several risk factors identified patients at risk of critical QTc prolongation. Despite this finding, life-threatening arrhythmia of TdP occurred rarely. Among the repurposed drugs studied, hydroxychloroquine or lopinavir-ritonavir alone or in combination with azithromycin clearly demonstrated to increase the risk of critical QT prolongation or induction of TdP.

## References


1. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30(3):269-271. doi: 10.1038/s41422-020-0282-0.
2. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W, Liu D. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Di. 2020;71(15):732-739. doi: 10.1093/cid/ciaa237.
3. Fintelman-Rodrigues N, Sacramento CQ, Ribeiro Lima C, Souza da Silva F, Ferreira AC, Mattos M, de Freitas CS, Cardoso Soares V, da Silva Gomes Dias S, Temerozo JR, Miranda MD, Matos AR, Bozza FA, Carels N, Alves CR, Siqueira MM, Bozza PT, Souza TML. Atazanavir, Alone or in Combination with Ritonavir, Inhibits SARS-CoV-2 Replication and Proinflammatory Cytokine Production. Antimicrob Agents Chemother. 2020 Sep 21;64(10):e00825-20. doi: 10.1128/AAC.00825-20.
4. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Tissot Dupont H, Honoré S, Colson P, Chabrière E, La Scola B, Rolain JM, Brouqui P, Raoult D. Int J Antimicrob Agents. 2020 Jul;56(1):105949. doi: 10.1016/j.ijantimicag.2020.105949.
5. Lagier JC, Million M, Gautret P, Colson P, Cortaredona S, Giraud-Gatineau A, Honoré S, Gaubert JY, Fournier PE, Tissot-Dupont H, Chabrière E, Stein A, Deharo JC, Fenollar F, Rolain JM, Obadia Y, Jacquier A, La Scola B, Brouqui P, Drancourt M, Parola P, Raoult D; IHU COVID-19 Task force. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis. Travel Med Infect Dis. 2020 Jul-Aug;36:101791. doi: 10.1016/j.tmaid.2020.101791.

6. Omrani AS, Pathan SA, Thomas SA, Harris TRE, Coyle PV, Thomas CE, Qureshi I, Bhutta ZA, Mawlawi NA, Kahlout RA, Elmalik A, Azad AM, Daghfal J, Mustafa M, Jeremijenko A, Soub HA, Khattab MA, Maslamani MA, Thomas SH. Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19. EClinicalMedicine. 2020 Dec;29:100645. doi: 10.1016/j.eclinm.2020.100645.
7. Self WH, Semler MW, Leither LM, et al. Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. *JAMA*. 2020;324(21):2165–2176. doi:10.1001/jama.2020.22240.
8. Self WH, Semler MW, Leither LM, Casey JD, Angus DC, Brower RG, eta l. Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. JAMA. 2020 Dec 1;324(21):2165-2176. doi: 10.1001/jama.2020.22240.
9. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al.; Coalition Covid-19 Brazil I Investigators. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med. 2020 Nov 19;383(21):2041-2052. doi: 10.1056/NEJMoa2019014.
10. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Li H, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Wang J, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020 May 7;382(19):1787-1799. doi: 10.1056/NEJMoa2001282.
11. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB,

Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC; ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020 Nov 5;383(19):1813-1826. doi: 10.1056/NEJMoa2007764.

12. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19-interim WHO Solidarity trial results. N Engl J Med. DOI: 10.1056/NEJMoa2023184.
13. Roden DM, Harrington RA, Poppas A, Russo AM. Considerations for Drug Interactions on QTc in Exploratory COVID-19 Treatment. Circulation. 2020 Jun 16;141(24):e906-e907. doi: 10.1161/CIRCULATIONAHA.120.047521.
14. Saleh M, Gabriels J, Chang D, Soo Kim B, Mansoor A, Mahmood E, Makker P, Ismail H, Goldner B, Willner J, Beldner S, Mitra R, John R, Chinitz J, Skipitaris N, Mountantonakis S, Epstein LM. Effect of Chloroquine, Hydroxychloroquine, and Azithromycin on the Corrected QT Interval in Patients With SARS-CoV-2 Infection. Circ Arrhythm Electrophysiol. 2020 Jun;13(6):e008662. doi: 10.1161/CIRCEP.120.008662.
15. O'Connell TF, Bradley CJ, Abbas AE, Williamson BD, Rusia A, Tawney AM, Gaines R, Schott J, Dmitrienko A, Haines DE. Hydroxychloroquine/Azithromycin Therapy and QT Prolongation in Hospitalized Patients with COVID-19. JACC Clin Electrophysiol. 2020 Aug 5. doi: 10.1016/j.jacep.2020.07.016. Epub ahead of print. PMCID: PMC7406234.
16. Chorin E, Wadhwani L, Magnani S, Dai M, Shulman E, Nadeau-Routhier C, Knotts R, Bar-Cohen R, Kogan E, Barbhaiya C, Aizer A, Holmes D, Bernstein S, Spinelli M, Park DS, Stefano C, Chinitz LA, Jankelson L. QT interval prolongation and torsade de pointes in patients with COVID-19 treated with hydroxychloroquine/azithromycin. Heart Rhythm. 2020 Sep;17(9):1425-1433. doi: 10.1016/j.hrthm.2020.05.014.
17. Postema PG, Wilde AA. The measurement of the QT interval. Curr Cardiol Rev. 2014 Aug;10(3):287-94. doi: 10.2174/1573403x10666140514103612.
18. Patel P, Borovskiy Y, Deo R. QTc, A novel method for correcting QT interval for QRS duration, predicts all-cause mortality. J Am Coll Cardiol 2015; 65 (10_Supplement) A336.

19. Nukoolkarn V, Lee VS, Malaisree M, Aruksakulwong O, Hannongbua S. Molecular dynamic simulations analysis of ritonavir and lopinavir as SARS-CoV 3CL(pro) inhibitors. J Theor Biol 2008;254:861e7. https://doi.org/10.1016/j.jtbi.2008.07.030.
20. Çelik HG, Keske Ş, Şener Ü, Tekbaş M, Kapmaz M, Şahin ŞT, Özyıldırım A, Aytekin S, Aytekin V, Ergönül Ö. Why we should be more careful using hydroxychloroquine in influenza season during COVID-19 pandemic? Int J Infect Dis. 2021 Jan;102:389-391. doi: 10.1016/j.ijid.2020.10.080.
21. Chinello P, Petrosillo N, Pittalis S, Biava G, Ippolito G, Nicastri E; INMI Ebola Team. QTc interval prolongation during favipiravir therapy in an Ebolavirus-infected patient. PLoS Negl Trop Dis. 2017 Dec 28;11(12):e0006034. doi: 10.1371/journal.pntd.0006034.
22. Çap M, Bilge Ö, Işık F, Burak C, Karagöz A, İnci Ü, Akyüz A, Aslan B, Altıntaş B, Altındağ R, Kaya İ, Adıyaman MŞ, Süleymanoğlu M, Kaya Ş, Baysal E. The effect of favipiravir on QTc interval in patients hospitalized with coronavirus disease 2019. J Electrocardiol. 2020 Nov-Dec;63:115-119. doi: 10.1016/j.jelectrocard.2020.10.015.
23. Gupta A K, Parker B M, Priyadarshi V, Parker J. Cardiac Adverse Events with Remdesivir in COVID-19 Infection. Cureus 12(10): e11132. DOI 10.7759/cureus.11132
24. Michaud V, Dow P, Al Rihani SB, Deodhar M, Arwood M, Cicali B, Turgeon J. Risk Assessment of Drug-Induced Long QT Syndrome for Some COVID-19 Repurposed Drugs. Clin Transl Sci. 2020 Sep 5. doi: 10.1111/cts.12882.
25. Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR, Kovacs RJ. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. Circ Cardiovasc Qual Outcomes. 2013 Jul;6(4):479-87. doi: 10.1161/CIRCOUTCOMES.113.000152. Epub 2013 May 28. Erratum in: Circ Cardiovasc Qual Outcomes. 2013 Nov;6(6):e57.
26. Naksuk N, Lazar S, Peeraphatdit TB. Cardiac safety of off-label COVID-19 drug therapy: a review and proposed monitoring protocol. Eur Heart J Acute Cardiovasc Care. 2020 Apr;9(3):215-221. doi: 10.1177/2048872620922784.

27. Torres V, Tepper D, Flowers D, Wynn J, Lam S, Keefe D, Miura DS, Somberg JC. QT prolongation and the antiarrhythmic efficacy of amiodarone. J Am Coll Cardiol 1986 Jan;7(1):142-7. doi: 10.1016/s0735-1097(86)80272-8.

28. Saleh M, Gabriels J, Chang D, Fishbein J, Qiu M, Mountantonakis SE, Epstein LM; Northwell COVID-19 Research Consortium. Safely Administering Potential QTc Prolonging Therapy Across a Large Health Care System in the COVID-19 Era. Circ Arrhythm Electrophysiol. 2020 Nov;13(11):e008937. doi: 10.1161/CIRCEP.120.008937.

**Table 1- Baseline clinical characteristics**

| Characteristic (n=2365) | Value |
|---|---|
| **Age (y)** | 59.6±16.4 |
| **Male gender** | 1303 (54.6) |
| **Nasopharyngeal PCR test** | 2059 (86) |
| **Positive PCR result** | 1586 (77) |
| **Lung CT scan** | 778 (33) |
| **COVID-19 pneumonia in lung CT scan** | 766 (98.5) |
| **Coronary artery disease** | 308 (13) |
| **Non-ischemic structural heart disease** | 355 (15) |
| **Heart failure** | 186 (7.8) |
| **Chronic kidney disease** | 174 (7.3) |
| **Chronic hepatic disease** | 16 (0.7) |
| **Hypertension** | 855 (35.8) |
| **Diabetes** | 742 (31) |
| **Creatinine level (mg/dL)** | 1.4±1.0 |
| **Potassium level (mEq/L)** | 4.3±2.0 |
| **Magnesium level (mEq/L)** | 2.1±0.74 |
| **Aspartate Aminotransferase level (u/L)** | 52±90 |
| **Alanine Aminotransferase level (u/L)** | 41±55 |
| **Bilirubin level** | 1.3±1.4 |

Continuous variables were presented as mean±SD. Categorical variables are presented as n (%).

Abbreviations: PCR=polymerase chain reaction; COVID-19=coronavirus disease 2019; CT=computed tomography

**Table 2- Electrocardiographic characteristics**

| ECG parameter | Baseline measurement | On-therapy measurement | P-value |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Heart rate (bpm)** | 90.5±28.0 | 90.2±20.0 | 0.51 |
| **PR interval (ms)** | 163.0±33.0 | 163.0±39.0 | <0.001 |
| **QRS width (ms)** | 84.5±22.0 | 86.5±25.0 | <0.001 |
| **QT interval (ms)** | 340.5±41.7 | 356.3±52.4 | <0.001 |
| **QTc interval (ms)** | 399.5±42.5 | 432.5±54.0 | <0.001 |

1 Variables were presented as mean±SD.

**Table 3- QT change with different COVID-19 pharmacotherapy**

| COVID drug | Baseline QTc | On-treatment QTc | ΔQTc | P-value |
|---|---|---|---|---|
| **Chloroquine (n=9)** | 389.8±33.0 | 447.6±35.0 | +57.8 | 0.002 |
| **Chloroquine monotherapy (n=6)** | 394.0±32.0 | 432.0±31.0 | +38 | 0.002 |
| **Chloroquine+Azithromycin (n=3)** | 381.6±40.0 | 479.3±17.0 | +97.7 | 0.002 |
| **Hydroxychloroquine (n=1430)** | 399.0±45.0 | 436.0±57.0 | +37 | <0.001 |
| **Hydroxychloroquine monotherapy (n=350)** | 394.4±44.0 | 428.4±59.0 | +34 | <0.001 |
| **Hydroxychloroquine+Azithromycin (n=1080)** | 400.5±45.0 | 438.9±56.5 | +38.4 | <0.001 |
| **Lopinavir/ritonavir (n=689)** | 395.5±38.5 | 422.5±49.0 | +27 | <0.001 |
| **Lopinavir/ritonavir monotherapy (n=483)** | 388±36.8 | 409.3±36.8 | +21.3 | <0.001 |
| **Lopinavir/ritonavir+Azithromycin (n=206)** | 413.9±36.6 | 453.5±39.3 | +39.6 | <0.001 |
| **Atazanavir/ritonavir (n=16)** | 427.0±28.5 | 456.5±32.3 | +29.6 | <0.001 |
| **Atazanavir/ritonavir monotherapy (n=12)** | 423.6±29.7 | 453.5±34.0 | +30 | <0.001 |
| **Atazanavir/ritonavir+Azithromycin (n=4)** | 437.2±38.2 | 465.7±28.6 | +28.5 | <0.001 |
| **Oseltamivir (n=121)** | 410.0±38.3 | 435.0±44.3 | +25 | <0.001 |
| **Oseltamivir monotherapy (n=18)** | 413.2±35.9 | 432.7±31.6 | +19.5 | <0.001 |
| **Oseltamivir +Azithromycin (n=103)** | 409.5±38.8 | 435.6±46.3 | +26.1 | <0.001 |
| **Favipiravir (n=33)** | 414.4±22.9 | 433.5±32.0 | +19.0 | <0.001 |
| **Remdesivir (n=67)** | 418.3±32.0 | 442.7±37.3 | +24.4 | <0.001 |

Continuous variables were presented as mean±SD. Categorical variables are presented as n (%).

**Table 4- Primary and secondary outcomes with different drug regimens**

| COVID drug | QTc≥500 ms | ΔQTc≥60 ms | TdP |
|---|---|---|---|
| **Chloroquine (n=9)** | 0 | 3 (33.0) | 0 |
| **Chloroquine (n=6)** | 0 | 2 (33.0) | 0 |
| **Chloroquine+Azithromycin (n=3)** | 0 | 1 (33.0) | 0 |
| **Hydroxychloroquine (n=1430)** | 196 (13.7) | 300 (21.0) | 4 (0.3) |
| **Hydroxychloroquine monotherapy (n=350)** | 41 (11.7) | 63 (18.0) | 0 |
| **Hydroxychloroquine+Azithromycin (n=1080)** | 155 (14.4) | 237 (22.0) | 4 (0.4) |
| **Lopinavir/ritonavir (n=689)** | 52 (7.5) | 90 (13.0) | 5 (0.78) |
| **Lopinavir/ritonavir (n=483)** | 27 (5.6) | 38 (8.0) | 0 |
| **Lopinavir/ritonavir+Azithromycin (n=206)** | 25 (12.0) | 52 (25.0) | 5 (2.4) |
| **Atazanavir/ritonavir (n=16)** | 3 (18.7) | 2 (12.5) | 0 |
| **Atazanavir/ritonavir (n=12)** | 2 (16.7) | 1 (8.3) | 0 |
| **Atazanavir/ritonavir+Azithromycin (n=4)** | 1 (25) | 1 (25) | 0 |
| **Oseltamivir (n=121)** | 8 (6.6) | 13 (10.7) | 0 |
| **Oseltamivir (n=18)** | 0 | 3 (16.7) | 0 |
| **Oseltamivir +Azithromycin (n=103)** | 8 (7.8) | 10 (9.7) | 0 |
| **Favipiravir (n=33)** | 1 (3.0) | 3 (9.0) | 0 |
| **Remdesivir (n=67)** | 6 (9.0) | 6 (9.0) | 0 |

Variables are presented as n (%).

**Table 5- Predictors of QTc≥ 500 ms**

| Risk factors | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | P-value | OR | 95% CI | P-value | OR | 95% CI |
| **Female gender** | 0.167 | 0.83 | 0.65-1.08 | 0.012 | 0.71 | 0.55-0.93 |
| **Coronary artery disease** | 0.096 | 1.35 | 0.95-1.90 | | | |
| **Heart failure** | <0.001 | 2.90 | 2.00-4.16 | <0.001 | 2.17 | 1.40-3.30 |
| **Chronic kidney disease** | 0.017 | 1.66 | 1.09-2.50 | | | |
| **Acute renal dysfunction** | <0.001 | 1.85 | 1.40-2.40 | | | |
| **Acute liver dysfunction** | <0.001 | 2.20 | 1.64-2.97 | <0.001 | 1.96 | 1.43-2.70 |
| **Hydroxychloroquine** | <0.001 | 1.96 | 1.47-2.60 | <0.001 | 1.78 | 1.29-2.44 |
| **Lopinavir-ritonavir** | <0.001 | 0.56 | 0.40-0.77 | | | |
| **Oseltamivir** | 0.098 | 0.54 | 0.26-1.13 | | | |
| **Azithromycin coadminstration** | <0.001 | 1.80 | 1.37-2.40 | 0.023 | 1.40 | 1.05-1.95 |
| **Furosemide** | <0.001 | 2.70 | 1.97-3.70 | 0.004 | 1.70 | 1.19-2.47 |
| **Hydrochlorothiazide** | 0.013 | 2.68 | 1.19-6.03 | | | |
| **Betablocker** | <0.001 | 2.28 | 1.75-2.98 | | | |
| **Calcium blocker** | 0.003 | 1.68 | 1.2-2.40 | | | |
| **Digoxin** | 0.096 | 1.85 | 0.88-3.86 | | | |

**Abbreviations:** OR-odds ratio; CI=confidence interval

**Table 6- Predictors of ΔQT≥60 ms**

| Risk factor | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | P-value | OR | 95% CI | P-value | OR | 95% CI |
| **Heart failure** | 0.078 | 1.39 | 0.96-1.99 | | | |
| **Chronic kidney disease** | <0.001 | 1.84 | 1.29-2.60 | | | |
| **Acute renal dysfunction** | <0.001 | 1.92 | 1.54-2.40 | <0.001 | 2.40 | 1.70-3.40 |
| **Acute hepatic dysfunction** | 0.002 | 1.53 | 1.17-2.00 | | | |
| **Hydroxychloroquine** | <0.001 | 1.85 | 1.47-2.34 | 0.086 | 1.50 | 0.94-2.40 |
| **Lopinavir-ritonavir** | <0.001 | 0.62 | 0.48-0.79 | | | |
| **Azithromycin coadministration** | <0.001 | 2.02 | 1.60-2.55 | | | |
| **Oseltamivir** | 0.041 | 0.55 | 0.30-0.98 | | | |
| **Remdesivir** | 0.059 | 0.45 | 0.19-1.05 | | | |
| **Furosemide** | <0.001 | 2.00 | 1.50-2.66 | | | |
| **Betablocker** | <0.001 | 1.60 | 1.27-2.02 | 0.023 | 1.50 | 1.05-2.10 |

**Abbreviations:** OR-odds ratio; CI=confidence interval

**Table 7. Predictors of torsade de pointes**

| Risk factor | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | P-value | OR | 95% CI | P-value | OR | 95% CI |
| **Nonischemic heart disease** | 0.012 | 4.66 | 1.24-17.40 | | | |
| **Coronary artery disease** | 0.068 | 3.38 | 0.84-13.6 | | | |
| **Heart failure** | 0.004 | 6.00 | 1.50-24.4 | | | |
| **Chronic kidney disease** | 0.003 | 6.40 | 1.60-26.0 | | | |
| **Chronic liver disease** | <0.001 | 19.5 | 2.30-165.8 | | | |
| **Lopinavir-ritonavir** | 0.080 | 3.05 | 0.82-11.40 | 0.006 | 8.2 | 1.84-36.0 |
| **Azithromycin coadministration** | 0.012 | 0.58 | 0.57-0.60 | | | |
| **Furosemide** | <0.001 | 9.08 | 2.40-34.0 | 0.030 | 4.83 | 1.16-20.0 |
| **Metolazone** | <0.001 | 36.6 | 4.10-328.4 | 0.028 | 34.7 | 1.46-826 |
| **QT prolonging drugs** | 0.021 | 4.47 | 1.11-18.0 | | | |
| **Amiodarone** | <0.001 | 31.3 | 7.54-130.0 | 0.002 | 14.5 | 2.74-77.0 |
| **Hypokalemia** | <0.001 | 8.40 | 2.10-34.0 | 0.006 | 8.50 | 1.84-39.3 |
| **Hypocalcemia** | 0.025 | 4.03 | 1.07-15.0 | | | |
| **Acute renal dysfunction** | 0.040 | 3.60 | 0.97-13.6 | | | |
| **QTc≥500 ms** | 0.036 | 3.97 | 0.99-16.0 | | | |
| **ΔQT≥60 ms** | <0.001 | 9.46 | 2.36-38.0 | | | |

**Abbreviations:** OR-odds ratio; CI=confidence interval

**Table 8. Predictors of mortality**

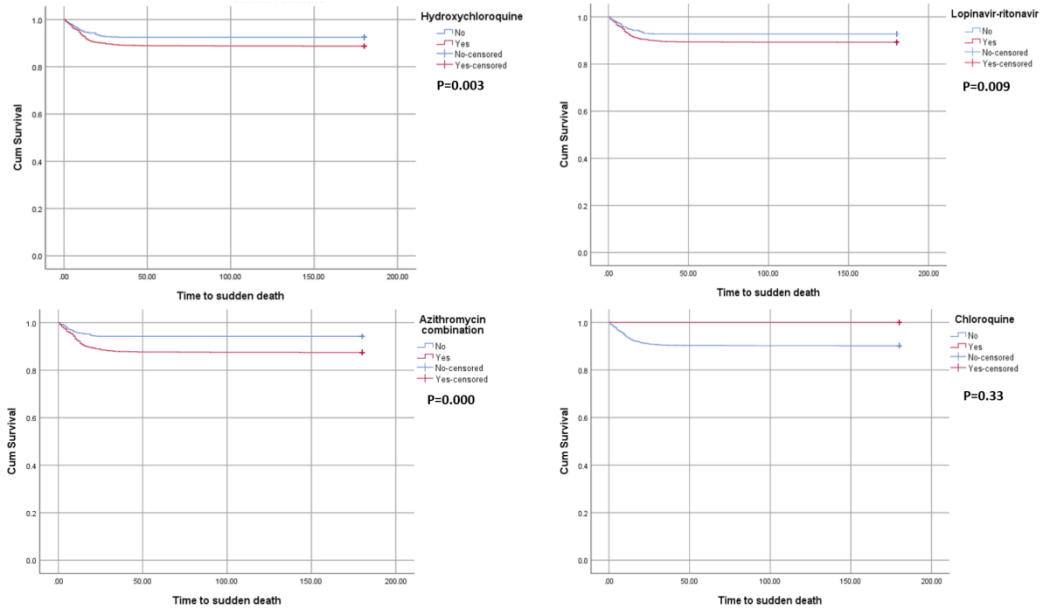
| Risk factor | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | P-value | OR | 95% CI | P-value | OR | 95% CI |
| **Age** | <0.001 | 10 | 9.0-13.0 | <0.001 | 1.03 | 1.02-1.04 |
| **Male gender** | 0.014 | 1.40 | 1.07-1.88 | | | |
| **Coronary artery disease** | <0.001 | 2.00 | 1.50-2.90 | | | |
| **Heart failure** | <0.001 | 2.40 | 1.60-3.56 | | | |
| **Chronic kidney disease** | <0.001 | 2.90 | 1.98-4.30 | | | |
| **Diabetes mellitus** | 0.012 | 1.40 | 1.08-1.89 | | | |
| **Hypertension** | 0.002 | 1.55 | 1.18-2.04 | | | |
| **Hydroxychloroquine** | 0.003 | 1.57 | 1.17-2.10 | | | |
| **Lopinavir/ritonavir** | 0.008 | 0.65 | 0.47-0.89 | | | |
| **Azithromycin coadministration** | <0.001 | 2.33 | 1.70-3.20 | <0.001 | 2.23 | 1.60-3.10 |
| **Furosemide** | <0.001 | 5.09 | 3.75-6.90 | <0.001 | 2.60 | 1.84-3.65 |
| **Amiodarone** | <0.001 | 4.65 | 2.37-9.15 | 0.033 | 2.37 | 1.07-5.27 |
| **Betablocker** | <0.001 | 2.46 | 1.86-3.25 | | | |
| **Digoxin** | <0.001 | 4.88 | 2.64-9.05 | | | |
| **Hypokalemia** | 0.002 | 1.60 | 1.18-2.20 | | | |
| **On-treatment QTc≥500 ms** | <0.001 | 2.84 | 2.03-3.97 | | | |
| **ΔQT≥60 ms** | <0.001 | 2.40 | 1.78-3.24 | | | |
| **Acute renal dysfunction** | <0.001 | 5.70 | 4.30-7.58 | <0.001 | 3.70 | 2.73-5.02 |
| **Acute hepatic dysfunction** | <0.001 | 1.77 | 1.27-2.45 | | | |

**Abbreviations:** OR-odds ratio; CI=confidence interval

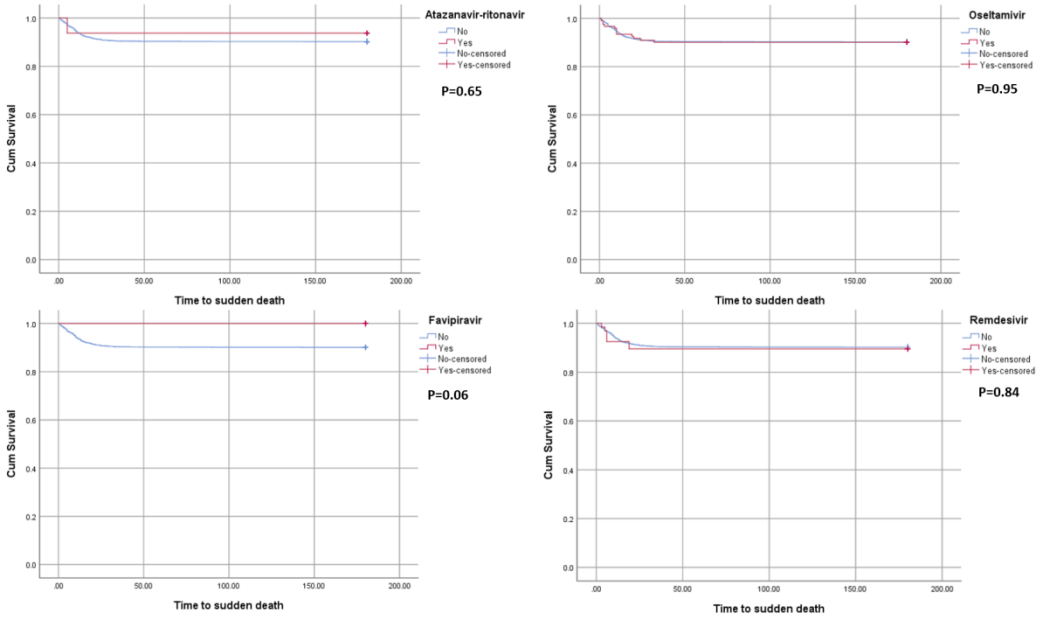
**Figure legend**

**Figure 1**- Survival function estimated by the Kaplan-Meier analysis among the eight different drug regimens used to treat COVID-19. Log-rank P-value was significant among the patients who

received hydroxychloroquine or lopinavir-ritonavir with and without azithromycin combination therapy.




ijcp_14182_f1a.tif




ijcp_14182_f1b.tif