

Figure 1. A: Events in patients with high or normal troponin levels depending on whether or not they have heart disease. B: relationship between troponin and the predicted probability of death and heart failure according to the presence or not of heart disease. HF, heart failure.

with a worse prognosis. This predictive power of risk of death or HF was particularly significant in patients without previous HD. Based on these results, TnI determination should be routinely included in patients hospitalized for COVID-19.

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Usefulness and safety of self-electrocardiographic monitoring during treatment with hydroxychloroquine and azithromycin in COVID-19 patients



Utilidad y seguridad de la automonitorización electrocardiográfica durante el tratamiento con hidroxiclороquina y azitromicina en pacientes con COVID-19

To the Editor,

Despite the lack of solid evidence on their efficacy, hydroxychloroquine (HCQ) and azithromycin (AZ) have been widely used as a first-line treatment for infection with SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19). The effect of these drugs on the QT interval and their potential to cause polymorphic ventricular arrhythmias has generated growing concern in the scientific community and until more robust evidence on their usefulness is available, we must employ strategies to ensure their safe use.¹ Recently, the Food and Drug Administration recommended the use of noninvasive remote monitoring devices to facilitate the monitoring of these patients, which minimizes contact with health care professionals, reduces the burden on health care services and allows more efficient use of resources.² To this end, the KardiaMobile 6L device, from AliveCor (California, USA), has been proposed, which can provide a 1- or

6-lead electrocardiogram (ECG), offering a simple and reproducible way to determine the corrected QT interval (QTc).³ Here in Spain, there are already protocols to support its use in these patients.⁴

During March and April of 2020, a study was conducted in our hospital to analyze the effect of treatment with HCQ (either alone or in combination with AZ) on the QTc and the incidence of ventricular arrhythmias in patients admitted with SARS-CoV-2 pneumonia who met the high-risk criteria for QTc prolongation (female, age > 65 years, history of heart disease, chronic renal disease, or diabetes, or taking both medications together). In line with the recommendations from the experts,³ a protocol was designed to minimize the arrhythmic complications of these drugs. This protocol included a series of precautions to be taken before and during treatment: a) review what other medications the patient is taking that could prolong the QTc; b) correct electrolyte imbalances; c) avoid bradycardia; and d) perform close electrocardiographic monitoring. A baseline 12-lead ECG was performed on admission. Later, the QTc was monitored using a 6-lead recording taken with the KardiaMobile 6L device, at 48 hours and 96 hours after starting the drugs (or more often if the QTc was > 480 ms, if there was an increase > 60 ms, or if the patient had possible symptoms of arrhythmia). The arrhythmia unit trained the nursing staff responsible for these patients using an informational video on the use of KardiaMobile 6L. After a brief explanation from the nursing staff, the patient performed the

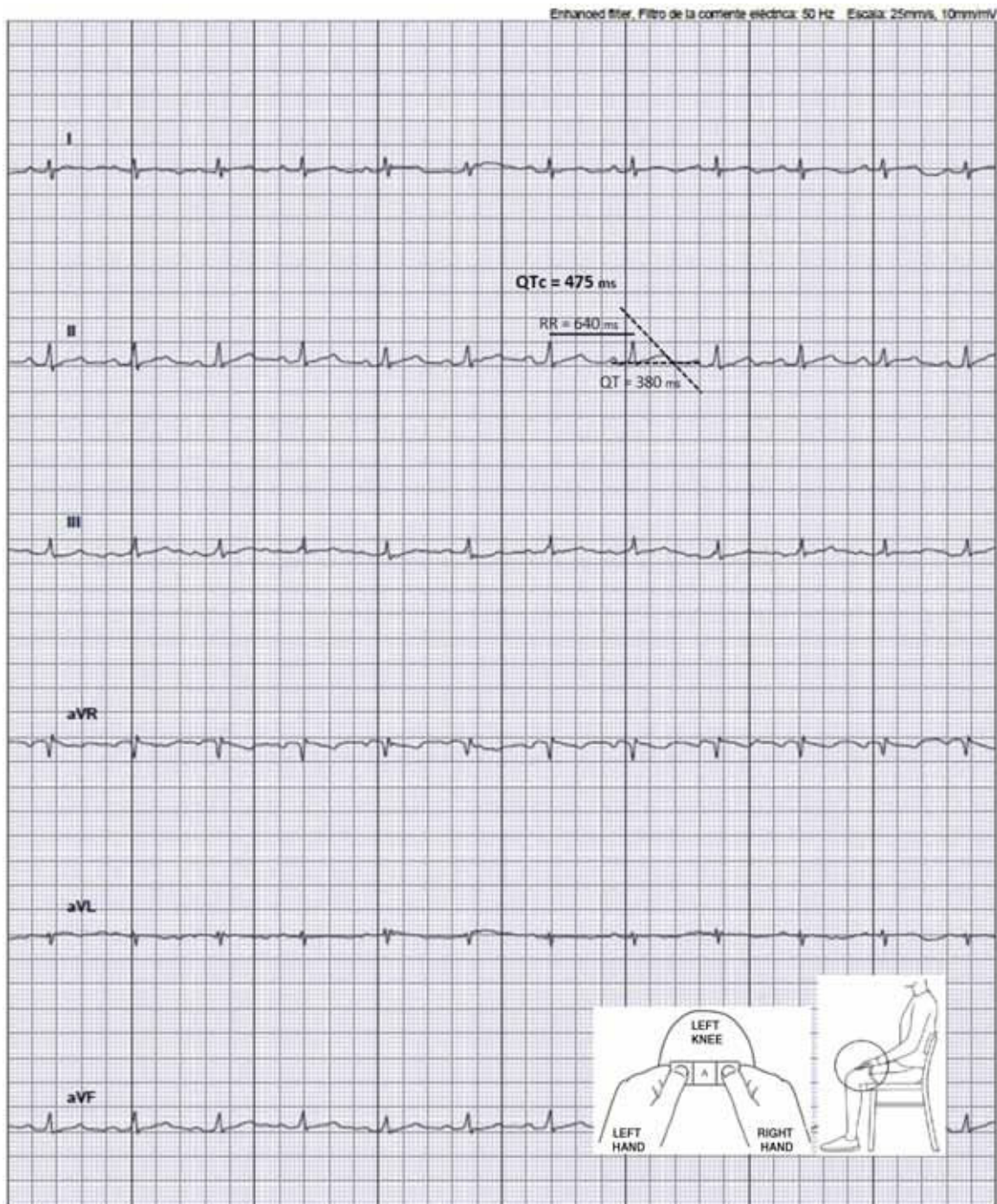


Figure 1. Measurement of the QTc interval on an electrocardiographic recording performed with the KardiaMobile 6L device. QTc, corrected QT interval.

recording, positioning the device on the left knee or ankle (as shown in [figure 1](#)). From outside the room, the nurse recorded the ECG on a tablet and transferred it to the electronic medical records. Four electrophysiologists analyzed the recordings and noted in the medical records the details of the ECG, the QTc measurement, and the recommendations on its treatment if they considered it necessary. For patients who were unable to perform the recording themselves, or when the tracing did not allow accurate measurement of the QTc, a 12-lead ECG was performed.

Of 306 patients admitted with COVID-19 pneumonia, 186 received HCQ and met criteria to be considered high risk. Of these,

78 were included in the electrocardiographic monitoring protocol (52 were taking the HCQ plus AZ combination). The baseline QTc was 425 (400–447) ms. Of all the patients, 48 (61.5%) had QTc prolongation on subsequent ECG; 18 (37.5%) were taking HCQ alone and 30 (62.5%) were taking HCQ plus AZ. The baseline characteristics of the study population are shown in [table 1](#), as well as the comparison between the groups with and without prolonged QTc.

No significant differences were found between the patients with and without prolonged QTc. The median QTc prolongation was 25.5 (16.8–57.5) ms, with no significant differences between the groups who were taking HCQ plus AZ and HCQ alone ($p = 0.38$).

Table 1
General characteristics of the patients admitted with COVID-19 who underwent electrocardiographic monitoring with the KardiaMobile 6L device (n = 78)

	Total population (n = 78)	QTc prolongation (n = 48)	No prolongation (n = 30)	P
Demographic characteristics				
Age, y	68.5 [55.0–78.2]	69.0 [54.2–80.0]	66.5 [56.5–75.0]	.39
Age ≥ 65 y	47/78 (60.3)	30/48 (62.5)	16/30 (53.3)	.61
Sex				
Male	46/78 (59.0)	28/48 (58.4)	18/30 (60.0)	
Female	32/78 (41.0)	20/48 (41.3)	12/30 (40.0)	.88
Comorbidities				
Hypertension	38/77 (49.3)	21/47 (44.6)	17/30 (56.7)	.27
Diabetes mellitus	17/78 (21.8)	12/48 (25.0)	5/30 (16.7)	.38
Obesity	20/64 (31.2)	11/37 (29.8)	9/30 (33.3)	.76
Cardiovascular disease	9/78 (11.5)	6/48 (12.5)	3/30 (10.0)	.74
Congestive heart failure	10/78 (12.8)	5/48 (10.4)	5/30 (16.7)	.43
Coronary artery disease	6/78 (7.7)	4/48 (8.3)	2/30 (6.7)	.79
Chronic renal disease	21/69 (31.4)	17/44 (38.4)	8/30 (26.7)	.24
Chronic pulmonary disease	21/78 (27.0)	13/48 (27.1)	8/30 (26.7)	.79
Charlson comorbidity index	3.0 [2.0–5.0]	3.5 [2.0–5.0]	3.0 [2.0–5.0]	.52
Charlson index ≥ 3	49/78 (62.8)	31/48 (64.6)	18/30 (60.0)	.68
Admission details				
Lung opacities > 50% on radiology	12/72 (16.7)	9/43 (20.9)	3/30 (10.0)	.08
Potassium, mmol/L	4.1 [3.8–4.3]	4.0 [3.7–4.2]	4.1 [3.9–4.3]	.42
Calcium, mg/dL	8.7 [8.4–9.1]	8.7 [8.6–9.0]	8.7 [8.4–9.1]	.18
PCR, mg/dL	6.52 [2.32–12.77]	6.26 [2.23–13.29]	7.22 [3.31–12.77]	.71
NT-proBNP, pg/mL	180.0 [46.75–1009.75]	176.0 [66.0–1138.0]	183.0 [36.5–924.0]	.65
CK, U/L	78.0 [56.0–148.0]	79.0 [56.0–153.0]	71.0 [56.0–141.5]	.98
hs-TnT, ng/L	14.5 [6.8–25.0]	15.0 [8.0–26.0]	13.0 [5.5–25.0]	.68
D-dimer, µg/mL	0.65 [0.39–1.08]	0.74 [0.29–1.28]	0.57 [0.35–0.87]	.08
Ferritin, µg/L	864.0 [370.8–1220.0]	880.0 [465.0–1508.5]	859.5 [348.7–1077.7]	.08
Procalcitonin, ng/mL	0.1 [0.05–0.2]	0.1 [0.06–0.2]	0.08 [0.04–0.2]	.43
Lymphocytes, cells/µL	1055 [790–1055]	1055 [800–1390]	1090 [697.5–1557.5]	.56
Other concurrent drugs that may prolong QTc	34/78 (43.6)	23/78 (48.0)	11/30 (36.7)	.33

CK, creatine kinase; hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCR, polymerase chain reaction. Values are expressed as n/N (%) or median [range].

The median QTc duration on monitoring was 450 (436–462) ms. Ten patients (12.8%) had a significant prolongation of the QTc (increase ≥ 60 ms or QTc ≥ 500 ms): 4 (5.1%) were taking HCQ alone and 6 (7.7%) were taking HCQ plus AZ. Five (6.4%) of these patients stopped the medication for this reason. We did not observe sustained ventricular arrhythmia or death due to arrhythmia in any of our patients during the monitoring period. Twelve patients (15.4%) required a conventional ECG due to difficulty interpreting the recording or not being able to use the device due to limited mobility.

According to our experience, HCQ and AZ treatment in patients admitted with COVID-19 is safe as long as measures are taken to minimize the risk of arrhythmia, including close electrocardiographic monitoring. Therefore, given the high burden on the healthcare system caused by this disease, and given its high rate of transmissibility, we think that ECG recording by the patients themselves with devices such as the KardiaMobile 6L can be a simple, useful strategy to avoid unwanted proarrhythmic effects of this treatment.

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APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.1016/j.rec.2020.08.020>

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◇ The list of investigators from the Alicante COVID-19 group can be viewed in the supplementary data. (A. García-Fernández).

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Drug-induced QT prolongation in COVID-19 pneumonia: influence on in-hospital survival



Prolongación del intervalo QT por fármacos en la neumonía por COVID-19: influencia en la supervivencia durante el ingreso

To the Editor,

The COVID-19 pandemic poses an epidemiological challenge and a problem for diagnostic and therapeutic decision-making. The drugs used in patients infected with SARS-CoV-2 have an arrhythmogenic risk associated with QT prolongation, even in patients with a previously normal QT.¹ Recent registries have confirmed that treatment with hydroxychloroquine (HCQ), whether in monotherapy or in combination with azithromycin, is associated with significant QT prolongation in COVID-19 patients.^{1–3} However, except in a few reported cases, its association with arrhythmia-related mortality is unclear, and some studies have noted a net neutral effect of these drugs on in-hospital mortality during the treatment of COVID-19 pneumonia,⁴ indicating the need for further studies of the arrhythmogenic risk of the treatments used.

Our objective was to determine the changes in QT interval from admission and their relationship with the combinations of drugs used in the treatment of COVID-19 pneumonia. We analyzed 1-month survival according to the degree of QT interval prolongation in the first 48 hours of hospitalization.

We retrospectively included all patients admitted to our center with COVID-19 pneumonia at the start of the pandemic (March 2020) and with available electrocardiogram (ECG) data at baseline and at 48 hours after treatment initiation (performed per protocol in our center). All ECGs were stored in digital format. The Bazett-

corrected QT interval (QTc) was measured automatically (DXL ECG Algorithm, TMV, Philips, The Netherlands) and confirmed by 2 independent cardiologists if there was doubt. The at-risk group was defined as patients with long QTc > 460 ms or with a QTc increase (iQTc) > 60 ms. Notably, other studies have defined patients with a QTc > 500 ms as being high risk and have recommended precaution with a QTc > 460 to 480 ms.⁴ We selected a less restrictive cutoff point to permit a stricter follow-up of the at-risk group in order to determine the arrhythmic behavior of patients with COVID-19.

In total, 226 patients were included between March 1 and March 20, 2020. Recruitment was halted when the number of daily admissions impeded an exhaustive follow-up. Finally, 65 patients were excluded due to the lack of a digitalized baseline or 48-hour ECG, leaving 161 patients for the statistical analysis. The most frequently used specific therapeutic regimen was dual therapy with HCQ and lopinavir/ritonavir (LPV/r) (n = 111; 68.9%), followed by triple therapy with HCQ, LPV/r, and azithromycin or a quinolone (n = 30; 18.6%). Monotherapy with azithromycin or LPV/r was the least commonly used strategy (n = 12; 7.5%). Eight patients (5.0%) received alternative combinations.

The drug dosages were similar to those used in other centers. HCQ was administered at 400 mg/12 h in the first 24 hours, followed by 200 mg/12 h. The LPV/r dosage was 400+100 mg/12 h, whereas that of azithromycin was 500 mg/24 h. Categorical variables were compared using the chi-square test and continuous variables using the *t* test. The survival analysis was an actuarial analysis using the Wilcoxon-Gehan test.

In general, the QTc interval was significantly higher at 48 hours than at admission (443 ± 30 vs 435 ± 25 ms; *P* = .001), with a mean iQTc of 8 ± 28 ms. No significant differences were found in the iQTc or in the QTc at 48 hours among the different drug combinations.

Table 1

Baseline characteristics of the study population

	All (n = 161)	Normal QT group (n = 124)	At-risk QT group (n = 37)	<i>P</i>
Male sex	103 (64)	80 (49.7)	23 (14.3)	.899
Age, y	63.9 ± 14.8	63.6 ± 15.6	64.7 ± 12.1	.709
Hypertension	71 (44.1)	52 (32.3)	19 (11.8)	.279
Diabetes mellitus	25 (15.5)	17 (10.6)	8 (5)	.235
Dyslipidemia	57 (35.4)	47 (29.2)	10 (6.2)	.214
Obesity (BMI > 30)	42 (26.1)	33 (20.5)	9 (5.6)	.785
COPD/asthma	26 (16.2)	19 (11.8)	7 (4.4)	.591
Heart disease	26 (16.2)	18 (11.2)	8 (5)	.293

BMI, body mass index; COPD, chronic obstructive pulmonary disease.