

Association of In-Hospital Antimalarial–Macrolide Therapy With 3–6-Month Cardiac Electrophysiological Outcomes in Survivors of Severe COVID-19: A Matched Retrospective Cohort Study

Shubhang Sharma Sharma

shubhang.sharma04@gmail.com

Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán

Julia Ramírez-González

Universidad Nacional Autónoma de México

Raúl Chávez-Fernández

Universidad Nacional Autónoma de México

Jaime Galindo-Urbe

Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán

Jaime Rivera-Figueroa

Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán

Gerardo Payro-Ramírez

Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán

Alejandra Hernández

Universidad Nacional Autónoma de México

Fátima Ramos-Pérez

Universidad Nacional Autónoma de México

Berenice Hernández-Franco

Universidad Nacional Autónoma de México

Diana Torres-Partida

Universidad Nacional Autónoma de México

Reyna Pacheco-Domínguez

Universidad Nacional Autónoma de México

Article

Keywords: COVID-19, hydroxychloroquine, chloroquine, macrolides, QT interval, arrhythmias, cardiac electrophysiology, heart rate variability

Posted Date: October 14th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11342547/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background: During the early phase of the COVID-19 pandemic, antimalarial agents and macrolide antibiotics were widely used because of their proposed antiviral and immunomodulatory effects. However, their potential to prolong ventricular repolarization and increase the risk of arrhythmias raised concerns about their cardiac electrophysiological effects. Available evidence has predominantly focused on electrophysiological effects during acute treatment, whereas post-recovery outcomes remain less well characterized.

Objectives: To evaluate cardiac electrophysiological outcomes 3–6 months after hospitalization for severe COVID-19 pneumonia and compare these outcomes according to in-hospital exposure to combined antimalarial–macrolide therapy.

Methods: We conducted a retrospective matched cohort study including adults hospitalized for severe COVID-19 pneumonia between March and June 2020. Patients exposed to hydroxychloroquine or chloroquine in combination with azithromycin or clarithromycin were matched 1:1 by sex and age (± 3 years) with patients who did not receive either drug class. Cardiovascular assessment 3–6 months after hospitalization included a 12-lead electrocardiogram and 24-hour Holter monitoring. QTc interval, conduction abnormalities, arrhythmias, and heart rate variability (HRV) were evaluated.

Results: Eighty-six patients were included (43 exposed and 43 unexposed). Follow-up QTc intervals were similar between groups (420.0 vs. 423.1 ms; $p=0.762$), and QTc prolongation was uncommon. No malignant ventricular arrhythmias or clinically significant conduction abnormalities were identified. Exposed patients had a higher prevalence of sinus bradycardia, a lower resting heart rate on electrocardiography, and higher HRV as assessed by the standard deviation of normal-to-normal intervals (SDNN). However, unexposed patients exhibited a greater inflammatory burden during hospitalization, more frequent intensive care unit admissions, and longer hospital stays.

Conclusion: In this cohort of survivors of severe COVID-19, short-term in-hospital exposure to combined antimalarial–macrolide therapy was not associated with persistent QTc prolongation or clinically significant electrophysiological abnormalities at 3–6 months. Differences in heart rate and HRV should be interpreted with caution, given potential residual confounding due to acute disease severity.

Introduction

During the early phase of the SARS-CoV-2 pandemic, the absence of proven antiviral therapies led to the widespread use of repurposed drugs with potential antiviral or immunomodulatory properties. Among the most frequently used agents were the antimalarials chloroquine and hydroxychloroquine, often administered in combination with macrolide antibiotics such as azithromycin or clarithromycin. Their initial use was supported by *in vitro* evidence of antiviral activity against coronaviruses and by their potential to modulate the inflammatory response associated with severe COVID-19.¹⁻⁴

Hydroxychloroquine and chloroquine may interfere with viral entry and intracellular processing by altering endosomal pH and lysosomal function. These agents also exert immunomodulatory effects, including attenuation of proinflammatory signaling pathways and reduced production of cytokines such as interleukin-6, interleukin-8, and tumor necrosis factor- α .² Macrolides have similarly demonstrated immunomodulatory properties beyond their antimicrobial effects, including modulation of inflammatory cytokine production and immune-cell responses in respiratory disease.^{5,6} Early observational studies suggested that hydroxychloroquine, either alone or in combination with azithromycin, might improve viral clearance or clinical outcomes in patients with COVID-19.^{4,5,7} However, subsequent randomized clinical trials and larger observational studies failed to demonstrate a clinically meaningful benefit in hospitalized patients.⁸

Despite the lack of established therapeutic efficacy, the electrophysiological effects of these drugs remain of clinical interest. Both antimalarial agents and macrolides may prolong ventricular repolarization, primarily by inhibiting the human ether-à-go-go-related gene (hERG) potassium channel, which encodes the rapid component of the delayed-rectifier potassium current (I_{Kr}).⁹ This effect may result in corrected QT (QT_c) interval prolongation and, in susceptible individuals, increase the risk of torsade de pointes and other malignant ventricular arrhythmias. Concomitant cardiovascular disease, electrolyte disturbances, bradycardia, or exposure to additional QT-prolonging medications may further amplify risk.^{10,11}

Interpretation of these effects in patients with COVID-19 is particularly complex because SARS-CoV-2 infection itself may alter cardiac electrophysiology. Systemic inflammation, myocardial injury, hypoxemia, electrolyte abnormalities, and autonomic dysfunction may independently affect ventricular repolarization and arrhythmogenic susceptibility.¹² Consequently, electrophysiological abnormalities observed during acute hospitalization may reflect an interaction between pharmacological exposure and the systemic effects of severe infection rather than a drug-specific mechanism alone.

Most studies examining the cardiac effects of hydroxychloroquine and macrolides in COVID-19 have focused on electrocardiographic changes occurring during treatment. Although varying degrees of QT_c prolongation have been reported, clinically significant ventricular arrhythmias appear to have been relatively uncommon.^{13–15} In contrast, evidence regarding persistent conduction or repolarization abnormalities after recovery from severe COVID-19 remains limited. In parallel, emerging evidence suggests that persistent autonomic abnormalities, including alterations in heart rate variability, may follow SARS-CoV-2 infection.¹⁶

Accordingly, the present study aimed to characterize cardiac electrophysiological findings 3–6 months after hospitalization for severe COVID-19 pneumonia and to compare QT_c duration, conduction abnormalities, arrhythmias, and heart rate variability according to previous in-hospital exposure to combined antimalarial–macrolide therapy.

Rationale:

The potential proarrhythmic effects of antimalarial and macrolide therapies used during the early COVID-19 pandemic were primarily evaluated during acute hospitalization. However, whether these drugs are associated with persistent abnormalities in cardiac repolarization, conduction, arrhythmia burden, or autonomic function after recovery remains uncertain. Because severe SARS-CoV-2 infection itself can alter electrophysiological and autonomic function, medium-term assessment is necessary to distinguish transient treatment-related effects from persistent post-infectious abnormalities. Accordingly, this study evaluated QTc interval, conduction disturbances, arrhythmias, and heart rate variability 3–6 months after severe COVID-19 according to previous in-hospital exposure to antimalarial–macrolide therapy.

Methods

Study design and population:

We conducted a retrospective matched cohort study including adult patients aged ≥ 18 years who were hospitalized for severe COVID-19 pneumonia at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán between March and June 2020.

All patients had SARS-CoV-2 infection confirmed by reverse-transcription polymerase chain reaction (RT-PCR), radiological evidence of pneumonia on chest computed tomography, and oxygen saturation $< 90\%$ at hospital admission.

The study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

Exposure definition:

A total of 86 patients were included. Patients were categorized according to their in-hospital exposure to combined antimalarial–macrolide therapy. The exposed group comprised patients who received hydroxychloroquine or chloroquine together with azithromycin or clarithromycin. Each exposed patient was matched 1:1 by sex and age (± 3 years) with a patient who had not received antimalarial or macrolide therapy during hospitalization.

Other supportive and pharmacological treatments were administered in accordance with the institutional protocols in effect during the study period.

Clinical and laboratory data:

Sociodemographic, anthropometric, and clinical variables were obtained from electronic medical records. These included age, sex, weight, body mass index (BMI), cardiovascular risk factors, comorbidities, and clinical indicators of COVID-19 severity.

Available laboratory measurements obtained on the fifth day of hospitalization included serum glucose, creatinine, estimated glomerular filtration rate (eGFR), electrolytes, hemoglobin, total leukocyte and

lymphocyte counts, high-sensitivity cardiac troponin I, C-reactive protein (CRP), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), ferritin, and D-dimer.

In-hospital outcomes included length of hospitalization, intensive care unit (ICU) admission, duration of ICU stay, and requirement for invasive mechanical ventilation. Clinical information was independently extracted by two investigators using standardized data-collection forms, and discrepancies were resolved by consensus.

Cardiovascular follow-up:

Between August and December 2020, surviving patients underwent a structured follow-up assessment that included evaluation of persistent post-COVID symptoms, a standard 12-lead electrocardiogram, and 24-hour ambulatory Holter monitoring. Experienced cardiologists interpreted Electrocardiographic and Holter recordings.

Persistent symptoms were assessed using a standardized questionnaire and included fatigue, dyspnea, palpitations, chest pain, syncope, tachycardia, perceived arrhythmias, and hypotension.

Electrocardiographic and Holter assessment:

QT intervals were manually measured using the tangent method and corrected for heart rate using Bazett's formula. Two investigators independently performed measurements.

QTc prolongation was defined as >450 ms in men and >470 ms in women.

In addition to ventricular repolarization, electrocardiographic analysis included heart rate, rhythm, PR interval, QRS duration, conduction abnormalities, bundle branch block, and repolarization patterns.

Heart rate variability was assessed from 24-hour Holter recordings using the standard deviation of normal-to-normal RR intervals (SDNN). Holter monitoring was also evaluated for supraventricular and ventricular arrhythmias, as well as conduction abnormalities.

Statistical Analysis:

Statistical analyses were performed using Stata® version 19 (StataCorp, College Station, TX, USA).

Categorical variables are presented as frequencies and percentages. Continuous variables are reported as mean $\pm$ standard deviation or median with interquartile range, according to their distribution. Normality was assessed using the Shapiro–Wilk test.

Between-group comparisons were performed using the chi-square test or Fisher's exact test for categorical variables and Student's *t*-test or the Mann–Whitney *U* test for continuous variables, as appropriate.

A multivariable logistic regression model was constructed to explore independent predictors of QTc prolongation. Covariates included systemic arterial hypertension, BMI, antimalarial exposure, diabetes mellitus, renal function, and cardiac troponin I levels.

A two-sided p-value <0.05 was considered statistically significant.

Results

Study population:

The study included 86 patients, with 43 patients in the exposed group and 43 in the unexposed group (Table 1).

Table 1
Demographic and main clinical characteristics of the study population

Variable	Exposed (n = 43)	Unexposed (n = 43)	p-value
Age (years), mean ± SD	51.2 ± 10.5	48.6 ± 12.3	0.281
Female sex, n (%)	25 (58.1)	21 (48.8)	0.517
Smoking, n (%)	6 (13.9)	9 (20.9)	0.570
Type 2 diabetes mellitus, n (%)	11 (25.6)	9 (20.9)	0.799
Hypertension, n (%)	11 (25.6)	10 (23.3)	0.063
BMI (kg/m ²), mean ± SD	28.9 ± 4.7	31.2 ± 6.9	0.085
Overweight, n (%)	22 (51.1)	18 (41.9)	0.387
Obesity, n (%)	14 (32.6)	20 (46.5)	0.186
Note: Qualitative variables are expressed as n (proportion). P value: Mann-Whitney rank sum test for continuous variables and Pearson’s chi-square test for categorical variables. p < 0.05 Abbreviations: BMI, Body Mass Index (kg/m ²); SD, Standard deviation.			

Demographic characteristics were generally comparable between groups. Mean age was 51.2 ± 10.5 years in exposed patients and 48.6 ± 12.3 years in unexposed patients (p = 0.281). Women accounted for 58.1% and 48.8% of the exposed and unexposed groups, respectively (p = 0.517).

The prevalence of smoking was 13.9% in exposed patients and 20.9% in unexposed patients (p = 0.570). Type 2 diabetes mellitus was present in 25.6% and 20.9%, respectively (p = 0.799), whereas systemic arterial hypertension was reported in 25.6% and 23.3%, respectively.

Mean BMI tended to be higher in the unexposed group (31.2 ± 6.9 vs. 28.9 ± 4.7 kg/m²), although the difference did not reach statistical significance (p = 0.0849). Overweight was more frequent among

exposed patients (51.1% vs. 41.9%), whereas obesity was more frequent among unexposed patients (46.5% vs. 32.6%); neither difference was statistically significant.

Laboratory characteristics during hospitalization:

Laboratory findings are summarized in Table 2. Mean glucose concentrations were higher in unexposed than in exposed patients (155.4 ± 78.2 vs. 130.5 ± 61.7 mg/dL; $p = 0.0165$). However, the proportion of patients with glucose > 130 mg/dL did not differ significantly between groups (39.5% vs. 25.6%; $p = 0.167$).

Table 2
Biochemical characteristics of participants.

Variable	Exposed	Unexposed	p-value
Glucose (mg/dL), mean $\pm$ SD	130.5 ± 61.7	155.4 ± 78.2	0.016*
Creatinine (mg/dL), mean $\pm$ SD	0.8 ± 0.2	0.8 ± 0.2	0.935
CRP (mg/L), mean $\pm$ SD	8.9 ± 7.7	13.5 ± 7.1	0.003*
CRP > 10 mg/L, n (%)	17 (39.5)	29 (67.4)	0.013*
LDH (U/L), mean $\pm$ SD	297.3 ± 94.4	418.6 ± 201.3	0.001*
LDH > 300 U/L, n (%)	24 (55.8)	31 (72.1)	0.004*
Leukocytes ($\times 10^9$ /L), mean $\pm$ SD	6.4 ± 2.8	11.2 ± 6.3	0.001*
Leukocytosis $> 10 \times 10^9$ /L, n (%)	3 (7.0)	16 (37.2)	0.001*
D-dimer (mg/L), mean $\pm$ SD	996 ± 2401	7136 ± 2993	0.001*
D-dimer > 500 mg/L, n (%)	13 (30.2)	33 (76.7)	$< 0.001^*$

Abbreviations: CPK, Creatine Phosphokinase; CRP, C-Reactive Protein; LDH, Lactate Dehydrogenase.

Renal function was generally preserved in both groups, with no significant differences in serum creatinine or in the proportion of patients with creatinine > 1.2 mg/dL (7.0% vs. 4.7%; $p = 0.645$).

Several markers of systemic inflammation and tissue injury were higher in unexposed patients. Mean CRP was 13.5 ± 7.1 mg/L in the unexposed group compared with 8.9 ± 7.7 mg/L in the exposed group ($p = 0.003$), and CRP > 10 mg/L was more frequent among unexposed patients (67.4% vs. 39.5%; $p = 0.013$).

Similarly, LDH was higher in the unexposed group (418.6 ± 201.3 vs. 297.3 ± 94.4 U/L; $p = 0.001$), and LDH > 300 U/L was observed in 72.1% and 55.8% of patients, respectively ($p = 0.004$).

Total leukocyte counts were also higher in unexposed patients (11.2 ± 6.3 vs. $6.4 \pm 2.8 \times 10^9$ /L; $p = 0.001$), with leukocytosis $> 10 \times 10^9$ /L occurring in 37.2% of unexposed and 7.0% of exposed patients ($p = 0.001$).

D-dimer concentrations were markedly higher in the unexposed group (7136 ± 2993 vs. 996 ± 2401 ; $p = 0.001$), and values above the predefined reference threshold were more frequent in unexposed patients (76.7% vs. 30.2%; $p < 0.0001$).

Ferritin and CPK concentrations were numerically higher among unexposed patients (807.7 ± 554.1 vs. 662.0 ± 332.9 ng/mL and 499.2 ± 722.7 vs. 287.9 ± 193.1 U/L, respectively), although these differences were not statistically significant. Lymphocyte counts were comparable between groups.

In-hospital outcomes and post-COVID symptoms:

Clinical outcomes are summarized in Table 3. Exposed patients had a shorter hospital stay than unexposed patients (10.2 days [95% CI, 8.1–12.3] vs. 15.7 days [95% CI, 11.7–19.7]; $p = 0.016$).

Table 3
Clinical Course

Variable	Exposed (n = 43)	Unexposed (n = 43)	p-value
Hospital stay (days), mean (95% CI)	10.2 (8.1–12.3)	15.7 (11.7–19.7)	0.016*
ICU admission, n (%)	6 (13.9)	14 (32.6)	0.041*
ICU stay (days), mean (95% CI)	14.8 (10.3–19.3)	18.8 (12.5–25.1)	0.805
Mechanical ventilation, n (%)	6 (13.9)	13 (30.2)	0.069

Abbreviations: ICU, Intensive Care Unit.

ICU admission was less frequent among exposed patients (13.9% vs. 32.6%; $p = 0.041$). Among patients requiring intensive care, ICU length of stay did not differ significantly between groups. Invasive mechanical ventilation was numerically more frequent in unexposed patients, although this difference did not reach statistical significance.

At follow-up, at least one persistent symptom was reported by 83.7% of patients in both groups ($p = 1.0$) (Table 4). Fatigue was the most frequently reported symptom, occurring in 69.8% of exposed and 79.1% of unexposed patients ($p = 0.458$).

Table 4
Post-Covid Symptoms

Variable	Exposed group (n = 43) Freq (%; 95% CI)	Unexposed group (n = 43) Freq (%; 95% CI)	P value
Any symptom	36 (83.7%; 69.3–93.2)	36 (83.7%; 69.3–93.2)	1.0
Presyncope	2 (4.7%; 0.6–15.8)	1 (2.3%; 0.1–12.3)	1.0
Hypotension	1 (2.3%; 0.1–12.3)	0	1.0
Fatigue	30 (69.8%; 53.9–82.8)	34 (79.1%; 64.0–90.0)	0.458
Dyspnea	6 (14.0%; 5.3–27.9)	9 (20.9%; 10.0–36.0)	0.57
Palpitations	11 (25.6%; 13.5–41.2)	8 (18.6%; 8.4–33.4)	0.603
Arrhythmias	1 (2.3%; 0.1–12.3)	0	1.0
Chest pain	4 (9.3%; 2.6–22.1)	1 (2.3%; 0.1–12.3)	0.169
Tachycardia	2 (4.7%; 0.6–15.8)	3 (7.0%; 1.5–19.1)	1.0
Variables are shown as means with 95% confidence intervals or as percentages. p-value: Mann-Whitney rank sum test for continuous variables and Pearson's chi-square test for categorical variables. $p < 0.05$			

Dyspnea (14.0% vs. 20.9%) and palpitations (25.6% vs. 18.6%) were also frequent, with no statistically significant between-group differences.

Chest pain was reported in 9.3% of exposed patients and none of the unexposed patients. Hypotension and perceived arrhythmias were each reported by 2.3% of exposed patients, whereas syncope and tachycardia were reported only in the unexposed group (2.3% and 7.0%, respectively). None of these differences reached statistical significance.

Electrocardiographic findings:

Electrocardiographic findings are presented in Table 5. Normal sinus rhythm was more frequent in unexposed patients (86.0% vs. 55.8%; $p = 0.0039$), whereas sinus bradycardia was more frequent in exposed patients (41.9% vs. 14.0%; $p = 0.0074$).

Table 5
Electrocardiogram Results

Variable	Exposed (n = 43)	Unexposed (n = 43)	p-value
Sinus rhythm, n (%)	24 (55.8)	37 (86.0)	0.003*
Sinus bradycardia, n (%)	18 (41.9)	6 (14.0)	0.007*
Sinus tachycardia, n (%)	1 (2.3)	0 (0.0)	1.000
Heart rate (bpm), mean (95% CI)	65.7 (61.4–69.9)	69.6 (66.7–72.5)	0.040*
Heart rate 60–100 bpm, n (%)	22 (51.2)	37 (86.1)	< 0.001*
PR interval (ms), mean (95% CI)	172.6 (166.9–178.2)	161.9 (154.6–169.1)	0.025*
P wave (ms), mean (95% CI)	95.5 (92.6–98.5)	93.9 (91.1–96.8)	0.949
P wave > 100 ms, n (%)	5 (11.6)	2 (4.7)	0.237
QT interval (ms), mean (95% CI)	403.7 (389.7–417.8)	394.4 (383.5–405.4)	0.111
QTc interval (ms), mean (95% CI)	420.0 (408.9–431.1)	423.1 (412.7–433.5)	0.762
QTc > 450 ms (men), n (%)	2 (4.7)	0 (0.0)	0.109
QTc > 470 ms (women), n (%)	0 (0.0)	1 (2.3)	0.270
QRS duration (ms), mean (95% CI)	86.7 (82.0–91.4)	86.2 (81.9–90.5)	0.987
QRS > 100 ms, n (%)	3 (7.0)	1 (2.3)	0.306
Bundle branch block, n (%)	3 (7.0)	1 (2.3)	0.699
ST-segment abnormalities, n (%)	19 (44.2)	22 (51.2)	0.517
Early atrial repolarization, n (%)	7 (16.3)	2 (4.7)	0.078
Flattened T wave / ST straightening, n (%)	4 (9.3)	3 (7.0)	0.693
Early ventricular repolarization, n (%)	2 (4.7)	8 (18.6)	0.044*
Combined atrial and ventricular repolarization, n (%)	3 (7.0)	2 (4.7)	0.645

Abbreviations: QTm, mean QT interval; QTc, Corrected QT interval.

Consistent with these findings, resting heart rate was lower in exposed patients (65.7 bpm; 95% CI, 61.4–69.9) than in unexposed patients (69.6 bpm; 95% CI, 66.7–72.5; $p = 0.040$).

The PR interval was modestly longer in the exposed group (172.6 vs. 161.9 ms; $p = 0.025$). However, no significant between-group differences were observed in QRS duration, bundle branch block, or other clinically relevant intraventricular conduction abnormalities.

An early repolarization pattern was more frequently observed in unexposed patients (18.6% vs. 4.7%; $p = 0.044$).

Importantly, QTc duration did not differ significantly between groups (420.0 ms in exposed vs. 423.1 ms in unexposed patients; $p = 0.762$), and QTc values exceeding sex-specific thresholds were uncommon. No clinically significant persistent abnormalities in ventricular repolarization were identified.

Holter monitoring:

Holter findings are summarized in Table 6. The proportion of Holter recordings classified as abnormal was lower among exposed patients (26% vs. 51%; $p = 0.0147$).

Table 6
Holter Record Results

Variable	Exposed (n = 43)	Unexposed (n = 43)	p-value
Abnormal Holter result, n (%)	11 (25.6)	22 (51.2)	0.015*
Heart rate variability (SDNN, ms), mean (95% CI)	126.1 (116.2–136.0)	113.6 (101.5–125.8)	0.014*
HRV < 100 ms, n (%)	7 (16.3)	17 (39.5)	0.016*
HRV 101–200 ms, n (%)	35 (81.4)	25 (58.1)	0.019*
HRV > 200 ms, n (%)	1 (2.3)	1 (2.3)	1.000
Sinus rhythm, n (%)	43 (100.0)	42 (97.7)	0.314
Average heart rate (bpm), mean (95% CI)	77.8 (75.1–80.5)	78.4 (75.7–81.2)	0.524
Heart rate < 60 bpm, n (%)	0 (0.0)	2 (4.7)	0.494
Heart rate 60–100 bpm, n (%)	43 (100.0)	40 (93.0)	0.241
Heart rate > 100 bpm, n (%)	0 (0.0)	1 (2.3)	1.000
QT interval (ms), mean (95% CI)	391.6 (384.9–398.4)	388.8 (379.1–398.5)	0.533
QTc interval (ms), mean (95% CI)	440.8 (435.2–446.4)	440.4 (431.1–449.8)	0.675
QTc > 450 ms (men), n (%)	5 (11.6)	4 (9.3)	0.470
QTc > 470 ms (women), n (%)	1 (2.3)	5 (11.6)	0.047*
Intranodal conduction disorder, n (%)	3 (7.0)	0 (0.0)	0.078
Intraventricular conduction disorder, n (%)	2 (4.7)	2 (4.7)	1.000
Bundle branch block, n (%)	3 (7.0)	2 (4.7)	0.645
Supraventricular arrhythmias, n (%)	14 (32.6)	8 (18.6)	0.138
Ventricular arrhythmias, n (%)	8 (18.6)	9 (20.9)	0.787

Abbreviations: QTm, mean QT interval; QTc, Corrected QT interval.

Heart rate variability, assessed by SDNN, was higher in the exposed group (126.1 ms; 95% CI, 116.2–136.0). An SDNN within the predefined normal range of 101–200 ms was more frequent among exposed patients (81.4% vs. 58.1%; $p = 0.019$), whereas reduced HRV, defined as SDNN < 100 ms, was less frequent (16.3% vs. 39.5%; $p = 0.016$).

Sinus rhythm predominated during Holter monitoring in both groups and mean 24-hour heart rate did not differ significantly (77.8 vs. 78.4 bpm; $p = 0.525$).

QT and QTc measurements obtained during ambulatory monitoring were also similar between groups. Among women, QTc > 470 ms was observed more frequently in the unexposed group (11.6% vs. 2.3%; $p = 0.047$).

Conduction abnormalities were uncommon. Three intranodal conduction abnormalities were identified in exposed patients and none in unexposed patients ($p = 0.078$), whereas intraventricular conduction disturbances and bundle branch blocks were infrequent in both groups.

Supraventricular arrhythmias were numerically more frequent among exposed patients (33% vs. 19%), although the difference was not statistically significant ($p = 0.138$). Ventricular arrhythmias were infrequent and similarly distributed between groups. No episodes of sustained ventricular tachycardia or ventricular fibrillation were detected during 24-hour Holter monitoring.

Predictors of QTc prolongation:

The multivariable logistic regression model is presented in Table 7. Systemic arterial hypertension, BMI, antimalarial exposure, diabetes mellitus, preserved renal function, and cardiac troponin I levels were evaluated as potential predictors of QTc prolongation. None demonstrated a statistically significant independent association with QTc prolongation.

Table 7
Multivariate logistic regression model assessing the association between clinical variables and QTc prolongation in COVID-19 survivors.

Variable	OR (95% CI)	p-value
Use of antimalarial	1.12 (0.25–4.90)	0.885
Diabetes mellitus	0.75 (0.15–3.69)	0.721
Hypertension	0.21 (0.04–1.01)	0.052
GFR > 90 ml/min	0.49 (0.06–3.79)	0.496
Troponin I	0.99 (0.97–1.01)	0.452
Body mass index (BMI)	1.14 (0.99–1.31)	0.053

Note: Odds ratios (ORs) with 95% confidence intervals (CIs) and p-values are presented. QTc prolongation was defined as QTc >450 ms in males and >470 ms in females. The model included antimalarial use (chloroquine/hydroxychloroquine), metabolic comorbidities (diabetes mellitus, hypertension), renal function (GFR >90 ml/min), troponin I levels, and body mass index (BMI). A p-value <0.05 was considered statistically significant.

Discussion

In this matched retrospective cohort study, we evaluated the cardiac electrophysiological profile of survivors of severe COVID-19 pneumonia 3–6 months after hospitalization, stratified by prior exposure to combined antimalarial–macrolide therapy. The principal finding was that short-term exposure to these agents was not associated with persistent QTc prolongation, malignant ventricular arrhythmias, or clinically significant conduction abnormalities during medium-term follow-up.

Cardiovascular concerns surrounding hydroxychloroquine, chloroquine, and macrolides became particularly relevant during the early phase of the COVID-19 pandemic because these agents can alter cardiac repolarization. Hydroxychloroquine, chloroquine, and several macrolides inhibit the hERG potassium channel and reduce the rapidly activating delayed rectifier potassium current (IKr), thereby prolonging the ventricular action potential and QT interval.^{9,11,17} In susceptible patients, particularly those with structural heart disease, bradycardia, electrolyte abnormalities, or concurrent exposure to other QT-prolonging medications, these effects can increase the risk of acquired long-QT syndrome and torsade de pointes.^{11,18}

Previous studies performed during acute SARS-CoV-2 infection demonstrated varying degrees of QTc prolongation among patients receiving hydroxychloroquine, particularly when combined with azithromycin. Nevertheless, malignant ventricular arrhythmias were relatively uncommon.^{13,14,19,20} Our findings are broadly consistent with these observations and extend the available evidence by evaluating patients several months after hospital discharge. We found no evidence of persistent QTc prolongation associated with prior antimalarial–macrolide exposure.

The absence of a persistent difference in QTc is biologically plausible. Drug-induced inhibition of cardiac potassium channels is primarily a pharmacological effect mediated by circulating drug concentrations. Although hydroxychloroquine has a prolonged terminal elimination phase, persistent repolarization abnormalities months after short-term exposure would not necessarily be expected in the absence of structural or sustained electrophysiological injury. Our results therefore suggest that the QT-prolonging effects described during acute treatment may not translate into persistent abnormalities after recovery in most patients.

Interpretation of electrophysiological findings in COVID-19 nevertheless requires consideration of the infection itself. Severe SARS-CoV-2 infection may influence cardiac repolarization and arrhythmogenic risk through systemic inflammation, myocardial injury, hypoxemia, metabolic and electrolyte abnormalities, and autonomic dysfunction.^{12,19,21} Inflammatory cytokines, particularly interleukin-6, may directly modulate cardiac ion-channel function and reduce repolarizing potassium currents, thereby contributing to acquired QT prolongation independently of pharmacological exposure.^{22,23}

This consideration is particularly relevant in our cohort because unexposed patients had higher CRP, LDH, leukocyte counts, and D-dimer concentrations during hospitalization. They also experienced longer hospitalization and more frequent ICU admission. Collectively, these findings suggest a greater burden

of acute systemic illness in the unexposed group. Consequently, differences observed during follow-up cannot be attributed solely to the absence or presence of antimalarial–macrolide therapy.

A second relevant finding was the higher prevalence of sinus bradycardia and the modestly longer PR interval among previously exposed patients. Antimalarial agents may affect sinoatrial automaticity and atrioventricular conduction by modulating sodium, calcium, and potassium currents.^{9,24} However, the magnitude of the observed abnormalities was small, and no progression to clinically significant atrioventricular block or major conduction disease was identified. Therefore, the clinical relevance of these differences appears limited.

Higher HRV was also observed in the exposed group. HRV reflects beat-to-beat variation in cardiac cycle length and is commonly used as a noninvasive marker of autonomic modulation. Reduced HRV has been associated with adverse cardiovascular outcomes and has also been reported after COVID-19, potentially reflecting persistent sympathovagal imbalance or post-infectious autonomic dysfunction.^{25–}

27

Although the higher SDNN observed among exposed patients could suggest more preserved autonomic modulation, this finding should not be interpreted as evidence of a beneficial pharmacological effect. The greater inflammatory burden and more severe clinical course observed among unexposed patients provide a plausible alternative explanation. Systemic inflammation and critical illness may both disrupt autonomic regulation and reduce HRV. Thus, residual confounding by acute disease severity is likely and limits causal interpretation of the association between treatment exposure and HRV.

Post-COVID symptoms were highly prevalent in both groups, with fatigue, dyspnea, and palpitations among the most common manifestations. This pattern is consistent with previous reports describing persistent cardiovascular and systemic symptoms following SARS-CoV-2 infection.^{16,30,31} Importantly, the high frequency of subjective cardiovascular symptoms contrasted with the low prevalence of clinically significant electrophysiological abnormalities on objective testing.

Taken together, our findings provide additional information regarding the post-acute electrophysiological profile of patients who received antimalarial–macrolide therapy during the initial phase of the pandemic. Although these drugs are no longer recommended for the treatment of COVID-19 due to a lack of demonstrated clinical efficacy, the present observations may help contextualize concerns about potential persistent electrophysiological consequences of their historical use.

Conclusion

Among survivors of severe COVID-19 pneumonia evaluated 3–6 months after hospitalization, previous short-term exposure to combined antimalarial–macrolide therapy was not associated with persistent QTc prolongation, malignant ventricular arrhythmias, or clinically significant conduction abnormalities.

Although previously exposed patients demonstrated a lower resting heart rate and greater heart rate variability, these differences should be interpreted cautiously because unexposed patients had evidence of greater acute inflammatory burden and more severe hospitalization.

These findings suggest that the electrophysiological effects associated with short-term antimalarial–macrolide administration during acute COVID-19 were not accompanied by detectable persistent repolarization abnormalities in this cohort.

Limitations:

Several limitations should be considered when interpreting these findings.

First, the retrospective and nonrandomized design introduces the possibility of selection bias and residual confounding. Although exposed and unexposed patients were matched by age and sex, the groups differed substantially in several markers of systemic inflammation and clinical severity. Evolving institutional practices may have also influenced treatment allocation during the early months of the pandemic.

Second, electrocardiographic data before SARS-CoV-2 infection and, importantly, detailed paired measurements obtained before and during pharmacological exposure were unavailable. Therefore, changes in QTc attributable specifically to treatment during the acute phase could not be quantified.

Third, the sample size was relatively small and insufficiently powered to detect rare events such as torsade de pointes, sustained ventricular tachycardia, or sudden cardiac death. The absence of these events should therefore not be interpreted as definitive evidence of absence of risk.

Fourth, 24-hour Holter monitoring provides only a limited sampling period and may fail to identify infrequent arrhythmic events.

Fifth, the multivariable model was limited by the number of participants and events and did not comprehensively adjust for markers of acute COVID-19 severity, concomitant QT-prolonging medications, electrolyte abnormalities, or other potential confounders.

Finally, the study population consisted exclusively of survivors who were able to undergo cardiovascular follow-up, introducing the possibility of survivor bias and limiting generalizability to patients with fatal or extremely severe disease.

Declarations

The study protocol was approved by the Ethics and Research Committees of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán on August 22, 2020. The study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice Guidelines, and the

Declaration of Istanbul. Written informed consent was obtained from all participants before study enrollment.

Acknowledgements:

The authors would like to thank all participants who voluntarily took part in this study. We also acknowledge the support of the Department of Cardiology of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, as well as the collaboration of the institutional staff involved in participant recruitment, blood pressure assessment, ambulatory blood pressure monitoring, and central aortic pressure measurements. The authors are also grateful to the Universidad Nacional Autónoma de México and its Faculty of Medicine for their academic support throughout the development of this research.

Funding:

This research received no specific funding from any public, commercial, or not-for-profit sectors.

Disclosures:

The authors have no financial or non-financial conflicts of interest to disclose.

References

1. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virology*. 2005 22;2. doi:10.1186/1743-422X-2-69
2. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases. *Lancet Infect Dis*. 2003;3(11):722. doi:10.1016/S1473-3099(03)00806-5
3. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269–71. doi:10.1038/s41422-020-0282-0
4. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. 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 Dis*. 2020;71(15):732–9. doi:10.1093/cid/ciaa237
5. Pani A, Lauriola M, Romandini A, Scaglione F. Macrolides and viral infections: focus on azithromycin in COVID-19 pathology. *Int J Antimicrob Agents*. 2020;56(2):106053. doi:10.1016/j.ijantimicag.2020.106053
6. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med*. 2020 1;26(10):1636–43. doi:10.1038/S41591-020-1051-917

7. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;14(1). doi:10.5582/BST.2020.01047
8. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med*. 2020;382(25):2411–8. doi:10.1056/nejmoa2012410
9. Sanguinetti MC, Tristani-Firouzi M. hERG potassium channels and cardiac arrhythmia. *Nature*. 2006;440(7083):463–9. doi:10.1038/nature04710
10. TeBay C, Hill AP, Windley MJ. Metabolic and electrolyte abnormalities as risk factors in drug-induced long QT syndrome. *Biophysical Reviews*. Springer Science and Business Media Deutschland GmbH; 2022. p. 353–67. doi:10.1007/s12551-022-00929-7
11. Tisdale JE, Chung MK, Campbell KB, Hammadah M, Joglar JA, Leclerc J, et al. Drug-Induced Arrhythmias: A Scientific Statement From the American Heart Association. *Circulation*. 2020;142(15):E214–33. doi:10.1161/CIR.0000000000000905
12. Kochav SM, Coromilas E, Nalbandian A, Ranard LS, Gupta A, Chung MK, et al. Cardiac Arrhythmias in COVID-19 Infection. *Circ Arrhythm Electrophysiol*. 2020;13(6):E008719. doi:10.1161/CIRCEP.120.008719
13. Maraj I, Hummel JP, Taoutel R, Chamoun R, Workman V, Li C, et al. Incidence and determinants of QT interval prolongation in COVID-19 patients treated with hydroxychloroquine and azithromycin. *J Cardiovasc Electrophysiol*. 2020;31(8):1904–7. doi:10.1111/jce.14594
14. Bessière F, Rocchia H, Delinière A, Charrière R, Chevalier P, Argaud L, et al. Assessment of QT Intervals in a Case Series of Patients with Coronavirus Disease 2019 (COVID-19) Infection¹⁸ Treated with Hydroxychloroquine Alone or in Combination with Azithromycin in an Intensive Care Unit. *JAMA Cardiol*. 2020;5(9):1067–9. doi:10.1001/JAMACARDIO.2020.1787
15. Chorin E, Dai M, Shulman E, Wadhvani L, Bar-Cohen R, Barbhaiya C, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. *Nat Med*. 2020;26(6):808–9. doi:10.1038/s41591-020-0888-2
16. Chen C, Haupt SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global Prevalence of Post-Coronavirus Disease 2019 (COVID-19) Condition or Long COVID: A Meta-Analysis and Systematic Review. *J Infect Dis*. 2022;226(9):1593–607. doi:10.1093/infdis/jiac136
17. Zequn Z, Jiangfang L. Molecular Insights Into the Gating Kinetics of the Cardiac hERG Channel, Illuminated by Structure and Molecular Dynamics. *Front Pharmacol*. 2021;12. doi:10.3389/FPHAR.2021.687007
18. Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR, et al. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. *Circ Cardiovasc Qual Outcomes*. 2013;6(4):479–87. doi:10.1161/CIRCOUTCOMES.113.000152
19. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(7):811–8.

doi:10.1001/jamacardio.2020.1017

20. Mercurio NJ, Yen CF, Shim DJ, Maher TR, McCoy CM, Zimetbaum PJ, et al. Risk of QT Interval Prolongation Associated with Use of Hydroxychloroquine with or without Concomitant Azithromycin among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5(9):1036–41. doi:10.1001/jamacardio.2020.183419
21. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. *JAMA.* 2020;323(24):2493–502. doi:10.1001/JAMA.2020.8630
22. Lazzerini PE, Boutjdir M, Capecchi PL. COVID-19, Arrhythmic Risk, and Inflammation: Mind the Gap! *Circulation.* 2020;142(1):7–9. doi:10.1161/CIRCULATIONAHA.120.047293
23. Lazzerini PE, Laghi-Pasini F, Boutjdir M, Capecchi PL. Cardioimmunology of arrhythmias: the role of autoimmune and inflammatory cardiac channelopathies. *Nat Rev Immunol.* 2019;19(1):63–4. doi:10.1038/s41577-018-0098-z
24. Capel RA, Herring N, Kalla M, Yavari A, Mirams GR, Douglas G, et al. Hydroxychloroquine reduces heart rate by modulating the hyperpolarization-activated current *I_f*: Novel electrophysiological insights and therapeutic potential. *Heart Rhythm.* 2015;12(10):2186–94. doi:10.1016/j.hrthm.2015.05.027
25. Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton R, et al. Autonomic dysfunction in ‘long COVID’: rationale, physiology and management strategies. *Clinical Medicine, Journal of the Royal College of Physicians of London.* 2021;21(1):E63–7. doi:10.7861/CLINMED.2020-0896
26. Barizien N, Le Guen M, Russel S, Touche P, Huang F, Vallée A. Clinical characterization of dysautonomia in long COVID-19 patients. *Sci Rep.* 2021;11(1). doi:10.1038/s41598-021-93546-520
27. Donniacuo M, De Angelis A, Rafaniello C, Cianflone E, Paolisso P, Torella D, et al. COVID-19 and atrial fibrillation: Intercepting lines. *Front Cardiovasc Med.* 2023;10:1093053. doi:10.3389/FCVM.2023.1093053
28. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet.* 2020;395(10229):1054–62. doi:10.1016/S0140-6736(20)30566-3
29. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020;18(4):844–7. doi:10.1111/JTH.14768
30. Nalbandian A, Sehgal K, Gupta A, Madhavan M V., McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. *Nat Med.* 2021;27(4):601–15. doi:10.1038/S41591-021-01283-Z
31. Lazzerini PE, Abbate A, Boutjdir M, Capecchi PL. Fir(e)ing the Rhythm: Inflammatory Cytokines and Cardiac Arrhythmias. *JACC Basic Transl Sci.* 2023;8(6):728. doi:10.1016/J.JACBTS.2022.12.004