Mitigating Arrhythmia Risk in Hydroxychloroquine and Azithromycin Treated COVID-19 Patients using Arrhythmia Risk Management Plan

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Abstract

Background: Hydroxychloroquine and Azithromycin use is associated with QT interval prolongation and arrhythmias. Despite ongoing multiple clinical trials for treatment of COVID19 infection, no definite cardiac safety protocols were proposed. The aim of our study was to assess cardiac safety in COVID-19 patients treated with the combination of Hydroxychloroquine and Azithromycin using close monitoring and arrhythmia risk management plan.

Methods and results: We retrospectively examined arrhythmia safety of treatment with Hydroxychloroquine and Azithromycin in the setting of pre-defined cardiac arrhythmia risk management plan. 81 patients were included from March 23rd to May 10th 2020. The median age was 59 years, 58.0% were female. The majority of the study population (82.7%) had comorbidities, 98.8% had radiological signs of pneumonia. 7 patients (8.6%) had QTc prolongation of ≥500 ms. The treatment was discontinued in 4 patients (4.9%). 14 patients (17.3%) experienced QTc≥480 ms and 16 patients (19.8%) had an increase of QTc≥60 ms. None of the patients developed ventricular tachycardia. The risk factors significantly associated with QTc≥500 ms were hypokalemia (p = 0.032) and use of diuretics during the treatment (p = 0.020). Three patients had a lethal outcome; none of them associated with ventricular arrhythmias.

Conclusion: We recorded a low incidence of QTc prolongation ≥500 ms and no ventricular tachycardia events in COVID-19 patients treated with Hydroxychloroquine and Azithromycin using cardiac arrhythmia risk management plan.

Background

Since the beginning of COVID-19 spread in December 2019, one of the therapies under investigation has been the combination of Hydroxychloroquine (HCQ) and Azithromycin (AZI). Both drugs have been associated with QT interval prolongation and arrhythmogenic effects (1,2). However, the actual risk of ventricular arrhythmias using this combination is unclear (3,4). Here we report QT interval prolongation and arrhythmia safety results in patients with COVID-19 treated with the combination of HCQ and AZI using close monitoring and arrhythmia risk management plan.

Methods

We retrospectively examined the cardiac safety of treatment using HCQ and AZI in consecutive patients with COVID-19 infection treated in Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania. Every patient consented to the treatment plan by signing an informed consent form and the hospital ethics committee individually approved the combination use in each patient. The data was acquired from the electronic medical records accessed through Vilnius University Hospital Santaros Klinikos Biobank. The study was approved by the regional ethics committee.

HCQ-AZI consisted of 5 days of oral azithromycin (once daily; initial dose 500 mg on the first day followed by 250 mg during the next 4 days) and 10 days of oral hydroxychloroquine 200 mg three times daily.

The cardiac arrhythmia risk management plan during HCQ-AZI treatment for each patient was as follows: 1) QT prolonging concomitant drugs (assessed using "CredibleMeds®" database (5)) were discontinued if possible; 2) ECG recording and QTcF (Fridericia) calculation was performed daily; 3) K^+ and Mg^{2+} were replaced if abnormal (hypokalemia and hypomagnesemia were defined as K^+ levels < 3.5 mmol/L and Mg^{2+} < 0.65 mmol/L in blood serum, respectively); 4) if QTcF reached 480 ms during HCQ-AZI treatment, K^+ and Mg^{2+} were replaced to reach maximum normal values, 5) if QTcF remained in the interval of 480 – 499 ms regardless of K^+ and Mg^{2+} replacement, the risk-benefit of continuing HCQ-AZI was reviewed individually, 6) HCQ-AZI was discontinued in patients with QTcF≥500 ms with the exception of patients treated in intensive care unit (ICU) who had continuous ECG monitoring and cardioversion equipment readily available at bedside.

In this study, we focused on QT prolongation and arrhythmias associated with HCQ and AZI use. ECG was reviewed and QT was measured in each ECG using the tangent method by 2 cardiologists and 2 resident doctors trained in QT measurement. QT was corrected using the Fridericia formula.

Our primary end point was arrhythmia safety during HCQ and AZI treatment measured as the number of patients with QTcF prolongation ≥500 ms within the period of 14 days from the start of HCQ-AZI treatment. Our secondary end points were change in QTcF≥60 ms, QTcF prolongation ≥480 ms, the number of ventricular tachycardia cases and cardiac mortality.

Statistical analysis

Frequency with percentage based on the total cohort was evaluated for categorical parameters while median (min – max) estimate was used for continuous variables. Univariate logistic regression model was used to evaluate odds ratio for QTcF prolongation. Factors found to be significant in univariate logistic regression analysis were entered into multivariate logistic regression model with forward model selection process. A two-tailed p-value less than 0.05 was considered to be significant. Statistical analysis was performed using R statistical package version 4.0.0.

Results

Demographics of the COVID-19 patients

81 consecutively hospitalized patients had been treated with HCQ and AZI combination from March 23rd to May 10th 2020 and were enrolled into the study (Table 1). The median age was 59 years (35 – 87), 58.0% (n=47) were female. The largest patient group according to age was the 60-69 years old group (24.7%). The median baseline Cumulative Illness Rating scale (CIRS) score (6) was 4 (0 – 15). The majority of the study population (82.7%) had comorbidities and half of the patients (50.6%) had

cardiological diseases. 33 patients (40.8%) were taking 1-2 and 10 patients (12.3%) 3-4 concomitant drugs.

Clinical data and laboratory findings of the COVID-19 patients

The median time from symptom onset to hospitalization and treatment with HCQ-AZI were both 7 days (-1 – 42) (Table 2). 80 patients (98.8%) had radiological signs of pneumonia. The median baseline National Early Warning score (NEWS) was 2 (0 – 13). On admission, 34 patients (42.0%) required low-flow oxygen, 2 patients (2.5%) had to be on invasive ventilation and 1 patient (1.3%) was connected to an extracorporeal membrane oxygenation (ECMO) to sustain oxygen saturation above 92%. 3 patients (3.7%) were admitted directly to ICU. Two-thirds of the patients (67.9%) had electrolyte imbalance during the follow-up period.

Cardiotoxicity of HCQ-AZI treatment

More than half of the patients (51.9%) were prescribed at least one additional QT interval prolonging drug during the hospitalization, the majority of these drugs (87.7%) being in the “conditional risk of TdP” group according to “CredibleMeds®” (Table 2).

The median baseline QTcF was 416 ms (365 – 498). The median QTcF was rising daily and the peak of 436 ms (333 – 483) was observed on the 10^{th} day of the HCQ-AZI treatment (Figure 1a). The highest median ΔQTcF was observed on the 8^{th} day (Figure 1b).

Seven patients (8.6%) had QTcF prolongation of ≥500 ms during the 14-day period from the initiation of the treatment (Table 3). Four of these cases were observed during and three immediately after the administration of HCQ-AZI. HCQ-AZI was discontinued in 4 patients (4.9%): one and three in 480-499 ms and ≥500 ms groups, respectively. None of the patients developed ventricular tachycardia. The risk factors significantly associated with QTcF≥500 ms were hypokalemia (p = 0.032) and the use of diuretics during the treatment (p = 0.020), the odds ratios (95% CI) were 6.188 (1.168-32.774) and 7.778 (1.388-43.595), respectively. Multivariate logistic regression analysis was not performed due to strong dependence between hypokalemia and the use of diuretics (phi = 0.4).

14 patients (17.3%) experienced QTcF≥480 ms (Table 3) and 16 patients (19.8%) had a change of QTcF≥60 ms. Higher baseline NEWS score, presence of cardiological comorbidities, higher number of concomitant medications, hypokalemia, use of diuretics during the treatment and higher baseline QTcF were associated with QTcF prolongation ≥480 ms in the univariate logistic regression model (Table 4). On multivariate analysis, cardiological comorbidities (p = 0.034) and hypokalemia (p = 0.008) were found to be independent factors for QTcF≥480 ms interval prolongation (Table 4, Figure 2).

Outcomes of the COVID-19 patients

11 patients (13.6%) were transferred to ICU and 3 patients (3.7%) were connected to ECMO. Cytokine adsorbtion using CytoSorb® filters was applied in 7 cases (8.6%) and interleukin-6-receptor inhibitor

Tocilizumab was administered in 4 patients (4.9%). 5 patients (6.2%) were still hospitalized and 73 patients (90.1%) were discharged from the hospital by the end of the follow-up on May 10th, 2020. 3 patients (3.7%) died, all cases were related to progression of multiple organ dysfunction syndrome and none were related to ventricular arrhythmias.

Discussion

After promising initial results (7) and despite worldwide empirical administration HCQ and AZI to treat COVID-19 patients, detailed arrhythmia risk mitigation guidelines have not been published. In order to reduce the risk of QTc and arrhythmia adverse events, we implemented a simplified HCQ-AZI arrhythmia risk management plan. With this approach, fourteen patients (17.3%) had QTc prolongation of ≥480 ms at least once. Among them only seven (8.6%) experienced extreme prolongation of QTc≥500 ms with no observed ventricular tachycardia episodes.

During randomized trial from Brazil of low-dose chloroquine (CQ) for 5 days vs. high-dose CQ for 10 days, prolonged QTc≥500 ms was documented in 4/36 (11.1%) vs. 7/37 (18.9%) and ventricular tachycardia in 0/36 vs. 2/37 (2.7%) patients, respectively (8). Many of these patients had severe COVID-19 infection, serious comorbidities or were elderly. Severe infection and concomitant medications with QT prolonging potential may have been the reason of early timing (1-4 day of treatment) of extreme QTc prolongation or arrhythmia. For example, 89.6% of patients were taking Oseltamivir for suspected influenza infection, which may have contributed to QT prolongation (9). In a retrospective HCQ and AZI treatment cohort of 90 patients with COVID-19, 11 of 53 (21%) subjects developed QTc≥500 ms and 7 of 53 (13 %) had ΔQTc≥60 ms (10). One case of torsades de pointes (TdP) which happened three days after discontinuation of treatment may indicate delayed risk possibly due to long half-life of HCQ (11). A larger retrospective cohort study of 251 subjects showed prolongation of QTc≥500 ms in 15.9 % of subjects with 1 case of TdP (12). The timing of peak ΔQTc of this study was at the end of the 5-day treatment scheme. Similarly, in our cohort the mean peak ΔQTcF was observed at the end of the treatment (day 8) (Figure 1b). Intensified ECG telemetry monitoring during the last days and immediately after treatment may thus be indicated. Importantly, QTc≥500 ms was observed less frequently (8.6%) under our risk management plan despite 10-day duration of HCQ-AZI treatment compared to both HCQ-AZI studies.

To the best of our knowledge, a well-known link between hypokalemia and QTc prolongation has not been demonstrated in COVID-19 population treated with HCQ and AZI. Low potassium levels were associated with extreme prolongation of QTcF≥500 ms ($p = 0.032$) in our cohort. Hypokalemia may be aggravated by the ability of SARS-CoV-2 virus to degrade angiotensin-converting enzyme 2 increase the action of angiotensin I/II and renin–angiotensin–aldosterone system resulting in a challenging renal K^+ loss (13). The study found a positive association between the degree of hypokalemia and the severity of COVID-19. The resolution of urine K^+ loss appeared to be a sensitive biomarker of good prognosis.

The generalizability of our findings may be limited to patients hospitalized and monitored daily in a tertiary level university hospital. Therefore, it may not be applicable to other populations where such

monitoring cannot be implemented. However, a simple to follow protocol, no routine co-administration of other QT prolonging drugs and good daily ECG and electrolyte testing compliance resulted in few cardiac adverse events compared to other cohorts.

In conclusion, there was a low incidence of extreme QTc prolongation ≥500 ms and no ventricular tachycardia events in COVID-19 positive patients treated with HCQ and AZI in the setting of cardiac arrhythmia risk management plan.

List Of Abbreviations

AZI – Azithromycin

CIRS – Cumulative Illness Rating scale

CQ – chloroquine

ECG – electrocardiogram

ECMO – extracorporeal membrane oxygenation

HCQ – Hydroxychloroquine

ICU – intensive care unit

NEWS – National Early Warning Score

TdP – torsades de pointes

QTcF – corrected QT interval (by Fridericia)

Declarations

Ethics approval and consent to participate

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the “Vilnius regional biomedical research ethics committee”. Every patient consented to the treatment plan by signing an informed consent form.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KM, UR and JB enrolled patients, collected, analyzed and interpreted the patient data, were major contributors in writing the manuscript.

EDM, EB, GK, MMJ, AD enrolled patients, collected patient data.

AZ, VP, LK, VK, DR, BZ, GM, LJ, LG conceived the presented idea, verified the analytical methods, enrolled patients, analyzed and interpreted the patient data, supervised the findings of this work. TZ conducted all statistical analysis, provided tables and figures.

All authors read, discussed and approved the final manuscript.

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Tables

Table 1. Demographics of the COVID-19 patients.

Parameter	Subgroup	Statistics	Total Cohort (N = 81)
Age		Median (min-max)	59 (35 – 87)
	18-44	n (%)	12 (14.8)
	45-49	n (%)	12 (14.8)
	50-59	n (%)	17 (21.0)
	60-69	n (%)	20 (24.7)
	70-79	n (%)	15 (18.5)
	≥80	n (%)	5 (6.2)
Sex	Female	n (%)	47 (58.0)
	Male	n (%)	34 (42.0)
CIRS		Median (min-max)	4 (0 – 15)
Comorbidities	Cardiological +/- other	n (%)	41 (50.6%)
	Non-cardiological	n (%)	26 (32.1%)
	None	n (%)	14 (17.3%)
Number of concomitant medications		Median (min-max)	1 (0 – 4)
	None	n (%)	38 (46.9)
	1-2	n (%)	33 (40.8)
	3-4	n (%)	10 (12.3)
	Antihypertensive medications	n (%)	39 (48.1)
	Antidiabetic medications	n (%)	11 (13.6)
	Antipsychotics	n (%)	4 (4.9)
	Antidepressants	n (%)	5 (6.2)
	Anticoagulants	n (%)	13 (16.0)
	Antiaggregants	n (%)	3 (3.7)
	Beta-mimetics	n (%)	5 (6.2)

Table 2. Clinical data and laboratory findings of the COVID-19 patients.

Parameter	Statistics	Total Cohort (N = 81)
Days from symptom onset to hospitalization	Median (min-max)	7 (-1 – 42)
Days from symptom onset to treatment initiation	Median (min-max)	7 (1 – 42)
Baseline NEWS score	Median (min-max)	2 (0 – 13)
Need for low-flow oxygen on admission	n (%)	34 (42.0)
Need for invasive ventilation on admission	n (%)	2 (2.5)
Need for extracorporeal membrane oxygenation on admission	n (%)	1 (1.3)
Radiologically confirmed pneumonia	n (%)	80 (98.8)
Additional antibiotics prescribed	n (%)	49 (60.5)
Laboratory findings		
Baseline absolute lymphocyte count (10^9/L)	Median (min-max)	1.14 (0.42 - 2.64)
Baseline CRP (mg/l)	Median (min-max)	33 (0.34 – 249.4)
Baseline Ferritin (µg/l) (n = 69)	Median (min-max)	356 (4.2 - 2678)
Baseline Interleukin-6 (ng/l) (n = 64)	Median (min-max)	15.3 (2 - 124)
Any electrolyte imbalance	n (%)	55 (67.9)
Ca^{2+} < 1.05 (mmol/l)	n (%)	47 (58.0)
K^{+} < 3.5 (mmol/l)	n (%)	11 (13.6)
Mg^{2+} < 0.65 (mmol/l)	n (%)	5 (6.2)
Symptoms		
Cough	n (%)	68 (84.0)
Rhinitis	n (%)	8 (9.9)
Diarrhea	n (%)	11 (13.6)
Nausea/vomiting	n (%)	3 (3.7)
Fever (37 °C -38 °C)	n (%)	61 (75.3)
Fever (>38 °C)	n (%)	43 (53.1)
Use of other QT prolonging drugs during hospitalization		
At least 1 drug	n (%)	42 (51.9)
Known risk of TdP	n (%)	13 (16.0)
Possible risk of TdP	n (%)	8 (9.9)
Conditional risk of TdP	n (%)	71 (87.7)

Table 3. Patients with QTcF≥480 ms.

Age	Sex[1]	CIRS	Comorbidities	CM prolonging QT	K^+ < 3.5 mmol/l	First QTcF ≥ 480 ms	Day of first QTcF ≥ 480 ms	Cumulated HCQ/AZI dosage until first prolonged QTcF (mg)	Had QTcF ≥ 500 ms	HCQ/AZI discontinued	Ventricular tachycardia
40s	F	7	Hypertension	No	Yes	516	7	4000/1500	Day 7	Day 7	No
60s	F	8	Hypertension; coronary heart disease; atrial fibrillation, obesity	Ranolazine	Yes	498	1	0/0	No	No	No
80s	F	7	Hypertension; coronary heart disease; atrial fibrillation	Omeprazole; Metoclopramide	No	482	2	600/750	No	No	No
60s	F	6	Diabetes mellitus; hypertension; coronary heart disease; atrial fibrillation; obesity	Metoclopramide	No	487	3	1400/750	No	Day 4	No
80s	F	6	Diabetes mellitus; hypertension	Furosemide	No	492	3	1200/750	Day 5	Day 5	No
70s	F	7	Cancer; hypertension; coronary heart disease; atrial fibrillation	No	No	486	1	0/0	No	No	No
60s	M	5	Hypertension; coronary heart disease; obesity	Piperacillin-Tazobactam	Yes	513	13	6000/1500	Day 13	No	No
70s	F	15	Cancer; diabetes mellitus; hypertension; coronary heart disease	Sertraline; Dasatinib, Metoclopramide; Omeprazole	No	492	1	0/0	Day 8	Day 8	No
50s	M	15	Cancer; diabetes mellitus; hypertension; coronary heart disease; chronic atrial fibrillation; chronic kidney disease	Piperacillin-Tazobactam; Furosemide; Quetiapine; Fluconazole; Propofol; Metoclopramide; Haloperidol; Esomeprazol	No	483	10	6000/1500	No	No	No
50s	M	5	Diabetes mellitus; hypertension; coronary heart disease; obesity	Amiodarone; Furosemide; Omeprazol; Propofol; Metoclopramide	Yes	493	5	3000/1500	No	No	No
70s*	M	6	Cancer; hypertension	Amiodarone; Haloperidol; Piperacillin-Tazobactam; Furosemide	No	509	14	6000/1500	Day 14	No	No
40s	M	0	None	None	Yes	480	2	1200/750	No	No	No
50s	M	4	Hypertension	Furosemide; Propofol	No	489	4	2400/1000	Day 13	No	No
50s	M	8	Diabetes mellitus; coronary heart	Furosemide; Propofol	Yes	496	4	2400/1000	Day 6	No	No

			disease; hypertension; obesity								

[1] F: Female, M: Male.

* Subject died on day 16 due to multiple organ failure.

Table 4. Logistic regression analysis of predictors for QTcF prolongation (≥480 ms) in COVID-19 patients.

Parameters	Univariate model			Multivariate model		
	Odds ratio		P-value	Odds ratio		P-value
	Estimate	95% CI		Estimate	95% CI	
Older age	1.043	0.995-1.093	0.081	ni		
Male sex	1.482	0.466-4.706	0.505	ni		
Higher baseline NEWS score	1.323	1.047-1.672	0.019	n-cs		
Presence of cardiological comorbidity	18.107	2.237-146.55	0.007	10.311	1.186-89.604	0.034
Higher number of concomitant medications[1]	2.017	1.214-3.352	0.007	ni		
Presence of hypocalcemia during treatment	0.675	0.212-2.144	0.505	ni		
Presence of hypomagnesemia during treatment	3.556	0.536-23.593	0.189	ni		
Presence of hypokalemia during treatment	9.300	2.301-37.588	0.002	8.116	1.718-38.347	0.008
Use of diuretics during treatment	6.814	1.968-23.587	0.002	n-cs		
Higher baseline QTcF	1.030	1.005-1.055	0.017	n-cs		

[1] Parameter was not included into multivariate analysis due to strong relation with subject's comorbidities.

ni: not included. n-cs: non-clinically significant. CI: confidence interval.

Figures

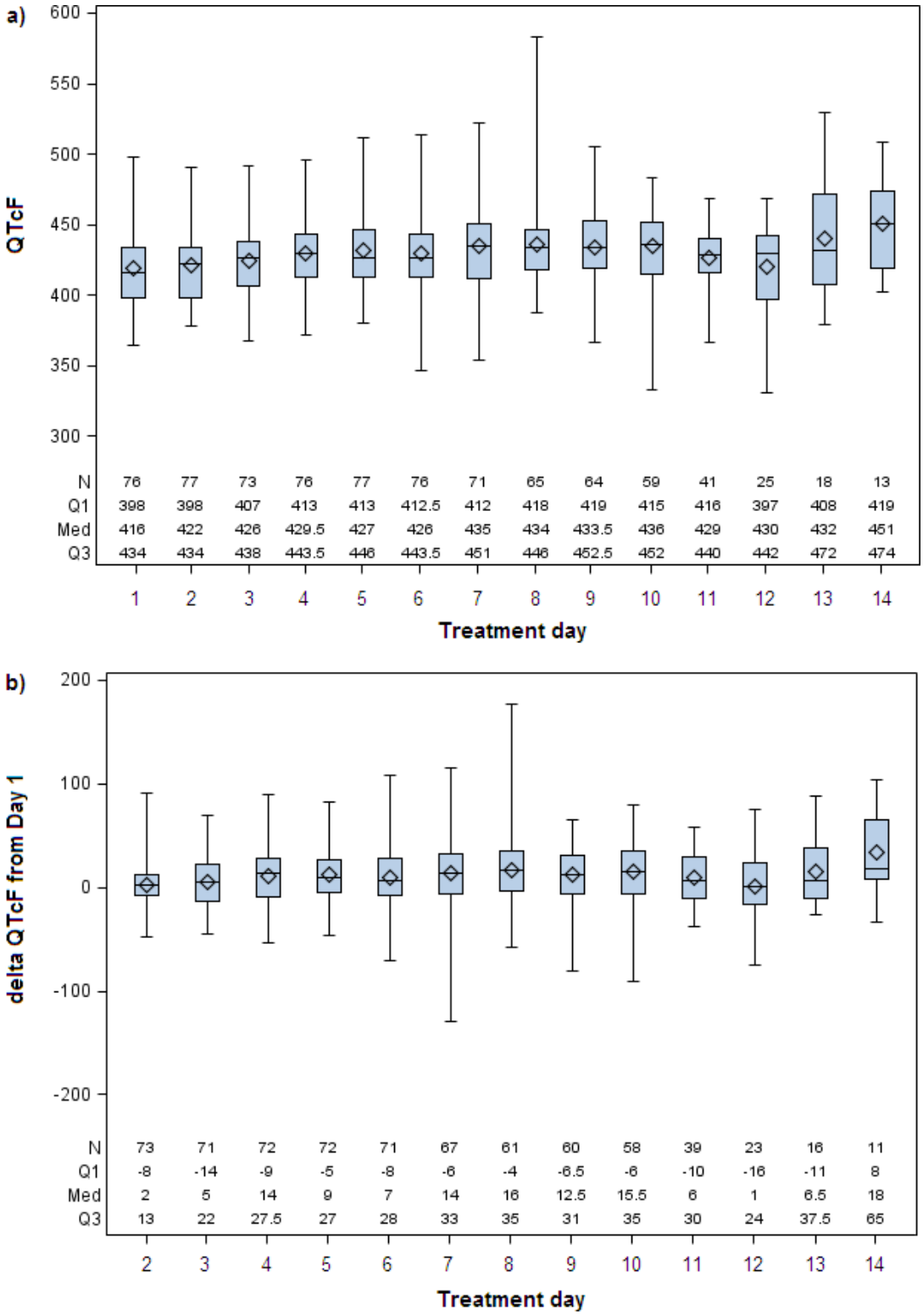

Figure 1

Daily QTcF change in COVID-19 patients: a) daily QTcF and b) ΔQTcF distributions.

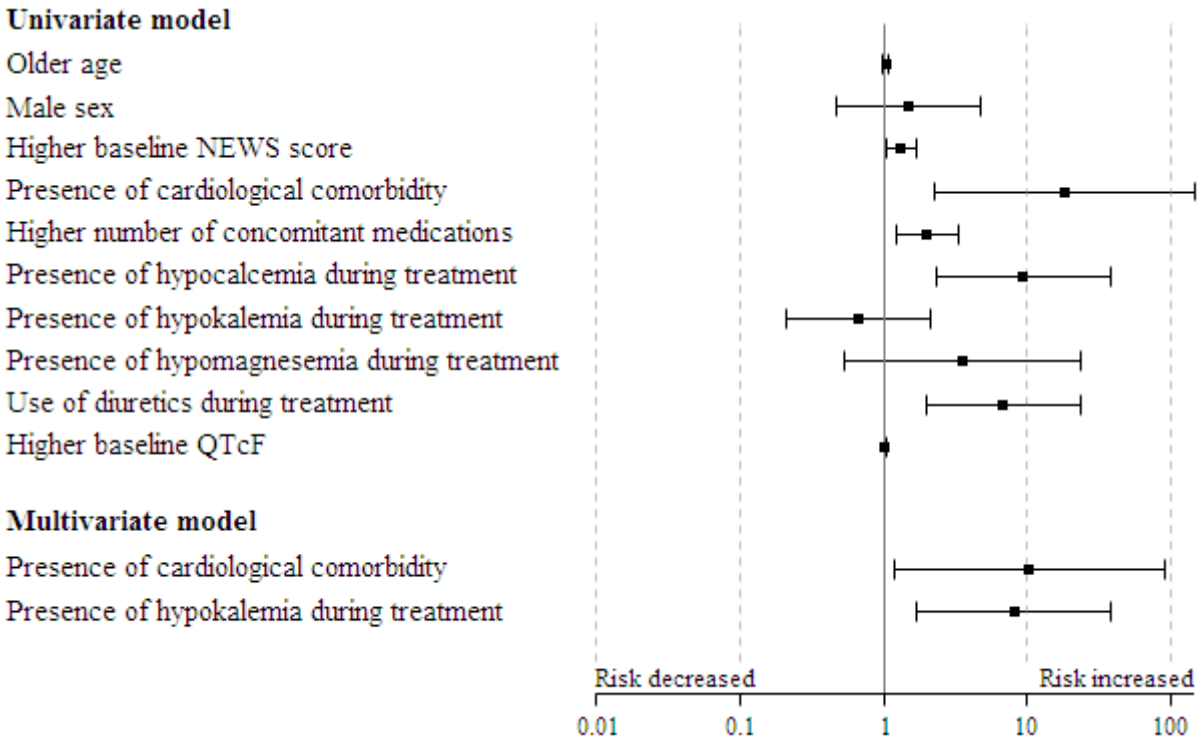

Figure 2

Forest plot of univariate and multivariate analysis for risk factors associated with QTcF interval prolongation ≥480 ms.