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Mitigating arrhythmia risk in Hydroxychloroquine and Azithromycin treated COVID-19 patients using arrhythmia risk management plan

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ABSTRACT

Aims: To assess cardiac safety in COVID-19 patients treated with the combination of Hydroxychloroquine and Azithromycin using arrhythmia risk management plan.

Methods and results: We retrospectively examined arrhythmia safety of treatment with Hydroxychloroquine and Azithromycin in the setting of pre-defined arrhythmia risk management plan. The data was analyzed using R statistical package version 4.0.0. A two-tailed p-value<0.05 was considered significant. 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. Fourteen patients (17.3%) experienced QTc $\geq$ 480 ms and 16 patients (19.8%) had an increase of QTc $\geq$ 60 ms. Seven patients (8.6%) had QTc prolongation of $\geq$ 500 ms. The treatment was discontinued in 4 patients (4.9%). None of the patients developed ventricular tachycardia. The risk factors significantly associated with QTc $\geq$ 500 ms were hypokalemia (p = 0.032) and use of diuretics during the treatment (p = 0.020). Three patients (3.7%) died, the cause of death was bacterial superinfection with septic shock in two patients, and disseminated intravascular coagulation with multiple organ failure in one patient. None of these deaths were associated with cardiac arrhythmias.

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

1. Introduction

Since the beginning of COVID-19 spread in December 2019, numerous treatment options have been studied worldwide. Based upon limited clinical data in case series, Hydroxychloroquine was recommended for treatment of hospitalized COVID-19 patients in several countries, and a number of national guidelines reported incorporating recommendations regarding use of this drug in the setting of COVID-19. Furthermore, on 28th March 2020 Hydroxychloroquine was authorized for emergency use by the U.S. Food and Drug Administration (FDA) during the COVID-19 pandemic [1]. Additional administration of macrolide antibiotic Azithromycin, seemed to reinforce the efficacy of Hydroxychloroquine [2].

Hydroxychloroquine in combination with Azithromycin or alone was used for COVID-19 treatment worldwide for almost 3 months. However, multiple large studies showed that the use

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of Hydroxychloroquine, either monotherapy or in combination with Azithromycin, did not improve clinical status as compared to the standard care [3,4]. Based on emerging scientific data, emergency use authorization for these drugs was revoked on 15th June 2020. Furthermore, Solidarity trial results showed that Hydroxychloroquine produced little or no reduction in the mortality of hospitalized COVID-19 patients when compared to standard of care and on 4th July 2020 World Health Organization (WHO) discontinued the trial's Hydroxychloroquine arm [5].

Despite the recall of Hydroxychloroquine by FDA and WHO, as of 1st November 2020, according to U.S. National Library of Medicine and European Union Clinical Trials Register, there are at least 45 interventional clinical trials for COVID-19 treatment with Hydroxychloroquine and Azithromycin that are active around the world. The drugs are studied in the setting of confirmed COVID-19 infection as well as in proactive prophylaxis. Although FDA and European Medicines Agency had warned to take precautions when using Hydroxychloroquine and Azithromycin [6,7], no definite cardiac safety protocols have been established yet. Here we report QT interval prolongation and arrhythmia safety results in COVID-19 patients treated with the combination of HCQ and AZI using close monitoring and arrhythmia risk management plan.

2. Methods

We retrospectively examined the cardiac safety of treatment using HCQ and AZI in consecutive adult patients with COVID-19 infection confirmed by qPCR treated in Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania. Every patient consented to the treatment plan by signing an informed consent form and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. 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 was designed by a multidisciplinary team which included a cardiologist – arrhythmia specialist. It was applied during HCQ-AZI treatment for each patient and was as follows: 1) QT prolonging concomitant drugs (assessed using "CredibleMeds®" database [8]) 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 $\geq$ 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. The HCQ-AZI dosing was not individually modified in any cases.

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 $\geq$ 500 ms within the period of 14 days from the start of HCQ-AZI treatment. Our secondary end points were change in QTcF $\geq$ 60 ms, QTcF prolongation $\geq$ 480 ms, the number of ventricular tachycardia cases and cardiac mortality.

2.1. 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<0.05 was considered to be significant. Statistical analysis was performed using R statistical package version 4.0.0.

3. Results

3.1. 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 [9] was 4 (0 – 15). The majority of the study population (82.7%) had comorbidities and half of the patients (50.6%) had cardiological diseases: 50.6% had arterial hypertension, 22.2% had coronary artery disease and 11.1% had a history of atrial fibrillation. 33 patients

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)

(40.8%) were taking 1–2 and 10 patients (12.3%) 3–4 concomitant drugs.

3.2. 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). The most common clinical symptoms were cough (84%) and fever (75.3%). Uncommon symptoms included diarrhea (13.6%), rhinitis (9.9%) and nausea (3.7%). 80 patients (98.8%) had radiological signs of pneumonia. The median baseline NEWS score 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.

3.3. 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 10th day of the HCQ-AZI treatment (Fig. 1a). The highest median ΔQTcF was observed on the 8th day (Fig. 1b).

Seven patients (8.6%) had QTcF prolongation of $\geq$ 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 $\geq$ 500 ms groups, respectively. None of the patients developed ventricular tachycardia. The risk factors significantly associated with QTcF $\geq$ 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 $\geq$ 480 ms (Table 3) and 16 patients (19.8%) had a change of QTcF $\geq$ 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 $\geq$ 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 $\geq$ 480 ms interval prolongation (Table 4, Fig. 2).

During the course of HCQ-AZI treatment minority of patients presented with atrial fibrillation (3.7%) or complete bundle branch block (1.2%). PR and QRS duration dynamics were analyzed but no statistically significant changes were observed. According to acquired data, HCQ-AZI treatment did not have a significant impact on atrioventricular or intraventricular conduction.

3.4. 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%). 78 patients (96.3%) were discharged from the hospital and three patients (3.7%) died. The lethal outcomes were considered

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 (>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)

* These drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended.
** These drugs can cause QT prolongation but currently lack evidence for a risk of TdP when taken as recommended.
*** These drugs are associated with TdP but only under certain conditions of their use (e.g. excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) or by creating conditions that facilitate or induce TdP (e.g. by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP).

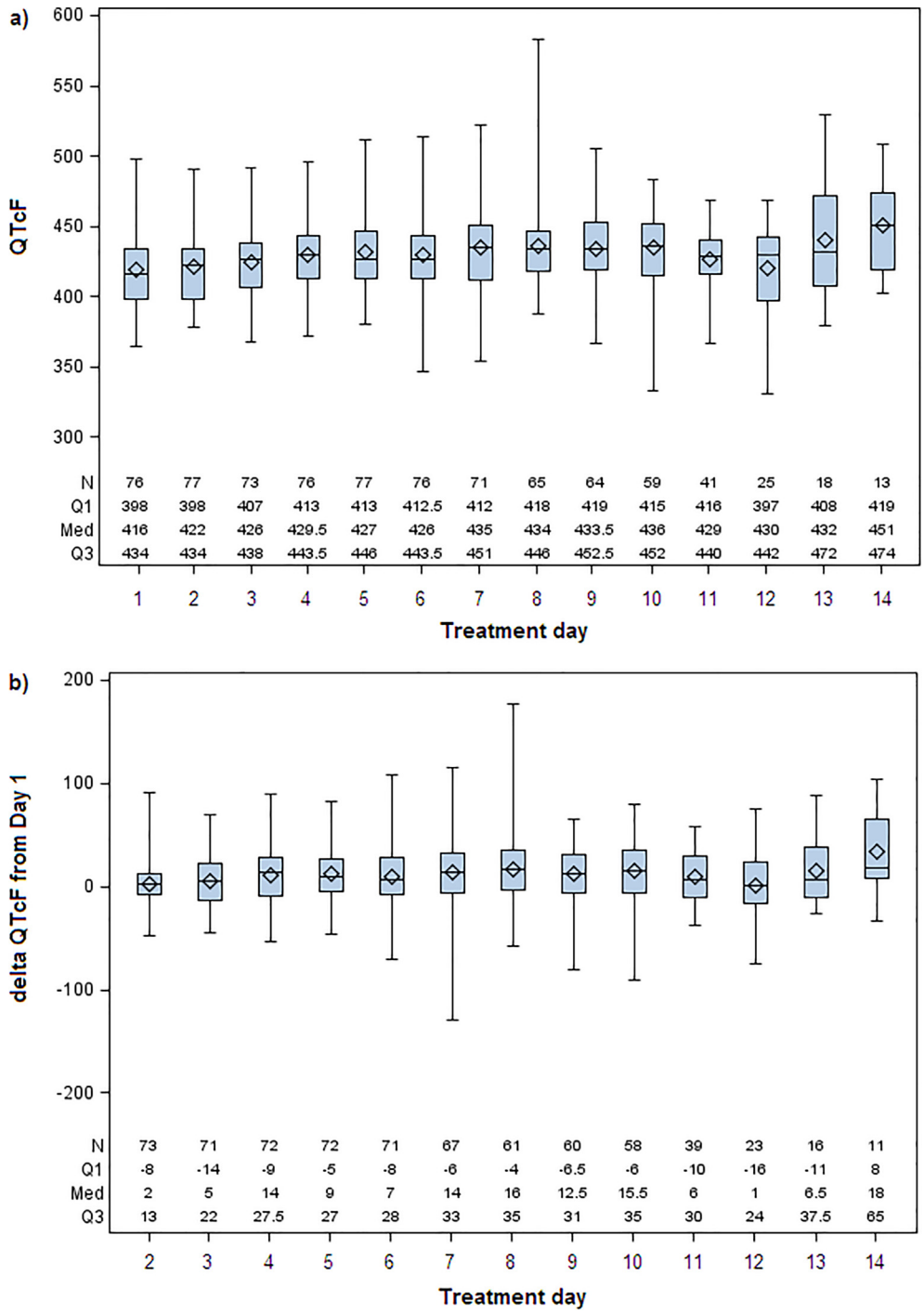

Fig. 1. Daily QTcF change in COVID-19 patients: a) daily QTcF and b) ΔQTcF distributions.

to be indirectly related to COVID-19: two patients died due to bacterial superinfection, septic shock and multiple organ failure; one patient's cause of death was disseminated intravascular coagulation, systemic inflammatory response syndrome and multiple organ failure.

4. Discussion

After promising initial results [2] and worldwide empirical administration of 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 prolongation and cardiac adverse events, we implemented a simplified HCQ-AZI arrhythmia risk management plan. With this approach, fourteen patients (17.3%) had QTc prolongation of $\geq$ 480 ms at least once. Among them only seven (8.6%) experienced extreme prolongation of QTc $\geq$ 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, alarming prolongation of QTc $\geq$ 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 [10]. Many of these patients had severe COVID-19 infection, serious comorbidities or were elderly. Severe infection and con-

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
40 s	F	7	Hypertension	No	Yes	516	7	4000/1500	Day 7	Day 7	No
60 s	F	8	Hypertension; coronary heart disease; atrial fibrillation, obesity	Ranolazine	Yes	498	1	0/0	No	No	No
80 s	F	7	Hypertension; coronary heart disease; atrial fibrillation	Omeprazole; Metoclopramide	No	482	2	600/750	No	No	No
60 s	F	6	Diabetes mellitus; hypertension; coronary heart disease; atrial fibrillation; obesity	Metoclopramide	No	487	3	1400/750	No	Day 4	No
80 s	F	6	Diabetes mellitus; hypertension	Furosemide	No	492	3	1200/750	Day 5	Day 5	No
70 s	F	7	Ovarian cancer; hypertension; coronary heart disease; atrial fibrillation	No	No	486	1	0/0	No	No	No
60 s	M	5	Hypertension; coronary heart disease; obesity	Piperacillin-Tazobactam	Yes	513	13	6000/1500	Day 13	No	No
70 s	F	15	Chronic myeloid leukemia; diabetes mellitus; hypertension; coronary heart disease	Sertraline; Dasatinib, Metoclopramide; Omeprazole	No	492	1	0/0	Day 8	Day 8	No
50 s	M	15	Renal cell carcinoma; 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
50 s	M	5	Diabetes mellitus; hypertension; coronary heart disease; obesity	Amiodarone; Furosemide; Omeprazol; Propofol; Metoclopramide	Yes	493	5	3000/1500	No	No	No
70 s*	M	6	Prostate cancer; hypertension	Amiodarone; Haloperidol; Piperacillin-Tazobactam; Furosemide	No	509	14	6000/1500	Day 14	No	No
40 s	M	0	None	None	Yes	480	2	1200/750	No	No	No
50 s	M	4	Hypertension	Furosemide; Propofol	No	489	4	2400/1000	Day 13	No	No
50 s	M	8	Diabetes mellitus; coronary heart disease; hypertension; obesity	Furosemide; Propofol	Yes	496	4	2400/1000	Day 6	No	No

* Subject died on day 16 due to multiple organ failure.
[1] F: Female, M: Male.

comitant 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 [11]. 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 [12]. 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 [13].

The Wuhan group presented 416 patients with COVID-19. A cardiac injury defined as blood levels of cardiac biomarkers (hs-TNI) above the 99th percentile upper reference limit occurred in 82 subjects (19.7%) and were associated with worse outcome

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

Parameters	Univariate model Odds ratio		P-value	Multivariate model 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		

ni: not included. n-cs: non-clinically significant. CI: confidence interval.
[1] Parameter was not included into multivariate analysis due to strong relation with subject's comorbidities.

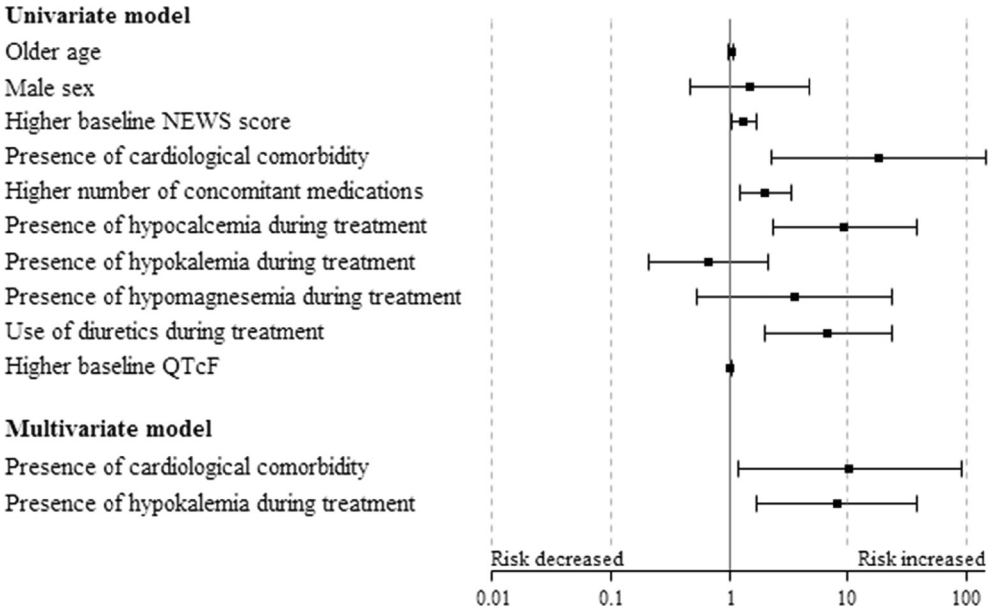

Fig. 2. Forest plot of univariate and multivariate analysis for risk factors associated with QTcF interval prolongation ≥ 480 ms.

[14]. However, a much higher extent of cardiac injury was observed in a prospective cohort of 100 COVID-19 patients for whom cardiac magnetic resonance was performed [15]. Puntmann et al. detected cardiac involvement in 78 individuals (78%) and an ongoing myocardial inflammation in 60 of them (60%), defined as abnormal native T1 and T2 measures. Interestingly, these findings had no relation to preexisting diseases, severity and course of the acute illness or the time from diagnosis. Although remote clinical outcomes of these lesions remain unclear, the high prevalence of perimyocarditis raises many practical questions. For instance, there is a need of consensus on safe timing to return to competitive sports after COVID-19 infection. In the series of 26 athletes, 4 (15%) presented with signs of myocarditis in cardiac magnetic resonance imaging [16]. 8 other patients (30.8%) showed late gadolinium enhancement without T2 elevation which is compatible with prior myocardial injury. These magnetic resonance findings demonstrate that cardiac injury in COVID-19 patients is frequent. It is feasible, that electrical conduction system of the heart can be additionally adversely affected by viral myocarditis.

QT prolongation is a well-known side effect of HCQ and AZI. A larger retrospective cohort study of 251 subjects showed prolongation of QTc ≥ 500 ms in 15.9% of subjects with 1 case of TdP [17]. The peak value of ΔQTc in this study was reached at the end of the 5-day HCQ and AZI treatment scheme. Similarly, in our cohort the peak mean ΔQTcF was observed at the end of the treatment (day 8) (Fig. 1b). Application of ECG telemonitoring during the last days and immediately after the treatment may thus be indicated. Importantly, using our risk management plan QTc ≥ 500 ms was observed less frequently (8.6%), despite longer duration of HCQ-AZI treatment compared to both studies mentioned above.

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 to degrade angiotensin-converting enzyme 2 and increase the action of angiotensin I/II and renin–angiotensin–aldosterone system resulting in a challenging renal K^+ loss [18]. 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 importance of electrolyte testing and correction aiming to prevent cardiac arrhythmias was further highlighted in a large observational study by Arshad et al. [19]

Authors emphasized that stringently applied electrolyte protocols were effective in controlling adverse events.

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. Our risk management plan aimed to prevent emerging cardiac arrhythmias. Structural myocardial damage related to COVID-19, such as myocarditis, may have a significant impact on prognosis. It was not evaluated in the mitigation protocol and its extent in our population remains unknown. However, a simple to follow protocol with no routine co-administration of other QT prolonging drugs, good daily ECG recording 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 $\geq$ 500 ms and no ventricular tachycardia events in COVID-19 patients treated with HCQ and AZI in the setting of cardiac arrhythmia risk management plan.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The data was acquired from the electronic medical records accessed through Vilnius University Hospital Santaros Klinikos Biobank.

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