Smartphone electrocardiogram for QT interval monitoring in Coronavirus Disease 2019 (COVID-19) patients treated with Hydroxychloroquine

Andy Tze Yang Ko, MRCP[1], Lean Seng Chen, MRCP[2], Ing Xiang Pang, MRCP[2], Hwei Sung Ling, MRCP[2,3], Tze Cheng Wong, MBBS[1], Tonnii Loong Loong Sia, MRCP[1], Keng Tat Koh, MRCP[2]

[1]Department of Medicine, Sarawak General Hospital, Malaysia, [2]Department of Cardiology, Sarawak Heart Centre, Malaysia, [3]Faculty of Medicine and Health Sciences, University Malaysia Sarawak, Malaysia

ABSTRACT

Introduction: The global pandemic of Corona Virus Disease 2019 (COVID-19) has led to the re-purposing of medications, such as hydroxychloroquine and lopinavir-ritonavir in the treatment of the earlier phase of COVID-19 before the recognized benefit of steroids and antiviral. We aim to explore the corrected QT (QTc) interval and 'torsadogenic' potential of hydroxychloroquine and lopinavir-ritonavir utilising a combination of smartphone electrocardiogram and 12-lead electrocardiogram monitoring.

Materials and Methods: Between 16-April-2020 to 30-April-2020, patients with suspected or confirmed for COVID-19 indicated for in-patient treatment with hydroxychloroquine with or without lopinavir-ritonavir to the Sarawak General Hospital were monitored with KardiaMobile smartphone electrocardiogram (AliveCor®, Mountain View, CA) or standard 12-lead electrocardiogram. The baseline and serial QTc intervals were monitored till the last dose of medications or until the normalization of the QTc interval.

Results: Thirty patients were treated with hydroxychloroquine, and 20 (66.7%) patients received a combination of hydroxychloroquine and lopinavir-ritonavir therapy. The maximum QTc interval was significantly prolonged compared to baseline (434.6±28.2msec vs. 458.6±47.1msec, p=0.001). The maximum QTc interval (456.1±45.7msec vs. 464.6±45.2msec, p=0.635) and the delta QTc (32.6±38.5msec vs. 26.3±35.8msec, p=0.658) were not significantly different between patients on hydroxychloroquine or a combination of hydroxychloroquine and lopinavir-ritonavir. Five (16.7%) patients had QTc of 500msec or more. Four (13.3%) patients required discontinuation of hydroxychloroquine and 3 (10.0%) patients required discontinuation of lopinavir-ritonavir due to QTc prolongation. However, no torsade de pointes was observed.

Conclusions: QTc monitoring using smartphone electrocardiogram was feasible in COVID-19 patients treated with hydroxychloroquine with or without lopinavir-ritonavir. The usage of hydroxychloroquine and lopinavir-ritonavir resulted in QTc prolongation, but no torsade de pointes or arrhythmogenic death was observed.

KEYWORDS:
Coronavirus disease 2019, hydroxychloroquine, lopinavir-ritonavir, long QT, torsade de pointes, smartphone electrocardiogram

INTRODUCTION

The global pandemic of coronavirus disease 2019 (COVID-19) has led to the "off label" re-purposing of medications, such as chloroquine, hydroxychloroquine, azithromycin, and lopinavir-ritonavir for COVID-19.[1,2] The latest National Institute of Health (NIH) guidelines had recommended against the use of the abovementioned medications following studies that showed equivocal or non-beneficial results. However, they were commonly used during the initial phase of the outbreak.[3] These medications are potentially associated with drug-induced torsade de pointes (DI-TdP) and sudden cardiac death through prolongation of QT interval which necessitates close electrocardiography monitoring.[4]

The mechanism of QT prolongation is due to the inhibition of human-Ether-a-go-go Related Gene (hERG), which is a subunit of the I_{Kr} channel, or aggravating the late sodium channel (I_{NA-L}) during the early depolarisation phase, leading to prolong QT interval. Risk factors contributing to the increased risk of DI-Tdp have been validated by Tisdal et al.[5] Study on QT interval prolongation associated with the use of hydroxychloroquine with or without azithromycin has been reported by Mercuro and co-workers[6] and Bessière and co-workers.[7] However, the QT-prolonging potential of hydroxychloroquine and lopinavir-ritonavir in COVID-19 patients, whether as a single agent or in combination, has never been described before.

The SARS-CoV-2 virus has a high risk of transmission via respiratory secretions and to a lesser extent, contact. There had been reports of healthcare personal being infected with the virus in the line of service.[8] Thus, there was major concern regarding the safety and exposure of healthcare personal conducting regular 12-lead electrocardiogram monitoring for QT interval during the widespread use of QT-prolonging medications. KardiaMobile smartphone electrocardiogram (AliveCor®, Mountain View, CA) was suggested as an alternative to a 12-lead electrocardiogram in monitoring the QT intervals.[4] Although it seems to be a feasible recommendation, the utility of this method has never been

This article was accepted: 29 Janaury 2021
Corresponding Author: Dr. Andy Ko Tze Yang
Email: andyko1989@gmail.com

described in any study on COVID-19 patients. We aimed to describe the use of a smartphone electrocardiogram in the monitoring of COVID-19 patients as well as the effect of the above mentioned medications on the QT interval.

MATERIALS AND METHODS

This was a single-centre, cross-section observational study evaluating patients with COVID-19 who were hospitalised at Sarawak General Hospital (SGH) in Sarawak, Malaysia. We included patients admitted between 16 of April to 30 of April 2020, who received hydroxychloroquine with or without lopinavir-ritonavir for COVID-19. Patients suspected to have COVID-19 and empirically started on hydroxychloroquine with or without lopinavir-ritonavir while waiting for nasopharyngeal polymerase chain reaction (PCR) test for COVID-19 were also included in the study. If the nasopharyngeal PCR tests for COVID-19 were repeatedly negative for two samples taken 24 hours apart, the treatment for COVID-19 was stopped. The standard regimen for hydroxychloroquine was 400mg twice daily on day-1, then 200mg twice daily for five days. The standard regimen for lopinavir-ritonavir was 400mg/100mg twice daily for 5 to 10 days.

Data on baseline demographic, routine blood investigations and clinical conditions were prospectively collected and updated daily. The first electrocardiogram (baseline) was taken before the initiation of hydroxychloroquine with or without lopinavir-ritonavir. The second electrocardiogram was taken 12 hours after the 1st dose of the medication(s). The electrocardiogram was recorded daily after that, until the last dose of the medication(s) for COVID-19 or until normalisation of the QTc interval (<470msec for male and <480msec for female).

The attending physician and nurses were given the options to monitor the QT intervals using a standard 12-lead electrocardiogram or the application of the KardiaMobile smartphone electrocardiogram. The utility of the KardiaMobile smartphone electrocardiogram in the isolation ward was described in Figure 1. Electrocardiogram was reviewed and manually evaluated by two cardiologists (L.H.S. and P.I.X.) to calculate the QTc intervals using the Bazett formula by electronic EP callipers. Both cardiologists performed an independent review of the electrocardiogram and were blinded to the baseline data of the patients. If there was a significant interobserver discrepancy in measurement, the final measurement was taken from the electrophysiologist (K.K.T.). QTc intervals of equal to or more than 500msec were immediately notified to the attending physician. The Tisdale score was applied retrospectively to evaluate QTc prolongation risk. Endpoints of interest were changes in QTc (delta QTc), maximum QTc interval, development of QTc interval of 500msec or more, interruption of hydroxychloroquine and/or lopinavir-ritonavir due to prolonged QTc, and event of torsade de pointes.

Patient information was de-identified and the study was carried out in accordance with the Helsinki Declaration 2013.

Statistical Analysis

Statistical analysis was performed using IBM® SPSS® Statistic version 16 (IBM Corp., Armonk, NJ, USA). Descriptive statistics were reported as the number with percentage or mean with standard deviation, whichever appropriate. Categorical variables were analysed using the chi-square test or Fisher's exact test. Continuous variables were analysed using the student t-test. Receiver Operator Characteristic (ROC) curve was used to analyse the predictive value of Tisdale score to QTc interval of ≥500msec. The QTc prolongation risk (≥500msec) was evaluated in the univariate and multivariate logistic regression model.

RESULTS

Thirty patients were treated with hydroxychloroquine, and 20 (66.7%) patients received a combination of hydroxychloroquine and lopinavir-ritonavir therapy. The mean (SD) age of the patient was 46.0 (22.2) years, 20 (66.7%) were female, mean (SD) lowest potassium level was 3.98 (0.44) mmol/L, one (3.4%) patient with atrial fibrillation and heart failure (Table I). The majority (46.7%) of the patients had symptomatic pneumonia on presentation. Patients on hydroxychloroquine and lopinavir-ritonavir had a significantly higher incidence of pneumonia on presentation (2 (20.0%) vs. 18 (80%), p<0.001). Median (IQR) Tisdale score upon treatment initiation was 4.0 (2.0).

The mean (Standard Deviation, SD) baseline QTc interval was 434.6 (28.2)msec. The maximum QTc interval was significantly prolonged compared to baseline (434.6±28.2msec vs 458.6±47.1msec, p=0.001) (Figure 2A). QTc interval of ≥500ms could happen from 12 hours to Day-5 after initiation of hydroxychloroquine with or without lopinavir-ritonavir (Figure 2B). The maximum QTc interval (456.1±45.7msec vs 464.6±45.2msec, p=0.635) and the delta QTc (32.6±38.5msec vs. 26.3±35.8msec, p=0.658) were not significantly different between patients on hydroxychloroquine or a combination of hydroxychloroquine and lopinavir-ritonavir. Five (16.7%) patients had QTc of 500msec or more, which was not significantly different between patients on hydroxychloroquine or a combination of hydroxychloroquine and lopinavir-ritonavir (10% vs. 20%, p=0.640). Four (13.3%) patients required discontinuation of hydroxychloroquine and three (10.0%) patients required discontinuation of lopinavir-ritonavir due to QTc prolongation. However, no event of torsade de pointes or arrhythmia-related cardiac death was observed.

The mean (SD) PR interval was 178.6 (37.6) msec. The mean (SD) maximum PR interval was significantly prolonged compared to baseline (186.6 (35.0) vs. 178.6 (37.6), p<0.001). The maximum PR interval and delta PR interval were not significantly different between patients on hydroxychloroquine or a combination of hydroxychloroquine and lopinavir-ritonavir therapy. No patients developed significant bradycardia requiring temporary pacing, initiation of chronotropic agents, or interruption of medications due to prolonged PR interval.

Table I: Baseline characteristics of the patients

	Total (n=30)	HCQ (n=10)	HCQ+Kaletra (n=20)	p-value
Age (years), mean (SD)	46.0 (22.3)	43.6 (21.1)	47.2 (23.4)	0.685
Female, n (%)	20 (66.7)	7 (70.0)	13 (65.0)	0.784
Ethics, n (%)				
Malay	19 (63.3)	6 (60.0)	13 (65.0)	
Chinese	7 (23.3)	3 (30.0)	4 (20.0)	
Iban	3 (10.0)	1 (10.0)	2 (10.0)	
Indian	1 (3.3)	0 (0)	1 (5.0)	0.847
Atrial fibrillation, n (%)	1 (3.3)	1 (10.0)	0 (0)	0.333
Heart failure, n (%)	1 (3.4)	1 (10.0)	0 (0)	0.333
Serum creatinine (umol/L), median (IQR)	69.5 (20.0)	71.5 (49.0)	69.5 (12.0)	0.746
Serum potassium level (mmol/L), mean (SD)	3.98 (0.44)	3.92 (0.48)	4.01 (0.43)	0.593
Serum magnesium level (mmol/L), mean (SD)	0.91 (0.09)	0.91 (0.10)	0.91 (0.09)	0.984
Serum calcium level (mmol/L), mean (SD)	2.30 (0.08)	2.26 (0.06)	2.32 (0.10)	0.143
Clinical Stage, n (%)				
Asymptomatic	2 (6.7)	0 (0)	2 (10.0)	
Symptomatic no pneumonia	8 (26.7)	8 (80.0)	0 (0)	
Symptomatic pneumonia	14 (46.7)	0 (0)	14 (70.0)	
Symptomatic pneumonia requiring oxygen	6 (20.0)	2 (20.0)	4 (20.0	<0.001
Tisdale score at treatment initiation, median (IQR)	4.0 (2.0)	4.0 (4.0)	4.5 (2.0)	0.559
Baseline QTc (msec), mean (SD)	434.6 (28.2)	423.5 (34.6)	438.3 (24.7)	0.187
Maximum QTc (msec), mean (SD)	458.6 (47.1)	456.1 (45.8)	464.6 (45.2)	0.635
Delta QTc (msec), mean (SD)	20.4 (33.2)	32.6 (38.5)	26.3 (35.8)	0.658
Maximum QTc≥500msec, n (%)	5 (16.7)	1 (10.0)	4 (20.0)	0.640
Baseline PR (msec), mean, SD	180.6(38.6)	184.3 (44.3)	178.8 (36.5)	0.720
Maximum PR (msec), mean, SD	189.0 (41.3)	194.6 (48.4)	186.2 (38.3)	0.608
Delta PR (msec), mean, SD	6.2 (32.8)	10.3 (32.1)	7.4 (36.1)	0.831

Abbreviations: HCQ=hydroxychloroquine; Kaletra=Lopinavir/Ritonavir; QTc=corrected QT interval.

Table II: Univariate and Multivariate Logistic Regression Model for Predicting QTc > 500ms

	Odds Ratio	95%CI	P-value	Adjusted Odds Ratio	95% CI	p-value
Tisdale Score	1.74	1.06-2.86	0.028	NT		
Tisdale Score ≥8	11.00	1.27-95.17	0.029	20.11	1.10-367.61	0.043
Female	2.25	0.22-23.32	0.497	3.242	0.17-63.15	0.438
Age=>68	2.667	0.35-20.51	0.346	2.25	0.15-33.19	0.555
With Kaletra	2.25	0.22-23.32	0.497	11.97	0.18-812.95	0.249
Baseline QTc≥450	2.111	0.28-15.77	0.466	NT		
Creatinine Level	1.006	1.00-1.01	0.203	NT		
Lowest Serum Potassium Level <3.5mmol/L	2.875	0.21-39.68	0.43	1.84	0.36-95.95	0.761

Abbreviations: NT: not tested; QTc: corrected QT interval; Kaletra: Lopinavir/Ritonavir

The likelihood of prolonged QTc (≥500msec) was greater with a Tisdale score of ≥8 (odds ratio, OR 11.0; 95% Confidence Interval, 95%CI 1.27, 95.17, p=0.029) (Table II). Tisdale score of ≥8 appeared to be the only independent variable to predict QTc interval ≥500ms (adjusted OR 20.11; 95%CI 1.10, 367.61, p=0.043). The Receiver Operating Characteristic curve for Tisdale score to predict QTc≥500ms has an area under the curve of 0.81 (95%CI, 0.59, 1.00, p=0.032) (Figure 3). Tisdale score of ≥8 has the NPV of 91.7%; PPV of 50%, specificity of 88%; and sensitivity of 60% in predicting QTc≥500ms.

DISCUSSION

QTc interval in COVID-19 patients treated with hydroxychloroquine and lopinavir-ritonavir

Our study showed that hydroxychloroquine and lopinavir-ritonavir resulted in significant QTc prolongation in COVID-19 patients. This contradicted an earlier observational study which showed no QT prolongation issues with chronic hydroxychloroquine usage in systemic lupus erythematosus (SLE) patients.[9] However, there was a case report on life-threatening severe QTc prolongation associated with hydroxychloroquine in SLE patients.[10] Concordant with the studies done by Mercuro, et al[6] and Bessière, et al.,[7] which showed that 20% and 18% of COVID-19 patients treated with hydroxychloroquine with or without azithromycin had QTc prolongation of ≥500msec respectively, 16.7% of our patients had the maximum QTc interval≥500ms after treated with hydroxychloroquine and lopinavir-ritonavir. On the other hand, Saleh M, et al.,[11] reported a lower number of patients (8.96%) with QTc≥500msec after treated with hydroxychloroquine or chloroquine with or without azithromycin.

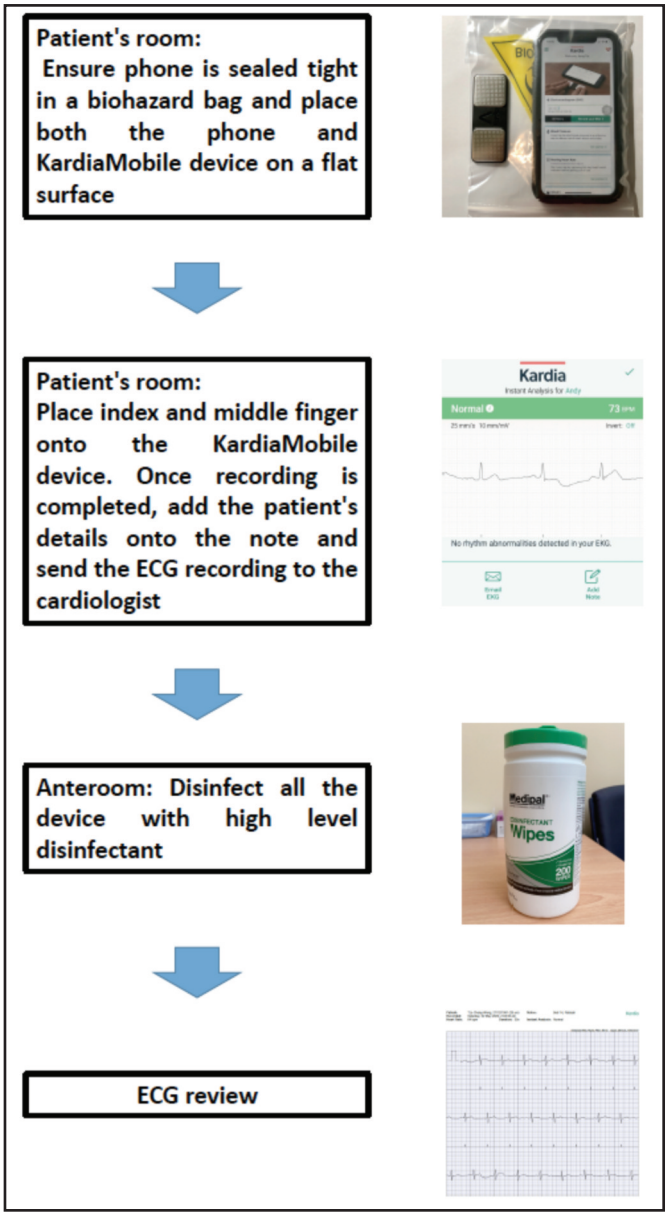

Fig. 1: Steps to use KardiaMobile device.

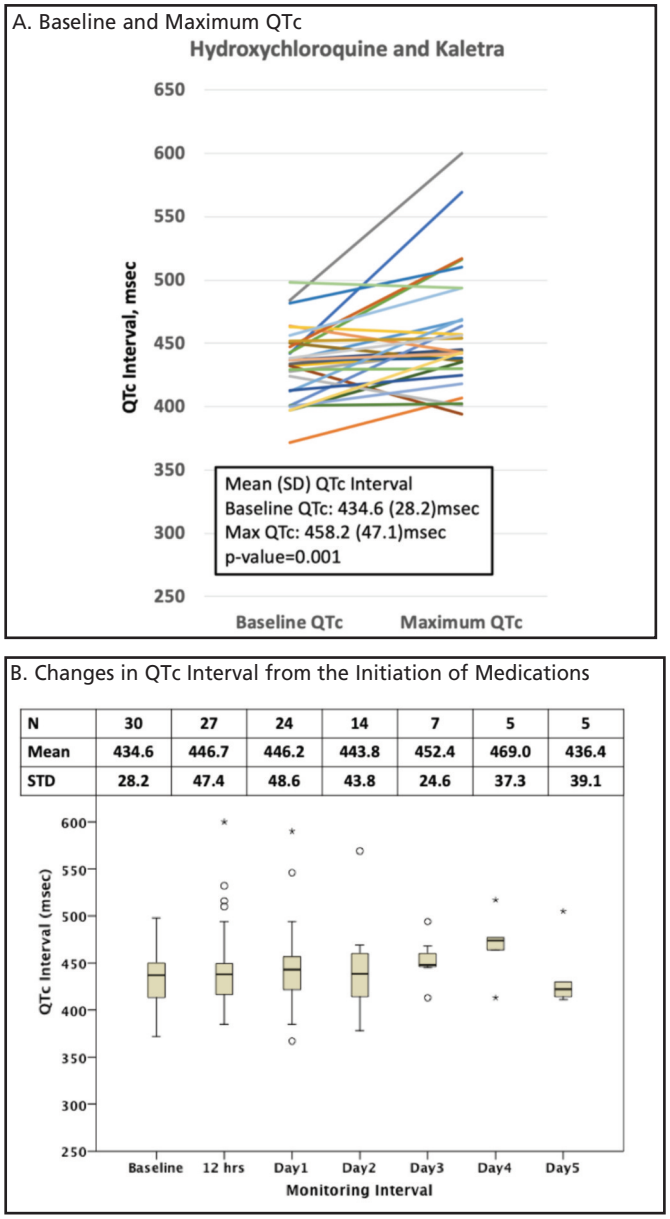

Fig. 2: (A) illustrates the changes in baseline QTc and maximum QT after hydroxychloroquine with or without lopinavir-ritonavir. The maximum QTc interval was significantly prolonged compared to baseline (434.6±28.2msec vs 458.6±47.1msec, p=0.001). (B) illustrates the serial monitoring of QTc interval after initiation of hydroxychloroquine with or without lopinavir-ritonavir. A prolonged QTc interval of ≥500ms could happen from 12 hours to Day 5 after initiation of hydroxychloroquine with or without lopinavir-ritonavir.

Our data showed that the combination of lopinavir-ritonavir did not significantly lead to a further increase in the QTc interval. This was contrary to azithromycin, which potentiated the prolongation property of hydroxychloroquine or chloroquine when used in combination.[6,7] Nevertheless, we observed a significant trend towards prolongation of PR interval in COVID-19 patients treated with hydroxychloroquine with or without lopinavir-ritonavir. The clinical implication of the PR prolongation was unknown because none of the patients developed haemodynamically significant bradycardia requiring temporary pacing or chronotropic support.

The increase in QTc could be seen as early as 12 hours after the first dose of medication, and as late as Day-5 after the initiation of medication. From our observation, the QTc interval usually normalized within 72 hours after stopping the medications. This finding was consistent with the description from the previous study.[11] The relationship between QTc interval and timing of medication is crucial in designing the recommendation for frequency and duration of QTc interval monitoring for future guidelines.

The Tisdale risk score[5] was the only independent variable associated with a QTc interval of ≥500msec. Tisdale risk score was validated to predict QT interval prolongation for

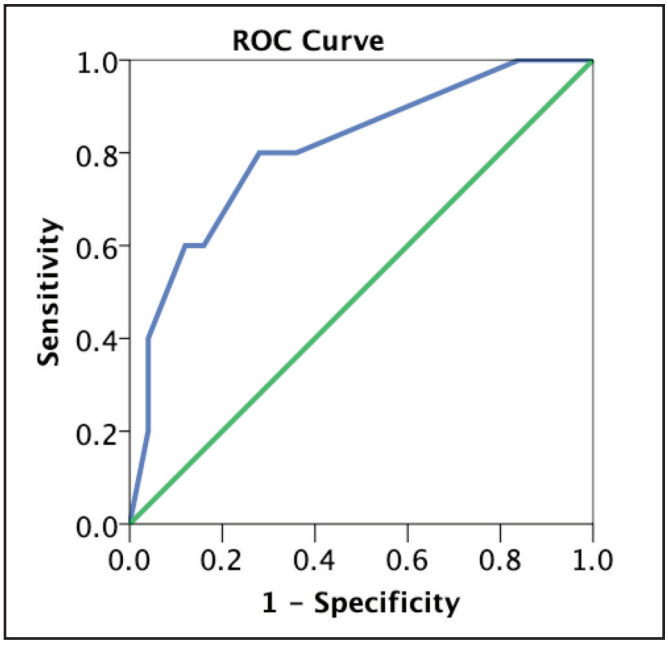

Fig. 3: Receiver Operating Characteristic Curve for Tisdale Score to QTc interval of ≥500msec. The area under the curve was 0.808 (95% confidence interval 0.59-1.00, p=0.032). Tisdale score of ≥8 has NPV of 91.7%; PPV of 50%, specificity of 88%; and sensitivity of 60% in predicting QTc≥500ms.

hospitalized patients. However, the utility of the Tisdale risk score was questionable in COVID-19 because there was only 2-3% of the study population was prescribed with 2 or more QT-prolonging medications. This situation is different in the COVID-19 pandemic in which COVID-19 patients were often put on two or more QT-prolonging medications.[4] The re-purposed medications for COVID-19 had put an unprecedented 'challenge test' for the QT interval. Nevertheless, our study showed that Tisdale risk score of ≥8 had a negative predictive value of 91.7%; positive predictive value of 50%, specificity of 88%; and sensitivity of 60% in predicting QTc≥500msec. In another words, the Tisdale risk score of <8 was a good predictor to predict QTc<500msec.

Monitoring of QTc interval

Our study demonstrated the utility of a smartphone electrocardiogram for monitoring QTc interval. Potential benefits include a lower risk of healthcare personal exposure, reduce the usage of resources (personal protective equipment and disinfectants), reduce manpower, and reduced electrocardiogram acquisition time. The limitations include loss of other valuable information on high-risk features of prolonging QT and its inapplicability in intensive care setting due to signal artifacts. In the context of managing patients with COVID-19, the fundamental component is that an intermittent single-lead electrocardiogram monitoring is better than no electrocardiogram monitoring.

Based on our study, QTc monitoring should include a baseline electrocardiogram done 12 hours after starting hydroxychloroquine and daily monitoring thereafter. The Tisdale score should also be calculated. We did not find added value on the calculation and monitoring of delta QTc. In the event of QTc≥500ms, drugs should be stopped. The monitoring should continue until the QTc normalized, which is usually seen within 72hrs. We did not identify any variable or score that can reliably exclude QTc monitoring. However, this approach requires further validation by future studies.

Risk of torsade de pointes and drug induced-sudden cardiac death

QTc prolongation is a surrogate for torsade de pointes and drug induced-sudden cardiac death. Interruption of hydroxychloroquine and lopinavir-ritonavir due to QTc prolongation of more than ≥500ms was seen in 10% of our patients. This was in concordance to the study done by Mercure et al (11%) and Bessière et al. (17%).[6,7] Saleh M et al., reported a lower incidence of discontinuation of medications (3.5%) due to QTc prolongation.[11]

No torsade de pointes was reported in our cohort of patients, similar to the majority of the previous studies.[7,11] This outcome may be due to our small sample size but may also be because QTc prolonging medications were stopped whenever the QTc was ≥500ms. However, Mercure et al reported a case of torsade de pointes three days after the combination of hydroxychloroquine and azithromycin was discontinued because of a QTc interval of 499 msec.[6] Nevertheless, our cohort of patients excluded severely ill patients requiring ICU care, which are more susceptible to malignant arrhythmias due to cytokine storms, myocarditis, or other factors.

LIMITATIONS

Our study population excluded COVID-19 patients requiring intensive care. Higher-risk groups may not have been represented. Hence the result may not be extrapolated to intensive care patients. Second, even though there was no outpatient treatment for COVID-19 in our study population due to local regulation, in which all patients diagnosed with COVID-19 by PCR are admitted, our study demonstrated the utility of smartphone electrocardiogram monitoring of QTc interval. This offers an alternative for monitoring the QT interval in countries practicing outpatient treatment for COVID-19. Lastly, our study had a small sample size. The result of our study may be hypothesis-generating, but these findings await validation from larger prospective studies.

CONCLUSION

QTc monitoring using Kardia smartphone electrocardiogram was feasible in COVID-19 patients treated with hydroxychloroquine with or without lopinavir-ritonavir. The use of hydroxychloroquine and lopinavir-ritonavir resulted in QTc prolongation, but no torsade de pointes or arrhythmogenic death was observed.

ACKNOWLEDGMENTS

We would like to thank all the front liners in Sarawak General Hospital and the Ministry of Health for their tremendous effort in taking care of COVID-19 patients.
We would like to thank all the medical officers who had contributed to the study.

We would like to thank the Director-General of Health Malaysia for permission to publish this manuscript.

SOURCE OF FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DISCLOSURE

None

CONFLICTS OF INTEREST

None

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