Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Experience of short-term hydroxychloroquine and azithromycin in COVID-19 patients and effect on QTc trend

Dear Editor,

We have read the paper on concerns in prescribing COVID-19 treatment in this journal with great interest.[1] With the scale of transmission and mortality risk, there is an urgent need to identify an effective antiviral. Combinational hydroxychloroquine and azithromycin emerge as potential therapy but yielded mixed results from clinical studies[2-5] and raising concerns over cardiovascular safety.[6,7] We would like to report risk profile, QTc trend and outcomes of 13 COVID-19 confirmed patients admitted to Taiping Hospital, Perak, Malaysia between 21 March 2020 and 13 April 2020, with mild to moderate diseases who were commenced on hydroxychloroquine with without azithromycin.

Diagnosis was confirmed by detection of SARS-CoV-2 from oropharyngeal and/ or nasopharyngeal swabs using reverse transcriptase- polymerase chain reaction (RT-PCR) tests. We assessed their clinical severity (Stage 1- 5) and monitored their disease progression monitor, according to the Malaysian Guideline for COVID-19 Management.[8] Hydroxychloroquine was initiated for all patients with 11 being co-prescribed with azithromycin. Dosage of hydroxychloroquine was initiated at 400mg with a second dose 12 hours apart followed by 200mg twice daily for five days,[8] or adjusted based on risk assessment, at the discretion of treating physician. Azithromycin was initiated at 500mg followed by 250mg daily for five days.[5]

We applied the 10-component Tisdale risk score[9] to assess the patients' risk of developing QT prolongation and monitored their daily 12-lead electrocardiogram up to three days post-treatment. QT interval was manually calculated from lead II of each electrocardiogram by trained clinicians and corrected for heart rate using Bazett's formula (QTc). QTc interval prolongation was defined as a QTc interval $\geq$500 ms or an increment of $\geq$60 ms compared to the baseline value at any time during hospitalization.[9] Drugs that prolong QTc interval were checked using CredibleMeds.org website while drug-drug interactions were examined using Liverpool COVID-19 Drug Interactions.

Among our 13 patients, 53.8% were male with a median age of 52 (27.5, 56.5) years. More than one-third (38.5%) had underlying co-morbidities, with hypertension being the commonest (30.8%), followed by diabetes (15.4%), end-stage renal failure on dialysis (15.4%), coronary artery diseases (7.7%), gout (7.7%) and benign prostatic hypertension (7.7%). None were smokers. Eleven cases had contact exposure to infected patients and two cases were detected through surveillance among patients presented severe acute respiratory tract infections.

Upon admission, 38.5% were asymptomatic (Stage 1), while 23.1% presented with mild symptoms of upper respiratory tract infection (Stage 2), 30.8% with evidence of pneumonia without needing oxygen support (Stage 3) and 7.7% with pneumonia requiring oxygen support (Stage 4). Half of those symptomatic patients presented with fever, cough and loss of appetite. Baseline blood investigations revealed lymphopenia in 15.4%, and raised C-reactive protein ($\geq$10mg/L) in 38.5% among whom three were treated concomitantly for bacteria sepsis with intravenous antibiotics.

During baseline assessment, their mean Tisdale risk score was 7.5$\pm$1.45, with 69.2% at intermediate risk of QT prolongation while the remaining patients profiled as low risk.

Their mean baseline QTc interval was 434.7$\pm$41.01 ms, with 30.8% having QTc$\geq$450 ms prior to therapy initiation. Fig. 1 illustrated daily progression of QTc interval monitoring. The average QTc interval peaked at day 4 of therapy with 445.9 $\pm$ 46.25 ms compared to baseline (p=0.390). QT prolongation was detected among 38.5% whom were profiled as low to intermediate Tisdale and normalized after treatment completion or discontinuation. Two end stage renal failure patients with elevated baseline QTc intervals had their hydroxychloroquine regimen initiated at 200mg twice daily without azithromycin. However, their regimens were discontinued after 3 days of therapy due to persistent QT prolongation. Another 91-year old patient with concomitant sepsis had a rise in QTc interval >60 ms on day 2 of treatment and persisted despite discontinuation of adjusted lower dose of hydroxychloroquine and azithromycin. He deteriorated and succumbed to pneumonia. None of the patients were commenced on other QT-prolonging medications. None developed cardiac arrhythmia or therapy-related side effects during hospitalization. Besides the deceased patient, all other patients recovered without disease progression until they were discharged from the hospitals with viral clearance.

Both hydroxychloroquine and azithromycin have long half-life in serum, 123.5 days and 68 hours, respectively (10). They both interact and known to prolong QTc interval which increases risk of *torsades de pointes*, a life-threatening polymorphic ventricular tachycardia, resulting in sudden cardiac arrest. Given their pro-arrhythmic risk in COVID-19 patients, risk-based approach in treatment initiation and monitoring is warranted when managing COVID-19 infection.

We illustrated the value of QTc interval monitoring at baseline and throughout treatment period coupled with clinical risk assessment in initiation of hydroxychloroquine with or without azithromycin in COVID-19 patients. Our patients were relatively younger with less co-morbidities. QTc interval prolongation occurred in COVID-19 patients prescribed with short term (five days) of hydroxychloroquine and azithromycin, despite short term usage and lower dose adjustment, regardless of patient's risk profile.

Drug-associated TdP is potentially a lethal outcome with QTc interval being the surrogate marker from electrocardiogram monitoring. The risk of arrhythmia is a not a linear function of QT du-

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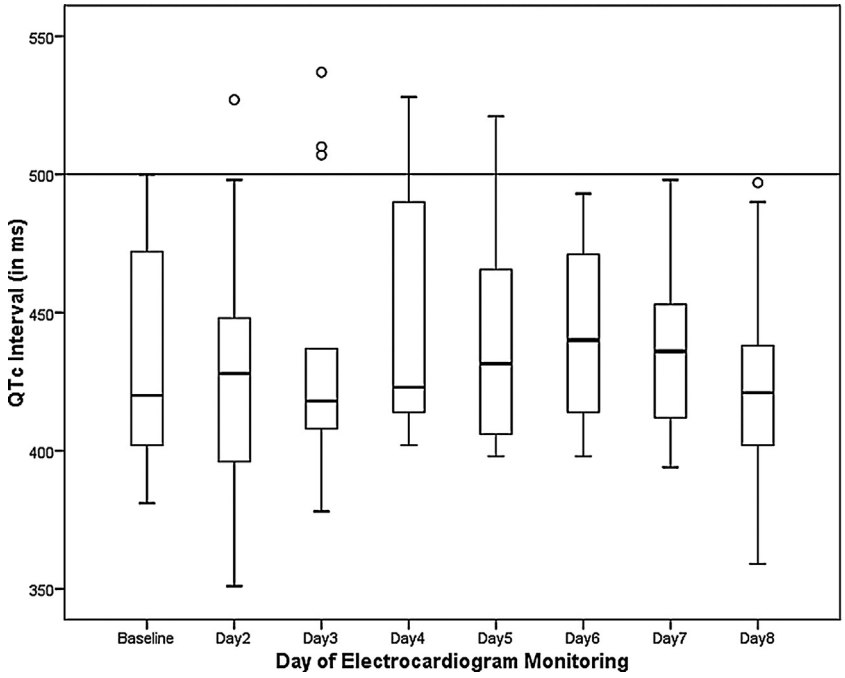

Fig. 1. Daily QTc interval monitoring for COVID-19 patients treated with hydroxychloroquine and azithromycin. denotes outliers.

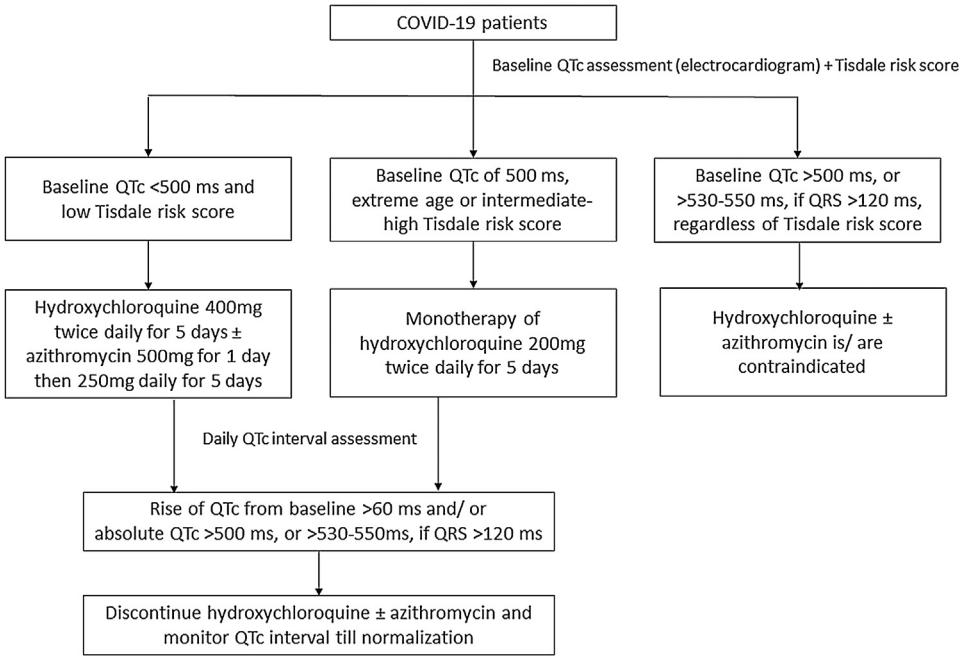

Fig. 2. Clinical decision support algorithm for treatment initiation and monitoring for hydroxychloroquine and azithromycin in COVID-19 patients.

ration nor the extent of change. The magnitude of QT-prolonged medication in potentially increasing risk of arrhythmia-associated death might be smaller than the potential benefits from the treatment of COVID-19 infection in view of faster viral clearance[5] and optimization of limited healthcare resources.

All other non-critical QT-prolonging medications should be avoided or discontinued prior to hydroxychloroquine initiation. If proton pump inhibitor is indicated, dosing should be spaced by four to six hours. Electrocardiogram and other blood investigations such as electrolytes, renal profile and liver enzymes should be monitored.

We propose a clinical decision support algorithm for treatment initiation to address the cardiovascular safety concerns in COVID-19 patients (Fig. 2), based on QTc interval monitoring. Combinational therapy with azithromycin should be based on clinical risk assessment for QT prolongation.

We acknowledge our limitation based on observational study with small study populations. Our experience of risk-based approach in guiding treatment and monitoring might provide insights for future trial or treatment design considerations on similar therapy for COVID-19 patients.

Declaration of Competing Interest

All authors declare no conflict of interest.

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