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## QT Interval Prolongation in COVID-19: Hypercytokinaemia is the Forgotten Culprit and Hydroxychloroquine Simply Add **Fuel to the Fire**

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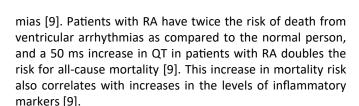
Accumulating data suggest an increased cardiovascular disease morbidity and mortality in Covid-19 patients [1]. In particular, growing evidence suggest that COVID-19 has a higher risk of arrhythmic events, with important implications for survival [1].

The prevalence of arrhythmias varies in COVID-19. In a study of 138 patients from Wuhan, who were hospitalized with COVID-19 related pneumonia, arrhythmias were reported in 17% of the general cohort and in 44% of patients admitted to an intensive care unit [2]. About 30% of patients with COVID-19 have myocardial injury [3] which predisposes to conduction abnormalities including prolonged QT interval. However, in intensive care unit patients, despite the high frequency of arrhythmias (≈50% of cases), only half have acute cardiac injury which suggests that factors other than myocardial damage are also involved in enhancing the arrhythmic risk in COVID-19.

A subgroup of patients with severe COVID-19 has a cytokine storm syndrome. Secondary Haemophagocytic lymphohistiocytosis (sHLH) is an under-recognized, hyper-inflammatory syndrome characterized by a fulminant and fatal hypercytokinaemia with multi-organ failure. In adults, sHLH is most commonly triggered by viral infections [4] and occurs in 3.7-4.3% of sepsis cases [5]. A cytokine profile resembling sHLH is associated with COVID-19 disease severity, characterized by increased interleukin (IL)-2, IL-7, granulocyte colony stimulating factor, interferon-y inducible protein 10, monocyte chemo-attractant protein 1, macrophage inflammatory protein 1- $\alpha$ , and tumor necrosis factor- $\alpha$  [6].

Excess levels of pro-inflammatory cytokines may play a role in causing prolongation of the QT interval [7]. It has been demonstrated that IL-6, tumor necrosis factor (TNF)  $\alpha$ , and IL-1 can prolong ventricular action potential duration by modulating the expression or function of several cardiomyocyte ion channels, specifically K+ and Ca2+ channels (inflammatory cardiac channelopathies) [8].

It has also been observed that patients with rheumatoid arthritis (RA) have a markedly increased incidence of QT prolongation and an increased mortality due to cardiac arrhyth-



In a study, Lazzerini, et al. [10] noted that patients with RA treated with tocilizumab, an IL6 blocker, had shortening of their previously prolonged QT interval, and this shortening was associated with concomitant decreases in inflammatory markers.

Haberman R, et al. [11] showed that the baseline use of biologics (anticytokine and other immunosuppressives) was not associated with worse Covid-19 outcomes in 86 established patients of immune-mediated inflammatory diseases at New York University Langone Health in New York City. In other words, Covid-19 patients on immunosuppressives, despite having higher risk, fared better, suggesting that these therapies minimized the effects of cytokine release in Covid-19 disease.

Data on hydroxychloroquine (HCQ) suggest it has a low risk of causing Torsades de Pointes (TdP), based on its use in rheumatoid arthritis, systemic lupus erythematosus, and anti-malarial therapy [12]. Torsade de pointes is a rare event, with an estimated annual crude rate of 3.2 per million pop-

Various studies [13-15] have suggested increased risk of QTc prolongation with use of HCQ with/without Azithromycin in Covid-19 patients. However, the risks of cardiac ad-

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verse events associated with HCQ are amplified in COVID-19 for several reasons [16]. Patients with SARS-CoV-2 infection have multiple risk factors for drug-induced proarrhythmia-hypokalemia, hypoxia, underlying cardiovascular disease and concomitant use of QT interval prolonging drugs. Although, QTc prolongation was more commonly seen in hospitalized patients esp. in ICU settings receiving HCQ with/without Azithromycin, none of the studies correlated QTc interval prolongation with cytokine levels.

Based on above observations, further studies need to be undertaken to address this issue: To what extent pro-inflammatory cytokines influence QTc interval prolongation in Covid-19? and will anti-cytokine therapies reduce mortality due to cardiac arrhythmias?

Putting blame solely on HCQ/Azithromycin on prolongation of QTc interval is not justified. The other risk factors also contribute to cardiac adverse effects. The knowledge gap needs to be answered in well-designed clinical trials.

## **Authors Declarations**

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