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Recent Findings on Cardiovascular Safety With the Use of Chloroquine and Hydroxychloroquine for COVID-19

In a recent review article, Aggarwal et al[1] discussed the implications for cardiovascular safety of the potential therapies for the treatment of patients with COVID-19. The authors highlight the potential toxicities and cardiovascular side effects of the controversial use of chloroquine (CQ) and hydroxychloroquine (HCQ) that should be taken into consideration before its use. At this time, other implications for cardiovascular safety, along with the prolongation of QT interval reported in small size studies,[2–7] have recently been addressed in regard to the use of CQ and HCQ, alone or in combination with a second-generation macrolide antibiotic (azithromycin or clarithromycin), for the treatment of COVID-19 and the discussion of the potential harm of these drugs is highly relevant and worthy of careful review.

Rosenberg et al[8] conducted a retrospective cohort study of 1,438 patients from 25 different hospitals in New York City, treated with HCQ plus azithromycin (AZ) (n = 735), HCQ alone (n = 271) AZ alone (n = 211), and none of these drugs (n = 221). and found no significant differences in the likelihood of abnormal electrocardiogram findings (defined as arrhythmia or prolonged QT interval) between groups, however, the researchers highlight that cardiac arrest was more likely in the group treated with HCQ plus AZ (adjusted odds ratio [OR] 2.13; 95% confidence interval [CI] 1.12 to 4.05). No significant differences in in-hospital mortality were found. To elucidate if the finding of cardiac arrest was mediated or not by mechanical ventilation, the authors performed a stratified analysis and indicated that in the group of patients who did not receive mechanical ventilation, the risk for cardiac arrest remained increased for HCQ alone compared with AZ alone (adjusted OR 3.01 95% CI 1.07 to 8.51). The analysis performed in this study was adjusted for likely confounders, including co-morbidities, demographics and disease severity. However, due to the observational study design it is possible that some amount of unmeasured confounding remains.

Later on, Mehra et al[9] reported a large international observational registry including data from 96,032 patients from 671 hospitals in 6 continents (mainly North America and Europe) who received CQ (n = 1,868); CQ plus macrolide (n = 3,783); HCQ (n = 3,016); HCQ plus macrolide (n = 6,221) versus none of these drugs (n = 81,144) and found that the use of CQ or HCQ with or without macrolides was independently associated with a higher risk of in-hospital mortality and an increased frequency of de-novo ventricular arrhythmia (nonsustained or sustained ventricular tachycardia or ventricular fibrillation). The authors state that the combination of CQ or HCQ with a macrolide increased the hazard of de-novo ventricular arrhythmias: CQ with a macrolide (hazard ratio [HR] 4.01; 95% CI 3.34 to 4.81); CQ alone (HR 3.56; 95% CI 2.76 to 4.59); HCQ with a macrolide (HR 5.10; 95% CI 4.10 to 5.98), and HCQ alone (HR 2.36; 95% CI 1.93 to 2.90). Predictors of ventricular arrhythmia were also investigated and the variables found to be independently associated with higher risk of de-novo ventricular arrhythmias were CQ or HCQ with or without macrolides and baseline co-morbidities such as coronary artery disease, congestive heart failure, history of cardiac arrhythmia, and chronic obstructive pulmonary disease. The researchers argue that the presence of underlying cardiovascular disease could represent a partial explanation of the cardiovascular toxicity associated with the use of CQ or HCQ particularly with the combination of macrolides. Notably, a propensity score matching analysis was conducted to mitigate potential confounders. Moreover, Cox proportional hazards models and a tipping-point analysis were performed to assess the robustness of the estimates. Clearly, this study represents a potential landmark regarding safety and efficacy of CQ and HCQ, either alone or in combination with macrolides, for the treatment of COVID-19. However, the observational retrospective design limits the study's implications.

In addition to the cardiotoxic considerations mentioned by Aggarwal et al,[1] relevant cardiovascular side effects and toxicities associated with the use of repurposing drugs for the treatment of COVID-19 have been stated by researchers of cardiovascular disease who stress the risk of QT interval prolongation, thrombocytopenia and anemia specifically with the use of CQ and HCQ.[10] In conclusion, it is not clear whether the risk of toxic effects may outweigh the benefits of potential COVID-19 treatments. A decisive answer still awaits the results of high quality large randomized controlled trials.

Disclosures

The authors have no conflicts of interest to disclose.

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Meta-Analysis of Relation of Creatine kinase-MB to Risk of Mortality in Coronavirus Disease 2019 Patients

A published paper by Dr. Li and colleagues[1] revealed that the elevated levels of creatine kinase-MB (CK-MB) were associated with the severity of coronavirus disease 2019 (COVID-19) patients. Recently, several emerging papers have focused on the association of the CK-MB levels with the risk of mortality in COVID-19 infected patients. However, the conclusions drawn from different studies are inconsistent.[2–4] In order to obtain a definitive conclusion on the association between the levels of CK-MB and the risk of mortality in COVID-19 patients, a quantitative meta-analysis was conducted on the basis of published data.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was strictly enforced throughout the design and implementation of this meta-analysis.[5] Chinese National Knowledge Infrastructure, Web of Science and PubMed databases were extensively searched by 2 of the authors (Li Shi and Ying Wang) prior to May 5, 2020 with the following keywords: "characteristics," "clinical," "laboratory," "SARS-CoV-2," "2019-nCoV," "COVID-19," "coronavirus 2019," "outcome," "death," and "mortality." The mean and standard deviation could be estimated by sample size, median and interquartile range according to Wan et al's paper.[6] The screening criterion was that studies provided mean (standard deviation) or median (interquartile range) for levels of CK-MB in both non-survival and survival COVID-19 infected patients. The pooled standardized mean difference and 95% confidence interval were used to assess the effect sizes, since the units of CK-MB are different among the eligible studies.[7] We chose different models based on the incongruity index (I^2; $I^2 < 50\%$ for the fixed-effects model; $I^2 \geq 50\%$ for the random-effects model).[8] In addition, sensitivity analysis was performed by sequentially omitting single study to test the stability of our final results.[9] The potential presence of publication bias was examined by Begg's regression test and Egger's linear regression test.[10,11] All statistical analyses were conducted by using the Stata 11.2 software package (StataCorp, College Station, Texas). $p < 0.05$ was regarded as statistical significance.

Five studies performed in China were finally included in this meta-analysis through detailed screening of 1,630 studies. A total of 1,170 COVID-19 infected patients including 280 non-survivors and 890 survivors were from the First People's Hospital of Jiangxia District,[3] Renmin Hospital,[12] Tongji hospital,[13] Jinyintan Hospital,[4] Zhongnan Hospital and Xishui Hospital.[2] More details of the included studies are demonstrated in Table 1.

Due to the high heterogeneity ($I^2 = 86\%$, $p < 0.001$), we chose a random-effects model to conduct this synthetic analysis. The overall results showed that the elevated levels of CK-MB were significantly associated with an increased risk of the mortality in COVID-19 infected patients (standardized mean difference 0.99; 95% confidence interval 0.57 to 1.42; $p < 0.001$; Figure 1). As indicated in Figure 1, no single study was found to have obvious effects on the overall results, which suggests the stability of our results. As for the publication bias, both Begg's test ($p = 0.806$) and Egger's test ($p = 0.642$; Figure 1) exhibited that there was no publication bias in our present meta-analysis.

Patients with severe pneumonia have varying degrees of myocardial injury due to hypoxemia and toxicity of the pathogen.[14–16] So do patients with COVID-19.[1,17,18] CK-MB mainly exists in the outer plasma layer of myocardial cells, and is the most specific enzyme in the myocardial enzyme spectrum for clinical diagnosis of myocardial injury.[19,20] A previous meta-analysis by Li et al observed that the elevated CK-MB levels were associated with the severity of COVID-19 patients.[1] Our present meta-analysis suggests that the elevated levels of CK-MB were significantly associated with an increased risk of the mortality in COVID-19 infected patients.

Table 1
Characteristics of the included studies

Author	Location	Case	Nonsurvival patients				Survival patients			
			n	Age (years)	Male	creatine kinase-MB	n	Age (years)	Male	Creatine kinase-MB
Wang D et al.[2]	China	107	19	73.0 (64.0-81.0)	16 (84%)	18 (13-44) U/L	88	44.5 (35.0-58.8)	41 (47%)	13 (9-16) U/L
Wang K et al.[3]	China	296	19	65.6±12.6	11 (58%)	17.5 (16.7-28.1) U/L	277	46.0±14.4	129 (47%)	13.5 (11.4-17.1) U/L
Wang L et al.[12]	China	339	65	76 (70-83)	39 (60%)	2.95 (1.30-4.30) ng/mL	274	68 (64-74)	127 (46%)	1.15 (0.81-1.91) ng/mL
Wang Y et al.[13]	China	344	133	70 (62-77)	74 (56%)	2.5 (1.2-6.1) ng/mL	211	57 (47-69)	105 (50%)	0.4 (0.3-1.2) ng/mL
Wu C et al.[4]	China	84	44	68.5 (59.3-75.0)	29 (66%)	17.00 (13.00-20.00) U/L	40	50.0 (40.3-56.8)	31 (78%)	16.00 (13.00-20.75) U/L

All values are n (%), median (IQR), or mean ± SD.