Risk factors of COVID-19 mortality: a systematic review of current literature and lessons from recent retracted articles


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Abstract. – OBJECTIVE: Recently, two influential articles that reported the association of (hydroxy)chloroquine or angiotensin converting enzyme (ACE) inhibitors and coronavirus disease 2019 (COVID-19) mortality were retracted due to significant methodological issues. Therefore, we aimed to analyze the same clinical issues through an improved research method and to find out the differences from the retracted papers. We systematically reviewed pre-existing literature, and compared the results with those of the retracted papers to gain a novel insight.

MATERIALS AND METHODS: We extracted common risk factors identified in two retracted papers, and conducted relevant publication search until June 26, 2020 in PubMed. Then, we analyzed the risk factors for COVID-19 mortality and compared them to those of the retracted papers.

RESULTS: Our systematic review demonstrated that most demographic and clinical risk factors for COVID-19 mortality were similar to those of the retracted papers. However, while the retracted paper indicated that both (hydroxy)chloroquine monotherapy and combination therapy with macrolide were associated with higher risk of mortality, our study showed that only combination therapy of hydroxychloroquine and macrolide was associated with higher risk of mortality (odds ratio 2.33; 95% confidence interval 1.63-3.34). In addition, our study demonstrat-
ed that use of ACE inhibitors or angiotensin 
receptor blockers (ARBs) was associated with re 
duced risk of mortality (0.77; 0.65-0.91).

CONCLUSIONS: When analyzing the same 
clinical issues with the two retracted papers 
through a systematic review of randomized con 
trolled trials and relevant cohort studies, we 
found out that (hydroxy)chloroquine monother 
apy was not associated with higher risk of mor 
tality, and that the use of ACE inhibitors or ARBs 
was associated with reduced risk of mortality in 
COVID-19 patients.

Key Words:
COVID-19, Risk factors, Mortality.

Introduction

Since the coronavirus disease 2019 
(COVID-19) outbreak first emerged in Decem 
ber 2019, many studies have confirmed the 
Among them, two studies conducted by the team 
of Mehra et al\textsuperscript{2,3} raised critical issues about the 
treatment of chloroquine or hydroxychloroquine 
and the use of angiotensin-converting enzyme 
(ACE) inhibitors or angiotensin receptor block 
ers (ARBs) in COVID-19 patients. The study of 
chloroquine or hydroxychloroquine treatment 
included 96,032 COVID-19 patients, and the 
results showed that chloroquine or hydroxychlo 
roquine treatment, when used alone or in com 
bination with a macrolide, had no clinical ben 
fits, but rather, a risk of increasing in-hospital 
mortality. The study was published in Lancet\textsuperscript{2}, 
and had a significant impact on clinical prac 
tice, halting other relevant clinical trials. The 
other study on the use of ACE inhibitors and 
ARBs enrolled 8,910 COVID-19 patients and 
demonstrated that there was no increased risk of 
in-hospital mortality associated with their use. 
The study was published in the New England 
Journal of Medicine (NEJM)\textsuperscript{3}. Unfortunately, 
these two articles were retracted due to critical 
ethical issues, not all authors were not granted 
access to the raw data, and the data could not be 
made available to a third-party auditor.

Thus, more reliable studies are needed through 
improved research methods. In this study, we 
tried to analyze the same clinical issues through 
a systematic review of randomized controlled 
trials (RCTs) and relevant cohort studies. Then, 
we aimed to find novel findings by comparing the 
studies of Mehra et al\textsuperscript{2,3}. 

Materials and Methods

Search Strategy

We identified risk factors associated with 
COVID-19 mortality, which were also previously 
evaluated in the studies of Mehra et al\textsuperscript{2,3}. Then, 
we performed literature search until June 26, 
2020 in PubMed by using several key terms. The 
search terms used were divided into three groups: 
the risk factors (i.e., “Age” “Age older than 65 
years” “Body mass index (BMI) greater than 35” 
“Male” “Ethnicity” “Black” “Hispanic” “Asian” 
“Cardiovascular diseases” “Cerebrovascular 
disease” “Cardiac injury” “Myocardial injury” 
“Congestive heart failure” “Diabetes mellitus” “Arterial hypertension” “Hypertension” “Hyperlipidemia” “Chronic obstructive pulmonary dis 
ease (COPD)” “Respiratory disease” “Smoking” 
“Autoimmune disease” “Cancer” “Cancer che 
motherapy” “Cancer immunotherapy” “Cortico 
steroid use” “ACE inhibitor use” “Angiotensin 
receptor blocker use” “ACE inhibitor/ARB” “Ox 
ygen saturation (SpO2) below 60%”, “Sequential 
organ failure assessment (SOFA)” “Chloroquine 
use” “Hydroxychloroquine use” or “Hydroxy 
chloroquine or macrolide” “Hydroxychloro 
quine and macrolide use in combination”) AND 
“mortality” AND COVID-19 related terms (i.e., 
“COVID-19” or “SARS-CoV-2”). The inclusion 
criterion for evaluating the eligibility of identified 
articles in the respect of study design included 
cohort studies, case-control studies, case series, 
and RCTs. The selection of articles based on 
study designs was performed with an emphasis 
on RCTs. Furthermore, the selection process of 
articles for evaluating the effects of risk factors 
on COVID-19 mortality was carried out by pri 
oritizing articles in a recent order and screening 
studies with a large number of participants. Fi 
nally, we selected studies reporting hazard ratio 
(HR), odds ratio (OR), and relative risk (RR) with 
a significant confidence interval (95% CI) and 
$p$-value ($p<0.05$), and then, we used studies with 
low $I^2$ value (Supplementary Table I).

Results

Summary of Systematic review on 
Risk Factors for Mortality in 
COVID-19 Patients

As for demographic and clinical risk factors, 
age greater than 65 years, BMI greater than 35, 
male sex, black race and Asian ethnicity, coronary
Risk factors of COVID-19 mortality

artery disease, congestive heart failure, diabetes mellitus, hypertension, COPD, current smoker, immunosuppressed condition by corticosteroids and high severity of illness (high score of SOFA or SpO2 <94%) were associated with higher risk of mortality in COVID-19 (Table I). As for medications, hydroxychloroquine with macrolide was associated with higher risk of COVID-19 mortality (OR 2.33; 95% CI 1.63-3.34). In contrast, the use of ACE inhibitors or ARBs was associated with reduced risk of mortality (OR 0.77; 95% CI 0.65-0.91) (Table II). No association was found for hyperlipidemia, cancer chemotherapy, and chloroquine or hydroxychloroquine monotherapy.

Comparison with the Studies of Mehra et al2,3 in Lancet and NEJM

The studies of Mehra et al2,3 in Lancet and the NEJM showed similar results in the demographic and clinical risk factors for COVID-19 mortality because they commonly used the data from the same multinational registry. In their study, variables associated with higher in-hospital mortality included advanced age, high BMI, black race or Hispanic ethnicity, coronary artery disease, congestive heart failure, arrhythmia, diabetes, hypertension, hyperlipidemia, COPD, current smoker, and SpO2 <94%. Favorable variables included female sex, Asian ethnicity and qSOFA <1 (Table I). The Lancet study2 comprised of five groups; control, chloroquine alone, hydroxychloroquine alone, chloroquine with macrolide, and hydroxychloroquine with a macrolide. Compared with the control group, chloroquine alone (HR 1.365; 95% CI 1.218-1.531), hydroxychloroquine alone (1.335; 1.223-1.457), chloroquine with macrolide (1.368; 1.273-1.469), and hydroxychloroquine with macrolide (1.447; 1.368-1.531) were independently associated with increased risk of in-hospital mortality (Table II). Mehra et al2 concluded that COVID-19 treatment based on chloroquine or hydroxychloroquine with or without macrolide had no clinical benefits and was associated with increased risk of in-hospital mortality. The study also showed the risk factors of clinically significant ventricular arrhythmias. Variables including coronary artery disease, congestive heart failure, arrhythmia, and COPD were independently associated with increased risk of de-novo ventricular arrhythmias during hospitalization. Compared with the control group, chloroquine alone (HR 3.561; 95% CI 2.760-4.596), hydroxychloroquine alone (2.369; 1.935-2.900), chloroquine with macrolide (4.011; 3.344-4.812), and hydroxychloroquine with macrolide (5.106; 4.106-5.983) were independently associated with an increased risk of de-novo ventricular arrhythmia during hospitalization2. These findings are consistent with previous studies that have shown the association between the given treatment regimens and QT interval prolongation that leads to ventricular arrhythmias4. As for the ACE inhibitors and ARBs, Lancet2 and the NEJM2 studies showed reduced risk of in-hospital mortality in the use of ACE inhibitors (Lancet: HR 0.566; 95% CI 0.514-0.624, NEJM: OR 0.33; 95% CI 0.20-0.54), whereas no association was found between ARBs and mortality. The studies also showed that the use of statin was associated with reduced risk of in-hospital mortality (Lancet: HR 0.793; 95% CI 0.736-0.855, NEJM: OR 0.35; 95% CI 0.24-0.52) (Table II).

In comparison with the studies of Mehra et al2,3, our systematic review showed similar trends for most demographic (Figure 1) and clinical variables (Figure 2). However, unlike the study of Mehra et al2, Asian ethnicity has been identified as an unfavorable risk factor in our study (HR 1.62; 95% CI 1.43-1.82). Furthermore, while the study of Mehra et al2 indicated that monotherapy with chloroquine or hydroxychloroquine was associated with increased risk of in-hospital mortality, our study showed that chloroquine or hydroxychloroquine monotherapy was not associated with higher risk of mortality. Our systematic review demonstrated that only combination therapy of hydroxychloroquine and macrolide was associated with higher risk of mortality. Our systematic review demonstrated that only combination therapy of hydroxychloroquine and macrolide was associated with higher risk of mortality. Our systematic review demonstrated that only combination therapy of hydroxychloroquine and macrolide was associated with higher risk of mortality. Our systematic review demonstrated that only combination therapy of hydroxychloroquine and macrolide was associated with higher risk of mortality. Our systematic review demonstrated that only combination therapy of hydroxychloroquine and macrolide was associated with higher risk of mortality.
Table I. Summary of systematic review on demographic and clinical risk factors of mortality in COVID-19 patients and comparison to the retracted papers from the Lancet¹ and the NEJM².

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Article type</th>
<th>No. of studies</th>
<th>Type of metrics</th>
<th>Summary effect size [95% CI]†</th>
<th>( I^2 ) (p-value)‡</th>
<th>Summary effect size in a retraction from the Lancet¹</th>
<th>Summary effect size in a retraction from the NEJM²²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>Meta-analysis</td>
<td>6</td>
<td>OR</td>
<td>4.59 (2.61-8.04)</td>
<td>67.1% (0.010)</td>
<td>1.010 (1.009-1.011)</td>
<td>1.93 (1.60-2.41)</td>
</tr>
<tr>
<td>BMI (per kg/m²)</td>
<td>Retrospective cohort</td>
<td>1</td>
<td>OR</td>
<td>2.56 (1.18-5.57)</td>
<td>–</td>
<td>1.063 (1.060-1.067)</td>
<td>–</td>
</tr>
<tr>
<td>Female</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.825 (0.793-0.858)</td>
<td>0.97 (0.65–0.95)</td>
</tr>
<tr>
<td>Male</td>
<td>Meta-analysis</td>
<td>5</td>
<td>OR</td>
<td>1.50 (1.06-2.12)</td>
<td>76.3% (0.002)</td>
<td>–</td>
<td>Reference</td>
</tr>
<tr>
<td>White</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.010 (1.009-1.011)</td>
<td>1.93 (1.60-2.41)</td>
</tr>
<tr>
<td>Black</td>
<td>Retrospective cohort</td>
<td>1</td>
<td>HR</td>
<td>1.71 (1.44-2.02)</td>
<td>–</td>
<td>1.344 (1.276-1.415)</td>
<td>–</td>
</tr>
<tr>
<td>Hispanic</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.495 (1.400-1.597)</td>
<td>–</td>
</tr>
<tr>
<td>Asian</td>
<td>Retrospective cohort</td>
<td>1</td>
<td>HR</td>
<td>1.62 (1.43-1.82)</td>
<td>–</td>
<td>0.717 (0.668-0.769)</td>
<td>–</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Meta-analysis</td>
<td>9</td>
<td>OR</td>
<td>3.72 (1.77-7.83)</td>
<td>89.1% (&lt;0.0001)</td>
<td>1.134 (1.082-1.188)</td>
<td>2.70 (2.08-3.51)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Retrospective cohort</td>
<td>1</td>
<td>OR</td>
<td>3.18 (1.46-6.93)</td>
<td>–</td>
<td>1.756 (1.609-1.915)</td>
<td>2.48 (1.62-3.79)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.626 (1.504-1.758)</td>
<td>1.95 (1.33-2.86)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Meta-analysis</td>
<td>9</td>
<td>OR</td>
<td>1.90 (1.37-2.64)</td>
<td>32% (0.16)</td>
<td>1.206 (1.151-1.264)</td>
<td>–</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Meta-analysis</td>
<td>8</td>
<td>OR</td>
<td>2.70 (1.40-5.24)</td>
<td>92.6% (&lt;0.0001)</td>
<td>1.302 (1.252-1.355)</td>
<td>–</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Retrospective cohort</td>
<td>1</td>
<td>OR</td>
<td>1.09 (0.57-2.10)</td>
<td>–</td>
<td>1.125 (1.081-1.171)</td>
<td>–</td>
</tr>
<tr>
<td>COPD</td>
<td>Meta-analysis</td>
<td>7</td>
<td>OR</td>
<td>3.53 (1.79-6.96)</td>
<td>72.2% (0.001)</td>
<td>1.190 (1.093-1.294)</td>
<td>2.96 (2.00-4.40)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>Meta-analysis</td>
<td>5</td>
<td>OR</td>
<td>2.04 (1.32-3.15)</td>
<td>0% (0.62)</td>
<td>1.268 (1.201-1.340)</td>
<td>1.79 (1.29-2.47)</td>
</tr>
<tr>
<td>Immunosuppressed condition</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.081 (0.985-1.187)</td>
<td>–</td>
</tr>
<tr>
<td>Cancer chemotherapy</td>
<td>Meta-analysis</td>
<td>5</td>
<td>OR</td>
<td>0.74 (0.40-1.39)</td>
<td>0% (0.88)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Meta-analysis</td>
<td>2</td>
<td>HR</td>
<td>2.30 (1.00-5.29)</td>
<td>0% (-)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SOFA</td>
<td>Retrospective cohort</td>
<td>1</td>
<td>OR</td>
<td>5.65 (2.61-12.23)</td>
<td>–</td>
<td>0.758 (0.726-0.792)</td>
<td>–</td>
</tr>
<tr>
<td>qSOFA &lt; 1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.664 (1.587-1.746)</td>
<td>–</td>
</tr>
</tbody>
</table>

CI: confidence interval, \( F \): heterogeneity, HR: hazard ratio, OR: Odds ratio, BMI: body mass index, COPD: chronic obstructive pulmonary disease, SOFA: the sequential organ failure assessment, qSOFA: quick the sequential organ failure assessment, SpO₂: pulse oxygen saturation. † Effect size (95% CI) of the largest study in each meta-analysis. ‡ \( I^2 \) metric of inconsistency (95% confidence intervals of \( I^2 \) ) and \( p \)-value of the Cochran Q test for evaluation of heterogeneity. Cells are “–” if the data was not reported in the meta-analyses or studies.
Table II. Summary of systematic review on the association of medications and mortality in COVID-19 patients, and comparison to the retracted papers from the Lancet\textsuperscript{1} and the NEJM\textsuperscript{2}.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Article type</th>
<th>No. of studies</th>
<th>Type of metrics</th>
<th>Summary effect size (95% CI)\textsuperscript{†}</th>
<th>(I^2) (p-value)\textsuperscript{‡}</th>
<th>Summary effect size in a retraction from the Lancet\textsuperscript{1} (HR, 95% CI)</th>
<th>Summary effect size in a retraction from the NEJM\textsuperscript{2} (OR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.566 (0.514-0.624)</td>
<td>0.33 (0.20-0.54)</td>
</tr>
<tr>
<td>ARB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.989 (0.914-1.071)</td>
<td>1.23 (0.87-1.74)</td>
</tr>
<tr>
<td>ACEi or ARB</td>
<td>Meta-analysis</td>
<td>24</td>
<td>OR</td>
<td>0.77 (0.65-0.91)</td>
<td>58.6% (0.013)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.793 (0.736-0.855)</td>
<td>0.35 (0.24-0.52)</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Retrospective cohort</td>
<td>1</td>
<td>OR</td>
<td>2.80 (0.90-8.50)</td>
<td>–</td>
<td>1.365 (1.218-1.531)</td>
<td>–</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Meta-analysis</td>
<td>6</td>
<td>OR</td>
<td>1.25 (0.65-2.38)</td>
<td>80% (0.0001)</td>
<td>1.335 (1.223-1.457)</td>
<td>–</td>
</tr>
<tr>
<td>Chloroquine/macrolide</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.368 (1.273-1.469)</td>
<td>–</td>
</tr>
<tr>
<td>Hydroxychloroquine/macrolide</td>
<td>Retrospective cohort</td>
<td>1</td>
<td>OR</td>
<td>2.33 (1.63-3.34)</td>
<td>0% (0.85)</td>
<td>1.447 (1.368-1.531)</td>
<td>–</td>
</tr>
</tbody>
</table>

CI: confidence interval, \(I^2\): heterogeneity, HR: hazard ratio, OR: Odds ratio, ACEi: angiotensin converting enzyme inhibitors, ARB: angiotensin II receptor blockers. \(†\) Effect size (95% CI) of the largest study in each meta-analysis. \(‡\) \(I^2\) metric of inconsistency (95% confidence intervals of \(I^2\)) and p-value of the Cochran Q test for evaluation of heterogeneity. Cells are “-” if the data was not reported in the meta-analyses.
Australia, the United Kingdom, and Turkey were higher than numbers reported by each country’s government. Critics have urged Surgisphere to disclose aggregated patient data at a hospital level, but the company failed to validate the integrity of its data. As a result, Lancet and the NEJM papers by the Mehra’s research team were retracted, and moreover, many researchers have still criticized that some clinical trials have been discontinued by the study of Mehra et al, although the study was not a RCT, and the results were significantly limited.

On the other hand, our study aimed to verify clinical risk factors related to COVID-19 mortality through a systematic literature review unlike the retracted papers in which analyzing data were collected by a single data company. Our study have selected relevant studies with an

![Figure 1](image-url)

**Figure 1.** Comparison of the effect of demographic characteristics on COVID-19 mortality between systematic review and Mehra et al studies. *In the retracted Lancet and NEJM papers, Mehra et al reported effect size based on female sex. **Publications that were reviewed in this study reported effect size based on male sex.

![Figure 2](image-url)

**Figure 2.** Comparison of the effect of underlying clinical conditions on COVID-19 mortality between systematic review and Mehra et al studies.
Risk factors of COVID-19 mortality

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Chemotherapy</td>
<td>0.74 (0.40-1.39)</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>2.50 (1.30-5.29)</td>
</tr>
<tr>
<td>ACEI</td>
<td>0.566 (0.514-0.634) 0.33 (0.20-0.54)</td>
</tr>
<tr>
<td>ARB</td>
<td>0.989 (0.914-1.073) 1.23 (0.8701-1.74)</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>0.77 (0.65-0.91)</td>
</tr>
<tr>
<td>Statin</td>
<td>0.793 (0.736-0.855) 0.35 (0.24-0.52)</td>
</tr>
<tr>
<td>Chloroquine Alone</td>
<td>1.365 (1.129-1.531) 2.80 (1.90-4.50)</td>
</tr>
<tr>
<td>Hydroxychloroquine Alone</td>
<td>1.335 (1.229-1.427) 1.25 (0.65-2.38)</td>
</tr>
<tr>
<td>Chloroquine and Macrolide</td>
<td>1.368 (1.279-1.469)</td>
</tr>
<tr>
<td>Hydroxychloroquine and Macrolide</td>
<td>1.447 (1.368-1.533) 2.33 (1.63-3.34)</td>
</tr>
</tbody>
</table>

Figure 3. Comparison of the effect of medications on COVID-19 mortality between systematic review and Mehra et al studies.

emphasis on RCTs even among various study designs and the cohort studies with a large number of participants to control the quality of data to be examined. As a result, our study confirmed that advanced age, high BMI, male sex, black race, current smoker, and comorbidities, such as hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, and COPD were still significant risk factors for increased mortality in COVID-19 patients. In addition, our study reported a conflicting result with the study of Mehra et al regarding ethnicity. In our study, Asian ethnicity appeared as a significant risk factor for COVID-19 mortality. A recent study also demonstrated that “South Asian ethnicity” had 1.45 times increased risk of COVID-19 mortality supporting our study result.

More noteworthy is the difference in the results on the relationship of chloroquine or hydroxychloroquine and COVID-19 mortality. Mehra et al showed that chloroquine or hydroxychloroquine monotherapy, as well as combination therapy with macrolide, was associated with higher in-hospital mortality. In addition, they showed that chloroquine or hydroxychloroquine was associated with the occurrence of ventricular arrhythmias during hospitalization, whether treated alone or in combination with macrolide. However, our study demonstrated that only combination therapy of hydroxychloroquine and macrolide was associated with higher risk of COVID-19 mortality.

Many researchers and clinicians have been concerned about the clinical risk of dangerous ventricular arrhythmias leading to mortality after the use of chloroquine or hydroxychloroquine in the treatment of COVID-19. The underlying mechanism has been known to be related to the pharmacologic effects whereby cardiac QT interval is prolonged. In particular, macrolide is also known to contribute to QT prolongation. Therefore, the combination treatment of chloroquine or hydroxychloroquine and macrolide is expected to increase significantly the pharmacologic effects that cause QT prolongation. In this regard, our study indicates that chloroquine or hydroxychloroquine monotherapy would not have a sufficient effect on the occurrence of clinically significant ventricular arrhythmia leading to mortality. A recent meta-analysis also showed that only combined use of hydroxychloroquine and azithromycin was associated with an increase in mortality, while hydroxychloroquine alone was not. Why did the study of Mehra et al show that chloroquine or hydroxychloroquine monotherapy was associated with mortality? Many researchers have pointed out the dosage of chloroquine or hydroxychloroquine used in the study of Mehra et al was higher than...
the recommended dosage. In the study of Mehra et al\textsuperscript{2}, the mean daily dose administered in monotherapy was 765 mg for chloroquine and 596 mg for hydroxychloroquine. Although the United States Food and Drug Administration (FDA) has currently canceled the Emergency Use of Authorization (EUA) for chloroquine and hydroxychloroquine to treat COVID-19, the dosage used in the study exceeded what has been previously recommended by FDA. The suggested maintenance dose in the EUA for chloroquine was 500 mg daily, and hydroxychloroquine was 400 mg daily\textsuperscript{10,11}. Although the optimal dosing of treatment of COVID-19 is not established, given that many other studies have followed the FDA’s recommendations, it is conceivable that higher dosage may have affected the results in the study of Mehra et al\textsuperscript{2}. Taken together, we believe that if not used with macrolide or used with appropriate dosage, chloroquine or hydroxychloroquine monotherapy as a treatment option for COVID-19 might have a low clinical risk for ventricular arrhythmias leading to mortality.

Nevertheless, the use of chloroquine or hydroxychloroquine in the treatment of COVID-19, whether alone or in combination, is still not recommended by recent findings. The recent review indicated that the evidence regarding the clinical benefit of hydroxychloroquine on COVID-19 was found to be weak and insufficient\textsuperscript{12-14}. Furthermore, on July 4, 2020, WHO discontinued hydroxychloroquine arm of the Solidarity trial because the interim result revealed that hydroxychloroquine produced no benefit over the mortality of hospitalized COVID-19 patients when compared to the standard of care\textsuperscript{15}.

The other important issue is the use of ACE inhibitors or ARBs in COVID-19 pandemic. Many researchers and clinicians have been concerned that the use of these drugs would worsen COVID-19 risk. However, our systematic review showed that the use of ACE inhibitors or ARBs was rather associated with lower risk of COVID-19 mortality. Due to the lack of pre-existing researches that examined ACE inhibitors or ARBs as distinct clinical factors, we could not identify the individual effect of ACE inhibitors or ARBs on COVID-19 mortality. ACE inhibitors and ARBs have been speculated to have a dual role in COVID-19 pathogenesis, as both medications may increase the expression of Angiotensin-converting enzyme 2 (ACE2). An increase in the number of ACE2 may enhance the risk of infection because ACE2 is a cellular receptor that Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) binds to when entering the host cell\textsuperscript{14}. On the contrary, ACE2 can exert anti-inflammatory effects, reducing the severity of lung damage caused by COVID-19\textsuperscript{17}. Although further investigation is needed to fully understand each medication’s role in COVID-19 pathogenesis and to identify the dominant effect of increased ACE2 expression, our study suggests the clinical safety and possible benefit of ACE inhibitors or ARBs in COVID-19.

Relating to study design, one limitation that we were not able to rule out was the possibility of selection bias. There are several tools that help to exclude selection bias and design a well-developed study. For example, PRISMA helps to set the inclusion criteria to avoid selection bias\textsuperscript{18}. Since our study did not establish inclusion criteria according to such protocols, there is a possibility of selection bias. Furthermore, quality assessment has not been done in the present study, and this also introduces the risk of selection bias. Another problem is that several studies used in our work were conducted with different research methods. This heterogeneity of the methods results in a broad range of CIs. Moreover, in Lancet, HR is used to assess the mortality risk, whereas, in the NEJM, it is assessed by OR. These reduce the credibility of the results given by our data, which also may have led to erroneous inferences on results.

**Conclusions**

In this study, we have verified risk factors for COVID-19 mortality through systematic review of RCTs and cohort studies in comparison with the studies of Mehra et al\textsuperscript{2,3}. Our data indicate that chloroquine or hydroxychloroquine monotherapy is not associated with increased risk of mortality, and ACE inhibitors or ARBs was associated with reduced risk of mortality in COVID-19 patients.

**Conflict of Interest**

The Authors declare that they have no conflict of interests.

**References**

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