European Review for Medical and Pharmacological Sciences 2020; 24: 13089-13097

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

K.H. LEE[1], J.S. KIM[2], S.H. HONG[3,4], D. SEONG[4], Y.R. CHOI[4], Y.T. AHN[4], K.S. KIM[4], S.E. KIM[4], S. LEE[4], W. SIM[4], D. KIM[4], B. JUN[4], J.W. YANG[2], D.K. YON[5,6], S.W. LEE[7], M.S. KIM[8,9], E. DRAGIOTI[10], H. LI[11], L. JACOB[12,13], A. KOYANAGI[13,14], R. ABOU GHAYDA[3,15], J.I. SHIN[1], L. SMITH[16]

[1]Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea
[2]Department of Nephrology, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea
[3]Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[4]Yonsei University College of Medicine, Seoul, Republic of Korea
[5]Department of Pediatrics, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea
[6]Department of Pediatrics, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea
[7]Department of Data Science, Sejong University College of Software Convergence, Seoul, South Korea
[8]Korea University, College of Medicine, Seoul, Republic of Korea
[9]Cheongsan Public Health Center, Ministry of Health and Welfare, Wando, Republic of Korea
[10]Pain and Rehabilitation Centre, and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping Sweden
[11]University of Florida College of Medicine, Gainesville, FL, USA
[12]Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux, Versailles, France
[13]Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, Barcelona, Spain
[14]ICREA, Pg. Lluis Companys 23, Barcelona, Spain.
[15]Urology Institute, University Hospitals System, Case Western Reserve University School of Medicine, Cleveland, OH, USA
[16]The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK

Keum Hwa Lee and Jae Seok Kim contributed equally

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-

Corresponding Author: Jae Il Shin, MD, Ph.D; e-mail: shinji@yuhs.ac

ed that use of ACE inhibitors or angiotensin receptor blockers (ARBs) was associated with reduced 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 controlled trials and relevant cohort studies, we found out that (hydroxy)chloroquine monotherapy was not associated with higher risk of mortality, 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 December 2019, many studies have confirmed the risk factors related to mortality in COVID-19[1]. Among them, two studies conducted by the team of Mehra et al[2,3] raised critical issues about the treatment of chloroquine or hydroxychloroquine and the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (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 hydroxychloroquine treatment, when used alone or in combination with a macrolide, had no clinical benefits, but rather, a risk of increasing in-hospital mortality. The study was published in Lancet[2], and had a significant impact on clinical practice, 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)[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[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[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 disease (COPD)" "Respiratory disease" "Smoking" "Autoimmune disease" "Cancer" "Cancer chemotherapy" "Cancer immunotherapy" "Corticosteroid use" "ACE inhibitor use" "Angiotensin receptor blocker use" "ACE inhibitor/ARB" "Oxygen saturation (SpO2) below 60%", "Sequential organ failure assessment (SOFA)" "Chloroquine use" "Hydroxychloroquine use" or "Hydroxychloroquine or macrolide" "Hydroxychloroquine 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 prioritizing articles in a recent order and screening studies with a large number of participants. Finally, 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

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 al[2,3] in Lancet and NEJM

The studies of Mehra et al[2,3] 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 SpO_2 <94%. Favorable variables included female sex, Asian ethnicity and qSOFA <1 (Table I). The Lancet study[2] 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 al[2] 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[2]. 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 hospitalization[2]. 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 arrhythmias[4]. As for the ACE inhibitors and ARBs, Lancet[2] and the NEJM[3] 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 al[2,3], our systematic review showed similar trends for most demographic (Figure 1) and clinical variables (Figure 2). However, unlike the study of Mehra et al[2], 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 al[2] 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 (Figure 3). As for the use of ACE inhibitors or ARBs, although we could not perform analysis for each drug separately, the results showed a better chance of survival with the use of ACE inhibitors or ARBs (Figure 3).

Discussion

Recent publications in the Lancet and the NEJM by the team of Mehra et al[2,3] were primarily based on a database run by an American healthcare analytics company named Surgisphere. Many clinicians and researchers around the world criticized Surgisphere for multiple reasons, including the company's refusal to disclose the raw data and making claims that did not match publicly available government reports. For example, Sugisphere's data on the number of Polymerase Chain Reaction-confirmed COVID-19 patients in

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 Lancet[1] and the NEJM[2].

Risk factors	Article type	No. of studies	Type of metrics	Summary effect size (95% CI)†	I^2 (*p*-value)‡	Summary effect size in a retraction from the Lancet[1] (HR, 95% CI)	Summary effect size in a retraction from the NEJM[2] (OR, 95% CI)
Age (per year)	Meta-analysis	6	OR	4.59 (2.61-8.04)	67.1% (0.010)	1.010 (1.009-1.011)	1.93 (1.60-2.41)
BMI (per kg/m^2)	Retrospective cohort	1	OR	2.56 (1.18-5.57)	–	1.063 (1.060-1.067)	–
Female	–	–	–	–	–	0.825 (0.793-0.858)	0.97 (0.65–0.95)
Male	Meta-analysis	5	OR	1.50 (1.06-2.12)	76.3% (0.002)		
White	–	–	–	–	–	Reference	
Black	Retrospective cohort	1	HR	1.71 (1.44-2.02)	–	1.344 (1.276-1.415)	–
Hispanic	–	–	–	–	–	1.495 (1.400-1.597)	–
Asian	Retrospective cohort	1	HR	1.62 (1.43-1.82)	–	0.717 (0.668-0.769)	–
Coronary artery disease	Meta-analysis	9	OR	3.72 (1.77-7.83)	89.1% (< 0.0001)	1.134 (1.082-1.188)	2.70 (2.08-3.51)
Congestive heart failure	Retrospective cohort	1	OR	3.18 (1.46-6.93)	–	1.756 (1.609-1.915)	2.48 (1.62-3.79)
Arrhythmia	–	–	–	–	–	1.626 (1.504-1.758)	1.95 (1.33-2.86)
Diabetes	Meta-analysis	9	OR	1.90 (1.37-2.64)	32% (0.16)	1.206 (1.151-1.264)	–
Hypertension	Meta-analysis	8	OR	2.70 (1.40-5.24)	92.6% (< 0.0001)	1.302 (1.252-1.355)	–
Hyperlipidemia	Retrospective cohort	1	OR	1.09 (0.57-2.10)	–	1.125 (1.081-1.171)	–
COPD	Meta-analysis	7	OR	3.53 (1.79-6.96)	72.2% (0.001)	1.190 (1.093-1.294)	2.96 (2.00-4.40)
Current smoker	Meta-analysis	5	OR	2.04 (1.32-3.15)	0% (0.62)	1.268 (1.201-1.340)	1.79 (1.29-2.47)
Immunosuppressed condition	–	–	–	–	–	1.081 (0.985-1.187)	–
Cancer chemotherapy	Meta-analysis	5	OR	0.74 (0.40-1.39)	0% (0.88)		
Corticosteroids	Meta-analysis	2	HR	2.30 (1.00-5.29)	0% (-)		
SOFA	Retrospective cohort	1	OR	5.65 (2.61-12.23)	–		
qSOFA < 1						0.758 (0.726-0.792)	–
SpO_2 < 94%	Retrospective cohort	1	OR	3.81 (1.45-10.00)	–	1.664 (1.587-1.746)	–

CI: confidence interval, I^2: 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, SpO_2: 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[1] and the NEJM[2].

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

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.

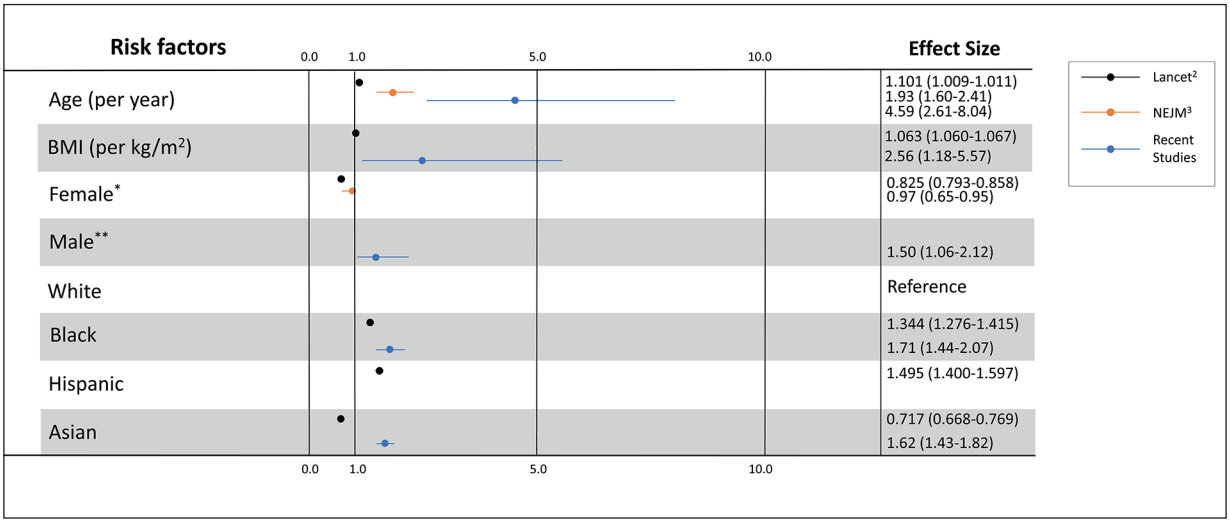

Figure 1. Comparison of the effect of demographic characteristics on COVID-19 mortality between systematic review and Mehra et al[2,3] studies. *In the retracted Lancet[2] and NEJM[3] papers, Mehra et al[2,3] reported effect size based on female sex. **Publications that were reviewed in this study reported effect size based on male sex.

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[5,6]. As a result, Lancet and the NEJM papers by the Mehra's research team[2,3] were retracted, and moreover, many researchers have still criticized that some clinical trials have been discontinued by the study of Mehra et al[2], 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

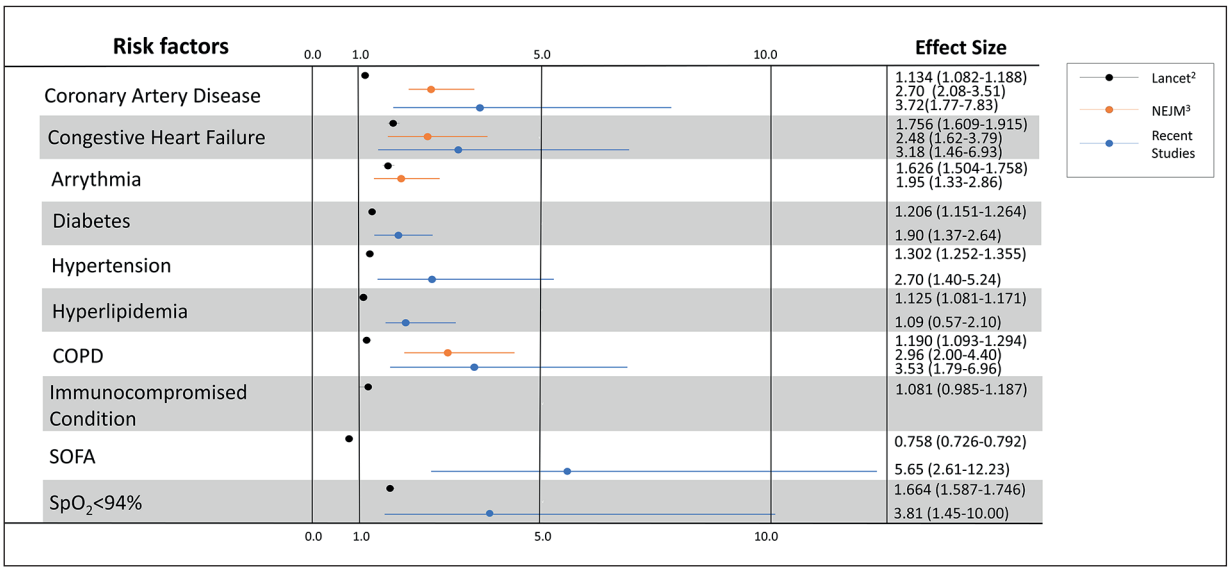

Figure 2. Comparison of the effect of underlying clinical conditions on COVID-19 mortality between systematic review and Mehra et al[2,3] studies.

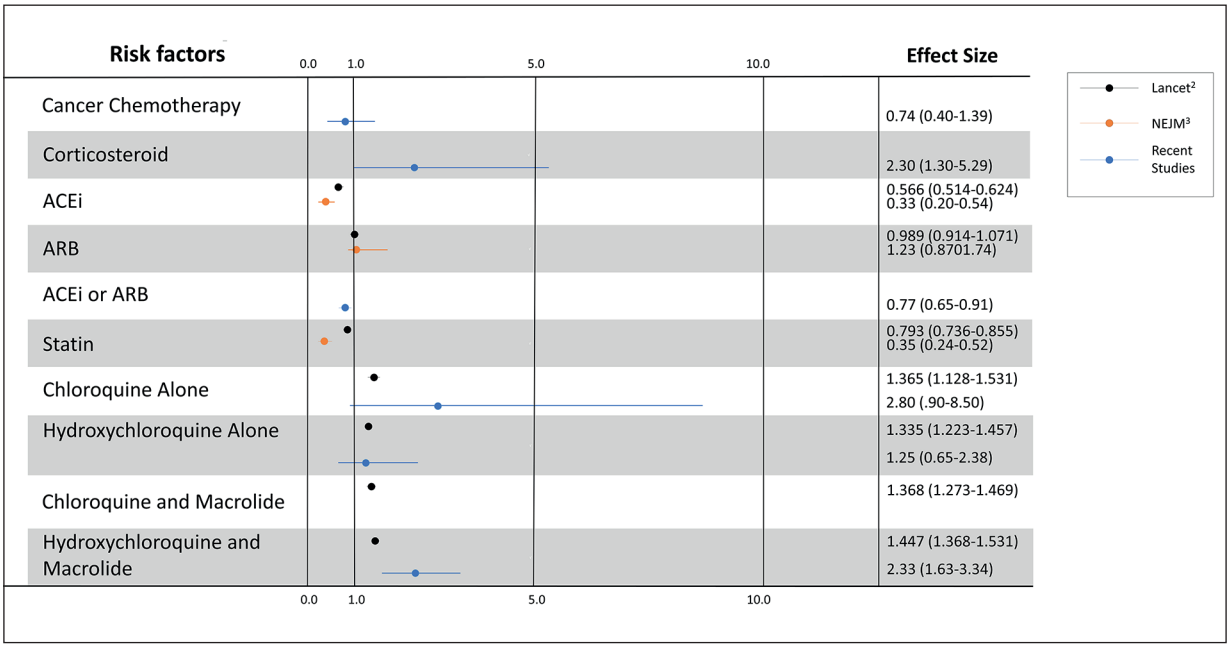

Figure 3. Comparison of the effect of medications on COVID-19 mortality between systematic review and Mehra et al[2,3] studies.

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[2] regarding ethnicity. In our study, Asian ethnicity appeared as a significant risk factor for COVID-19 mortality. A recent study[7] 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[2] 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[4]. In particular, macrolide is also known to contribute to QT prolongation[8]. 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[9]. Then, why did the study of Mehra et al[2] 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[2] was higher than

the recommended dosage. In the study of Mehra et al[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[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[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[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[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[16]. On the contrary, ACE2 can exert anti-inflammatory effects, reducing the severity of lung damage caused by COVID-19[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[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[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

1) Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020; 46: 846-848.

2) Mehra MR, Desai SS, Ruschitzka F, Patel AN. Retracted: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet 2020; S0140-6736(20)31180-6.

3) Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Retraction: cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med 2020; 382: 2582.

4) Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc-prolonging and torsadogenic potential of possible pharmacotherapies for coronavirus disease 19 (COVID-19). Mayo Clin Proc 2020; 95: 1213-1221.

5) Watson J (on behalf of 201 signatories). An open letter to Mehra et al and The Lancet. Zenodo 2020. doi: 10.5281/zenodo.3871094.

6) Watson J (on behalf of 174 signatories). An open letter to Mehra et al and The New England Journal of Medicine. Zenodo 2020. doi: 10.5281/zenodo.3873178.

7) Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J, McDonald HI, MacKenna B, Tomlinson L, Douglas IJ, Rentsch CT, Mathur R, Wong AYS, Grieve R, Harrison D, Forbes H, Schultze A, Croker R, Parry J, Hester F, Harper S, Perera R, Evans SJW, Smeeth L, Goldacre B. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020; 584: 430-436.

8) Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012; 366: 1881-1890.

9) Patel TK, Barvaliya M, Kevadiya BD, Patel PB, Bhalla HL. Does adding of hydroxychloroquine to the standard care provide any benefit in reducing the mortality among COVID-19 patients?: a systematic review. J Neuroimmune Pharmacol 2020; 15: 350-358.

10) United States Food and Drug Administration (2020). Revoked: EUA Chloroquine Phosphate Health Care Provider Fact Sheet, version date 4/27/2020. Available from: https://www.fda.gov/media/136535/download. Last accessed: 27 October 2020.

11) United States Food and Drug Administration (2020). Revoked: EUA Hydroxychloroquine sulfate Health Care Provider Fact Sheet, version date 4/27/2020. Available from: https://www.fda.gov/media/136537/download. Last accessed: 27 October 2020.

12) Das S, Bhowmick S, Tiwari S, Sen S. An updated systematic review of the therapeutic role of hydroxychloroquine in coronavirus disease-19 (COVID-19). Clin Drug Investig 2020; 40: 591-601.

13) Hernandez AV, Roman YM, Pasupuleti V, Barboza JJ, White CM. Hydroxychloroquine or chloroquine for treatment or prophylaxis of COVID-19: a living systematic review. Ann Intern Med 2020; 173: 287-296.

14) Alexander PE, Debono VB, Mammen MJ, Iorio A, Aryal K, Deng D, Brocard E, Alhazzani W. COVID-19 coronavirus research has overall low methodological quality thus far: case in point for chloroquine/hydroxychloroquine. J Clin Epidemiol 2020; 123: 120-126.

15) WHO Solidarity trial consortium, Pan H, Peto R, Karim QA, Alejandria M, Henao-Restrepo AM, García CH, Kieny M, Malekzadeh R, Murthy S, Preziosi M, Reddy S, Periago MR, Sathiyamoorthy V, Røttingen J, Swaminathan S, as the members of the Writing Committee, assume responsibility for the content and integrity of this article. Repurposed antiviral drugs for COVID-19 interim WHO SOLIDARITY trial results. medRxiv 2020.10.15.20209817. [this article is a preprint and has not been peer-reviewed]. [cited October 28, 2020]. Doi: https://doi.org/10.1101/2020.10.15.20209817.

16) Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu N, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181: 271.

17) Guo J, Huang Z, Lin L, and Lv J. Coronavirus Disease 2019 (COVID-19) and cardiovascular disease: a viewpoint on the potential influence of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection. J Am Heart Assoc 2020; 9: e016219.

18) Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.