Hypertension as a prognostic factor in the prediction of mortality in patients with COVID-19: A systematic review and meta-analysis

Carmela D. Pagdanganan, Uriel Gem A. Paguio, Maria Angelica C. Palaspas, Nina Rose G. Palmares, Jonaima S. Panalondong, Vita Iris A. Salvacion, Louriz Maveric S. Samonte, Pia Loraine P. San Felipe, Mary Ann D. San Juan, Maria Emelyn P. San Miguel, Patricia Anne C. San Pedro, Izza Anamiel V. Sanchez, and Jose Ronilo G. Juangco, MD, MPH

Abstract

Introduction Hypertension was identified by the CDC to be one of underlying medical conditions that might pose an increased risk for severe illness from COVID-19. This study aimed to determine the effect of hypertension on the morbidity of COVID-19 patients to help physicians in adjusting the management plans for a better prognosis.

Methods Participants included all COVID-19 patients with hypertension as a pre-existing medical condition. Studies were selected based study design, participants, exposure, outcome, timing, setting and language. MEDLINE and CINAHL, ScienceDirect, Clinical Key, OVID database, Wiley Online library, and UpToDate were searched. The risk of bias in selection, comparability and outcomes were evaluated. All information gathered were collated and evaluated using the Newcastle-Ottawa Quality Assessment Scale and CEBM.

Results There was a statistically significant positive association between mortality and hypertension as a prognostic factor (OR = 5.25, 95% CI 2.42, 11.40; HR = 2.21, 95% CI 1.75, 2.80). Individual studies all showed a significant relationship between hypertension and mortality in COVID-19 patients with OR ranging from 1.75 to 28.88, and HR of 1.49 to 3.32.

Conclusion Hypertension as a comorbid condition is a significant prognostic factor in the prediction of mortality in hospitalized COVID-19 patients.

Key words: COVID-19, hypertension, mortality, prognosis

Correspondence:
Carmela D. Pagdanganan, Department of Preventive and Community Medicine, College of Medicine, University of the East Ramon Magsaysay Memorial Medical Center, Inc., 64 Aurora Boulevard, Barangay Doña Imelda, Quezon City, PH 1113. Tel: 09276539247; Email: pagdangananc1208@uerm.edu.ph

Department of Preventive and Community Medicine, College of Medicine, University of the East Ramon Magsaysay Memorial Medical Center, Inc., Quezon City, PH

From December 2019 to the present, various countries have experienced a second and third wave of the COVID-19 pandemic. Although there have been almost 25 million recoveries, there have been at least one million deaths.[1] With the alarming increase in the number of cases and deaths worldwide, the possible risk factors should be determined to have a general idea of those who are more susceptible to develop COVID-19. Initially, only the old and

immunocompromised were identified to be at risk for more severe outcomes. However, as the months progressed, more studies revealed that people with other comorbidities were just as at risk. Hypertension was identified by the Centers for Disease Control and Prevention (CDC) to be one of underlying medical conditions that might pose an increased risk for severe illness from COVID-19.[2] This study aimed to determine the effect of hypertension on the morbidity of COVID-19 patients to help physicians in adjusting the management plans for a better prognosis.

Methods

This meta-analysis was done according to the fundamentals laid in the Cochrane Handbook for Systematic Reviews of Interventions and as stated by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[3] Studies were selected based on study design, participants, exposure, outcome, timing, setting and language. Only case control and cohort studies reported in English from 2019 onwards were included. Participants included all patients admitted in hospitals who were diagnosed with COVID-19 and had hypertension as their pre-existing medical condition. The association between patient mortality or death rate and hypertension was the main outcome for this research.

MEDLINE and CINAHL using the EBSCO search engine, ScienceDirect using the Elsevier network, Clinical Key, OVID database, Wiley Online library, and UpToDate were searched from June to August 2020 for case control and cohort studies. The search strategies used Medical Subject Headings (MeSH) terms like COVID-19, comorbidities, hypertension, and mortality. Twelve authors independently screened the titles and the abstracts yielded by the search against the inclusion criteria gathered. Full reports were obtained for all the titles that met the inclusion criteria or where there was any uncertainty. Review author pairs then screened the full text reports if the initial screening suggested that they may be suitable for inclusion in the final meta-analysis. Figure 1 shows the reasons for exclusion at the level of full-text review. Any discrepancies among the reviewers were thoroughly discussed and subsequently resolved.

Data from the studies were extracted independently using standardized forms and a detailed instruction manual specific for RevMan.[4] Critical appraisal of each article was done using the Centre for Evidence Based Medicine Critical Appraisal tool for prognosis.[5] Variables extracted were socio-demographic, clinical characteristics and total number of the participants. The number of participants with hypertension, mortality-related outcomes, the effect size and statistical analysis utilized in each study were also extracted.

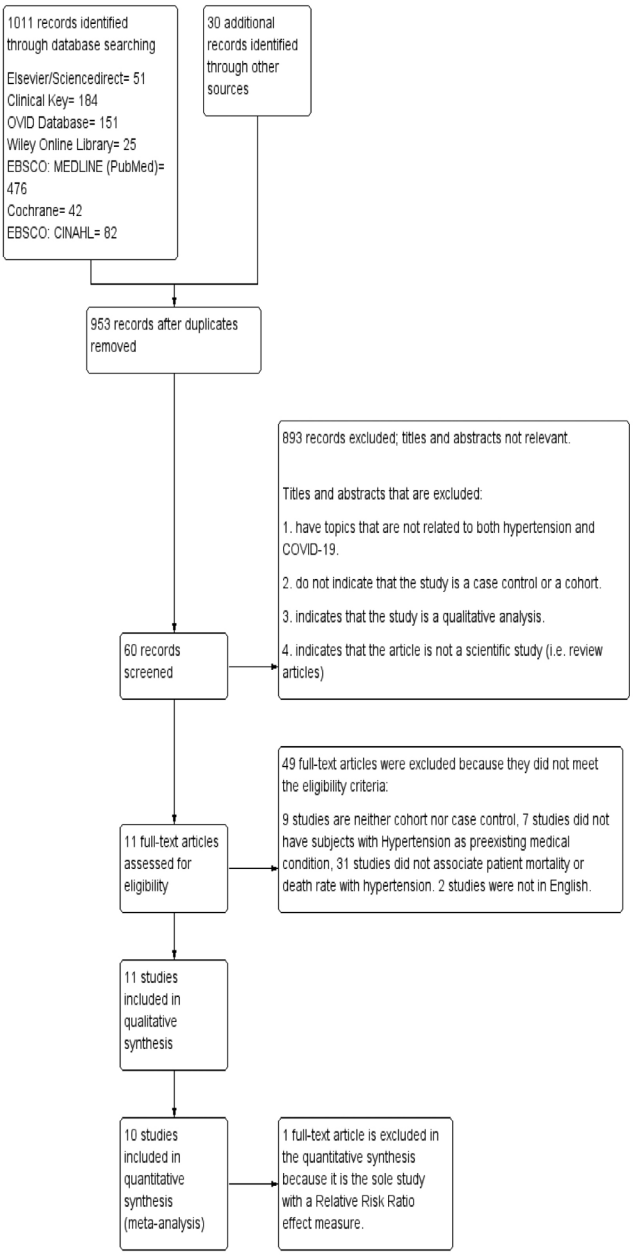

Figure 1. Flowchart of study selection

The risk of bias of each article was determined using the Newcastle-Ottawa scale and Centre for Evidence Based Medicine (CEBM) Critical Appraisal tools.[5,6] The chosen domains for risk evaluation were selection bias, comparability bias and outcome bias. To standardize the assessment process among evaluators, guide questions regarding the selection of patients, definition and determination of non-exposed cohort, cases and controls, handling of confounding variables and assessment of outcome or exposure were set. Features describing low, high and unclear risk were established as criteria for judging each study across the three bias domains.

The odds ratio for death was computed for each case control study using two-by-two tables. For cohort studies, the hazard ratio was pooled together using generic inverse variance. The data set was encoded in REVMAN 5.4 for analysis. The Mantel-Haenszel method was used for pooling the effect of individual data using odds ratio while the generic inverse variance was used for data using hazard ratio. Statistical significance was set at $p < 0.05$ level together with the 95% confidence interval. An odds ratio and hazard ratio of > 1.00 was deemed as a positive outcome which would indicate an association of hypertension with increased risk of mortality in patients with COVID-19. Random or fixed effects model was determined by the statistical heterogeneity which was evaluated by chi-square and I-test. An I^2 value of 0 < 40% was considered as not significant, 30-60% is taken as moderate heterogeneity, 50-90% considered as substantial heterogeneity and 75-100% was considered as significant heterogeneity. The authors used an I^2 result of > 75% and a x^2 result with $p < 0.01$ as indicative of statistical heterogeneity.[7]

Results

The search of the databases listed yielded 1011 articles; 30 additional records were identified through other sources and references of above titles, leaving 953 articles after removal of duplicates. Eight hundred ninety-three records were excluded due to irrelevance of the titles and/or abstracts. Of the remaining 60 articles, 49 were excluded as they did not meet the eligibility criteria. Eleven full-text articles were assessed for relevance and included in qualitative synthesis and 10 studies were included for meta-analysis. One article was excluded because it reported relative risk instead of odds ratio.

Table 1 shows the type of study, participants, other co-morbidities, number of participants with and without hypertension, exposure, outcome, outcome measures, and effect size. Ten studies consisting of 6 concurrent cohort, 3 non-concurrent cohort, and 1 non-concurrent observational study were included. All studies defined their subjects as patients diagnosed with COVID-19, with or without hypertension. All studies used Kaplan-Meier curves to determine probability of patient survival and Cox proportional hazard regression models or univariable and multivariable models to determine associated risk factors with mortality and odds ratios, respectively. All studies defined hypertension as having a blood pressure of > 140 mm Hg systolic and > 90 mm Hg diastolic measured on two separate days. The ten studies involved 8,999 participants, of which 3,032 had hypertension. Each study showed a positive association (OR > 1) between hypertension and mortality.

The criteria used to determine selection bias were: 1) representativeness of cases or exposed cohort, 2) ascertainment of exposure (for cohort) or definition of control and cases (for case control), and 3) selection of the non-exposed cohort (cohort) or same methods of ascertainment of cases/controls. A study was considered low risk for the first criterion when the disease severity was a common point in the course of the disease. Half of the studies were high risk because the disease severity varied among subjects, some studies classified the disease severity as mild, moderate and severe while some studies categorized the disease as severe, not severe or critical. Ten percent of the studies were low risk and the rest had unclear risk because no description of the derivation of the cohort was provided. A study was considered low risk for the second criterion when all subjects were drawn from the same community as the exposed cohort. All studies were low risk because all subjects were derived from the same community or hospital. A study was considered low risk for the third criterion when there were secured records, structured interviews for cohorts or independent validation for case controls. All studies were considered low risk. The criterion for outcome bias was the presence of assessment of outcome for cohort studies or ascertainment of exposure for case control studies. All studies were considered low risk because in-hospital deaths were considered as the outcome. Figure 2 shows the summary of the risk of bias.

Table 1. Summary of article characteristics.

ARTICLE FILENAME	METHODS	PARTICIPANTS	OTHER COMORBIDITIES	NUMBER OF TOTAL PARTICIPANTS	NUMBER OF PARTICIPANTS W/ HTN	EXPOSURE	OUTCOME	OUTCOME MEASUREMENT	EFFECT SIZE
Ciceri, et al. 2020 (Italy)	Cohort study	COVID-19 patients, 18 y/o & above (56-75 y/o, median=65)	coronary artery disease, diabetes, COPD, CKD, cancer	410	203	Hypertension	Mortality where main causes were: refractory hypoxia, massive pulmonary thrombosis, and multiple organ failure; Still admitted; and discharged	Kaplan-Meier curves were used to estimate the probability of survival. To evaluate the association between patients characteristic and i-hospital death, univariable and multivariable models were calculated.	Hazard Ratio=2.6
Gao et al. 2020 (China)	Retrospective observational study	COVID-19 patients consecutively admitted, with mean ages of 55.38 (non-hypertensive) and 64.24 (hypertensive)	diabetes, stroke, angina, renal failure, previous revascularization, peripheral vascular disease, chronic heart failure, COPD, pneumonia, Obstructive sleep apnea, asthma, cancer, smoking, alcoholism	2877	850	Hypertension	All cause mortality of patients during hospitalization collected from patients' documented medical files; associated with higher risk for patients not under anti-hypertensive treatment	Survival was estimated by the Kaplan-Meier method. Variances in outcomes between exposure cohorts were assessed by the multivariable Cox proportional hazards model. Covariates in the multivariable model included age, sex, medical history of diabetes, insulin-treated diabetes, MI, treatment by percutaneous coronary intervention (PCI) or CABG, renal failure, chronic heart failure, asthma, COPD, and stroke. Cox proportionality assumptions were met in all models.	Hazard Ratio=2.06 P: 3.45
Pan et al. 2020 (China)	Retrospective cohort study	Covid-19 patients consecutively admitted (ages 60-75 when matched)	DM, CHD, arrhythmia, COPD, asthma, cerebrovascular disease, CKD, chronic liver disease, malignancy, organ transplant	996	256	Hypertension	Death extracted from electronic medical records; covid-19 patients with hypertension were associated with more severe secondary infections, cardiac and renal dysfunction, and depletion of CD8+ cells on admission	Kaplan-Meir curved wee used to compare the cumulative risk rate. Cox proportional hazard regression models were applied to determine the potential risk factors associated with all-cause mortality, and the results are reported as the hazard ratio and 95% CI	Hazard Ratio=2.24
Wang et al. 2020 (China)	Cohort study	Covid-19 patients over 60 years old (65-76 y/o, median=69)	hypertension, diabetes, cardiovascular disease, cerebrovascular disease, CKS, chronic liver disease, COPD, malignancy, autoimmune disease	339	138	Hypertension	survival/non-survival; shorter length of stay associated with deaths; dyspnea, comorbidities, COPD, and ARDS were strong predictors of death cardiac injury was defined if the serum level of cardiac troponin I (cTn1)was above the 99th percentile upper reference limit ARDS was defined according to the Berlin definition Arrhythmia was defined as emerging premature beat, tachycardia, atrial fibrillation, and clinically significant bradycardia according to ECG or medical records; transient sinus tachycardia associated with fever was excluded Cardiac insufficiency was defined when the serum level of NT-pro BNP exceeded the normal range and the presence of associated symptoms such as dyspnea, orthopnea, and pedal edema	Multivariate Cox regressions were subsequently performed for comorbidities and complications, in which "age" factor was added to correct the models and only variables with statistical significance in univariate analysis were included. all significance levels were computed for 2-tailed testing and the cutoff of significance was set at P<0.05	Hazard Ratio=1.494
Yang et al. 2020 (China)	Cohort study	COvid-19 patients with mean ages of 49.93 (survivors) and 67.82 (non-survivors)	hypertension, t2dm, coronary heart disease, COPD	226	84	Hypertension	Survival/non-survival obtained by patient discharge records; non-survivors had significantly higher serum N counts and higher levels of CRP, AST, sCr, NUB, and D-dimer, and higher neutrophil to lymphocyte ratio; serum ALB levels and L counts of non-survivors were lower than those of survivors	Kaplan-Meier (K-M) method to evaluate the relationships between variables and outcome and Cox proportional-hazard model (CPHM) analysis to clarify the effects of each factor on outcome	Hazard Ratio=3.317
Borobia et al. 2020 (Spain)	Cohort	COVID-19 patients, 18 y/o & above (46-78 y/o, median=61)	CHD, DM, rheumatological disease, solid malignant disease, obesity, CKD, COPD, hematological malignant disease, asthma, liver disease, HIV infection	2226	920	Hypertension	Mortality increased with age (over 60% for patients over 80 years of age), abnormal laboratory findings such as elevated D-dimer, lymphopenia, procalcitonin, ferritin, ans CRP levels	Multivariate logistic regression model: for analysis of predictors of in-hospital death	Odds Ratio=1.105
Chilimuri, et al. 2020 (United States)	Retrospective Cohort Study	COVID-19 patients (19-97 y /o, median=63)	DM, CVD, CKD, HIV/AIDS, CLD	888	225	Hypertension	Mortality associated with older age, admission D-dimer levels > 1000 ng/mL, admission CRP levels > 200 mg/L, admission lymphopenia, microembolic disease	Univariable and multivariable regression to measure relation between risk factors and in-hospital mortality	Odds Ratio=U: 2.43 M: 1.46
Hu et al. 2020 (China)	Retrospective Cohort Study	COVID-19 patients (23-91 y/o, median=61)	Cirrhosis, DM, malignancy, cerebrovascular disease, COPD, CKD, CLD, CVD, digestive system disease, endocrine system disease, nervous system disease, respiratory system disease	323	105	Hypertension	Mortality/ Disease Progression or Survival/ Disease Improvement: Survival time defined as the interval from the date of admission to the date of death or discharge;	Kaplan-Meier method and Log-rank Test: for associated of risk factors with outcome Univariate and multivariate logistic regression models for OR	Odds Ratio=4.388
Salacup et al. 2020 (United States)	Cohort study	COVID-19 patients, (58-75 y/o, median=66)	COPD, asthma, HF, arterial fibrillation, liver cirrhosis, diabetes, CKD, coronary artery disease, hypertension, obesity	242	180	hypertension	Inpatient mortality: associated with higher baseline CRP, requirement of mechanical ventilation, vasopressor use, and continuous renal replacement therapy/hemodialysis (CRRT/HD)	Multivariate logistic regression: for association of inflammatory baseline markers with in-patient death	Odds Ratio=1.056
Xiong, et al. 2020 (China)	Cohort study	COVID-19 patients (32-53.5 y/o, median=43)	hypertension, DM, coronary artery disease, cerebrovascular disease, COPD	472	71	hypertension	Composite endpoint (admission to ICU, need for mechanical vent, or death)	Multivariate logistic regression model to determine OR and CI for covariates with the composite endpoint (admission to ICU, need for mechanical ventilation, or death)	Odds Ratio=2.82

Individual studies all showed a significant relationship between hypertension and mortality in COVID-19 patients. Odds ratios ranging from 1.75 to 28.88, and hazard ratios ranging from 1.49 to 3.32 were noted. Five case control studies were included, consisting of 4247 subjects, 1501 of whom were hypertensive. As shown in Figure 3, there was a significant positive association with an overall odds ratio of 5.25 (95% CI = 2.42, 11.40 p < 0. 001), indicating that hypertensive patients were five times more likely to die than patients who were not hypertensive. There was significant heterogeneity (I^2 = 91%). As shown in Figure 4, five cohort studies had hazard ratios ranging from 1.49 to 3.32 with an overall significant positive association (HR = 2.21, 95% CI = 1.75, 2.80, p < 0.001). This means that the risk of mortality is two times higher for COVID-19 patients with hypertension compared to those without hypertension as a comorbid condition. Heterogeneity was minimal (I^2 = 10%).

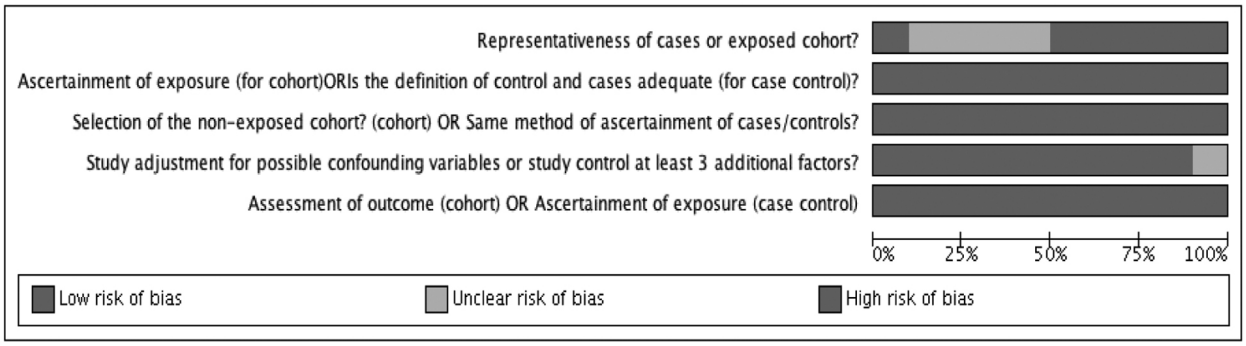

Figure 2. Risk of bias summary.

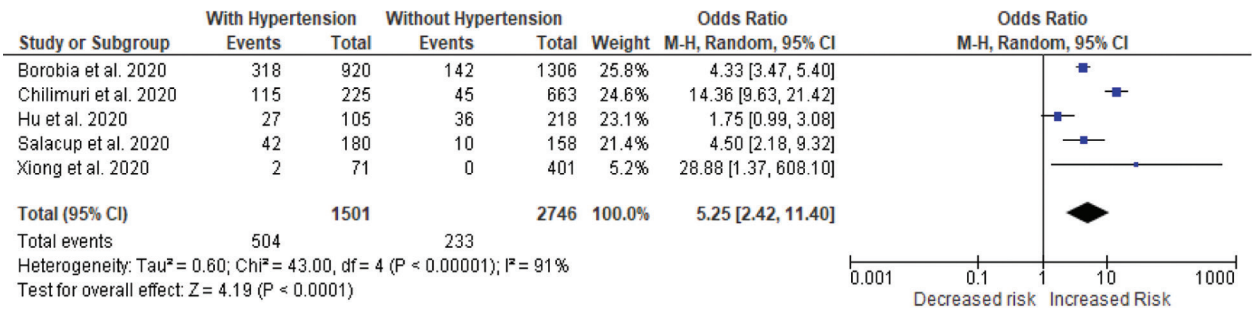

Figure 3. Forest plot of the odds ratio of mortality with hypertension.

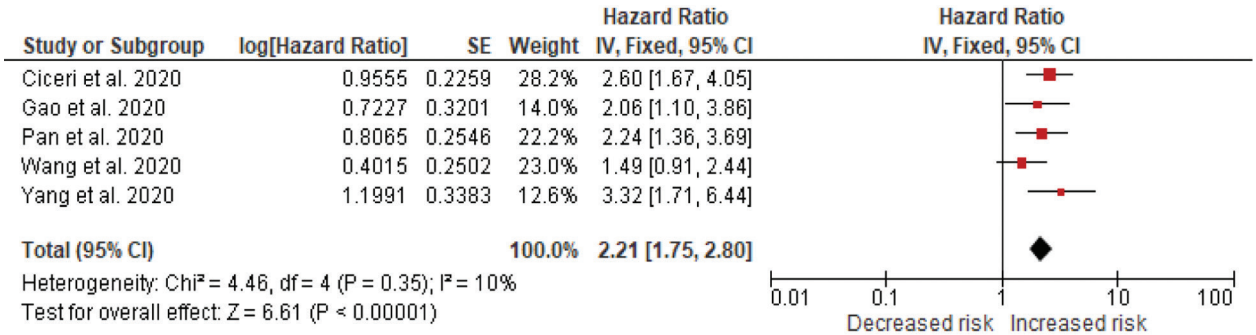

Figure 4. Forest plot of the hazard ratio of mortality with hypertension.

Discussion

Hypertension as a prognostic factor in the prediction of COVID-19 patients' mortality is still undergoing numerous studies as the number of cases continue to rise since it first made an appearance in Wuhan, China.[8] The aim of this meta-analysis was to determine the number of patients previously diagnosed with hypertension who tested positive for COVID-19, and to determine the number of deaths among COVID-19 patients with diagnosed hypertension in the included studies. The ten studies that were included evaluated the number of COVID-19 patients with hypertension and measured the outcome of mortality. The findings of five case control studies demonstrated a significant positive association with an overall odds ratio suggesting that the odds of mortality in COVID-19 patients with hypertension was five times higher. The five cohort also demonstrated a significant positive association suggests a two-fold increased risk of mortality in COVID-19 patients with hypertension.

Earlier studies on COVID-19 have shown how a comorbidity affects the severity of the disease progression. Patients will have different clinical profiles and underlying conditions making it difficult to point out whether the adverse effect of comorbidities came from the COVID-19-comorbidity interaction or from the pathological interactions between the patients' comorbidities.[9] Hypertension is one of the more common comorbidities among patients with COVID-19. However, previous studies have not been able to clearly delineate whether the poor outcomes were caused directly by the cardiovascular condition itself or by other comorbidities present. The typical patient profile of non-survivors includes older age and the presence of the following comorbidities - hypertension, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), coronary artery disease, and heart failure.[10] In patients with hypertension, there is a 2.5-fold higher risk of developing a severe disease or progressing to death from SARS-CoV-2 infection.[11]

However, other studies have reported that this 2.5-fold risk has a relatively weaker association compared to other comorbidities, such as the 5-fold higher risk in COPD and the 3-fold higher risk in CKD.[12,13] While mortality is predicted by age and the presence of comorbidities, hypertension and the use of anti-hypertensives did not significantly affect COVID-19 lethality.[9] These claims however do not disregard the fact that there is still a positive association between hypertension and the occurrence of poor outcomes. In another study involving 46,248 COVID-19 patients, the pooled OR of hypertension in severely-ill patients was 2.36 (95% CI = 1.46, 3.83) compared to non-severe patients, suggesting that hypertension is a risk factor for severity. It mentioned that hypertension was one of the acute respiratory distress syndrome (ARDS) predictors in patients with severe acute respiratory syndrome (SARS). However, the study also clarified that the role of hypertension in the progression of the illness was unclear but remained to be an important factor contributing to the mortality.[14]

The strength of this meta-analysis is that it comprises case control and cohort studies with a large sample size from different databases. The use of standardized methodology and validation of the systematic review using the PRISMA checklist allows for more reliable results. A limitation of this meta-analysis is the lack of age-adjusted data in relation to hypertension and disease severity. Since the mean age of all the patients found in this meta-analysis is 63, the results may be construed and attributed to the severity or progression of hypertension with advancing age.

The result of this meta-analysis shows that hypertension is a comorbid condition which has a prognostic significance in predicting mortality among patients hospitalized for COVID-19. Although there is inadequate explanation of the pathophysiology and its role in the disease progression, its significance as a contributory factor for poorer outcomes in hospitalized COVID-19 patients should not be disregarded.

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