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COMMENTARY

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Is hypertension without any other comorbidities an independent predictor for COVID-19 severity and mortality?

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Early reports from China found that both established cardiovascular disease and its risk factors, such as hypertension and diabetes mellitus, were common pre-existing conditions in patients with COVID-19.[1,2] The high prevalence of these comorbidities was confirmed in subsequent studies.[3] Remarkably, the prevalence of these pre-existing conditions was higher in critically ill patients and in those who died.[2,4,5] In the analysis performed by Wu and McGoogan, including 44 672 patients with confirmed COVID-19, the overall case fatality rate was 2.3%, and increased with comorbid conditions: 10.5% for cardiovascular disease, 7.3% for diabetes, and 6% for hypertension.[6] The connections between cardiovascular disease, hypertension, age, and vascular aging are complex. The association between hypertension and COVID-19 mortality or severity could be explained in part by the increased age and higher prevalence of cardiovascular disease, both well-known risk factors for mortality in critical patients. Therefore, in order to identify independent predictors of COVID-19 mortality or severity, models should be properly adjusted to exclude potential confounding effects.[7]

The study by Sun and colleagues[8] published in *The Journal of Clinical Hypertension* added new information to this relevant topic. They performed a retrospective analysis of 3400 adults with confirmed COVID-19 hospitalized at two hospitals in Wuhan, China. Patients with type 1 diabetes mellitus were excluded. The authors used a multivariate logistic analysis in order to estimate the effect of hypertension, type 2 diabetes mellitus and their combination on the risk of developing death (it was the primary outcome), respiratory failure, and severe COVID-19 infection. Compared to patients having neither hypertension nor diabetes, the risk of mortality was significantly higher in patients with diabetes alone (OR 5.26 [95% CI: 2.39–12 11.58]) or with diabetes in combination with hypertension (OR 3.02, [95% CI: 1.48–6.15]). Moreover, diabetes was a risk factor for development of respiratory failure and severe infection, but hypertension alone only conferred the risk for the development of severe infection (OR 1.22 [95% CI: 1.00–1.51]). Advanced age, male sex, history of cardiovascular diseases, and chronic kidney disease were also independent risk factors for adverse outcomes. To exclude possible confounding effects of these comorbid conditions, the authors performed a sensitivity analysis among 2304 patients who did not have any other identified comorbidities beyond hypertension or diabetes. This analysis confirmed that diabetes, but not hypertension, increased the risk of death.

The lack of relationship between hypertension and severe/lethal COVID-19 found by Sun and colleagues[8] was contradictory with some previously published studies. Guan et al found in 1099 patients with confirmed COVID-19 that hypertension was a more prevalent condition in those who had a primary composite end point (admission to critical care unit, use of mechanical ventilation or death), 35.8% versus 13.7%.[5] Ruan and colleagues also described in 150 patients with confirmed COVID-19 that cardiovascular disease and hypertension were more frequent in patients who died compared with those who were discharged (19% versus 0%, $P < .001$, and 43% versus 28%, $P = .07$, respectively).[9] Moreover, a systematic review and meta-analysis that included 46 248 infected patients found that hypertension was associated with COVID-19 poor outcome (OR 2.36 [95% CI 1.46–3.83]).[10] However, none of these studies performed a multivariable adjustment. Guan and colleagues found, using Cox regression model, that both hypertension (HR 1.58, 95% CI 1.07–2.32) and diabetes (HR 1.59, 95% CI 1.03–2.45) were predictors for poor outcome to a similar degree.[11] However, the adjustment was only performed for age and smoking. Thus, the

effect of arterial hypertension on the severity or mortality could be explained by potential confounders. Rodilla and colleagues, in a retrospective analysis of 12 226 patients who required hospital admission in Spain, found that hypertension, diabetes, coronary heart disease, heart failure, atrial fibrillation, stroke, and chronic kidney disease were significantly more frequent in non-survivals.[12] Using multivariable analysis adjusted for age and sex, the authors stated that pre-existing hypertension (but not diabetes) had an independent prognostic value for mortality in patients with COVID-19 who required hospitalization.

On the other hand, data of some studies using multivariate logistic regression models to identify independent clinical predictors for mortality or severity support the results of Sun and colleagues The studies by Chen and colleagues[13] and by Zhou and colleagues[2] found that hypertension was a predictor of COVID-19 severity or mortality in the univariate analysis; in both studies, however, hypertension was not an independent predictor of risk in the multivariate logistic regression model. Moreover, the Italian Society of Hypertension performed a cross-sectional, observational, multicenter, nationwide survey including 1591 patients diagnosed with COVID-19, admitted in 26 hospitals. Older age, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, coronary artery diseases, and heart failure were more frequent in non-survivors than in survivors. After adjustment for multivariate analysis, age (P = .0001), diabetes (P = .004), and chronic kidney disease (P = .004), but not hypertension, predicted mortality.[14] Remarkably, in this study, the prevalence of hypertension among COVID-19 patients is comparable to that expected based on the data recorded in the general population during the World Hypertension Day in Italy from 2010 to 2018. A meta-analysis including 16 studies with 3994 patients shows that hypertension (OR 2.95), diabetes mellitus (OR 3.07), cardiovascular disease (OR 4.58), and chronic kidney disease (OR 5.32) lead to a higher risk of developing serious events. However, diabetes mellitus (OR 2.78) but not hypertension had a significant impact on the mortality rate.[15]

While the roll of hypertension without any other comorbidities in predicting death among COVID-19 patients seems debatable, diabetes appears as a well-established risk factor. The results found by Sun and colleagues[8] was consistent with many previously published studies. Since the initial COVID-19 outbreak in China several retrospective studies,[11,16,17] cohort studies,[18] and metanalysis[19] support the association between diabetes and COVID-19 mortality or severity. Although initial reports were mainly on people with type 2 diabetes, recent surveys have shown that individuals with type 1 diabetes are also at risk of severe COVID-19.[18]

However, individuals with diabetes often had comorbidities such as hypertension, obesity, and cardiovascular disease. In a retrospective analysis of patients with COVID-19, those with diabetes had a greater prevalence of hypertension (56.9% vs 28.8%), cardiovascular disease (20.9% vs 11.1%), and cerebrovascular disease (7.8% vs 1.3%) than those without diabetes.[18] Moreover, specifically in patients with diabetes, non-survivors had a greater prevalence of comorbidities than survivors. Consistent with the study by Sun and colleagues,[8] in a Cox regression analysis performed on patients with diabetes hypertension was and independent risk factor for in-hospital death (HR 3.10, 95% CI 1.14–8.44).[18]

Remarkably, in most studies, cardiovascular disease was strongly associated with poor COVID-19 outcome in univariate and multivariate analysis. The prevalence of diabetes, hypertension, and cardiovascular disease increases with age and frequently coexists in the same patient. Thus, age, vascular aging, and cardiovascular disease could be a linchpin between diabetes, hypertension, and COVID-19 poor outcomes.

Beyond the controversies regarding which are independent predictors for risk, in the clinical practice hypertension, diabetes, and chronic cardiac and renal disease identify a subset of subjects at risk of developing severe COVID-19. However, for some clinical decisions, a fine-tuning of our knowledge could be necessary. Understanding the clinical characteristics that anticipate the worse outcome of COVID-19 is necessary for an appropriate use of the resources. For instance, when effective vaccines become available, priorities for vaccination should be defined. In this context, to identify independent risk factors appears as a critical issue, especially if a supposed risk factor is highly prevalent. Hypertension is the most prevalent risk factor: roughly one-third of the population in developed and developing countries is expected to be affected by this condition; the global prevalence of hypertension was estimated to be 1.13 billion in 2015.[20] Also, in many regions, >60% of the population above 60 years old is hypertensive.[21] While individuals with diabetes and/or established cardiovascular disease undoubtedly emerge as priorities for vaccination, the risk of individuals with hypertension without established cardiovascular disease or end-organ damage seems less well defined.

In this matter, the study of Sun and colleagues[8] does not support a significant effect of hypertension on COVID-19 mortality. However, their conclusion should not be generalized for many reasons. First, it was a retrospective analysis performed in two hospitals of a single region of China. The prevalence of hypertension varies widely between ethnic groups and regions. Moreover, regional differences in the level of hypertension knowledge, treatment and control could modify the prevalence of established cardiovascular disease and, in consequence, the risk for severe or fatal COVID-19. Second, the study had a surprisingly low rate of fatal events, and comparisons with other studies could be non-appropriate. For example, the study by Rodilla and colleagues[12] had 10 times higher mortality than the study by Sun and colleagues[8] Also, the scarce number of fatal events made the multivariable analysis less confident. Finally, since it was a retrospective analysis, several sources of bias related with levels of blood pressure, treatments and end-organ damage cannot be discharged. The possibility of this bias was suggested by the unexpected lower risk of diabetes plus hypertension compared to diabetes alone. Beyond these limitations, the study by Sun and colleagues[8] highlights the importance of encouraging the development of regional well designed, multivariable adjusted studies in order to identify accurate predictors for severe or fatal COVID-19 on different populations.

In conclusion and regarding the initial question, "Is hypertension an independent predictor of COVID-19 severity and mortality?" I believe that we cannot count on a single answer for the wide spectrum of patients with hypertension. Thus, it is probable that the answer will vary according to the severity of hypertension and the presence of other risk factors, such as end-organ damage or established cardiovascular disease. Also, the published analysis was based on self-reported or casual and office blood pressure recordings; the presence of white coat and masked hypertension could modify the relationship between hypertension and COVID-19 poor outcomes. Finally, hypertension prevalence increases with age as well, and so do other risk factors, such as diabetes mellitus, chronic kidney disease, and cardiovascular disease. How to correct the effect caused by age, established end-organ damage, level of blood pressure and treatments, is an unresolved issue; possibly due to the high collinearity of these conditions and the inherent limitations of multivariate regression analysis.

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CONFLICTS OF INTEREST

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