

# The influence of diabetes and hypertension on outcome in COVID-19 patients: Do we mix apples and oranges?

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The pandemic of COVID-19 raised many questions about the impact of comorbidities on susceptibility, severity, and outcome in these patients. Hypertension and diabetes are considered as the most prevalent comorbidities in COVID-19 patients.<sup>1,2</sup> It is not fully clarified whether hypertension and diabetes are independent predictors of severity and outcome in COVID-19 patients or they have synergistic negative effect in this population.<sup>3,4</sup>

In the current issue, Sun et al<sup>5</sup> reported that neither hypertension nor elevated blood pressure was an independent risk factor for mortality or acute respiratory distress syndrome (ARDS) and respiratory failure. Hypertension was associated only with increased risk of severe COVID-19 infection. On the other hand, diabetes alone or in combination with hypertension was independent predictor of mortality.<sup>5</sup> The investigators divided all participants into 4 groups: (i) patients without hypertension and diabetes, (ii) patients with hypertension alone, (iii) patients with diabetes alone, and (iv) patients with concomitant diabetes and hypertension. Cardio- and cerebrovascular diseases were more prevalent in patients with hypertension and diabetes alone than in those without these conditions, and the highest prevalence was reported in patients with both conditions.<sup>5</sup> Chronic kidney disease was more prevalent in patients with diabetes with or without hypertension, as well as in patients with diabetes and hypertension in comparison with hypertensive patients.

Analyses restricted to hypertensive patients and those with neither hypertension nor diabetes showed no elevation of risk associated with hypertension, independent of whether other comorbidities were or were not included in the analysis. Even when patients were grouped according to blood pressure values and glucose levels, only glucose level, but not blood pressure, was risk factor for mortality in COVID-19 patients. Diabetes alone or in

combination with hypertension increased the risk of ARDS and respiratory failure. Diabetes and elevated glucose level, but not arterial hypertension and elevated blood pressure, were independent predictors of ARDS and respiratory failure in COVID-19 patients.<sup>5</sup> The multivariable analysis showed the diabetes alone or in combination with hypertension increased the risk of severe COVID-19 infection. Nevertheless, hypertension was also associated with a mild increase in risk of severe infection. Elevated fasting blood glucose, but not elevated blood pressure, was a risk factor for the development of severe COVID-19 infection independently of other comorbid conditions.

Recent meta-analysis included 18 012 COVID-19 patients and revealed that diabetes mellitus and hypertension were moderately associated with severity and mortality for COVID-19, whereas the existence of cardiovascular disease was strongly related to both severity and mortality.<sup>6</sup> However, the authors did not have possibility to investigate the influence of each of these comorbidities in the same model, which did not allow us to conclude whether hypertension and diabetes were independently associated with severity and outcome in COVID-19 patients.<sup>6</sup> Systematic review that involved 15 794 COVID-19 participants showed that hypertension and diabetes were associated with admission in intensive care and mortality in unadjusted model.<sup>7</sup> However, neither hypertension nor diabetes or their combination was not related to COVID-19 severity. Meta-analysis included 310 494 patients and analyzed the relationship between large number of variables and mortality.<sup>3</sup> These parameters included demographics, signs, and symptoms and related morbidities, vital signs, laboratory findings, imaging studies, and underlying diseases. The authors reported that older age, hypertension, and diabetes significantly increased risk of mortality among patients with

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COVID-19. However, the multivariate analysis showed that only diabetes was independently associated with increased mortality.<sup>3</sup>

The main question that arises is whether hypertension and diabetes independently of sex, age, and other comorbidities are associated with severity and adverse outcome of COVID-19. In the current study, Sun et al<sup>5</sup> tried to overcome this problem by separating patients with diabetes and hypertension from other cardiovascular and cerebrovascular diseases, chronic lung, liver, and kidney diseases, endocrine and immune system disorders, or cancer. In these circumstances, hypertension or elevated blood pressure was not recognized as an independent predictor of severity or mortality in COVID-19 patients. Recently published study that included large number of patients with type 1 and type 2 diabetes in England revealed that hypertension was not related to mortality in patients with type 1 diabetes.<sup>8</sup> Interestingly, hypertension was weakly associated with lower COVID-19-related mortality in patients with type 2 diabetes.<sup>8</sup> Furthermore, the use of antihypertensive drugs was related to increased mortality and the use of statins was associated with lower mortality in type 2 diabetes, whereas the relationship with type 1 diabetes was insignificant.<sup>8</sup> The authors stated that drawing conclusions about the possible effects of antihypertensive drugs or statins on COVID-19-related mortality was not possible due to potential confounding factors. Nevertheless, these medications reduce cardiovascular and renal disease, which is why their use can help to decrease not only non-COVID-19-related mortality, but could contribute to the reduction in COVID-19-related mortality, because these findings also revealed that a history of cardiovascular disease and impaired renal function was related to COVID-19-associated mortality.<sup>8</sup>

There are some important limitations of the current study that deserve further discussion. Therapeutic approach in hypertension and diabetes could interfere with final results. Namely, the authors provided information regarding main antihypertensive classes and reported significant differences between groups.<sup>5</sup> Angiotensin-converting enzyme inhibitors (ACEI) and calcium channel blockers (CCB) were used more frequently in patients with hypertension and diabetes than in participants with only one of these conditions. Similar differences were found in the use of beta-blockers and diuretics between patients with both conditions and those with only hypertension or diabetes.<sup>5</sup> ACEI were used significantly less frequently than CCB in the present population that differs from common clinical practice in Western countries, which should be considered during the analysis of obtained findings. Hypoglycemic drugs except insulin were more frequently used in patients with both conditions than in patients with isolated diabetes.<sup>5</sup> Medications, except ACEI, were not included in multivariable analysis and therefore it is not possible to exclude them as a potential confounding factor in this analysis. Furthermore, the influence of obesity was not investigated and body mass index (BMI), as the main parameter of obesity, was not provided in this investigation. This is a very important point because previous studies showed that underweight and obese patients (BMI <20 kg/m<sup>2</sup> and BMI >30 kg/m<sup>2</sup>) were under increased risk of mortality in type 2 diabetes.<sup>8</sup> The investigators included only type

2 diabetic patients and excluded patients with type 1 diabetes, and therefore, obtained results do not have to be necessarily applied to type 2 diabetic patients. Underweight and obesity potentially could be a significant confounding factor in this study group. One should also notice that Asian and black races were important predictors of COVID-related mortality in patients with type 2 diabetes in previous studies.<sup>8</sup> Considering the fact that current study is performed in the Asian population, the obtained findings should be interpreted with caution and possibly could not be fully applied worldwide.

The persisting problem present also in the current study is lack of information about the percentage of patients with hypertension and diabetes prior to hospitalization for COVID-19. Patients with persistent hypertension and diabetes have significantly more pronounced endothelial damage, which is essential in pathogenesis of complications related to COVID-19. On the other hand, chronic patients have more prevalent target organ damage, which increases susceptibility for COVID-19 and risk of adverse outcome in these patients. Data regarding the impact of chronic and newly diagnosed hypertension in COVID-19 patients are scarce. Ran et al recently investigated only chronic hypertensive COVID-19 patients and reported that poor blood pressure control was independently associated with adverse outcome in these patients.<sup>9</sup> Another study showed that stage I pre-diagnosed hypertension existed in only 37% of hospitalized COVID-19 patients, while the percentage of pre-diagnosed stage II and stage III hypertension was significantly higher among these patients (61% and 70%, respectively).<sup>10</sup> This confirms our hypothesis that hypertension is diagnosed concomitantly with COVID-19 in significant portion of these patients. Nevertheless, the authors showed that adverse outcomes (septic shock, respiratory failure, ARDS, ICU admission) and mortality gradually increased with blood pressure elevation, despite the fact that hypertension was diagnosed and treated before hospitalization due to COVID-19.<sup>10</sup>

It is even more complicated relationship between pre-existing and new onset of diabetes among COVID-19 patients. Pre-existing diabetes increases risk of severe COVID-19. However, COVID-19 could also induce new onset of diabetes with metabolic complications and necessity for insulin therapy. Li et al<sup>11</sup> reported that newly diagnosed diabetes was related to higher mortality than known diabetes or hyperglycemia in hospitalized patients with COVID-19. Similar findings were revealed from the Italian group of authors.<sup>12</sup> These studies raised many questions that remained unanswered.

It seems that the role of antihypertensive and anti-diabetic therapy, whenever it has been initiated—before or during COVID-19-related hospitalization, is clearer. The influence of acute and chronic therapy could also impact final results. Ran et al<sup>9</sup> did not find any influence of chronic use of RAAS inhibitors on outcome in hypertensive COVID-19 patients. Findings from diabetic population showed that adequate blood glucose regulation was essential in this population, irrespective of when anti-diabetic therapy was initiated.<sup>13</sup> However, differences between various antihypertensive medications remain to be determined.

There is a consensus about high prevalence of hypertension and diabetes among (i) all COVID-19 patients, (ii) COVID-19 patients who

were admitted in intensive care unit due to complicated course of disease, and (iii) COVID-19 patients with lethal outcome. However, there is no agreement about the role of hypertension and diabetes as independent predictors of outcome in COVID-19 patients. Current study reported independent role of diabetes, but not hypertension, on mortality in COVID-19 patients. This emphasizes the importance of glucose regulation in chronic and newly diagnosed diabetic patients. Interestingly patients with diabetes demonstrated higher risk of mortality than those with concomitant diabetes and hypertension, which is not expected due to negative influence of both conditions in COVID-19 patients. There was no difference in insulin therapy between these two groups of patients, but all antihypertensive classes (ACEI, ARB, CCB, and BB) were used significantly more frequently in patients with both conditions. The latter might be responsible for lower mortality risk in patients with hypertension and diabetes, and therefore, beneficial influence of antihypertensive agents should not be forgotten in COVID-19 patients.

Even though the present study did not reveal independent effect of hypertension on severity and mortality of COVID-19, one should be careful in interpretation of obtained results and should not neglect the importance of hypertension and antihypertensive medications in these patients. Longitudinal multicenter studies with larger number of COVID-19 patients of different races and more detailed information regarding duration of hypertension and diabetes are necessary to investigate isolated and joined effect of hypertension and diabetes irrespective of other common comorbidities and therapy.

#### CONFLICT OF INTEREST

No conflict of interest.

#### AUTHOR CONTRIBUTIONS

Marijana Tadic wrote the review paper. Cesare Cuspidi contributed to detailed review with constructive remarks that substantially changed the review paper.

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