COMMENT

Resistant hypertension and COVID-19: tip of the iceberg?

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Since the outbreak of COVID-19 pandemic many epidemiological studies revealed that common cardiovascular risk factors are frequently seen in these patients, but it was not clear which of them represented an independent predictor of adverse outcomes including mortality [1, 2]. Data coming from China indicated that arterial hypertension might be responsible for worse outcome irrespective of other risk factors and comorbidities, including age, diabetes, coronary artery disease, and renal dysfunction [2]. However, this was not confirmed in studies and some authors claimed that this relationship was a consequence of other confounding factors that frequently meet in hypertensive patients, including antihypertensive treatment, which was at the early stage of pandemic considered responsible for increased admissions in intensive care unit and even higher mortality [3]. This mainly referred to angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor II blockers (ARBs) [4, 5]. However, many studies and meta-analysis that followed the first false alarm dismissed any relation between the aforementioned drug classes and cardiac injury and adverse outcomes in COVID-19 patients [6]. Moreover, investigations showed the beneficial effect of ACEIs and ARBs on the outcome in COVID-19 patients [7]. Many questions still remained unanswered.

In this issue of the Journal, Işik et al. investigated the influence of resistant arterial hypertension on in-hospital mortality in large cohort of COVID-19 patients [8]. The authors used the definition of the American Heart Association for resistant arterial hypertension [8]. Therefore, resistant hypertension was diagnosed in all patients with blood pressure (BP) ≥ 130/80 mmHg who were treated with three antihypertensive drugs including a diuretic or reached <130/80 mmHg with at least four antihypertensive medications [8]. The influence of resistant hypertension on outcomes in COVID-19 patients has not been investigated so far. In the present study the mortality of COVID-19 was surprisingly high (18.7%) in the whole population of 1897 patients. Interestingly, there were no many significant differences in demographic and clinical characteristics between regulated and resistant hypertensive patients [8]. The patients with resistant hypertension had higher prevalence of heart failure and, by definition, higher percentage of different antihypertensive medications than their controlled counterparts. Frequently seen comorbidities in hypertensive patients such as diabetes, coronary artery disease, congestive heart failure, atrial fibrillation, chronic renal failure, cerebrovascular diseases and chronic obstructive pulmonary disease were predictors of mortality due to COVID-19. However, advanced age, resistant hypertension and chronic renal failure were the only independent predictors of lethal outcome in this population [8]. From laboratory parameters, only procalcitonin level was the independent predictor of mortality in the patients.

There are many controversies about the relationship between arterial hypertension and outcomes in COVID-19 patients. The large study that involved 45,418 COVID-19 patients showed that 11,950 of them had controlled BP, 17,025 prehypertension, 13,173 stage 1 hypertension and 3270 stage 2 hypertension [9]. Patients with stage 1 uncontrolled BP had lower risk of COVID-19 death compared with patients with well-controlled BP. There was no association between BP control and COVID-19 diagnosis or hospitalization. Interestingly, stage 1 uncontrolled hypertension in patients older than 70 years, without diabetes, chronic kidney disease and cardiovascular disease was associated with the risk reduction of COVID-19-related death. These findings revealed an inverse relationship between recent BP control and COVID-19–related mortality. This might suggest that BP control can be related with worse COVID-19 outcomes, possibly due to more advanced target organ damage that was not possible to assess in this study [9]. These unexpected results were explained by the authors as a consequence of the fact that patients with well-controlled BP were older, with more comorbidities and had hypertension for a longer time [9]. There was no significant difference in antihypertensive treatment between different groups, which excluded the possibility of any (positive or negative) effect of these medications on the outcomes in the large cohort of patients. Nevertheless, this study included only 28-day outcome and possible many relevant outcomes were missed because they occurred afterwards.

The investigation from Wuhan, the source of pandemic, reported that average systolic BP was independent predictor of heart failure development, but not mortality, in hypertensive COVID-19 patients [10]. Nevertheless, increased BP variability was related with higher mortality and ICU admission. Interestingly, the risk of COVID-induced heart failure was significantly higher in patients with high systolic BP, but not in those patients with elevated diastolic BP [10]. This finding implies that high BP variability perhaps might be more important parameter than BP in prediction mortality and ICU admissions.

Chen et al. showed mortality, septic shock, ARDS, respiratory failure, mechanical ventilation and ICU admission gradually increased from normotensive COVID-19 patients, across those with grade I hypertension, to those with grade II and III hypertension [11]. However, the significant difference was not noticed between normotensive subjects and patients with grade I hypertension, as well as between patients with grade II and III hypertension. The important finding is that the length of COVID-19

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disease and severity of symptoms gradually increased with level of hypertension. Hypertension grade ≥2 was independently associated with adverse events in multivariable analysis [11].

In the present study, Işik et al. did not provide data about the duration of hypertension or target organ damage in studied population, which might enlighten the relationship between resistant hypertension and higher mortality [8]. It is expected that atherosclerosis and target organ damage are more pronounced in patients with resistant hypertension and this may partly explain higher mortality in this group of patients. The authors did not provide correlation between BP level and mortality risk, which would clarify whether higher BP level was responsible for worse outcomes or mortality in patients with resistant hypertension. Considering the fact that BP in patients with resistant hypertension was ~130/80 mmHg, one may assume that BP levels probably did not have decisive role in higher mortality in COVID-19 patients. Coronary artery disease and stroke were more prevalent among resistant hypertensive patients, which indicate advanced atherosclerosis in these patients, but might be also associated with COVID-related hypercoagulability that was detected in these patients [12]. Resistant hypertension is associated with hyperactivation of bio-humoral systems such as sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) [13], which may lead to unfavorable outcomes—development of heart failure, myocardial infarction, stroke, and other cardiovascular complications. Interestingly, in the present study only resistant hypertension, but not cardiovascular and cerebrovascular events, was independently associated with COVID-related mortality.

The obesity is an important risk factor of resistant hypertension, which may be also associated with worse outcome in COVID-19 patients. Unfortunately, its impact was not investigated in this study [8]. In the recent large study that included >2.5 millions of participants in Catalonia showed proportional relationship between body mass index (BMI) and risk of COVID-19 infection, as well as hospitalization due to COVID-19 [14]. The association between BMI and subsequent COVID-related mortality was J-shaped, with a modestly higher risk among patients with BMI ≤ 19 kg/m^2 and a significantly higher risk in patients with BMI ≥ 40 kg/m^2 [14]. It is possible that obesity had an important influence on mortality in the present study considering the high prevalence of overweight and obesity in Turkish population [15].

The current research is a single-center retrospective study and therefore associated with all limitations typical for this kind of investigation, such as limited application of reported findings outside of this population and possible bias during inclusion in this investigation. Different criteria were used for hospitalization due to COVID-19 in different countries and criteria significantly varied over time, which is difficult to assess, but might be important confounding factor. Treatment protocols were also not presented, which might have a very important impact on outcome of COVID-19 patients. The lack of therapeutic data makes difficult the comparison of the current findings with similar studies in other populations. Furthermore, all data about taking antihypertensive medications regularly, before hospitalization due to COVID-19, were self-reported by the patients, which might be a significant source of bias. In these circumstances was difficult to differentiate low adherence and compliance to antihypertensive therapy, particularly during period that preceded hospitalization, from resistant hypertension.

Even though hypertension represents one of the most prevalent comorbidity in COVID-19 patients, the role of hypertension in outcome of these patients has not been clarified yet. Conflicting data from different studies do not clearly show which parameter is the most responsible for adverse outcomes—presence of hypertension, BP level, BP variability, resistance on antihypertensive treatment, or hypertension in combination with other risk factors. Well-conducted investigations with a significant number of hypertensive patients are required to resolve ongoing uncertainties in the association between hypertension and COVID-19.

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China medical treatment expert group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20.
2. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan. China JAMA Intern Med. 2020;180:934–43.
3. Sun Y, Guan X, Jia L, Xing N, Cheng L, Liu B, et al. Independent and combined effects of hypertension and diabetes on clinical outcomes in patients with COVID-19: a retrospective cohort study of Huoshen Mountain Hospital and Guanggu Fangcang Shelter Hospital. J Clin Hypertens (Greenwich). 2021;23:218–31.
4. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5:811–8.
5. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with different severities: a multicenter study of clinical features. Am J Respir Crit Care Med. 2020;201:1380–8.
6. Savarese G, Benson L, Sundström J, Lund LH. Association between renin-angiotensin-aldosterone system inhibitor use and COVID-19 hospitalization and death: a 1.4 million patient nationwide registry analysis. Eur J Heart Fail. 2021;23:476–85.
7. Wang Y, Chen B, Li Y, Zhang L, Wang Y, Yang S. et al. The use of renin-angiotensin-aldosterone system (RAAS) inhibitors is associated with a lower risk of mortality in hypertensive COVID-19 patients: a systematic review and meta-analysis. J Med Virol. 2021;93:1370–7.
8. Işik F, Çap M, Akyüz A, Bilge Ö, Aslan B, İnci Ü, et al. The effect of resistant hypertension on in-hospital mortality in patients hospitalized with COVID-19. J Hum Hypertens. 2021 [in Press].
9. Sheppard JP, Nicholson BD, Lee J, McGagh D, Sherlock J, Koshiaris C, et al. Association between blood pressure control and coronavirus disease 2019 outcomes in 45 418 symptomatic patients with hypertension: an observational cohort study. Hypertension .2021;77:846–55.
10. Ran J, Song Y, Zhuang Z, Han L, Zhao S, Cao P, et al. Blood pressure control and adverse outcomes of COVID-19 infection in patients with concomitant hypertension in Wuhan, China. Hypertens Res. 2020;43:1267–76.
11. Chen R, Yang J, Gao X, Ding X, Yang Y, Shen Y, et al. Influence of blood pressure control and application of renin-angiotensin-aldosterone system inhibitors on the outcomes in COVID-19 patients with hypertension. J Clin Hypertens (Greenwich). 2020;22:1974–83.
12. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. Thromb Res. 2020;194:101–15.
13. Papademetriou V, Tsioufis K, Gradman A, Punzi H. Difficult-to-treat or resistant hypertension: etiology, pathophysiology, and innovative therapies. Int J Hypertens. 2011;2011:438198.
14. Recalde M, Pistillo A, Fernandez-Bertolin S, Roel E, Aragon M, Freisling H, et al. Body mass index and risk of COVID-19 diagnosis, hospitalisation, and death: a cohort study of 2 524 926 Catalans. J Clin Endocrinol Metab. 2021;23:dgab546. https://doi.org/10.1210/clinem/dgab546. Epub ahead of print.
15. Hatemi H, Yumuk VD, Turan N, Arik N. Prevalence of overweight and obesity in Turkey. Metab Syndr Relat Disord. 2003;1:285–90.

AUTHOR CONTRIBUTIONS

MT wrote the paper and CC revised it and added substantial scientific contribution.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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