

Brief updates regarding the links between arterial hypertension and COVID-19 disease

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Background

Hypertension is one of the most common comorbidities in hospitalized COVID-19 patients and its role as one of the significant drivers of mortality in COVID-19 has been disputed since initial cohort analyses. In addition to this, there is growing evidence of how hypertension and COVID-19 share complex pathways of immune-mediated inflammation that ultimately promote the development of cytokine storm syndrome (CSS) in severe cases of COVID-19. The potentially negative prognostic role of renin-angiotensin system (RAAS) inhibition has sparked concern during preliminary reports regarding SARS-CoV-2 cell entry mechanisms. We seek to briefly scrutinize evidence regarding three aspects of the COVID-19 and hypertension relationship.

Section 1 – Hypertension as a disputed cause for worse COVID-19 prognosis

Initial exploratory reports concerning COVID-19 prognosis reported hypertension as the most preva-

lent (20–30%) comorbidity in Chinese-hospitalized patients and an independent contributor to higher mortality relative risk of the infectious disease [1–3]. Hypertensive patients had higher rates of severe disease and more frequent ICU admissions. [4, 5]. Higher values of systolic or diastolic blood pressure (BP) at admission (in addition to age, hsCTnI, hsCRP and lactic acid values) predicted mortality [5, 6]. This was supported by several subsequent unadjusted analyses in which hypertension generated a more than two-fold higher rate of ICU admission and mortality in COVID-19 patients [7, 8].

However, subsequently published papers (such as the Italian SARS-RAS study) [9, 10] disputed the undifferentiated role of hypertension (and of RAAS inhibitors) as a mortality factor for patients with COVID-19, as only age, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD) independently predicted mortality. After adjusting for confounding factors, hypertension was not associated with higher mortality risk.

More recent data stemming from the CAPACITY registry, which analysed a large number of cohorts (n=9,197) of hospitalized patients, reassessed the impact of pre-existing hypertension on COVID-19 prognosis [11]. Whereas hypertension did provide incremental in-hospital mortality in crude analysis, adjustment for only age and, in a subsequent analysis, for age, gender, DM, CKD, COPD and heart failure (HF) demonstrated no excess risk of death generated by hypertension or by RAAS inhibitors treatment. Interestingly, RAAS inhibitors significantly reduced mortality risk by 12% in COVID-19 hospitalized patients after adjusting for the aforementioned factors. This led

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to hypothesis that hypertension itself does not induce incremental mortality, which was further substantiated by larger-scale prospective Spanish population-based cohort studies [12]. In reality, advanced age and more extensive hypertension-mediated target organ damage (HMOD) may justify the worse prognosis in hypertensive patients.

Interestingly, in an apparent paradox, patients with strictly controlled blood pressure showed a higher risk of death in one of the largest community-dwelling cohorts regarding COVID-19 outcomes [13]. This was explained by more advanced age, a longer history of hypertension and thus, more numerous systemic consequences (*i.e.*, atherosclerosis). Hence, elder-controlled hypertensive patients may be at risk for a worse COVID-19 prognosis because they represent a much more fragile population.

In conclusion, hypertension single-handedly does not appear to provide a higher risk of death in COVID-19 hospitalized patients. However, the consequences of long-acting hypertension represented by HMOD, such as CKD, cerebrovascular disease and heart failure, can independently predict worse outcomes, especially in older infected patients.

Section 2 – Immune-mediated inflammation as a link between hypertension and COVID-19 disease

Extensive research has underlined the critical play of immune-mediated hyper-inflammation leading to cytokine storm as a cause of acute severe acute respiratory syndrome development (ARDS) and subsequent multisystem organ failure (MSOF) in COVID-19 [14, 15]. The concept of COVID-19 cytokine-storm syndrome (CSS) is supported by at least three pillars of evidence [15]. Firstly, higher levels of inflammation and immune mediators (CRP, IL-6) have been repeatedly associated with respiratory failure and death. Secondly, autopsy studies have shown minimal viral presence, despite histological signs of tissular hyperinflammation. Thirdly, specific anti-inflammatory or immunomodulatory treatments (starting with corticosteroids and tocilizumab in RECOVERY trial) have improved survival in severe cases of COVID-19 [16–19].

Interestingly, a growing body of clinical and experimental evidence is now supporting the contribution of highly complex immune mechanisms to the development of hypertension. Essentially, immune cell migration to perivascular fat, kidneys, heart and brain may promote chronic inflammation, which disrupts blood pressure physiology. Danger-associated molecular patterns (DAMPs) and hypertension-specific neoantigens, which can result from non-immune pathways (moderate transient increases in blood pressure, oxidative stress), can lead

to multi-cellular hyperactivation [macrophages via NLRP3 inflammasome activation, dendritic cells and subsequently various type of B and T cells (cytotoxic T cells, abnormally function regulatory T cells, natural killer T cells)] which promote inflammation, fibrosis, vessel tone (providing stiffening and dysfunction), renal sodium reabsorption and autoantibody effects [20]. In the clinical context, data derived from meta-analyses have shown how higher levels of CRP, hs-CRP and IL-6 are associated with the risk of hypertension [21].

The landmark CANTOS trial recently documented the potential opportunity provided by the control of immune-mediated inflammation for improving cardiovascular disease outcomes [22]. Canakinumab improved cardiovascular outcomes via interleukin-1 β -modulation of the NLRP3 inflammasome function in patients with previous myocardial infarction. With regard to hypertension, pharmacological inhibition of the NLRP3 inflammasome reduced BP and limited renal inflammation, dysfunction and fibrosis in animal models [23].

In this context, the worse potential outcome in hypertensive patients may also be explained from a hyper-inflammatory state point of view. COVID-19 may contribute to ACE/Ang II/AT1R activation and inhibition of the ACE-2/Ang1-7/Mas axis in hypertensive patients, leading to immune cell hyperactivation leading to tissular infiltration and accumulation, gut leakiness, micro thrombosis and endothelial dysfunction, ROS generation and oxidative stress and ultimately to CSS development, particularly in those affected by HMOD [24, 25].

Section 3 – The controversial role of antihypertensive treatment and COVID-19 prognosis

Extensive controversy and concerns emerged during the initial phase of the COVID-19 pandemic due to fear of higher COVID-19 virulence by over-expression of ACE-2, which is part of RAAS but is also the primary receptor for both SARS-CoV viruses. This has caused ACE-I/ARB therapy empirical interruption, which may have impacted hypertension or HF chronic treatment. Subsequent reports have clarified that there is no deleterious effect of pre-existing ACE-I/ARB therapy in patients that become infected with SARS-CoV2 [26, 27]. Reassuringly, the European Society of Cardiology (ESC) issued clear recommendations supporting the continuation of ACE-I/ARB treatment.

Two landmark randomized clinical trials (BRACE-CORONA and REPLACE-COVID) have provided indisputable evidence supporting the continuation of ACE-I/ARBs after contracting COVID-19 [28, 29]. No higher risk of ICU

admission or death was documented in patients who continued treatment. Moreover, in-depth analyses provided by the CAPACITY-COVID Consortium show that treatment with ACE-I or ARBs had no detrimental effect in hypertensive COVID-19 patients and, if anything, may actually exhibit a trend of protective effect against mortality [OR 0.88 (CI 95% 0.78–0.99)].

Consequently, ESC recommendations regarding managing hypertensive patients during COVID-19 have recently been updated. It is clearly stated that there is no need to adjust or stop ACE-I/ARBs in the absence of hypotension or acute renal injury [30]. Furthermore, the importance of telemedicine is underlined as there is growing evidence of improving outcomes in hypertension management [31, 32].

Conflict of Interest

The authors declare no conflict of interest.

References

1. L. Bao *et al.*, “Reinfection could not occur in SARS-CoV-2 infected rhesus macaques”, bioRxiv, 2020, doi: 10.1101/2020.03.13.990226.
2. J. Chen *et al.*, “Hypertension as an independent risk factor for severity and mortality in patients with COVID-19: a retrospective study”, *Postgrad. Med. J.*, vol. 98, no. 1161, pp. 515 LP – 522, Jul. 2022, doi: 10.1136/postgradmedj-2021-140674.
3. F. Zhou *et al.*, “Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study”, *Lancet*, 2020, doi: 10.1016/S0140-6736(20)30566-3.
4. W. Guan *et al.*, “Clinical Characteristics of Coronavirus Disease 2019 in China”, *N. Engl. J. Med.*, 2020, doi: 10.1056/nejmoa2002032.
5. J. Ran *et al.*, “Blood pressure control and adverse outcomes of COVID-19 infection in patients with concomitant hypertension in Wuhan, China”, *Hypertens. Res.*, no. 923, pp. 1267–1276, 2020, doi: 10.1038/s41440-020-00541-w.
6. A. Caillon *et al.*, “High Systolic Blood Pressure at Hospital Admission Is an Important Risk Factor in Models Predicting Outcome of COVID-19 Patients”, *Am. J. Hypertens.*, vol. 34, no. 3, pp. 282–290, Apr. 2021, doi: 10.1093/ajh/hpaa225.
7. S. Bae, S. R. Kim, M.-N. Kim, W. J. Shim, and S.-M. Park, “Impact of cardiovascular disease and risk factors on fatal outcomes in patients with COVID-19 according to age: a systematic review and meta-analysis”, *Heart*, vol. 107, no. 5, pp. 373 LP – 380, Mar. 2021, doi: 10.1136/heartjnl-2020-317901.
8. R. Pranata, M. A. Lim, I. Huang, S. B. Raharjo, and A. A. Lukito, “Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: A systematic review, meta-analysis and meta-regression”, *JRAAS - J. Renin-Angiotensin-Aldosterone Syst.*, vol. 21, no. 2, 2020, doi: 10.1177/1470320320926899.
9. C. Mancusi *et al.*, “Determinants of healing among patients with coronavirus disease 2019: the results of the SARS-RAS study of the Italian Society of Hypertension”, *J. Hypertens.*, vol. 39, no. 2, pp. 376–380, Feb. 2021, doi: 10.1097/HJH.0000000000002666.
10. G. Iaccarino, G. Grassi, C. Borghi, C. Ferri, M. Salvetti, and M. Volpe, “Age and Multimorbidity Predict Death Among COVID-19 Patients: Results of the SARS-RAS Study of the Italian Society of Hypertension”, *Hypertens. (Dallas, Tex. 1979)*, vol. 76, no. 2, pp. 366–372, Aug. 2020, doi: 10.1161/HYPERTENSIONAHA.120.15324.
11. E. McFarlane *et al.*, “The impact of pre-existing hypertension and its treatment on outcomes in patients admitted to hospital with COVID-19”, *Hypertens. Res.*, vol. 45, no. 5, pp. 834–845, 2022, doi: 10.1038/s41440-022-00893-5.
12. U. Fresán, M. Guevara, C. Trobajo-Sanmartín, C. Burgui, C. Ezpeleta, and J. Castilla, “Hypertension and Related Comorbidities as Potential Risk Factors for COVID-19 Hospitalization and Severity: A Prospective Population-Based Cohort Study”, *J. Clin. Med.*, vol. 10, no. 6, 2021, doi: 10.3390/jcm10061194.
13. J. P. Sheppard *et al.*, “Association Between Blood Pressure Control and Coronavirus Disease 2019 Outcomes in 45 418 Symptomatic Patients With Hypertension: An Observational Cohort Study”, *Hypertens. (Dallas, Tex. 1979)*, vol. 77, no. 3, pp. 846–855, Mar. 2021, doi: 10.1161/HYPERTENSIONAHA.120.16472.
14. D. Ragab, H. Salah Eldin, M. Taeimah, R. Khattab, and R. Salem, “The COVID-19 Cytokine Storm; What We Know So Far”, *Frontiers in Immunology*, vol. 11, 2020.
15. L. Y. C. Chen and T. T. T. Quach, “COVID-19 cytokine storm syndrome: a threshold concept”, *The Lancet Microbe*, vol. 2, no. 2, pp. e49–e50, Feb. 2021, doi: 10.1016/S2666-5247(20)30223-8.
16. B. Schurink *et al.*, “Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study”, *The Lancet Microbe*, vol. 1, no. 7, pp. e290–e299, Nov. 2020, doi: 10.1016/S2666-5247(20)30144-0.
17. B. J. Webb *et al.*, “Clinical criteria for COVID-19-associated hyperinflammatory syndrome: a cohort study”, *Lancet Rheumatol.*, vol. 2, no. 12, pp. e754–e763, Dec. 2020, doi: 10.1016/S2665-9913(20)30343-X.
18. L. Y. C. Chen, R. L. Hoiland, S. Stukas, C. L. Wellington, and M. S. Sekhon, “Confronting the controversy: interleukin-6 and the COVID-19 cytokine storm syndrome”, *The European respiratory journal*, vol. 56, no. 4, Oct-2020, doi: 10.1183/13993003.03006-2020.
19. RECOVERY Collaborative Group, “Dexamethasone in Hospitalized Patients with Covid-19”, *N. Engl. J.*

- Med., vol. 384, no. 8, pp. 693–704, Jul. 2020, doi: 10.1056/NEJMoa2021436.
20. G. R. Drummond, A. Vinh, T. J. Guzik, and C. G. Sobey, “Immune mechanisms of hypertension”, *Nat. Rev. Immunol.*, vol. 19, no. 8, pp. 517–532, 2019, doi: 10.1038/s41577-019-0160-5.
 21. A. Jayedi, K. Rahimi, L. E. Bautista, M. Nazarzadeh, M. S. Zargar, and S. Shab-Bidar, “Inflammation markers and risk of developing hypertension: a meta-analysis of cohort studies”, *Heart*, vol. 105, no. 9, pp. 686–692, May 2019, doi: 10.1136/heartjnl-2018-314216.
 22. P. M. Ridker *et al.*, “Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease”, *N. Engl. J. Med.*, vol. 377, no. 12, pp. 1119–1131, Aug. 2017, doi: 10.1056/NEJMoa1707914.
 23. S. M. Krishnan *et al.*, “Pharmacological inhibition of the NLRP3 inflammasome reduces blood pressure, renal damage, and dysfunction in salt-sensitive hypertension”, *Cardiovasc. Res.*, vol. 115, no. 4, pp. 776–787, Apr. 2019, doi: 10.1093/cvr/cvy252.
 24. S. Muhamad, A. Ugusman, J. Kumar, D. Skiba, A. Cristina, and S. E. Silva, “COVID-19 and Hypertension: The What, the Why, and the How”, vol. 12, no. May, pp. 1–11, 2021, doi: 10.3389/fphys.2021.665064.
 25. M. Peng, J. He, Y. Xue, X. Yang, S. Liu, and Z. Gong, “Role of Hypertension on the Severity of COVID-19: A Review”, *J. Cardiovasc. Pharmacol.*, vol. 78, no. 5, pp. e648–e655, Nov. 2021, doi: 10.1097/FJC.0000000000001116.
 26. J. Hippisley-Cox *et al.*, “Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people”, *Heart*, vol. 106, no. 19, pp. 1503 LP – 1511, Oct. 2020, doi: 10.1136/heartjnl-2020-317393.
 27. M. Vaduganathan, O. Vardeny, T. Michel, J. J. V McMurray, M. A. Pfeffer, and S. D. Solomon, “Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19”, *N. Engl. J. Med.*, vol. 382, no. 17, pp. 1653–1659, Apr. 2020, doi: 10.1056/NEJMsr2005760.
 28. R. D. Lopes *et al.*, “Effect of Discontinuing vs. Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19: A Randomized Clinical Trial”, *JAMA*, vol. 325, no. 3, pp. 254–264, Jan. 2021, doi: 10.1001/jama.2020.25864.
 29. J. B. Cohen *et al.*, “Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial”, *Lancet Respir. Med.*, vol. 9, no. 3, pp. 275–284, Mar. 2021, doi: 10.1016/S2213-2600(20)30558-0.
 30. The Task Force for the management of COVID-19 of the European Society of Cardiology, “ESC guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 2—care pathways, treatment, and follow-up”, *Eur. Heart J.*, vol. 43, no. 11, pp. 1059–1103, Mar. 2022, doi: 10.1093/eurheartj/ehab697.
 31. R. J. Mcmanus *et al.*, “Home and Online Management and Evaluation of Blood Pressure (HOME BP) using a digital intervention in poorly controlled hypertension : randomised controlled trial”, pp. 1–13, 2021, doi: 10.1136/bmj.m4858.
 32. S. Omboni, E. Panzeri, and L. Campolo, “E-Health in Hypertension Management: an Insight into the Current and Future Role of Blood Pressure Telemonitoring”, *Curr. Hypertens. Rep.*, vol. 22, no. 6, p. 42, Jun. 2020, doi: 10.1007/s11906-020-01056-y.