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LETTER TO THE EDITORS

No adequate evidence indicating hypertension as an independent risk factor for COVID-19 severity

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The meta-analysis of Li and colleagues entitled *Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China* indicated that patients with hypertension are more likely to develop severe/ICU cases after 2019-nCoV infection. Hypertension accounted for 28.8% of ICU/severe cases, but 14.1% of non-ICU/severe cases. Moreover, the proportion of hypertension was about twofold higher in ICU/severe cases than in their non-ICU/severe counterparts (risk raio (RR) 2.03 (1.54–2.68), $p < 0.00001$) [1]. However, these pooled results were obtained by analyzing data from only three studies, and moderate heterogeneity was shown ($I^2 = 41\%$). More importantly, none of the three included studies adjusted baseline confounding factors between ICU/severe cases and non-ICU/severe cases, so a large number of confounders such as age and gender may seriously affect the effect size of this association. In more recent studies, Chen and colleagues [2] reported that critically ill patients were more likely to have coexisting hypertension compared to mild cases (35 (27.8%) versus 14 (58.3%), $p = 0.003$). Univariate logistic regression analysis indicated that hypertension was significantly associated with the severity of COVID-19 (OR 3.64 (1.48–8.96), $p = 0.005$). However, statistical significance was not reached in multivariate logistic regression model (OR 2.59 (0.61–10.98), $p = 0.198$), i.e. comorbid hypertension was not an independent risk factor for the severity of COVID-19 in this study. A recent retrospective cohort study reported that coexisting hypertension was more commonly seen in patients with ARDS than in those without it (16 (13.7%) versus 23 (27.4%), $p = 0.02$) [3]. Bivariate Cox regression analysis showed that comorbid hypertension was significantly associated with higher incidence of ARDS (HR 1.82 (1.13–2.95), $p = 0.005$). However, this study did not adjust potential confounding factors, making the real magnitude of the independent association unknown. Therefore, the results from aforementioned studies need to be interpreted cautiously due to the potential bias and limited power. In brief, currently there is no direct evidence indicating comorbid hypertension as an independent risk factor for the severity of COVID-19. Further studies with an appropriate design and adequate power are required to robustly investigate this relationship.

It is suggested by Fang and colleagues that patients with hypertension who are often treated with RAS inhibitors may have an increased risk for COVID-19 infection [4], since treatment of RAS inhibitors was reported to increase the expression of ACE2, through which SARS-CoV-2 bind to the target cells [5]. On the other hand, previous study demonstrated that ACE2 expression is suppressed following SARS infection, inducing excessively activation of RAS and aggravation of pneumonia [6]. Thus, whether RAS inhibitors increase or decrease the risk for SARS-CoV-2 infection and disease progression has been a recent topic of intense debate. Fang et al. proposed that patients with COVID-19 should be monitored for ACEIs and ARBs, and anti-hypertensive calcium channel blockers could be a suitable alternative treatment [4]. Nevertheless, based on current evidences, we do not suggest arbitrary withdrawl or alteration of usual anti-hypertensive treatment, as complications induced by poorly controlled blood pressure might cause exacerbation of COVID-19 and even death. Indeed, the Council on Hypertension of European Society of Cardiology (ESC) also recommended that treatment with usual anti-hypertensive therapy should be continued, because there is no evidence suggesting the discontinuation of treatment with RAS inhibitors because of the COVID-19 infection [7].

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