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COMMENT

Association between blood pressure and COVID-19 severity

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With the worldwide prevalence of COVID-19, concerns were reported about not only increased blood pressure might be due to increased emotional stress, increased alcohol consumption, less physical activity and less medical care, but also its associated increased cardiovascular events in patients with hypertension and COVID-19 [1]. Although hypertension was reported to be one of the associated factors for COVID-19 severity, there were also reports on the less or no association; thus, confirmation of a close relationship between hypertension and COVID-19 severity has not yet been obtained [2]. Furthermore, although low blood pressure also was reported to be associated with COVID-19 severity [3], there were few reports evaluating an effect of hypotension on COVID-19 severity in Japanese patients. Sakurai et al. found that pre-existing hypertension was associated with critical outcomes defined by high-flow oxygen use, non-invasive and invasive positive-pressure ventilation, extracorporeal membrane oxygenation or death during hospitalization, while in patients with preexisting hypertension, blood pressure and pulse pressure themselves at their admission were not associated with critical outcomes [4]. However, interestingly, in patients without preexisting hypertension, high or low blood pressure and high pulse pressure at their admission were associated with critical outcomes [4]. These findings must be important for assessing the risk of critical outcomes when starting to treat patients with COVID-19.

Hypertension was reported to be more frequent as a sequela of COVID-19 than in non-COVID-19 patients, and COVID-19 was considered to be a risk factor for the development of hypertension [5, 6]. The details of the mechanisms of blood pressure elevation are unknown, although it has been suggested that increased activation of renin system and reduced renal function may be involved. Renin-angiotensin system (RAS) inhibitors, especially angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, have been reported to increase organ angiotensin converting enzyme 2 (ACE2) expression in the experimental animal studies [7]. Furthermore, since ACE2 plays an important role in the mechanism of COVID-19 infection, it has been suggested that RAS inhibitors increase the risk of COVID-19 infection and may also be associated with COVID-19 severity [8]. In the clinical observational studies, RAS inhibitors were reported to have aggravative effects on COVID-19 severity, while others reported an opposite effect, indicating that unidirectional effect has not been identified as a result of the meta-analysis [9]. Randomized control trials (RCTs) have also been conducted to investigate the effect of RAS inhibitors on COVID-19 severity [10, 11]. A small intervention study reported that telmisartan reduced mortality by its anti-inflammatory effects [10], while a larger intervention study reported the conflicting finding of a lower hospital survival rate in the angiotensin receptor blockers group than in the control group [11], indicating that there is no consensus to recommend for continuation, discontinuation or new introduction of RAS inhibitors in patients with hypertension and COVID-19. Since the ACE2 gene is located on the X chromosome, ACE2 expression is known to be different between male and female and is more highly expressed in Asian women than in other ethnic groups [12]. There have also been reports of sex differences in the efficacy of RAS inhibitors [13], an area where further detailed studies are expected. The figure shows some of the most important findings of the study by Sakurai et al. and the unclarified issues in terms of association of blood pressure and COVID-19 severity (Fig. 1). The involvement of differences among race, ethnicity, and sex, the involvement of virus mutant strains, antihypertensive drugs, treatments for COVID-19, and vaccination status are expected to be

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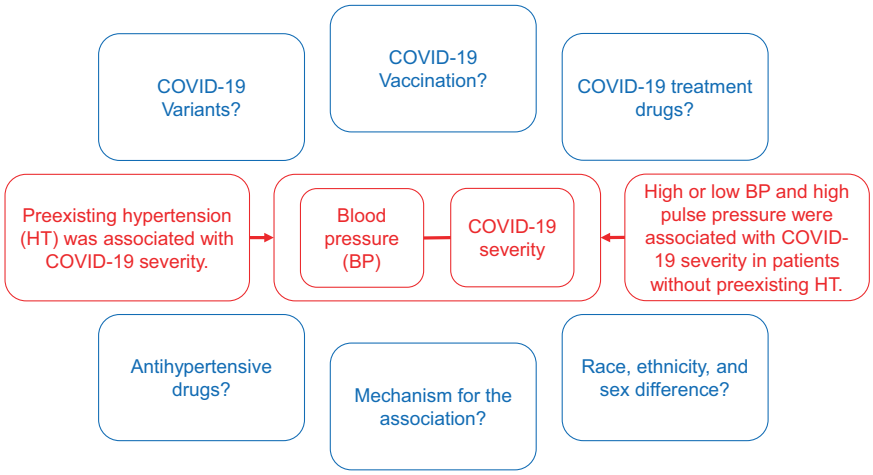

Fig. 1 Association between blood pressure and COVID-19 severity. The red text indicates the regions identified in the study by Sakurai et al. [4], whereas the blue text indicates unclarified issues

evaluated and also to clarify mechanisms of the association between blood pressure and COVID-19 severity.

Compliance with ethical standards

Conflict of interest FY reports research funding from AstraZeneca K. K. and Ono Pharmaceutical Co., Ltd outside the submitted work.

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