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COMMENT

The necessity of investigations to clarify sex and racial disparities in pathophysiology of Long COVID

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As of November 2023, people's daily lives are returning to pre-COVID-19 conditions without the behavioral restrictions that were imposed at the beginning of the COVID-19 pandemic. Conversely, as of March 2023, the cumulative number of COVID-19 patients was approximately 676 million worldwide [1], with an estimated 6.2% (roughly 40 million) suffering from long COVID symptoms [2]. A recent report from the United Kingdom estimated that the annual primary care expenditure for long COVID in the United Kingdom is approximately 23 million pounds (Japanese yen equivalent: approximately 4.4 billion yen) [3], underscoring its persistent global challenge.

Nonetheless, owing to the extremely heterogeneous symptoms of long COVID, the pathophysiology, diagnostic approaches, and therapeutic strategies of long COVID are not yet well established. In addition, sex differences in long COVID risk and symptoms have been indicated. Multiple studies have reported that women are more prone to develop long COVID than men, despite men exhibiting greater severity and mortality in COVID-19's acute phase [4]. A meta-analysis involving 13,340 patients (women: 47.6%) from 20 studies highlighted that women were more affected by long COVID than men. In this meta-analysis, the occurrence of any symptoms of long COVID was 56.3% in women compared to 45.5% in men, and female sex was significantly associated with any symptoms (odds ratio [OR] 1.52, 95% confidence interval [CI] 1.27–1.82), respiratory symptoms (OR 1.20, 95% CI 1.20–1.45), mental health symptoms (OR 1.67, 95% CI 1.21–2.29), and fatigue (OR 1.54, 95% CI 1.32–1.79) [5]. The underlying mechanisms of sex differences in the risk of long COVID have not been clarified. However, sex-specific immunological differences driven by the X chromosome and sex hormones may be one of these mechanisms [4]. Also, sex-related social factors and worse health self-perception in women than in men may contribute to some of the major symptoms of long COVID, such as anxiety, depression, and pain [4]. Furthermore, from an epidemiological standpoint, survival bias and higher mortality of older men compared to women during the acute phase may influence the association of sex and risk of long COVID [4]. Therefore, to clarify the risk factors and etiology of long COVID by sex might be important.

Ozawa et al. investigated sex-specific risk factors for long COVID in a Japanese cohort of 981 hospitalized COVID-19 patients (median age: 52 y, men: 63.2%). Long COVID symptoms were assessed using a self-reported questionnaire during hospitalization, 3, 6, and 12 months after COVID-19 diagnosis. They suggested that women with hypertension were significantly less likely to develop long COVID symptoms than those without hypertension (OR 0.51, 95% CI 0.27–0.98, $p = 0.043$), and that Ca channel blocker (CCB) administration, rather than having hypertension, was significantly associated with a reduction in the frequency of alopecia (OR 0.14, 95% CI 0.03–0.67, $p = 0.015$), memory impairment (OR 0.14, 95%CI 0.02–0.82, $p = 0.029$), sleeping disorders (OR 0.17, 95% CI 0.04–0.67, $p = 0.012$), tinnitus (OR 0.23, 95% CI 0.05–0.98, $p = 0.047$), sputum (OR 0.31, 95% CI 0.10–0.92, $p = 0.035$), and fever (OR 0.33, 95% CI 0.12–0.93, $p = 0.036$). In contrast, the risk factors for long COVID in men appeared unrelated to hypertension or CCB use, but rather linked to the necessity for supplemental oxygen during hospitalization (OR 2.02, 95% CI 1.47–2.76, $p < 0.001$) [6].

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A previous report from the Japanese Society of Hypertension Project team on COVID-19 summarized that COVID-19 evokes systemic vascular damage via endothelial dysfunction, abnormalities of the coagulation-fibrinolytic system, etc., and induces damage to the cardiovascular system, kidney, and other hypertension-related organs in both acute and chronic phases [4]. Although it has not been clarified whether hypertension is a risk factor for COVID-19 severity in the acute phase or long COVID, it is quite promising that COVID-19 and hypertension share some of the same pathophysiology [4]. On the other hand, the association between antihypertensive treatment and severity/mortality of COVID-19 has been the focus of attention since the beginning of the pandemic, as SARS-CoV-2 incorporates into cells in the respiratory tract via angiotensin-converting enzyme 2 (ACE-2) and the negative impacts of the use of ACE inhibitors or angiotensin receptor blockers (ARB) have been of concern. Despite initial concerns, subsequent observational studies and randomized trials have indicated that treatment with ACE inhibitors or ARB has a neutral impact on the prognosis of patients with COVID-19.

Wojciechowska. et al. also reported that patients with hypertension already treated with any first-line antihypertensive drug (ACE inhibitors, ARBs, beta-blockers, CCBs or thiazide/thiazide-like diuretics) had a significantly lower risk of in-hospital death (OR 0.25, 95% CI 0.2.0.3, $p < 0.001$) compared to non-treated hypertensive. Pre-hospitalized use of all classes of antihypertensive medications (ACE inhibitors, ARBs, beta-blockers, thiazide/thiazide-like diuretics) was associated with a lower risk of in-hospital death, and pre-hospitalized use of CCB was associated with lower mortality compared to non-treated hypertensive patients with an OR of 0.61 (95% CI 0.4–0.8) in this study [7]. As this study suggests, many guidelines recommend continuation of antihypertensive medication in COVID-19 patients, regardless of the class of antihypertensive medication. On the other hand, a meta-analysis by Kow et al. compared the effect of preadmission/prediagnosis use of CCBs on the clinical outcomes in hypertensive patients with COVID-19 consisting of 17 observational studies until July 2021 and failed to reveal significant differences in the prognosis of COVID-19 in hypertensive patients with prediagnosis use of CCBs compared to non-use of CCBs [8]. However, subgroup analysis of this meta-analysis revealed that studies originating from East Asia showed a significant reduction in the odds of all-cause mortality (pooled OR 0.50, 95% CI 0.37–0.68) and the odds of severe illness (pooled OR 0.51, 95% CI 0.33–0.78) in the prediagnosis use of CCBs [8]. The mechanisms underlying this finding have not yet been fully clarified. As the authors speculated in their discussion, it is possible that there are racial differences in the effects of CCBs on the prognosis of COVID-19. Also, calcium (Ca2+) modulates the interaction of the SARS-CoV-2 S protein with human ACE-2, and Ca2+ is required to enhance the fusion process of SARS-CoV-2. In addition, some important inflammatory factors involved in SARS-CoV-2 infection are dependent on Ca2+ levels [9]. Therefore, blocking calcium channels may have potential therapeutic effects on COVID-19 prognosis [10]. Furthermore, the vasodilatory effects of CCBs in the pulmonary and systemic vasculature could mitigate the effects of inflammation, hypercoagulation, edema, and local vasoconstriction, developed as a response to SARS-CoV-2 infection, and facilitate oxygen delivery and survival of host cells. However, after a meta-analysis by Kow et al., drastic changes in the environment surrounding COVID-19, such as the development of vaccines and new treatments for COVID-19, as well as the emergence of mutant strains of SARS-CoV-2, can have a substantial influence on the effects of CCBs on COVID-19 prognosis. Further investigations are needed to clarify the effects of antihypertensive drugs on COVID-19 prognosis. On the other hand, a few studies have evaluated the relationship between antihypertensive medication and the risk of developing long COVID. Therefore, the findings from Ozawa et al. were quite interesting that the use of CCBs was associated with a lower risk of developing long COVID only in women [6]. For the mechanism of this finding, as the authors suggested in their discussion, CCBs may contribute to maintaining hair follicle blood supply by dilating the vessels around the hair follicles and preventing telogen effluvium [6]. In addition, the potential effects of CCBs during COVID-19 acute phase, which we have already discussed in this commentary, could contribute to some of the protective effects of CCBs on the progression to long COVID. Nonetheless, the numbers of events, especially in the subgroup analysis stratified by sex, in the study by Ozawa. et al. were not large enough and thus, it is the state of being premature to determine robustness of their findings. In addition, we still lack sufficient information for the potential racial differences in the risk, pathophysiology, and treatment efficacy of long COVID. In fact, some studies from Western countries have reported racial differences in the risk of long COVID [11]. However, these results may be influenced by socioeconomic factors and the health care system in each country, and we have not obtained enough evidence to reveal pure biological racial differences in the pathophysiology of long COVID.

With the normalization of people's lives, attention to COVID-19 and long COVID has been gradually diminishing. However, the worldwide problem associated with long COVID still has substantial and immeasurable impacts on society, owing to its wide variation of symptoms and high morbidity. Regarding the heterogeneity of long

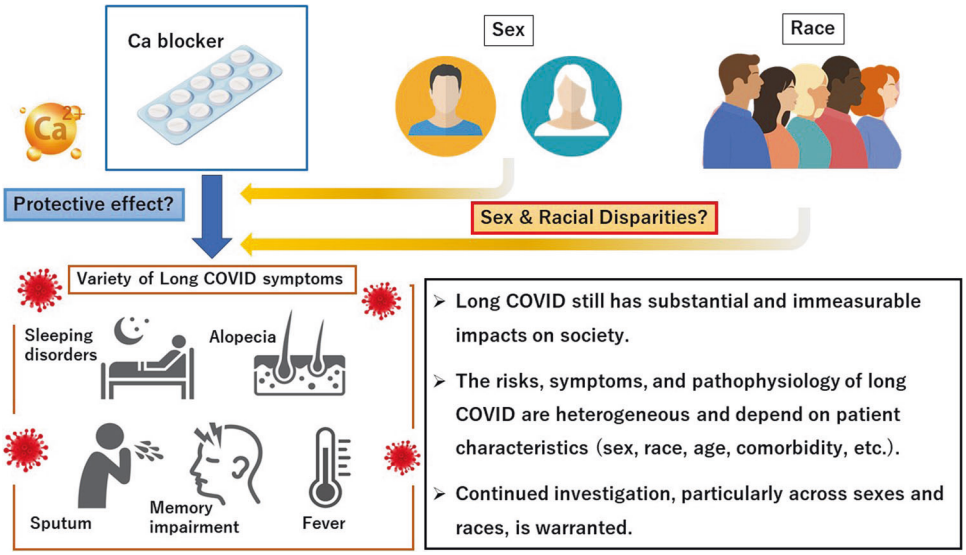

Fig. 1 Potential sex and racial disparities in the protective effect of Ca channel blockers on long COVID

COVID risks, symptoms, and pathophysiology, continued investigation particularly across sexes and races, is warranted (Fig. 1).

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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