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REVIEW ARTICLE

Long COVID and hypertension-related disorders: a report from the Japanese Society of Hypertension Project Team on COVID-19

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Abstracts

The coronavirus disease 2019 (COVID-19) affects infected patients even after the acute phase and impairs their health and quality of life by causing a wide variety of symptoms, referred to as long COVID. Although the evidence is still insufficient, hypertension is suspected to be a potential risk factor for long COVID, and the occurrence of cardiovascular diseases seems to be a key facet of multiple conditions observed in long COVID. Nonetheless, there are few reports that comprehensively review the impacts of long COVID on hypertension and related disorders. As a sequel to our previous report in 2020 which reviewed the association of COVID-19 and hypertension, we summarize the possible influences of long COVID on hypertension-related organs, including the cardiovascular system, kidney, and endocrine system, as well as the pathophysiological mechanisms associated with the disorders in this review. Given that the clinical course of COVID-19 is highly affected by age and sex, we also review the impacts of these factors on long COVID. Lastly, we discuss areas of uncertainty and future directions, which may lead to better understanding and improved prognosis of clinical problems associated with COVID-19.

Keywords Long COVID · Hypertension · Cardiovascular disease · Kidney · Endocrine · Frailty · Sex difference

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Graphical Abstract

Graphical Abstract for:

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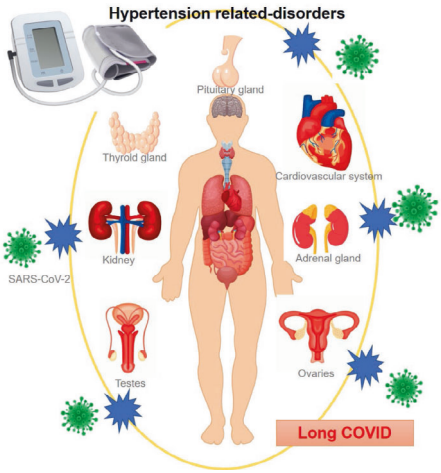

This article summarizes and discuss recent findings on

- Long COVID and hypertension-related disorders
- The pathophysiological mechanisms associated with the disorders
- The effects of age and sex on long COVID

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global pandemic, resulting in more than 20 million confirmed cases in Japan and 600 million cases in the world (as of Sep 2022) [1]. Emerging data indicate that COVID-19 affects patients even after an acute phase and impairs their quality of life, refers to as "long COVID" (also called post-COVID conditions or post-acute COVID-19 syndrome). Long COVID includes a wide range of ongoing health problems that last weeks or even several years and it has become a serious global problem.

In this COVID-19 pandemic era, hypertension has been receiving increased attention. As we summarized in our previous report in 2020 which reviewed the association of COVID-19 and hypertension [2], complications of COVID-19 can be recognized as vascular disorders [2, 3]. In addition, hypertension-related diseases, including cardiovascular disease (CVD) and chronic kidney disease (CKD), are among the most common risk factors for severe COVID-19 [4, 5]. Also, even the evidence of hypertension as a potential risk factor for long COVID is still insufficient [5], one observational study reported that pre-existing hypertension was a predictor of long COVID [6]. Moreover, recent evidence suggests that hypertension and related diseases might occur as the sequelae of COVID-19 [4, 5, 7]. Multiple studies reported elevated blood pressure [8] and excess burdens of hypertension as a post-acute sequelae of COVID-19 [9, 10]. Given that hypertension is a systemic disease and closely associated with multiple organs (brain, heart, vasculature, kidney, endocrine systems, etc.), whether and how long COVID impacts these organs is an important issue that needs to be addressed. As a sequel to our previous report on COVID-19 and hypertension in 2020 [2], we here summarize recent findings on the relationship between long COVID and hypertension-related disorders, and describe its possible mechanisms. We also review the influences of age and sex on long COVID, as these biological factors are reported as potential factors that affect risk of long COVID. Along with this review, the updated information on the impact of COVID-19 on hypertension is discussed as a separate manuscript [5]. In that manuscript, we discussed the relationship between long COVID and hypertension itself [5]. We also discussed other important issues relating hypertension and COVID-19 (e.g. COVID-19 and the use of the renin-angiotensin system (RAS) inhibitors, COVID-19 vaccines in patients with hypertension, lifestyle changes during COVID-19 pandemic and its influence on hypertensive patients, and the role of telemedicine) [5].

For the definition of "long COVID", recently World Health Organization (WHO) defined long COVID (Post COVID-19) as "a clinical condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis" [11]. Nonetheless, before WHO released this definition, there was no clear definition of this disorder and each study has defined long COVID according to their own methods [12]. We generally

considered studies published by June 2022, defining long COVID as a condition that exists 3 months or longer from the onset of COVID-19 in this review.

Long COVID and hypertension-related organs

Long COVID and cerebral/cardiovascular disease

COVID-19-associated CVD such as acute coronary syndromes (acute myocardial infarction or unstable angina), heart failure, arrhythmias, stroke, and thromboembolism, occurs not only in the early stages of infection but also several months later [13]. In a UK study, 13.3% of 4182 predominantly community patients experienced at least one persistent symptom beyond four weeks of infection, of which half were considered cardiac in origin [14]. In an international online survey study of 3762 patients, cardiac symptoms including chest pain (~53%), palpitations (~68%), and fainting (~13%) were observed in up to 86% of patients by seven months from infection [15]. The prevalence of long COVID among 2550 patients using a social media survey demonstrated that cardiopulmonary symptoms were reported by 89% of participants in their study [16]. A prospective study report from Italy found that only 13% had complete recovery of symptoms, 53% had general fatigue, 43% had dyspnea, and chest pain in 22% [17]. A follow-up study of 1733 hospitalized patients from Wuhan, China, showed that 63% of patients reported fatigue, 26% breathlessness, and 5–9% experienced chest pain and palpitations at six months post-infection [18]. By 12 months, the same investigators of the study showed that symptoms of breathlessness (30%) and chest pain (7%) were slightly more common, while fatigue had improved (20%) [19]. In a study from the UK, only 29% showed improvement in their pre-symptomatic state, 56% complained of fatigue, 48% of dyspnea, and 39% of worsening pain symptoms [20]. Thus, the complication rate of CVD and cardiopulmonary symptoms associated with COVID-19 varied widely depending on the severity of the patient, the time of infection and the region [13].

Recently, Xie and colleagues found an increased risk and excess burden of incident CVD among all subgroup of patients with COVID-19 compared with the control group [21]. This cohort study of the US Department of Veterans Affairs (VA) national healthcare database consisted of 153,760 COVID-19 survivors and two control groups, 5,637,647 non-SARS-CoV-2 infected subjects and 5,859,411 historical cohort (before the COVID-19 pandemic), reported that patients with COVID-19 were at increased risk of incident CVD at one year after infection, even among patients who were not hospitalized during the acute phase of the infection. These diseases included atrial fibrillation [(hazard ratio (HR) 1.71, 95% confidence interval (95% CI) 1.64–1.79)], ischemic heart disease (HR 1.72, 95% CI 1.56–1.90), pericarditis (HR 1.85, 95% CI 1.61–2.13), myocarditis (HR 5.38, 95% CI 3.80–7.59), heart failure (HR 1.72, 95% CI 1.65–1.80), thromboembolic disease (HR 2.93, 95% CI 2.73–3.15), stroke (HR 1.52, 95% CI 1.43–2.62), and transient ischemic attacks (TIA) (HR 1.49, 95% CI 1.37–1.62) [21]. Moreover, the increased risk of CVD was observed both in the presence and absence of cardiovascular risk factors or pre-existing CVD [21]. Although cardiovascular risk increases in parallel with the severity of the acute COVID-19, even individuals with mild COVID-19 are at increased risk of CVD [22]. These studies indicate that COVID-19 can increase the risk of developing CVD after the acute infection, even in individuals who were at low risk of CVD before having COVID-19.

Regarding the cardiovascular function, a case-matched study from Germany comprehensively assessed the intermediate-term impact of a mild to moderate course of COVID-19 on multiple organ-specific function [23]. The study reported that the left and right ventricular function was slightly lowered, and the concentrations of troponin and N-terminal pro-brain natriuretic peptide (NT-proBNP) were significantly higher in post-COVID-19 [23]. As for the vascular system, sonographically non-compressible femoral veins, suggesting deep vein thrombosis, were substantially more frequent after COVID-19 [23]. Also, in a prospective cohort study over a six-month follow-up, COVID-19 patients were shown to develop endothelial dysfunction (as assessed by flow-mediated dilatation; FMD), which, though improved, remained impaired compared to healthy controls subjects [24]. Among adult patients with COVID-19 who were admitted to the hospital and required oxygenation with moderate disease or higher, cardiac magnetic resonance imaging (MRI) revealed cardiac involvement in 78% and ongoing myocardial inflammation in 60%, independent of preexisting conditions, severity and overall course of the acute illness, and time from the original diagnosis [25]. In patients with symptomatic long COVID-19 (three months after an acute phase), cardiac MRI showed (post-) inflammatory cardiac sequelae in 28% patients, with signs of myocarditis (such as nonischemic late gadolinium enhancement or pathologic findings in T1 or T2 mapping) [26]. Wang et al. showed that myocardium injury (depressed left ventricular global circumferential strain and peak right ventricular strains) existed in 30% of COVID-19 patients at three-month follow-up [27]. Although there is a possibility that myocardial damage or heart failure may have occurred before SARS-CoV-2 infection, myocardial damage due to myocarditis or other causes should be considered, and cardiac MRI strain analysis can be a sensitive tool to evaluate the recovery of left and right ventricular dysfunction.

Recent guidance from the European Society of Cardiology indicated that cardiopulmonary symptoms including chest pain, shortness of breath, fatigue, and autonomic manifestations such as postural orthostatic tachycardia are common and associated with significant disability and heightened anxiety [28]. Possible pathophysiological mechanisms for delayed cardiovascular complications are not well understood, which will be covered later.

As for brain and neurological sequela of COVID-19, various symptoms and disorders, such as "brain fog", headache, neurocognitive dysfunction, mood and sleep disorders, and fatigue are known [29]. Also, development of dysautonomia including blood pressure abnormality, such as hypertension, postural hypotension, among patients with COVID-19 was reported [30, 31] Furthermore, while patients with COVID-19 have an increased risk of stroke, post-stroke depression and anxiety may explain some parts of symptoms of long COVID. The mechanisms for the extensive damages of COVID-19 on neurological aspects are not well known. Yet, direct viral invasion of the brain and vascular structures, abnormal immune and inflammatory reaction, neurological consequences secondary to hypoxia and multi-organ failure, and social isolation during the pandemic may explain some parts of neurological sequela of COVID-19 [32, 33].

Long COVID and the kidney

Acute kidney injury (AKI) has been reported to be a frequent observation in patients with COVID-19 at an acute phase, which significantly influences the clinical outcomes. Moreover, CKD is one of the independent factors for severe COVID-19, highlighting the close association between COVID-19 and kidney diseases. As for the cause of kidney injury that accompanies COVID-19, both direct and indirect mechanisms have been proposed. In the former, it has been demonstrated that SARS-CoV-2 RNAs are present in renal parenchyma and that the virus can directly enter renal cells [34]. In the latter, multiple factors such as acute respiratory distress syndrome (ARDS), systemic inflammatory response, endothelial injury, and hypercoagulation contribute to the deterioration of renal function.

Several studies have been identified that describe the mid-term kidney outcome (from three months up to one year) in COVID-19 patients (Table 1) [18, 35–39]. In an initial study by Hultstrom et al., 60 patients with COVID-19 admitted to ICU were assessed for renal function (average follow-up time of 18 weeks) [37]. In these patients, those who had stage 3 AKI during the ICU stay were more likely to progress to a higher CKD stage. In another study, Stockmann et al. retrospectively analyzed renal outcomes in 74 patients with COVID-19 who had AKI requiring kidney replacement therapy [39]. After a median follow-up of 151 days, 36 (49%) patients died, one patient was still hospitalized, and 37 patients (50%) had been discharged. Among those who were alive and out of hospital at the follow up, 23 patients had full recovery of kidney function, whereas three patients were dependent on kidney replacement therapy. These data suggest that, although renal recovery is common following AKI in COVID-19, a significant portion of patients can have a variable degree of reduced kidney function at a post-acute phase.

The study by Bowe et al. provided largest and detailed data on kidney outcomes in a post-acute phase [35]. The authors analyzed the US Department of Veterans Affairs national healthcare databases for the assessment of post-acute sequelae of COVID-19, and found that the patients have increased risks and burdens of AKI and CKD at 6 months after SARS-CoV-2 infection [9]. In a more detailed analysis on the kidney outcome that included 89,216 patients, the authors found that 30-day survivors of COVID-19 exhibited a higher risk of AKI, eGFR decline, end-stage kidney disease, and major adverse kidney outcome (defined as eGFR decline of 50% or more, end-stage kidney disease, or all-cause mortality) compared with non-infected controls after adjustment for baseline characteristics [35]. The study concluded that patients with COVID-19 exhibited increased risk of kidney diseases in the post-acute phase of COVID-19.

Gu et al. provided data on 1-year outcome of kidney function in patients with COVID-19 [36]. In this study, 1,734 participants with COVID-19 discharged from hospital were invited to follow up at 6 and 12 months after the onset (the median follow-up duration was 342 days). After multivariable adjustment, the primary outcome, which was the percentage of eGFR decreased from acute phase to follow-up, was 8.3% (95% CI 6.0–10.6) higher among patients who had AKI than those without AKI at the acute phase. Participants with AKI had an odds ratio (OR) of 4.6 (95% CI 2.1–10.1) for reduced renal function (defined as an eGFR of less than 60 ml/min/1.73 m^2) and an OR of 2.5 (95% CI 1.3–5.1) for proteinuria (defined as 1+ proteinuria or higher on urine dipstick testing) at follow-up visit. The risk for reduced renal function at follow-up increased along with the AKI stage, with OR of 22.1 for those who had AKI stage 3. The authors concluded that AKI at an acute phase of COVID-19 was closely related to the longitudinal decrease in kidney function at 1 year after the onset.

Nugent et al. compared the rate of change in eGFR after discharge in patients with COVID-19-associated AKI ($n = 182$) and those with AKI not associated with COVID-19 ($n = 1430$) [38]. In this retrospective cohort study, median duration of follow-up was 93 days for those with COVID-19 and 61 days for those without COVID-19. The study found that patients with COVID-19-associated AKI had a greater decrease in eGFR in the unadjusted model

Table 1 Summary of studies on Long COVID and hypertension related organs/disorders

Study	Related hypertension related organs/disease	Study setting	Sample size	Participants' age	Duration	Results
Cerebral and cardiovascular system						
Xie et al. [21]	Cardiovascular disease	Prospective study	(1) 153,760 COVID-19 patients (2) 5,637,647 contemporary controls (3) 5,8589,411 historical controls	(1) 61.42 ± 15.64 (COVID-19) (2) 63.46 ± 16.23 (contemporary control) (3) 62.90 ± 16.48 (historical control)	Median follow up: (1) 347 days (COVID-19) (2) 348 days (contemporary control) (3) 347 (historical control)	Patients who survived the first 30 days of COVID-19 had increased risk of CVD (HR, 95% CI): composite cerebrovascular outcomes (1.53, 1.45–1.61), atrial fibrillation (1.71, 1.64–1.79), composited of dysrhythmia (1.59, 1.64–1.75), ischemic heart disease (1.66, 1.52–1.80), thrhomboembolic disorders (2.39, 2.27–2.51), stroke (1.52, 1.43–1.62), TIA (1.39, 1.37–1.62)
Ikonomidis et al. [22]	Marker of Cardiovascular function (PWV, FMD, CFR, LVGLS, myocardial global work capacity, etc.)	Prospective study	(1) 70 COVID-19 patients (2) 70 healthy controls	54.53	12 months	Comparing to control, COVID 19 had higher PBR, GWW, MDA, and lower FMD, GWE, LVGLS
Petersen et al. [23]	pulmonary, cardiac, vascular, renal, and neurological status	Prospective study	(1) 443 non-hospitalized SARS-CoV-2 infected patients (2) 1328 matched controls	SARS-CoV-2 infected patients: median 55, control: median 57	9.6 months	Comparing to control, COVID-19 patients revealed lower lung volume, left ventricular ejection fraction, right ventricular function, glomerular filtration rate, higher airway resistance, high sensitivity troponin I, NT-proBNP, and signs of prior deep vein thrombosis
Oikonomou et al. [24]	FMD	Prospective study	73 hospitalized COVID-19 patients	Patients hospitalized medical ward; 56.4 ± 12.3, ICU: 68.0 ± 10.4	6 months (after hospital discharge)	FMD remained impaired compared to control at 6 months post hospital discharge
Puntamann et al. [25]	CMR findings, cardiac blood markers	Prospective study	(1) 100 COVID-19 patients (2) 50age-sex matched healthy controls (3) 57 risk-factor matched controls	(1) COVID-19 patients: 49 ± 14 (2) controls: 47 ± 16	Median 71 (IQR: 64–92) days	Compared with control, COVID-19 patients had lower left ventricular ejection fraction, higher left ventricle volumes, and raised native T1 and T2
Wang et al. [27]	CMR findings	Prospective study	(1) 44 COVID-19 patients (2) 31 healthy controls	(1) COVID-19 patients: 47.6 ± 13.3 (2) controls: 47.1 ± 11.0	3 months	Myocardium injury existed in 30% of COVID-19 patients and these patients revealed depressed LV GCS and peak RV strains at the 3-month follow-up
Kidney						
	Kidney function	Ambidirectional study		57.0 (IQR: 47.0–65.0)	153 (146–160)	

Table 1 (continued)

Study	Related hypertension related organs/disease	Study setting	Sample size	Participants' age	Duration	Results
Huang et al. [18]			1,733 Patients with confirmed COVID-19 who had been discharged between Jan 7, 2020 and May 29, 2020			107 of 822 participants without AKI and with eGFR 90 mL/min/1.73 m^2 or more at acute phase had eGFR less than 90 mL/min/1.73 m^2 at follow-up
Hulstrom et al. [37]	Kidney function	Prospective study	60 COVID-19 ICU admitted patients	60 ± 12	18 ± 3 weeks	Creatinine remained higher in patients with stage 3 AKI than those who never developed AKI during the ICU-stay
Stockmann et al. [39]	Renal outcomes	Retrospective study	74 Hospitalized patients with COVID-19 and AKI requiring kidney replacement therapy	65 (IQR:57–74)	151 (IQR: 128–192)	Among 74 patients, 36 patients died and one patient continued to be in hospital. In 37 patients who discharged, 3 patients (8.1%) were dependent on kidney replacement therapy and 34 patients (91.9%) had renal recovery
Bowe et al. [35]	Kidney function		(1) 89.216 30-day survivors of COVID-19 from March 1, 2020 to March 15, 2021 (2) 1,637467 non-infected control	68.5 (IQR: 56.8–74.3)	172 (IQR: 133–281)	Survivors of COVID-19 exhibited a higher risk of AKI, eGFR decline, ESKD, and MAKE (defined as eGFR decline of ≥50%, ESKD, or all-cause mortality) compared with non-infected controls after adjustment for baseline characteristics
Gu et al. [36]	Kidney function	Ambidirectional study	1,734 COVID-19 survivors discharged between Jan 7, 2020 and May 29, 2020 and completed the follow-up survey	57.0 (IQR: 47.0–65.0)	342 (IQR:223–358)	Percentage of eGFR decreased from acute phase to follow-up was 8.3% higher among AKI participants than those without AKI at acute phase after multiple adjustment. Participants with AKI had an odds ratio of 4.6 of reduced renal function at follow-up
Nugent et al. [38]	Kidney function	Retrospective study	1,612 Admitted and discharged patients between March 10 and August 31, 2020, who received a PCR test for SARS-CoV-2 and developed AKI during hospitalization according to KDIGO criteria	(1) With COVID-19: 67.4 (IQR: 58.3–80.1) (2) Without COVID-19: 69.9 (IQR:59–78.7)	(1) With COVID-19, 93 (IQR: 53–128) (2) without COVID-19, 61 (IQR: 30–103)	Patients with COVID-19-associated AKI had a greater decrease in eGFR after adjusting for baseline comorbidities, peak creatinine level, and in-hospital dialysis recruitment
Endocrine						
	Pituitary functions	Prospective study			5.6 ± 1.3 months	

Table 1 (continued)

Study	Related hypertension related organs/disease	Study setting	Sample size	Participants' age	Duration	Results
Urhan et al. [42]			(1) 49 SARS-Cov-2 infected patients 11healthy controls	(1) Patients: 44.28 ± 10.76 (2) Control: 44.18 ± 12.41		Secretions of ACTH, cortisol, and growth hormone were significantly decreased in patients with COVID-19 at least 3 months after the diagnosis of this disease than healthy controls
Clarke et al. [43]	Cortisol after Synahyroid function	Prospective study	70 COVID-19 patients	55.9 ± 13.0	3 months	Adrenal and thyroid function ≥3 months after presentation with COVID-19 was preserved
Khoo et al. [50]	Thyroid function	Prospective study	334 COVID-19 hospitalized Patients	64.8 ± 19.3	79 days (range 52–108 days)	Mild reductions in TSH and FT4 in keeping with a nonthyroidal illness syndrome was observed in COVID-19 patients; in survivors of COVID-19, thyroid function tests at follow-up returned to baseline
Sunada et al. [51]	Thyroid function, ACTH, GH	Prospective study	186 COVID-19 patients	40 (IQR: 25–51)	83 days (IQR:56–117)	TSH level was higher and the ratio of FT4/TSH was lower in patients with severe COVID-19 symptoms and suffering from the long COVID symptoms
Dhiindsa et al. [67]	Testosterone, estradiol, insulin like growth factor1 (IGF-1)	Prospective study	152 COVID-19 patients	63 ± 16	28 days	Hormone concentrations at study baseline and 28 days follow up in COVID-19 patients with severe symptoms were not different; lower testosterone concentrations during hospitalization were associated with increased disease severity and inflammation in men
Hajizadeh et al. [68]	seminal biomarkers and reproductive function in male	Prospective study	(1) 84 COVID-19 male patients (2) 105 controls	(1) COVID-19 patients: 34.7 ± 6.3 (2) Controls: 33.9 ± 7.5	60 days	Impairments in semen volume, progressive motility, sperm morphology, sperm concentration, and the number of spermatozoa in male patient with COVID-19

HR hazard ratio, *95% CI* 95% confidence interval, *CVD* cardiovascular disease, *TIA* transient ischemic attacks, *IQR* interquartile range, *PWV* pulse wave velocity, *FMD* flow mediated dilation, *CFR* coronary flow reserve, *LVGLS* left ventricular global longitudinal strain, *PBR* perfused boundary region, *GWW* myocardial global wasted work, *GWE* myocardial global work efficacy, *MDA* malondialdehyde, *CMR* cardiovascular magnetic resonance, *GCS* global circumferential strain, *RV* right ventricular, *AKI* acute kidney injury, *ESKD* end-stage kidney disease, *eGFR* estimated glomerular filtration rate, *ACTH* adrenocorticotropin, *GH* growth hormone, *TSH* thyroid stimulating hormone, *FT4* free thyroxine, *DHEA-S* dehydroepiandrosterone

(difference in slope, −11.3 ml/min/1.73 m^2/y), and the significant difference in slope was also observed in the fully adjusted model (−14.0 ml/min/1.73 m^2/y). These data support that AKI associated with SARS-CoV-2 infection can have a significant impact on kidney function also at a post-acute phase.

Long COVID and endocrine disease

In humans, both angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) are expressed in several endocrine glands, including the pituitary gland, thyroid gland, adrenal gland, testes and ovaries [40]. Several studies suggest that the endocrine system is affected by SARS-CoV-2 infection, both acutely and chronically.

Pituitary gland

Studies have shown that an acute impairment of adrenocorticotropic hormone (ACTH) secretion from the pituitary was observed in 32% of inpatients with COVID-19 [41]. As for the long-term effects, secretion of ACTH and growth hormone was significantly decreased in patients with COVID-19 at three months after the acute phase than healthy controls [42]. However, in another study, thyroid stimulating hormone (TSH) secretion is reported to be preserved [43]. Therefore, the degrees of perturbation in pituitary function seem variable at a post-acute phase, which requires further study.

Thyroid gland

There are several case reports of thyroid disorder associated with COVID-19, such as subacute thyroiditis [44], non-thyroidal illness syndrome [45], and Graves' thyrotoxicosis [46]. Although the precise mechanisms are unclear, these can be caused either by direct infection of the SARS-CoV-2 to the thyroid or by autoimmune effects mediated by cytokine storm [47]. Interleukin 6, which is likely to be involved in cytokine storm in COVID-19 [48], are also shown to be elevated in Graves' disease [49]. Regarding the persistent effects of COVID-19, transient reductions in TSH and free thyroxine (FT4) were shown to be normalized at a post-acute phase (median time, 79 days; interquartile range, 52–108 days) [50]. In relation to long COVID, one study reported that the thyroid function was normal and was not associated with chronic symptoms at least 3 months after the diagnosis of COVID-19 [43]. However, in a retrospective analysis involving 186 patients with COVID-19, the ratio of FT4/TSH was decreased in patients with long COVID symptoms, suggesting that the hormonal changes may be associated with the persistent symptoms [51].

Adrenal gland

Primary adrenal insufficiency has been reported in several cases with COVID-19 either by the direct invasion of SARS-CoV-2 or by acute adrenal infarction and acute adrenal hemorrhage [52–54]. It is also possible that exogenous steroid used for the treatment of COVID-19 may impair adrenal function by suppressing the hypothalamic-pituitary-adrenal axis. As for the long-term effect of COVID-19, adrenal function was preserved in all COVID-19 survivors at least 3 months after presentation with COVID-19 [43]. However, Salzano et al. described adrenal insufficiency in a patient with COVID-19 who was treated with dexamethasone and was suffered from long COVID symptoms persisting for 3 months [55]. Therefore, adrenal insufficiency may need to be considered in patients with long COVID symptoms [56].

Reproductive system (testes and ovaries)

SARS-CoV-2 infection can cause damage to the testes [57]. Significant loss of germ cells but not Sertoli cells was observed at postmortem in patients with COVID-19 [57]. In addition, several case reports have documented that patients with COVID-19 can present with testicular pain, which was associated with orchitis, epididymo-orchitis, and testicular infarction [58–62]. COVID-19 may reduce spermatogenesis [63] and serum levels of total testosterone [64] or free testosterone [65] either directly, via hypothalamic-pituitary dysfunction, or via impaired secretion of gonadotropin releasing hormone, a phenomenon known to occur with physiological stressors [66]. Despite acute reduction in testosterone in patients with COVID-19, one study suggests that any fall in testosterone levels resolves spontaneously after recovery from acute illness [67]. However, a prospective, longitudinal cohort study with a follow-up time of 60 days reported impairments in semen volume, progressive motility, sperm morphology, sperm concentration, and the number of spermatozoa in male patient with COVID-19 [68]

Survey for women of reproductive age indicated that nearly half of the participants experienced the change in the menstrual cycle after the COVID-19 pandemic, highlighting the impact of the psychological distress on reproductive health [69]. However, it is currently unclear whether SARS-CoV-2 infection itself can affect female reproductive system. In one study that involved female patients with COVID-19 and non-infected subjects, serum levels of several hormones such as anti-Müllerian hormone (AMH), testosterone, and prolactin were altered, and the changes in these hormones were significantly associated with COVID-19 in multivariate analysis [70]. In another study, on the other hand, there were no differences in sex hormones such

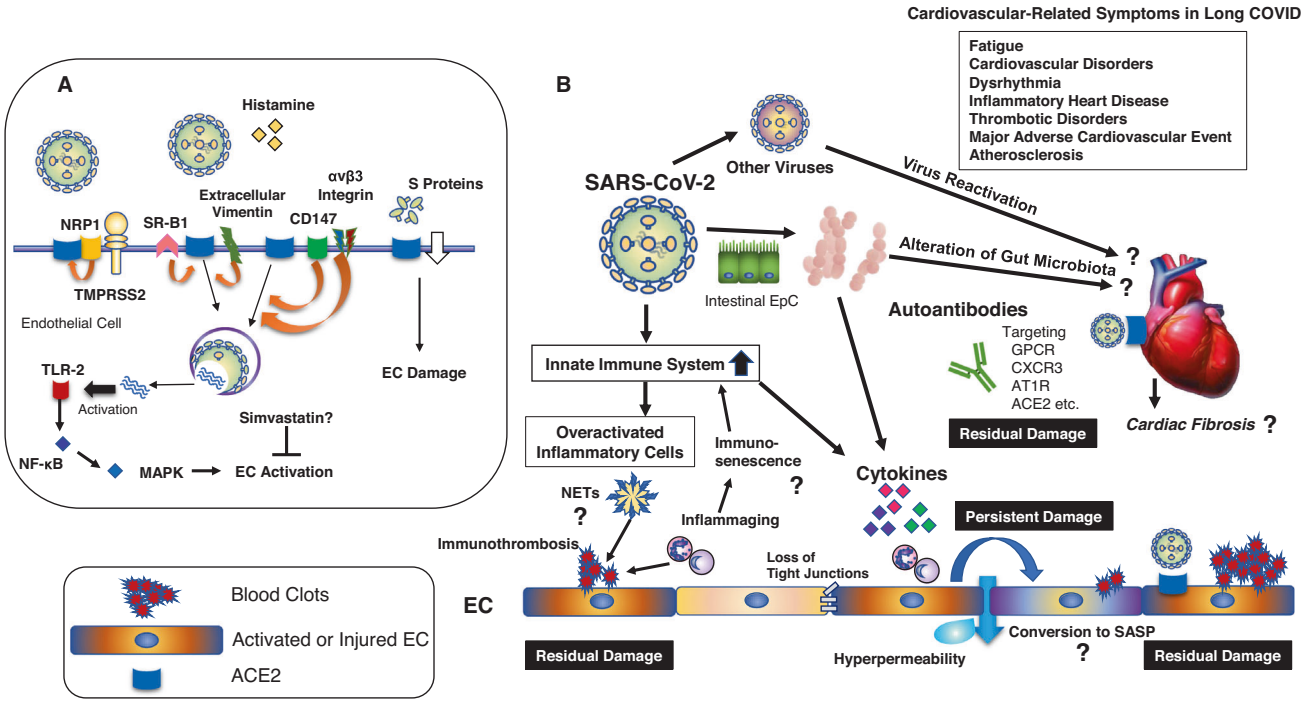

Fig. 1 Possible mechanism of cardiovascular complications in long COVID. **A** Influence of SARS-CoV-2 infection on endothelial cells. **B** SARS-CoV-2-induced cytopathic effects and cardiovascular-related symptoms. ACE2 angiotensin-converting enzyme 2, AT1R angiotensin II type 1 receptor, CXCR3 chemokine (C-X-C motif) receptor 3, EC endothelial cell, EpC epithelial cell, GPCR G protein-coupled receptors, MAPK mitogen-activated protein kinase, NETS neutrophil extracellular traps, NF-κB nuclear factor-kappa B, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, SASP senescence-associated secretory phenotypes, SR-B1 scavenger receptor B type 1, TLR-2 toll-like receptor 2, TMPRSS2 transmembrane serine protease 2

as follicle-stimulating hormone, estradiol, testosterone, progesterone and AMH compared with age-matched controls [71]. In an international cohort study on long COVID, prolonged menstrual issues such as abnormally irregular periods, heavy periods, and post-menopausal bleeding have been reported [15]. However, given the susceptibility of the hypothalamic-pituitary-gonadal axis to physical and psychological stress, it is unclear to what extent these issues are attributable to the biological effect of SARS-CoV-2 infection.

Mechanisms for long COVID and cardiovascular damage

Pathophysiological mechanisms for long COVID are still poorly understood. As possible pathogenesis of the long COVID, residual organ damage by the acute phase of COVID-19, viral persistence, delayed resolution of inflammation, autoimmunity, and overlapping each other have been estimated [72]. Moreover, risk factors of long COVID at the time of initial COVID-19 diagnosis are also reported as follows: (1) type 2 diabetes, (2) SARS-CoV-2 RNAemia, (3) Epstein-Barr virus viremia, and (4) specific autoantibodies [4]. Subjects with either low total immunoglobulin (Ig) M or low total IgG3 as an immunoglobulin signature, older age, history of asthma, and five symptoms (fever, fatigue, cough, shortness of breath, and gastrointestinal symptoms) at the primary infection are also predicted to have an increased risk of developing long COVID [73]. However, the detailed mechanisms of this intractable symptom are still an enigma. Here, we discuss the possible mechanisms of long COVID associated with CVD.

Endothelial damage

Possible direct SARS-CoV-2 infection to endothelial cells has been reported [74, 75]; however, there are few reports that show the presence of viral protein in endothelium [76]. The expression of ACE2 is observed in vascular endothelial cells (ECs) and vascular smooth muscle cells [77]. There are other several potential host entry factors on ECs as well as ACE2 (Fig. 1A): neuropilin-1 (NRP1), which is a promoter of virus entry in the presence of ACE2 and TMPRESS2 [78, 79], scavenger receptor B type 1 (SR-B1) [80, 81] and extracellular vimentin [82], which facilitate ACE2-dependent virus entry; CD147 [83] and αvβ3 integrin [84], which mediate virus entry by endocytosis; and liver/lymph node-specific ICAM-3 grabbing nonintegrin

(L-SIGN), which are highly expressed on human liver sinusoidal endothelial cells and serve as the virus receptor [85]. Histamine also contributes to the entry of spike protein into ECs [86]. Moreover, nucleocapsid protein (NP), which is one of the most crucial structural components of SARS-CoV-2 activates human ECs through toll-like receptor (TLR) 2/nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling [87]. Interestingly, a lipid-lowering agent, simvastatin works as a potent inhibitor of NP-induced endothelial activation [87]. SARS-CoV-2 spike protein alone damages ECs by downregulation of ACE2 due to the impaired mitochondrial function [88]. Thus, vaccination could inhibit EC injury via the protection of the binding of S protein to EC, while vaccination causes a temporal increase in inflammatory markers and deterioration of endothelial function [89, 90]. On the other hand, Wagner et al. demonstrated ACE2 expression was only observed in human coronary artery ECs (HCAECs) among several ECs tested, and the variant SARS-CoV-2 B.1.1.7, but not wild type SARS-CoV-2, reduced the HCAEC cell number by cytotoxic effect [91]. However, even such a variant did not replicate in HCAECs, indicating that SARS-CoV-2 may show an abortive infection in endothelial cells [91, 92].

These virus-induced cytopathic effects in the acute phase impairs endothelial function, and the residual EC damage in the post-acute phase can predispose patients to cardiovascular and thrombotic events (Fig. 1B) [93]. As noted previously, EC dysfunction assessed by brachial artery FMD remained impaired even at 6 months post-hospital discharge [24]. Such long-term EC damage is also considered to cause cardiovascular complications of long COVID such as stroke, ischemic heart attacks, and thromboembolic disorders [21]. Inflammatory cytokines and leukocyte activation lead to EC activation and endothelial dysfunction via multiple mechanisms such as direct damage, loss of tight junctions, and hyperpermeability [94]. Viral pathogen-associated molecular patterns such as viral proteins, double-stranded RNA, and single-stranded RNA initially activate the innate immune system [95]. Activating the innate immune response to eradicate the virus induces overproduction of pro-inflammatory cytokines; however, the overactivation of immune cells such as neutrophils, monocytes and lymphocytes induces cytokine storm [96], resulting in EC damage in the acute phase of COVID-19. Endothelial dysfunction could be a trigger for immunothrombosis that induces coagulopathy in long COVID patients [97]. Immunothrombosis induced by activated neutrophils and monocytes that interact with platelets enhances the coagulation cascade and leads to intravascular clot formation in small and larger vessels [97]. For example, neutrophil extracellular traps (NETs), which are composed of DNA-histone complexes and proteins released by activated neutrophils, are one of the key players in COVID-19-associated immunothrombosis [98]. Adrover et al. demonstrated the preventive effect of disulfiram, a drug for alcohol use disorder, on acute lung injury in a rodent model via reduction of NETs and perivascular fibrosis in the lungs, and downregulation of coagulation pathways [99]. Fogarty et al. demonstrated the association between persistent EC damage and long COVID pathogenesis, such as persistent procoagulant effects independently of active NETosis; [93] however, NETs may contribute to the residual organ damage in COVID-19. Thus, a therapeutic approach targeting NETs has been expected to prevent residual multiple organ damage, resulting in less severity of long COVID [100].

Cardiomyocyte damage

Lingering symptoms regarding the cardiovascular system in long COVID include arrhythmias, palpitations, hypotension, venous thromboembolic diseases, myocarditis and heart failure [21]. Using longer-duration wearable sensor data, Radin et al. showed that subjects with COVID-19 exhibited transient bradycardia followed by a prolonged tachycardia, which did not return to baseline until 79 days on average after the symptom onset [101]. It has been reported that patients with long COVID showed increased sympathetic activity and parasympathetic reduction [102]. Recently, Mills et al. demonstrated that bromodomain and extra-terminal protein (BET) family inhibitors prevented diastolic dysfunction and death in a mouse cytokine-storm model via reduction of SARS-CoV-2 infection of cardiomyocytes by decreasing ACE2 expression [103]. Thus, residual cardiac damage by acute COVID-19 is a cause of cardiac persistent symptoms (Fig. 1B).

Innate immune response releases cytokines, chemokines, interferons, and induces further activation and homing of innate immune cells such as mast cells, neutrophils, dendritic cells, monocytes and macrophages to the heart [104]. Persistent elevation of proinflammatory cytokines induces chronic inflammation and may lead to cardiac remodeling [105] or cardiac dysrhythmias [106]. Upregulation of serum transforming growth factor-beta (TGF-β) 1 is observed in severe COVID-19 patients [107] and an increase in TGF-β inhibits natural killer cell function, resulting in uncontrol against virus infection. TGF-β1 plays an important role in tissue fibrosis in various organ systems [108]. Although the detailed mechanism of cardiac fibrosis by TGF-signals in long COVID has not been well investigated compared to lung fibrosis, cardiac fibrosis may be a key player in a long-term cardiac consequence of COVID-19 inducing functional and structural changes in the heart [109]. On the other hand, the persistence of proinflammation induces long-term persistent immune activation and may contribute to the

development of latent and overt autoimmunity [110]. An anti-heart antibody increase was observed in 73.5% of patients with COVID-19 pneumonia, and among them, anti-cardiomyocyte antibodies and anti-smooth muscle antibodies had a significant correlation with the lethality of COVID-19 [111]. Moreover, autoantibodies targeting G protein-coupled receptors (GPCR) and the renin-angiotensin system (RAS)-related molecules especially chemokine (C-X-C motif) receptor 3 (CXCR3) and angiotensin II type 1 receptor are the most important predictors associate with the COVID-19 severity [112]. On the other hand, Arthur et al. reported that ACE2 autoantibodies are developed after SARS-CoV-2 infection, suggesting the reduction of the RAS protective arms [113]. Thus, the presence of the ACE2 autoantibodies is also a predictor of COVID-19 severity.

Virus reactivation is also a hot topic in long COVID (Fig. 1B). Reactivations of Epstein–Barr virus (EBV), cytomegalovirus (CMV) and human-herpes virus-6 (HHV-6) DNAemia are detected in intensive care unit (ICU) patients [114] and EBV reactivation may be associated with the severity of COVID-19 [115]. Patients with chronic active EBV infection show cardiac complications [116–118]. Although the relation between EBV reactivation and cardiovascular complications in long COVID is unclear, EBV reactivation may have a role in cardiac dysfunction after COVID-19. Cytomegalovirus infection is also associated with a significantly increased relative risk of CVD [119]. Moreover, a cardiotropic virus such as HHV-6 was detected by biopsy of the myocardium of patients with left ventricular (LV) dysfunction. Interestingly, spontaneous viral elimination in endomyocardial biopsy sample was associated with a significant improvement in LV function of patients with regionally or globally impaired myocardial function [120]. The effect of virus-reactivation by COVID-19 on heart diseases is not well known; however, there may be one of the possible mechanisms of cardiac dysfunction in long COVID.

Organ senescence after virus infection

SARS-CoV-2-infected cells trigger paracrine senescence and induce senescence of surrounding non-infected cells. These senescence cells transfer to senescence-associated secretory phenotypes (SASPs) that express high levels of inflammatory factors [121]. Moreover, virus-infected cells evoke senescence as a universal host cell response to viral stress and play as a pathogenic trigger of COVID-19-related organ damage [122]. Thus, senolytic drugs which selectively eliminate senescent cells are expected to reduce mortality after SARS-CoV-2 infection. In fact, the beneficial effect of senolytics, such as fisetin and senolytic cocktail, Dasatinib plus Quercetin contribute to improved outcomes in old mice exposed to virus-pathogen [123].

A pro-inflammatory status that is characterized by high levels of pro-inflammatory markers in cells and tissues (inflammaging) contributes to immunosenescence, which is defined as changes to the immune system, including a reduced ability to respond to new antigens and uncontrolled activation of innate immune response, resulting in tissue damage such as CVD [124].

Alterations of microbiota

SARS-CoV-2 can infect the gastrointestinal tract [125] and prolonged presence of SARS-CoV-2 mRNA was observed even after throat swab samples were negative [126]. Although most children develop mild symptoms or are asymptomatic at an acute phase, some children develop multisystem inflammatory syndrome in children (MIS-C), which leads to multiple organ failures driven by zonulin-dependent loss of gut mucosal barrier and subsequent superantigen-mediated T cell activation [127]. Such a leaky gut symptom leads to the translation of intestinal bacteria and antigens into circulation and induces systemic inflammation, resulting in the development of CVD [128]. Recently, it was reported that persistent alterations in the fecal microbiome occurred in patients with SARS-CoV-2 infection [129]. Liu et al. demonstrated the association between gut microbiome composition and long COVID symptoms up to 6 months after clearance of the SARS-CoV-2 virus [130]. In patients with long COVID, higher levels of *Ruminococcus gnavus*, *Bacteroides vulgatus*, and lower levels of *Faecalibacterium prausnitzii* were observed, while patients without long COVID showed gut microbiome profiles that were comparable to that of non-infected control subjects. However, the effect of the alteration of gut microbiota on the cardiovascular complication of long COVID is not well known and further investigation will be expected (Fig. 1B).

Effects of age and sex on long COVID

Older population and long COVID (frailty and long COVID)

In terms of the life-threatening risk, older population, which has a high prevalence of hypertension, has been most severely affected by the COVID-19 pandemic. When treating hypertension, it is important to consider the functional status of older patients regardless of chronological age, as the decline of functional status, recently termed frailty, could alter the treatment strategy of hypertension [131, 132]. Of note, it has been shown in multiple

observational studies [133–155] and systematic reviews [156–162] that frailty is an independent determinant of severity and mortality in older patients with COVID-19. To determine the level of frailty, most studies used clinical frailty scale (CFS) alone [133–148], while others used the CFS in combination with other frailty measures [149, 150, 155] or with other frailty measurements alone [151–154]. It has been shown in most studies that frailty status independently predicts severity and mortality of COVID-19, and the influence is even higher than chronological age. Nevertheless, it should be noted that frailty classified by CFS primarily includes older subjects who are functionally dependent and even have limited life expectancy. This is different from the concept of frailty as determined by other frailty measures, including frailty index and Cardiovascular Health Study Index; the latter measures target older people who are functionally independent and capable of robust recovery. Some studies focused on multimorbidity, the coexistence of 2 or more chronic conditions, on the outcome of patients with COVID-19 [143, 146, 155, 163], reporting that multimorbidity is also an independent factor of disease severity or mortality.

Several reports have suggested that frailty is also a risk of long COVID. CFS-based frailty predicted late mortality more strongly than the severity of COVID-19 [164]. Frailty was also associated with poor mental health [165], poor exercise capacity [166], reduced quality of life [167], and sustained symptom of COVID-19 [168]. Conversely, COVID-19 is reported to increase the risk of frailty [169–172]. In patients with COVID-19 who received treatment in ICU, 74% reported physical symptoms, 26% mental symptoms, and 16% cognitive symptoms in the 1-year follow-up questionnaires [170]. The CFS significantly increased from baseline at a follow-up period after discharge in patients with COVID-19 [169, 171]. In nursing home residents, COVID-19-infected residents had a greater decline in handgrip, walking speed, and a greater increase in Frail-NH scores compared with uninfected control [172]. Thus, the relationship between COVID-19 and frailty is bidirectional.

It should also be noted that the social distancing during COVID-19 pandemic has caused the reduced activity of older population that may have contributed to the development of frailty even among those who have no history of COVID-19. A systematic review of 25 observational studies indicated that physical activity reduced during the COVID-19 pandemic in the older people, which was consistent across studies [173]. In Japan, the total physical activity time decreased by up to 40% in older adults during the pandemic, and those who were living alone and socially inactive had the greatest decline in physical activity [174]. The percentage of patients who went out at least once a week decreased after the outbreak from 91 to 87%, from 65 to 46%, and from 47 to 36% in the non-frail, frail, and nursing care requirement groups, respectively [175]. Approximately 10% of older people showed new transitions to frailty defined by the Frailty Screening Index over 6 months during the COVID-19 pandemic in Japan [176]. In addition, psychological distress increased after COVID-19 pandemic in older adults, and persistence or development of frailty and multimorbidity was associated with psychological distress [177].

Given these multifactorial bidirectional influences of COVID-19 on frailty and related conditions, it is important for physicians to be aware of changes in the functional status of older hypertensive patients. In particular, it should be noted that frailty is not considered to trigger hypertension, but rather orthostatic hypotension, which increases the risk of falls and fractures along with the impaired physical condition [178–180].

Sex difference in long COVID and COVID-19 sequelae

In spite of equivalent probability of being infected by SARS-CoV-2 in women and men, current evidence suggests sex difference in severity and mortality of patients infected with SARS-CoV-2. Multiple studies reported that men tend to develop more severe disease with increased mortality than women in the acute phase [181–184]. Etiology responsible for sex difference in the prognosis of COVID-19 in the acute phase is still uncertain. However, fewer cardiovascular risk factors, higher immune response, lower expression of ACE2 in women than men, and gender difference in social behavior (lower levels of smoking/drinking, more undertaking of preventive measures; frequent hand washing, wearing masking, etc. in women than men) may explain some part of sex difference in the prognosis of COVID-19 in acute phase [185].

Meanwhile, sex difference in the risk of long COVID has been also suggested. Although some small-scale studies failed to reveal sex difference in the risk of long COVID [186, 187], multiple large-scale studies reported women are more prone to develop long COVID than men. A multicenter cohort study from Spain consisted of 1,969 COVID-19 survivors (mean age: 61 years, women: 46.4%) during the first wave of pandemic reported that the long-COVID symptoms were observed up to 60% of patients [188]. The average number of long-COVID symptoms was 2.25 for women and 1.5 for men, and female sex was associated with ≧3 long-COVID symptoms (OR 2.54, 95% CI 1.67–3.86), fatigue (OR 1.51, 95% CI 1.04–2.21), dyspnea (OR 1.43, 95% CI 1.08–1.89, OR 1.41, 95% CI 1.11–1.79), pain (OR 1.35, 95% CI 1.06–1.72), hair loss (OR 4.53, 95% CI 2.78–7.37), ocular problems (OR 1.98, 95% CI 1.19–3.31),

depressive levels (OR 1.61, 95% CI 1.00–2.57) and worse sleep quality (OR 1.63, 95% CI 1.10–2.43) at 8 months after infection even after adjustment for covariates [188]. A retrospective cohort study (end of follow up: December 2020) based on electronic health records data from 81 million patients including 273,618 COVID-19 survivors (mean age: 46.3 ± 19.8 years, women: 55.6%) in the United States revealed that women were significantly more likely to have headaches, abdominal symptoms, and anxiety/depression, whereas men were significantly more likely to have breathing difficulties and cognitive symptoms during the whole 6-month period [189]. Also, meta-analysis involving 13,340 patients (women: 6213, 47.6%) from 20 studies reported that women was 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 (OR 1.52, 95% CI 1.27–1.82, I^2 68%, Heterogeneity $P < 0.01$), respiratory symptoms (OR 1.20, 95% CI 1.20–1.45, I^2 65%, Heterogeneity $P < 0.01$), mental health symptoms (OR 1.67, 95% CI 1.21–2.29, I^2 58%, Heterogeneity $P < 0.01$), and fatigue (OR 1.54, 95% CI 1.32–1.79, I^2 49%, Heterogeneity $P = 0.07$) [190]. However, as this meta-analysis exhibited moderate to high heterogeneity measured by I^2 statistic test, heterogeneity of previous studies evaluating the risk of long COVID is not negligible. The use of different definitions and classifications for evaluation of long COVID and its symptoms, wide range of follow-up period, diverse characteristics of studied subjects (severity of disease, race, age, inclusion of control subjects), different study design, etc., may have substantial impacts on the results of previous studies. Yet, the accumulating evidence still suggests higher risk of developing long COVID in women compared to men.

Underlying mechanisms explaining the sex difference in the risk of long COVID has not been clarified. However, several potential factors are considered. First, sex-specific immunological differences driven by X chromosome and sex hormones can be one of the mechanisms. Women generally exhibit greater immune responses to infection and this could explain part of the lower mortality at acute phase of COVID-19 in women compared to men. This sex-related difference in immune system can also contribute to increased susceptibility to inflammation in women. Clinical data from Mayo Clinic reported more frequent persistent (å 3 month) elevation of IL-6 levels in SARS-CoV-2 infected women compared to those in men. This study also revealed that fatigue, the most common symptoms of long COVID, was associated with elevated IL-6 levels and with women [191]. Second, sex-related social factors and worse health self-perception in women compared to men may contribute to anxiety/depression, lower health-related quality of life, and pain, which are also major symptoms of long COVID [192]. Also, from the epidemiological stand point, the exclusion of high number of diseased patients, mainly older men due to their higher mortality during the acute phase may influence the association of sex and risk of long COVID.

As cardiovascular complications of COVID-19 in acute phase have been well documented, the increasing studies report post-acute cardiovascular manifestations of COVID-19. Previously mentioned cohort study of the US Department of VA revealed that risks of CVD, dysrhythmias, ischemic and non-ischemic heart disease, heart failure, thromboembolic disease, and MACE (composite of myocardial infarction, stroke and all-cause mortality and any cardiovascular outcomes,) were elevated in COVID-19 patients at one year after infection. However, for the sex difference in the risk of long-term cardiovascular outcomes after SARS-CoV-2 infection, this study suggested this risk was evident regardless of sex [21]. On the other hand, another large-scale claim data-based study suggested sex difference in the risk of cardiovascular sequelae during post-acute phase of COVID-19. A claim data-based study enrolling 87,337 SARS-CoV-2 infected individuals over 65 years old in the US estimated the excess risk for sequelae including CVD caused by infection with SARS-CoV-2 at 120 days after the acute phase. They reported that elderly subjects infected by SARS-CoV-2 had higher risk of hypertension, cardiac rhythm disorders, hypercoagulability, and kidney injury compared to control group matched by propensity score. They also reported risk of cardiac rhythm disorders, coronary disease, and hypercoagulability (deep vein thrombosis, pulmonary embolism, peripheral arterial occlusions) were higher in men than women with significant interaction between sex and SARS-CoV-2 infection. The risk difference (RD) of cardiac rhythm disorders, coronary disease, and hypercoagulability between SARS-CoV-2 infected group and control group at one year were, cardiac rhythm disorders; women; RD 1.86, 95% CI 1.32–2.35, men: RD 3.02, 95% CI 2.43–3.73, coronary disease; women: RD 0.58, 95% CI 0.30–0.88, men: RD 1.08, 95% CI 0.72–1.45, hypercoagulability; women: RD 2.08, 95% CI 1.63–2.50 men: RD 2.59, 95% CI 2.09–3.15, respectively (all P values for interaction were <0.05) [7]. However, even though accumulating evidence suggests increased risk of CVD [7] and impaired cardiovascular function (i.e. endothelial dysfunction, myocardium injury) secondary to COVID-19 [24, 27], few study focus on the sex difference in long-term cardiovascular outcome secondary to COVID-19. Also, sex difference in the risk of hypertension after COVID-19 has not been reported at present. As recognition and consideration of sex difference in prevention and treatment of disease are fundamental steps toward precision medicine, further evidence of sex

difference in Long COVID and cardiovascular outcomes secondary to COVID-19 are warranted.

Conclusion and areas of uncertainty

As reviewed in this manuscript, accumulating evidence suggests that long COVID affects the clinical course of hypertension-related disorders, such as CVD, kidney diseases, and endocrine diseases. Studies thus far also indicate that long COVID has greater impacts on older population and women. Nonetheless, there are several clinical issues that require further investigation. The majority of studies evaluating long COVID and hypertension-related organs were conducted in the early phase of pandemic and few studies investigated the influence of new variants of coronavirus on the association of long COVID and hypertension-related organs. For example, a recent study of self-reported data to COVID Study app suggested that the prevalence of long COVID of the Omicron variant (majority was BA.1variant) was lower than that of Delta variant [193]. On the other hand, one article suggests that the BA.2 variant, which took place of recent wave after the wave of the Omicron BA.1 variant, caused approximately same rate of long COVID as the Delta variant [194]. In addition, the drastic changes in the environment surrounding COVID-19, e.g., the development of vaccines and new treatments for COVID-19, as well as the change in society and people's behavior, can have profound impacts on the risk of long COVID. Nonetheless, the effect of vaccination on long COVID is still controversial [195]. It also needs to note that no studies thus far evaluated the effects of third or fourth boosters on long COVID.

Also, currently there are no established treatments of long COVID. As many clinical trials evaluating the effects of variety of treatments on long COVID are currently in progress [13], the results of these trials are highly anticipated. To overcome COVID-19, clinicians, researchers, and various specialists in the world have been concentrating their wisdom. Yet, we are still in the half way towards the adaptation to the world with COVID-19, and we need more evidence to recover from the huge impacts of COVID-19.

Compliance with ethical standards

Conflict of interest The Department of Health Development and Medicine in Osaka University is an endowed department supported by Anges, Daicel, and FunPep. The authors declare no competing interests.

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