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REVIEW

Long COVID and the cardiovascular system—elucidating causes and cellular mechanisms in order to develop targeted diagnostic and therapeutic strategies: a joint Scientific Statement of the ESC Working Groups on Cellular Biology of the Heart and Myocardial and Pericardial Diseases

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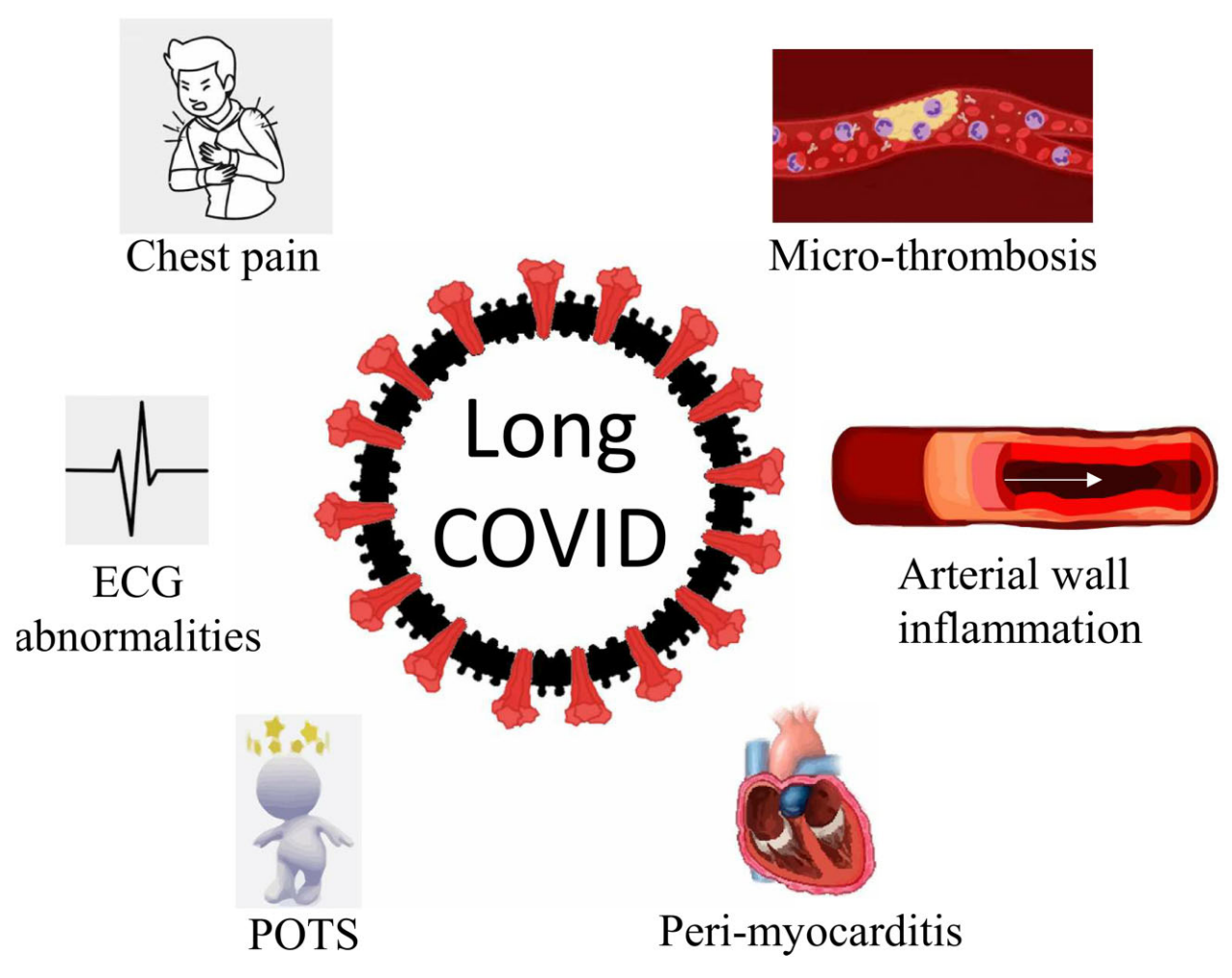
Abstract

Long COVID has become a world-wide, non-communicable epidemic, caused by long-lasting multiorgan symptoms that endure for weeks or months after SARS-CoV-2 infection has already subsided. This scientific document aims to provide insight into the possible causes and therapeutic options available for the cardiovascular manifestations of long COVID. In addition to chronic fatigue, which is a common symptom of long COVID, patients may present with chest pain, ECG abnormalities, postural orthostatic tachycardia, or newly developed supraventricular or ventricular arrhythmias. Imaging of the heart and vessels has provided evidence of chronic, post-infectious perimyocarditis with consequent left or right ventricular failure, arterial wall inflammation, or microthrombosis in certain patient populations. Better understanding of the underlying cellular and molecular mechanisms of long COVID will aid in the development of effective treatment strategies for its cardiovascular manifestations. A number of mechanisms have been proposed, including those involving direct effects on the myocardium, microthrombotic damage to vessels or endothelium, or persistent inflammation. Unfortunately, existing circulating biomarkers, coagulation, and inflammatory markers, are not highly predictive for either the presence or outcome of long COVID when measured 3 months after SARS-CoV-2 infection. Further studies are needed to understand underlying mechanisms, identify specific biomarkers, and guide future preventive strategies or treatments to address long COVID and its cardiovascular sequelae.

Graphical Abstract



Keywords COVID-19 • Long COVID • Post COVID • Cardiovascular • Cardiac

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1. Long-COVID syndrome

1.1 Epidemiology

As of May 2022, over 500 million people world-wide have been infected with the SARS-CoV-2 virus and its mutant variants. COVID-19, the disease caused by SARS-CoV-2, is burdened by an overall mortality rate of 1%,[1] and in 2020 represented the third and second leading cause of mortality amongst people aged 45–84 or over 85 years old in US, respectively.[2] In some countries, including France, Spain, and the UK, COVID-19 was the leading cause of death in the last 2 years.[3,4] Studies have estimated that 4.5–36.6% of all COVID-19 patients continue to suffer from symptoms more than 3 months post-infection, a condition referred to as 'post COVID' or 'long COVID' (defined below).[5–9] This rises as high as 76% amongst those who required hospitalization during the infectious phase.[10–14] A recent retrospective analysis of 273 618 patients with proven prior SARS-CoV-2 infection revealed that 36.6% had long COVID, with at least one of the nine predefined, typical long-COVID symptoms recorded in electronic health record (EHR) data between 3 and 6 months post-infection.[12] Notably, in a matched control population of 106 578 patients who previously had influenza, 29.7% experienced at least one of the symptoms during the same period of observation.[12]. Considering the possibility of selection and reporting bias, this suggests that many aspects of long COVID are similar to other post-viral diseases, even if there are significant differences in prevalence, clinical manifestation, or disease duration between post-viral syndromes.[7,8] A particular feature of SARS-COV-2 infection is that a single patient can be infected several times within a relatively short time despite effective vaccination. A further alarming observation is, that the morbidity, mortality, and development of long COVID are largely not predictable, especially in young patients.

Successful wide-spread vaccination against SARS-CoV-2 has reduced the severity of acute infection, although concern remains about the possible escape of viral mutants with greater infectivity.[15] Furthermore, the population of acutely infected individuals increasingly includes younger individuals who are unvaccinated, and those whose immunity is waning post-vaccination.[16,17] Therefore, more patients with long COVID and possibly a shift in the age distribution of long-COVID patients to those of younger age may be anticipated.

Several clinical cardiovascular manifestations of long COVID have been reported in small studies with questionable clinical relevance. However, a recent analysis of 153 760 individuals in national healthcare databases from the US Department of Veterans Affairs, with comparison to over 10 million contemporary and historical controls, revealed a significant increase in the incidence of cardiovascular disease in surviving patients, and a 55% increase in the combined cardiovascular outcome, 1 year after COVID-19.[18] Notably, increased risk was observed even in non-hospitalized patients, with risk related to the severity of the acute infection.[18]

Clinical implication: Long COVID will clearly lead to an enormous health care burden on top of the costs of acute COVID-19 medical support, which are already substantial. There is therefore an urgent need to improve the diagnosis and treatment of long COVID, especially in the cardiovascular domain.[19]

In this document, we discuss the main proposed mechanisms of long COVID, with a special emphasis on the cardiovascular sequelae of COVID-19.

1.2 Definition of acute, post-acute, and long COVID

The post-viral convalescence of COVID-19 can last for several months up to a year or even longer. There is no unique definition of this syndrome, and several different terms are used (*Table 1*). Most commonly, the post-SARS-CoV-2 viral period is divided into 'acute' (<4 weeks), 'post-acute', 'new', or 'ongoing' (4–12 weeks) and 'chronic (or long or post) COVID' (lasting 12 weeks or longer) phases.[20,21] Additionally, patients hospitalized during severe SARS-CoV-2 infection and still hospitalized several weeks or months after the acute infection due to severe complications when no longer infected, are usually called 'in-hospital post-COVID patients'. In this document, we use the term 'long COVID' where signs and symptoms continue beyond the acute phase of COVID-19, in line with the definition by NICE and the NIH (who refer to it as post-Acute Sequelae of SARS-CoV-2 infection or PASC).[22,23] A strict definition of long COVID requires confirmation of the previous

Table 1 Major clinical definitions for patients with signs and symptoms of COVID-19 beyond the period of acute SARS-CoV-2infection

Defining organization	Proposed term	Definition	References
NIH	Post-acute sequelae of SARS-CoV-2 infection (PASC)	Signs and symptoms of COVID-19 beyond 4 weeks from the onset of symptoms.	Herrera *et al.*[22]
NICE	Ongoing symptomatic COVID-19	Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks	NIfHaCE[23]
NICE	Post-COVID-19 syndrome	Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis	NIfHaCE[23]
NICE	Long COVID	Signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more)	NIfHaCE[23]
WHO	Post-COVID	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. Symptoms may be new onset (…) or persist.	[194]
CDC/WHO	Multisystem inflammatory syndrome in children (MIS-C) or adults (MIS-A)	Symptoms appear between 2 and 6 weeks (4 weeks on average) after COVID-19 infection.	[195,196]

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infection with SARS-CoV-2, either with evidence of prior positivity for polymerase chain reaction (PCR) or nucleocapsid antigen.

1.3 General symptoms of long COVID

The clinical presentation of long-COVID patients varies considerably. A diverse range of over 200 symptoms have been reported for long COVID, involving all organs, which suggests that long COVID is a systemic, multiorgan disease. Many symptoms are mild, non-specific, and reversible but moderate, severe, and persistent symptoms have also been reported, including thromboembolic consequences, lung fibrosis, chronic inflammatory myocarditis, cardiovascular autonomic vegetative dysregulation (e.g. postural orthostatic tachycardia syndrome or POTS), and chronic post-viral fatigue syndrome (similar to myalgic encephalomyelitis/chronic fatigue syndrome, ME/CFS) leading to chronic disability.[10,24–27] The most common symptoms are of neurologic–neuropsychiatric character (e.g. fatigue, brain fog, cognitive disorders, insomnia, depression, post-exercise malaise, decrease of general health condition), followed by pneumological (e.g. dyspnoea, cough) and cardiovascular symptoms (e.g. hypotonia, palpitation, tachycardia, chest pain). Neuronal infection and intracerebral viral invasion may also contribute to neurological-related symptoms affecting the heart–brain axis.[28] Further typical symptoms are joint and muscle pain, hair loss, dermatological, or other organ-related manifestations.

Clinical implication: Cardiovascular symptoms are common in long-COVID patients and are the third-most-frequent manifestation of the disease.

1.4 Risk factors

Although more men experience symptoms from *acute* COVID-19 disease, 55–75% of long-COVID patients are women, with the greatest prevalence in those aged 40–60 years.[12,29] Other predictors of long COVID include: a greater body-mass index, older age, presence of combined symptoms from five or more different organs during the SARS-CoV-2 infection, and, importantly severe COVID-19 disease requiring hospitalization (*Table 2*).[5,10,12,24–26,30] A combination of several factors, including the severity of the illness during acute COVID-19 infection, clinical symptoms, and lower SARS-CoV-2 IgG level, have been found to be predictive for the development of PASC or long-COVID syndrome.[31] Risk can be estimated using the PASC score (a clinical symptom-based score combined with antibody signature) or other calculated score.[5,32] However, all risk factors investigated, especially the laboratory parameters, have been assessed in patients who were either hospitalized or had an outpatient visit due to severe symptoms. Since ~90% of patients were not medically seen or isolated during the acute infection because of a mild–moderate diseases course, an exact estimation of long-COVID risk factors for non-hospitalized patients is not possible.

Clinical implication: The risk of long COVID can be calculated for patients with severe COVID-19, based on associated risk factors, but is difficult to predict for mild and non-hospitalized cases.

1.5 Diagnosis and patient management

The main diagnostic process for long COVID aims to either verify or exclude objective organ disorders, such as newly developed autoimmune or post-inflammatory chronic myocarditis or lung fibrosis, or unexpected progression of pre-existing diseases, e.g. chronic obstructive lung disease, coronary artery disease, chronic kidney dysfunction, diabetes mellitus, reactivation of autoimmune or endocrine disorders. Detailed guidelines for general diagnosis of long COVID, artificial intelligence-based diagnostic or prediction models for patient management have been published in several specific journals, addressing primary, secondary, and tertiary care workers, and specific medical professionals.[23,30,33–41]

Table 2 Risk factors for development of long-COVID syndrome

Risk factors	References
Detected during active infection	
High level of SARS-CoV-2 RNAemia	148,197
High level of EBV RNAemia (latent EBV reactivation)	148
High level of INFα	148
Specific autoantibodies (e.g. ANA)	148
Low IgM and IgG Subtype 3	32
Lower level of SARS-CoV-2 IgG	31
Anosmia	31
Diarrhoea	31
Severe COVID-19 disease requiring hospitalization	5
Presence of five symptoms from different organs during acute infections (fatigue, headache, dyspnoea, hoarse voice, myalgia, but also loss of smell in pts age >70 years)	5,10,12,24–26,30
High PASC score	32
General	
Diabetes mellitus	5,148
Female gender	12,29
Greater body-mass index	5
Older age	5
Any previous comorbidities if age > 70 years	5
Previous comorbidities: asthma, heart diseases	5,32

Studies with highly selected patient groups (e.g. hospitalized and/or intensive care unit treatments, older age, or significant comorbidities, as inclusion criteria) were excluded. EBV, Epstein-Barr Virus; INFa, interferon-alpha; ANA, antinuclear antibody; Ig, immunoglobulin; PASC, post-acute sequelae of SARS-CoV-2 infection.

2. Cardiovascular manifestations of long COVID

The *cardiovascular symptoms* of long COVID are a consequence of multiple cardiac and extracardiac pathological sequelae (*Figure 1*), including residual respiratory abnormalities with abnormally low peak-of-maximal oxygen consumption, pulmonary hypertension, muscular deconditioning, cytokine dysregulation, left or right ventricular dysfunction, chronotropic incompetence, altered parasympathetic tone, or increased heart rate variability (*Table 3*).[19,21,42–49] Generally, patients who required hospitalization during the acute COVID-19 phase present with more severe cardiovascular symptoms in long COVID, and with much higher incidence than in mild-to-moderate or asymptomatic patients.[18,50–53] For hospitalized patients who had elevated cardiac troponin T, the in-hospital, 6-month, and 12-month mortality rates were 28.6, 32.2, and 33.2%, respectively, compared with 4.1, 4.9, and 4.9% mortality of patients with low-level positive troponin T and 0% mortality in those with undetectable troponin T.[53] Patients with high troponin T during index hospitalization were re-hospitalized significantly more often and developed long-term symptoms.[53]

Clinical implication: There are currently few randomized studies of long-COVID symptoms. Reports of cardiovascular symptoms are based entirely on individual subjective assessment, with the challenge being to verify the underlying cause.

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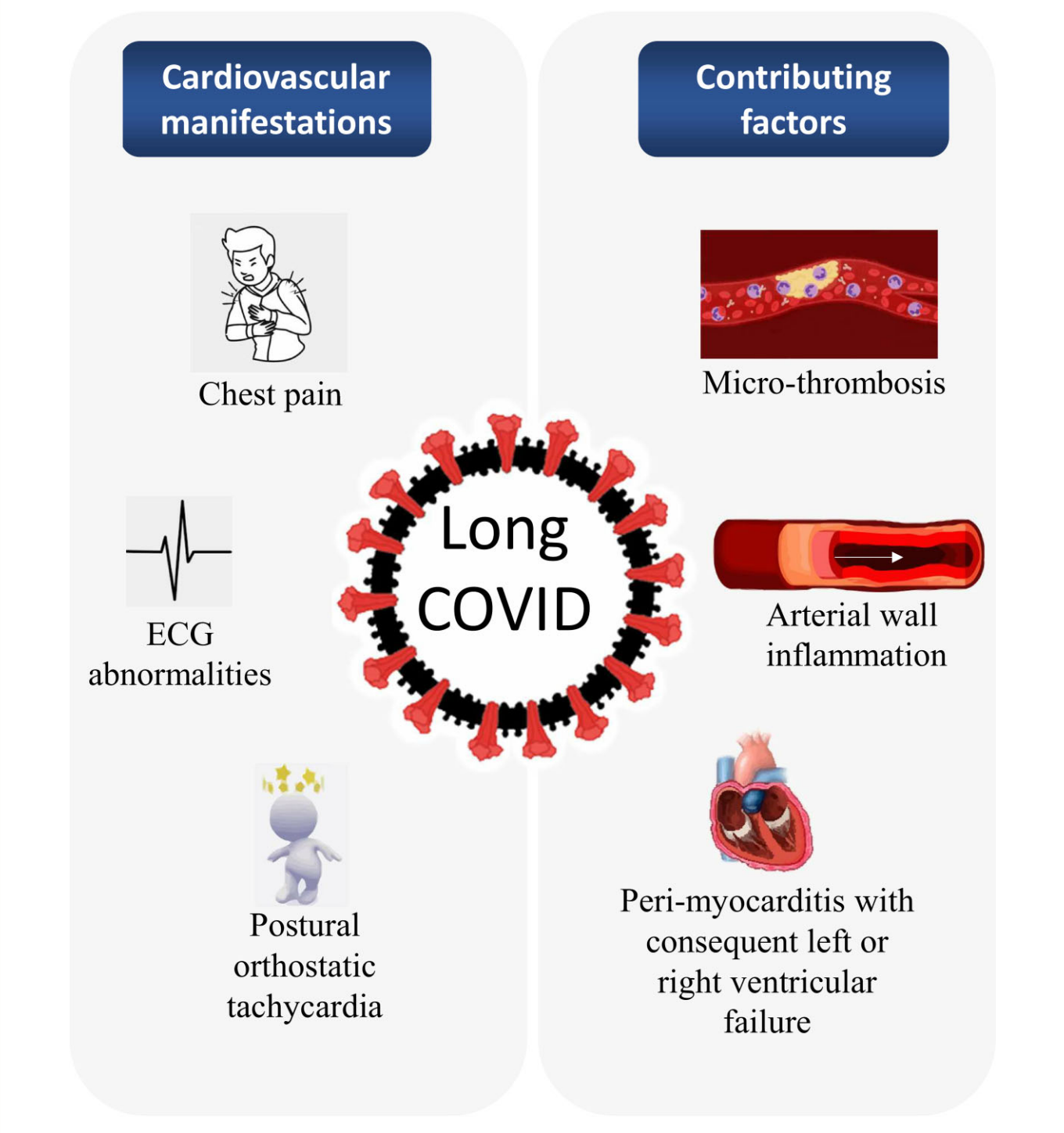

Figure 1 **The major cardiovascular manifestations in patients with long COVID (left side), and likely mechanistic contributing factors (right hand side).**

Several studies have reported *cardiac manifestations* in patients affected by long COVID, although their prevalence varies according to the population studied and the methodology with which the data were collected (*Table 4*). Temporary or persistent ECG and Holter–ECG abnormalities have been described in some long-COVID patients, at a frequency ranging from <1% in young athletes to as high as 27.5% in patients requiring hospitalization due to cardiovascular complications.[54,55] The prevalence of ECG changes depends on the time since acute COVID-19 infection, the patient population, and pre-existing cardiovascular abnormalities. The changes detected include sinus tachycardia, unspecific ST-changes, ST-elevation without signs of myocardial ischaemia, T-wave abnormalities, prolonged QT interval, low voltage, development of new complete or incomplete bundle branch block.[24,54,55] ECG combined with tilt table test is useful for the diagnosis of POTS.[56]

Although most COVID-19-related acute abnormalities in ventricular size, geometry, and function resolve over time, some abnormal

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Table 3 Cardiac-related manifestations based on patient symptoms and their prevalence in long-COVID patients

Long COVID						
Post-acute COVID (4–12 weeks since COVID-19)				Post COVID		
Cardiac manifestations	Symptomatic (%)	Patients included in study (*n*)	References	Symptomatic (%)	Patients included in study (*n*)	References
Chest pain	12.7–28.9%	81–287	24,198–201,204	5–30%	120–1733	10,25,46,120,202–207
Palpitation, tachycardia, atrial fibrillation	10–32%	51–2113	54,199,201, 204,208	0.3–20%	92–1733	10,25,202,204,209,210–212
Dyspnoea	13.1–92.1%	33–3290	13,20,24,97,193,200,201,204, 208,213–215,216	4.1–70%	66–2649	10,25,31,203,204,205–207,209,212,217,218, 219–221
Cough	9–42.3%	110–3290	13,97,198,204,213,216	4.2–16.7%	120–958	31,203,207,212
Exercise-induced dyspnoea, exercise-induced ventilatory inefficiency	51%	51	54	14.6–29%	28–55	112,222
Dysautonomia				15.2–25%	92–205	212,223
Postural tachycardia syndrome, orthostatic intolerance, inappropriate sinus tachycardia				11–41%	27–1890	49,212,224–226

Studies with highly selected patient groups (e.g. only hospitalized and/or intensive care unit treatments, older age, or significant comorbidities, as inclusion criteria) were excluded.

echocardiographic findings may remain, including adverse left and right ventricular remodelling, diastolic and systolic dysfunction, pulmonary hypertension, pericardial effusions, or reduced left ventricular (LV) or right ventricular (RV) global longitudinal strain.[47,50,57–59] It has been suggested that such late pathological findings can be correlated with the severity of the acute COVID-19, the time since the acute illness and the number of persisting symptoms.[60]

In-depth characterization of cardiac involvement by cardiac magnetic resonance imaging (cMRI) has revealed ongoing myocardial oedema, inflammation, fibrosis, impaired LV and RV function, and pericardial enhancement and/or effusions in some patients studied after the acute phase of COVID-19. Some studies were relatively small with <50 patients, and conflicting results have been reported regarding the actual prevalence. Accordingly, the significance of these findings depends on patient population and time between COVID-19 disease and imaging time (*Table 4*).[27,61–65] Furthermore, even in hospitalized severe COVID-19 patients, myocarditis-like injury was limited to three or less myocardial segments in 88% of cases, with no associated LV dysfunction.[27] A recent meta-analysis of cardiac involvement of long-COVID syndrome assessed by cMRI reported decreased LV and RV function in non-athlete, long-COVID patients as compared with healthy controls.[66] The cMRI abnormalities seen in patients recovered from acute COVID-19 are not always associated with pre-existing comorbidities, other chronic clinical conditions, severity of the acute COVID-19 illness, or persistence of symptoms.[63,67] A prospective case–control cMRI study of 149 healthcare workers found that cardiovascular abnormalities were no more common in seropositive vs. seronegative individuals 6 months following mild COVID-19.[68] The exact prevalence and incidence of these cardiovascular signs in long-COVID patients is still unclear, due to substantial differences between studies, cMRI protocols, timing of disease, and patient selection criteria.

Table 4 Cardiac complications and their prevalence in patients with long COVID

Cardiac complications	Patients with cardiac complications (%)	Patients included in study (*n*)	References
Chronic myocarditis	0.4–28.9%	48–543	24,27,46,54,66,227–230
Chronic pericarditis	1.9–27%	26–105	74,231
Myocardial oedema	15.4%	26	231
Myocardial fibrosis or scar	4%	26	231
Systolic or diastolic LV dysfunction	0.06–35%	51–8983	54,59,66,79,199,204,207,228,210,232–235
RV systolic dysfunction	7–22.6%	50–1414	59,66,204,207,210,230
LV thrombus	2%	51	57
Coronary artery disease	8%	51	57
Acute myocardial infarction	1.5–8%	51–47 780	46,57,83
Persistent systemic endothelial dysfunction	2.5–6.1%	72–133	236,237
Coronary microvascular disease	18%	22	238
Heart failure	0.1–2%	543–8983	46,79
Pulmonary hypertension	10–50%	102–145	21,233,239

Studies with highly selected patient groups (e.g. only hospitalized and/or intensive care unit treatments, older age, or significant comorbidities, as inclusion criteria) were excluded. LV, left ventricular; RV, right ventricular.

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Table 5 Newly diagnosed cardiovascular complications and their prevalence in patients with long COVID

Cardiovascular complications	Patients with CV complications (%)	Patients included in study (*n*)	References
Hypertension	1.28–1.3%	512–538	202,240
Diabetes mellitus	0.64–2.4%	287–512	24,240
Stroke	0.1–6.7%	30–8983	79,80
Venous thromboembolism	0.2–12.5%	1062–8983	79,82,232
Hospitalization	4.5–29.4%	1062–47 780	82,83
Paediatric or adult multisystem inflammatory syndrome with/without Kawasaki in children and adults	Ca. 0.15%	International health records	86

Studies with highly selected patient groups (e.g. only hospitalized and/or intensive care unit treatments, older age, or significant comorbidities, as inclusion criteria) were excluded.

To complement cMRI information, functional positron emission tomography (PET)/computed tomography (CT) studies could be useful to demonstrate PET tracer uptake in active inflammatory lesions.[69,70] However, to date, this specific application has rarely been employed in the clinical context of long COVID.[71] [18F]-FDG-PET/CT imaging of 10 patients with persisting long-COVID symptoms exhibited significantly higher target-to-blood pool ratio in the thoracic aorta, right iliac artery, and femoral arteries, compared with controls.[72] Whole-body [18F]-FDG PET/CT images of long-COVID patients revealed increased [18F]-FDG uptake in several tissues (lung, mediastinal lymph node, large vessels) in a subgroup of patients, and a brain hypometabolism of individuals suffering from persistent anosmia and/or ageusia.[73] Cardiac 18F-FDG PET/CT of five patients with cardiac symptoms in the post-acute COVID phase displayed higher 18F-FDG-PET uptake of the LV lateral and inferolateral walls, suggesting 'myocardial fatigue syndrome'.[74]

Clinical implication: Although cardiac manifestations occur in some patients affected by long COVID, in some cases these might have already existed before they had COVID-19, even if the patients did not have previous corresponding complaints, but this is difficult to assess, due to missing individual comparative baseline measures. Additionally, several diagnostic investigations have been performed in highly pre-selected patient populations and their wider applicability is difficult to ascertain.

Table 5 summarizes the newly diagnosed *cardiovascular manifestations* during the long-COVID phase. New hypertension and diabetes mellitus have been diagnosed in up to 10 and 2.4% of individuals, respectively. Indirect haemodynamic consequences may be caused by chronic kidney disease,[75–77] or gastrointestinal disorders.[78] Several case reports and small case series report stroke,[79,80] microangiopathy,[81] venous thromboembolism,[79,82] heart failure,[79] or need for hospitalization.[82] In a large retrospective study, mean 140 days post-discharge, 29.4% of patients required re-hospitalization, with a mortality rate 7.7-fold greater than those in a control group with matched clinical characteristics.[83] Cardiovascular involvement with Kawasaki syndrome (especially in children) has been reported in delayed multisystem inflammatory syndrome (MIS) induced by COVID-19 disease.[84,85] The Kawasaki-like, MIS in children (MIS-C, also called paediatric MIS or PMIS) and in adults (MIS-A) is a very rare (2 in 100 000) complication of SARS-CoV-2 infection, which manifests in the post-acute phase of infection and is characterized by generalized hyperinflammation with cardiovascular involvement.[86–89]

Clinical implication: Multiorgan diagnostic screening procedures may reveal hidden systemic diseases and the presence of risk factors. The increased prevalence of risk factors in a predominantly young- or middle-aged population warrants attention and suggests the importance of ongoing systematic and cardiovascular assessment of long-COVID patients.

3. Circulating clinical biomarkers predictive for cardiovascular manifestations of long COVID

Several studies have evaluated whether standard clinical biomarkers can predict the severity and duration of long COVID. Only a few of these studies have considered novel biomarkers using unbiased approaches to predict cardiovascular manifestations associated with long COVID. Overall, these studies suggest that circulating inflammatory and coagulation biomarkers may persist during long COVID, and therefore potentially indicate altered cardiac metabolism and increased thromboembolic and cardiovascular risks. However, most biomarker studies are based on small patient datasets and are lacking either: laboratory confirmation of prior SARS-CoV-2 infection; longitudinal evaluation; appropriate match-controlled groups to ascertain specificity for long COVID; replication with independent data sets; and/or evaluation of biomarker correlation with specific manifestations of long COVID, notably cardiovascular. Further studies are therefore required to assess the longitudinal evolution of these biomarkers during the time course of long COVID. Ongoing large-scale studies, including BIOMARK-COVID (NCT04664023), French COVID Cohort (NCT04262921), MOIST Study (NCT04525404), PHOSP-COVID, follow-up study of the ISARIC cohort,[90] COVIDOM-study[91] and the use of large-scale screening technologies will hopefully provide more conclusive data.

3.1 Circulating inflammatory and cardiac-related markers

There are some indications that levels of proinflammatory markers remain elevated in patients with long COVID[92] (*Table 6*). In particular, several inflammatory markers that are typically elevated during the acute disease, including C-reactive proteins (CRP) and interleukins (IL), may remain elevated when measured 2 or more months post-disease onset.[93–95] However, the percentage of long-COVID patients with elevated inflammatory markers reported by various studies varies widely, from 10 to 73%, and some inflammatory markers, such as IL-6, show inconsistent association with long-COVID symptoms.[13,95–103] It is important to note that most published biomarker studies that have examined the association with patient outcome (e.g. CRP[99,104] and ferritin[101,105]) are very preliminary and inconclusive due to small patient numbers, the presence of confounding factors, or lack of appropriate control groups. One notable exception is the study by Phetsouphanh *et al.*,[106] in which inflammatory markers in long-COVID patients were compared with matching populations of individuals who recovered from COVID-19,

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Table 6 Circulating biomarkers characterizing long-COVID syndrome

Cardiac biomarkers	Comments and detection time post-infection	References
Troponin T/I	Depending on elevated troponin during hospitalization, interval between hospital discharge and labour measurements; 57–71 days	63,204,232
n-Terminal pro-brain natriuretic peptide (proBNP)	9.6 months	232
Inflammatory biomarkers		
C-reactive protein (CRP)	30 days to 3 months	93,94,99,101,104,241
Interleukins general (IL)	15 days to 3 months	93,94,241,242
IL-6	Inconsistent association with long-COVID symptoms; over 3 months	13,84,96–99,101–103
Ferritin	Associated with patient outcome in small cohort; over 3 months	101,105
IFN-β, IFN-λ1,	Combination of inflammatory markers are predictive for long COVID; 8 months	106
CXCL9 and CXCL10	Was also elevated in asymptomatic post-COVID patients; 8 months	106
IL-8	Was also elevated in asymptomatic post-COVID patients; 8 months	106
TIM-3	Was also elevated in asymptomatic post-COVID patients; 8 months	106
Plasma ACE2 activity	Was also elevated in asymptomatic post-COVID patients; 3–8 months	106,243
PTX3	8 months	106
Procalcitonin	Correlated with microvessel disease, 3 months	99
Coagulation biomarkers		
D-Dimer	2–3 months	98,101,109,113
Factor VIII, vWF; Thrombomodulin	Returned to normal in >90% patients in convalescent phase; 68–81 days	98,109,113
Novel biomarkers		
Taurine	3 months	113
Reduced glutamine/glutamate ratio	3 months	113
Lower nitrite, nitrite/nitrate	4 months	114
Molecular biomarkers (long non-coding RNA, microRNA)	Suggestive, not validated	115–117

IFN, interferon; CXCL, chemokine (C–X–C motif) ligand; TIM-3, soluble T-cell immuno-globulin mucin Domain 3; ACE, angiotensin-converting enzyme; PTX, pentraxin; vWF, von Willebrand Factor.

unexposed controls, and individuals infected with other coronaviruses. Time-dependent elevations of inflammatory biomarkers were detected, and combinations of the plasma levels of interferon (IFN)-β, PTX3 (pentraxin-3), IFN-γ, IFN-λ2/3, and IL-6 characterized long COVID with 78.5–81.6% accuracy. Finally, amongst the various efforts to identify new diagnostic biomarkers for long COVID, small-scale mass spectrometry-based multiplex assays and machine learning studies have been conducted but so far these remain explorative studies and far from clinical translation.[107,108]

3.2 Circulating coagulation biomarkers

Elevated blood levels of coagulation markers (D-dimer, Factor VIII, von Willebrand factor, plasma soluble thrombomodulin) have been detected during long COVID,[13,98,109] together with increased erythrocyte sedimentation rate,[101] altered vascular responsiveness,[100] and structural membrane homeostasis of red blood cells,[110] raising the possibility of long-term risks of thromboembolic diseases and endotheliopathy for long-COVID patients (*Table 6*). Persistently elevated D-dimer was found in three reported cases of STEMI in post-COVID patients with no prior cardiovascular risk factors.[111] Higher levels of D-dimer at acute COVID-19 admission also correlated with persistent lung damage in long-COVID patients.[112]

3.3 Current research on novel biomarkers of long COVID

Metabolic phenotyping approaches have been deployed to find novel predictive markers of long COVID (*Table 6*), but are all at the exploratory research level and require validation. An elevated blood taurine level with a reduced glutamine/glutamate ratio at 3 months post-COVID was identified, potentially reflecting liver, heart, and muscle damage.[113] Lower nitrite and nitrite/nitrate levels were found in recovered COVID-19 patients.[114] Since nitric oxide (NO) plays an important role in the cardiovascular system, further research is warranted to elucidate whether NO levels could reflect cardiovascular damage.

Potential molecular biomarkers that could help predicting cardiovascular outcomes of patients with SARS-CoV-2 infection are non-coding RNAs, due to their dynamic regulation in response to disease. In fact, several microRNAs and lncRNAs that could potentially influence symptoms were reported to be differentially expressed in acutely infected patients. Up-regulation of miR-21, miR-155, miR-208a, and miR-499 in COVID-19 patients was suggested to be a predictor of chronic myocardial damage and inflammation.[115,116] Most of these targets still require validation for their predictive value regarding the onset of short- and/or long-term cardiovascular events following SARS-CoV-2 infection.[117]

Clinical implication: Currently there are no specific biomarkers of long COVID. The diverse, organ-specific, circulating biomarkers that have been detected are a consequence of the COVID-19 infection-related organ disorders, with their established diagnostic and predictive values.

4. Cellular and molecular mechanisms of cardiovascular long-COVID manifestations

Increasing research data are available about the cellular and molecular mechanisms that may drive cardiac and vascular injuries associated with long COVID (*Figure 2*). An *in silico* study by Hachim *et al.*[118]

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identified several genes to be differentially expressed in various cell types which are known to play roles in endothelial cell function and cardioprotection, namely in migration and regulation of cellular response to stress, and in viral infection. However, it is conceivable that different causes and underlying mechanisms may be responsible for the different clinical manifestations of long COVID, leading to multiple types of disease presentations.

4.1 Cellular response

Table 7 summarizes the cellular dysregulation that occur in long-COVID syndrome. Long-COVID manifestations involve autoimmune responses, with self-damaging effector responses by autoreactive T cells and autoantibodies to self-antigens produced by plasma cells. Several research groups investigated the B- and T-cell populations in different time intervals after infection onset. Files *et al.*[119] found increased expression of Programmed Cell Death protein (PD1) in convalescent individuals lasting up to 45 days, while Yao *et al.*[120] detected SARS-CoV-2-specific memory B cells and interferon-γ-secreting T cells in 70% of patients up to 9 months. Lack of naïve T- and B-cells expressing CD127 and TIM-3, as well as an increase in activated myeloid cells, and plasmacytoid dendritic cells were reported.[106] Interestingly, expression of several B- and T-cell surface molecules persisted in longitudinal samples, suggesting a role for prolonged cellular dysregulation in long-COVID patients.[119] New onset autoantibodies appear in hospitalized patients with COVID-19[121] and may continue following infection,[122] but their contribution to long COVID remains to be determined.

The sequelae of other viral infections (e.g. influenza, parvo-virus B19, Epstein-Barr, Dengue, or Ebola) are usually shorter and present fewer and less severe symptoms over time.[9,12,75,123] Nevertheless, the clinical similarities with long COVID suggest autoimmune reactive inflammation associated with the release of autoantigens by activated or dying neutrophils, elevation of neutrophils to lymphocytes ratio and neutrophil extracellular traps, which lead to the conversion of acute SARS-CoV-2 infection to long COVID.[124,125]

SARS-CoV-2 infection activates mast cells. Since acquired mast cell clonality is characterized by aggravation of inflammation and generalized allergy, causing chronic multiorgan manifestation and typically fatigue syndrome, activation of mast cells has been proposed as one of the possible causes of long-COVID syndrome.[126] However, since systemic mastocytosis is difficult to diagnose from blood samples, the significance of this hypothesis is weak, and remains to be confirmed.

An additional immune mechanism contributing to long COVID could involve epigenetic reprogramming of haematopoietic progenitors, which alters the phenotype of blood cells. A recent, real-time deformability cytometry analysis of blood samples from a small number of patients (17 acute COVID-19 patients, 14 recovered and 20 healthy volunteers), showed that COVID-19 infection caused significant changes in the size and stiffness of red blood cells and leucocytes.[127]

Scientific implication: The hypothesis that immune dysregulation is involved in the cardiovascular manifestation of long COVID is currently highly speculative, but may provide a possible explanation for the multiorgan character of the long-COVID syndrome, and justifies further investigation.

4.2 Molecular pathomechanisms and cellular senescence

The majority of long-COVID patients suffers from CFS, a disease entity very similar to ME/CFS. ME/CFS has been suggested to be related to mitochondrial dysfunction and oxidative stress, and the same pathomechanism has therefore been suggested for fatigue in long COVID (*Table 7*).[128]

The clear vulnerability of most elderly patients to the devastating impact of SARS-CoV-2 and long COVID indicates a possible effect of infection on accelerated senescence of the immune system.[129,130] It is possible that the viral infection enhances the diffuse proinflammatory status in organs susceptible to ageing. Most cardiomyocytes are terminally differentiated and, with ageing, release inflammatory cytokines related to the senescence-associated secretory phenotype (SASP),[131] causing various cardiac dysfunctions.[132] A correlation has been observed between the degree of 'biological' ageing, as determined by telomere length, and severity of acute COVID-19.[133,134] Even more alarming is evidence that prior infection with SARS-CoV-2 may accelerate the epigenetic 'clock'[135] by increasing methylation at age-sensitive DNA CpG islands and by shortening telomeres,[136] since significant telomere shortening in blood cells and an acceleration of biological ageing (5 years above normality) have been reported in COVID-19 survivors,[136] suggesting that COVID-19-induced epigenetic alterations could contribute to long-COVID symptoms.

Although the molecular mechanisms underlying this effect are far from being elucidated, it is possible that interaction of the viral S-protein with SARS-CoV-2 cellular receptors[137] induces replicative senescence and overexpression of SASP factors,[138,139] with long-lasting consequences on cardiomyocyte function or persistent activation of cardiac-resident fibroblasts.[140] In this respect, the use of senolytic drugs to eliminate senescent cells from tissues could help to limit the consequences of accelerated tissue senescence in long COVID, as recently demonstrated in animal models of SARS-CoV-2 infection.[141,142] However, this research remains at an early stage and current senolytics are unlikely candidates as they are generally untested clinically and present some unwanted toxicity.

Scientific implication: The molecular pathomechanisms of the cardiovascular manifestations of long COVID are largely unexplored, due to the lack of respective cell culture or animal models.

4.3 Persistence of viral particles and the role of hidden reservoirs

Although the SARS-CoV-2 virus is typically cleared within the first weeks of infection, viral particles can persist in some patients,[143] leading to sustained T- and B-cell activation and potentially causing long COVID.[78] Viral persistence might be facilitated by immunosuppressive treatment, or by residence within immune-privileged sites or hidden reservoirs such as the intestines.[78,144,145] Another possibility is immune exhaustion following prolonged antigen stimulation.[146] The presence of a viral superantigen within SARS-CoV-2 has also been suggested, which could overstimulate the immune response thereby inducing a paradoxical, negative immunological feedback loop.[147] In some patients, reactivation of latent Epstein-Barr virus (EBV) or cytomegalovirus infection occurs during acute COVID-19. EBV reactivation anticipates some symptoms of long COVID, despite little viral mRNA remaining in the blood.[148] Nevertheless this suggests antivirals during the acute phase may lessen some long-COVID effects, at least in certain patients.

The extent to which cells of the myocardium can be virally infected during the acute phase is debated. There is some evidence for infection of cardiomyocytes in cardiac biopsies,[149–151] but differentiating true myocyte infection from stromal, vascular, or inflammatory cell infection precludes any definite conclusions. Furthermore, whether any

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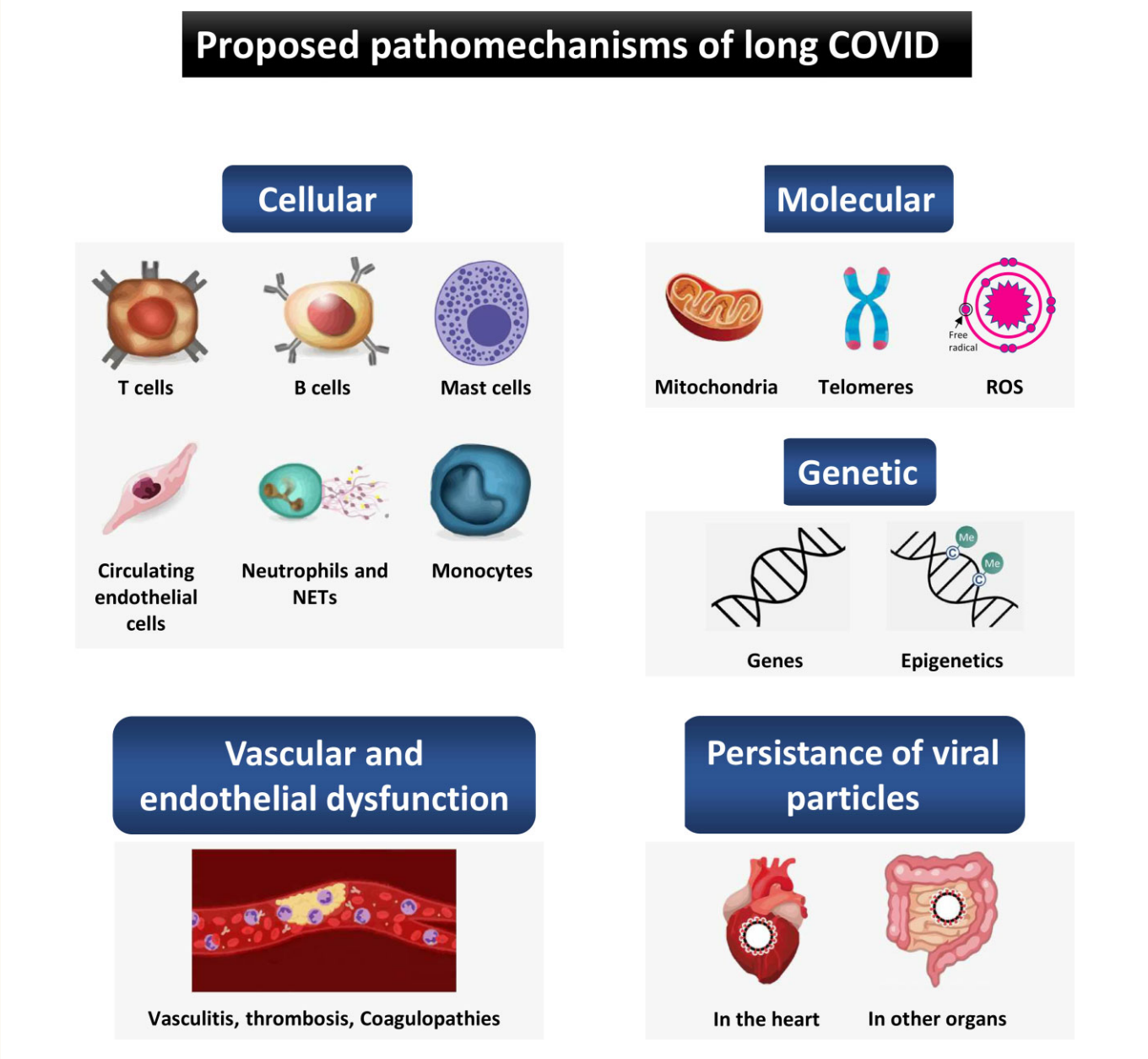

Figure 2 The major mechanisms that may drive long COVID, and how they may interact. Potential cellular mechanisms may involve: T-cells (interferon-gamma, IF-beta, IF-delta1 secretion, activation of CD8+, T-cell exhaustion); B-cells (dysregulation of SARS-CoV-2-specific memory B cells); haematopoietic progenitors (epigenetic reprogramming); activated CD38 + HLA-DR+ myeloid cells; plasmacytoid dendritic cells (pDCs) expressing CD86 and CD38; mast cell activation; circulating endothelial cells; neutrophils (release of autoantigens, NETs); activated monocytes; protracted immunosuppression by latent virus reactivation. *Molecular mechanisms* may involve: mitochondrial dysfunction; senescence; telomere shortening of blood cells; oxidative stress. *Genetic mechanisms* may involve: X-chromosome-associated ACE-2 receptor; genes coding Type I interferon immunity; ABO blood group genetic locus; epigenetic mechanisms. *Vascular and endothelial mechanisms* may involve: endotheliopathy; deterioration of capillary integrity (capillary flow disturbance, heterogeneity of capillary transit time); vasculitis; coagulopathies or thrombosis. Persistence of viral particles may contribute to the mechanism, either in myocardial tissue or hidden reservoirs in other organs.

viral particles isolated would be replication competent is not clear.[140,143,152] However, when assessed according to established criteria, there is little evidence for acute or persistent lymphocytic myocarditis even amongst patients with persistent cardiac symptoms after a COVID-19 infection.[153] Since SARS-CoV-2 infects alveolar macrophages,[154] and increased numbers of macrophages have been detected in hearts of patients deceased with COVID-19, another possibility is that there is a unique type of myocarditis associated with diffusely infiltrative cells of monocytes/macrophage lineage.[155]

Scientific implication: Based on current evidence it is unlikely that viral persistence in myocardium contributes to post-acute COVID-19 cardiovascular sequelae. However, the long-term consequences of the viral infected myocardium should be further evaluated.

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Table 7 Proposed pathomechanisms of long-COVID syndrome

Pathomechanism	Comments and detection time post-infection	References
Cellular pathomechanism		
Dysregulation of SARS-CoV-2-specific memory B cells	9 months	120
Interferon-γ-secreting T cells, elevated INF-beta, INF-delta1	9 months	120
CD8+ T-cell activation expressing PD-1 and TIM3	45 days, 8 months	119,106,242
Lack of B and T cells expressing CD127 and TIM-3	8 months	106
T-cell exhaustion with reduced cytokine production	Starts during acute infection	244,245
Epigenetic reprogramming of haematopoietic progenitors	8 months	127
Elevated level of activated CD38 + HLA-DR+ myeloid cells	8 months	106
Activated CD14 + CD16 + monocytes	8 months	106,155
Persistent activation of cardiac-resident fibroblasts	n.r.	151
Higher number of plasmacytoid dendritic cells (pDCs) expressing CD86 and CD38	8 months	106
Mast cell activation	n.r.	126
Increased levels of circulating endothelial cells (CD45–/CD31+/CD133–/DNA+)	27–46 days	242
Elevation of neutrophils to lymphocytes ratio (NLR)	n.r.	124
Development of NET	n.r.	124,246
Release of autoantigens by neutrophils	n.r.	124
Persistent antibodies	9 months	120
Protracted immunosuppression (PICS) by latent virus reactivation		48
Molecular pathomechanisms		
Mitochondrial dysfunction	n.r.	128
Oxidative stress	n.r.	128
Telomere shortening of blood cells	n.r.	136
Epigenetic alterations	n.r.	136
Overexpression of SASP factors	n.r.	131,140

IFN, interferon; PD, programmed death; TIM-3, soluble T-cell immuno-globulin mucin Domain 3; NET, neutrophil extracellular trap; SASP, senescence-associated secretory phenotype; n.r., not reported.

4.4 Persistence of vascular and endothelial dysfunction and pro-thrombotic complications

The endothelium has been proposed to underly the pathology behind the clinical presentation in severe COVID-19 and contribute to long-term cardiovascular complications.[156–158] (*Table 8*). Importantly, several pathologic processes persist even once SARS-CoV-2 is no longer detectable. These processes include microthrombosis, deterioration of capillary integrity, capillary flow disturbance, and heterogeneity of capillary transit time with reduced oxygen extraction.[159] The end result is microvascular and alveolar gas exchange malfunction, further leading to hypoxaemia of diverse organs including heart, brain, lung, and kidney, and sequelae of the disease.[159]

Endotheliopathy and coagulation markers remain elevated in a significant proportion of convalescent patients,[98,109] suggesting that the infection creates a chronic coagulopathy, endotheliitis, or microangiopathy with

Table 8 Vascular and endothelial dysfunction

	Comments and detection time post-infection	References
Endothelial dysfunction		
Endotheliopathy	Together with coagulopathy parameters, endothelial cell activation occurs mostly in hospitalized patients; 68 days to 4 months	98,109,156,158,159,247
Reduced oxygen extraction	In spite of normal resting lung function and imaging	159,248
Vascular dysfunction		
Capillary flow disturbance, heterogeneity of capillary transit time, deterioration of capillary integrity	Blood-flow limiting conditions, reduced oxygen exchange; 4 months	156–159
Vasculitis	In several organs	72,249
Coagulopathies, thrombosis		
Coagulopathy	With elevated D-dimer, mostly in hospitalized patients; 68–80 days	98,109
Microthrombosis	In several organs; 80 days	159
Activation of neutrophil extracellular traps (NETs)	Circulating markers were elevated in acute COVID but returned to baseline by 4 months	125

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microthrombosis which may drive myocardial dysfunction,[18] although so far, the effect on heart function appears to be relatively minimal.[27] This condition should be appropriately monitored in the future by studies in larger patient cohorts, taking advantage of advanced imaging systems such as cMRI.

Clinical implication: Micro- and macro-vessel changes are associated with endothelial dysfunction, coagulopathy, and microthrombi, and are likely to be major factors in the persistence of cardiovascular manifestations of long-COVID syndrome.

4.5 Genetic underpinnings of long COVID

Women tend to be at higher risk for long COVID,[90] despite the mortality rate being higher for men during the acute phase.[160,161] Genetic variants were implicated in shaping the immune response in several viral diseases,[162] and preclinical data indicate that ACE2 expression levels are sex dependent.[160] Despite the involvement of ACE2 in SARS-CoV-2–host cell interaction, no association between serum ACE activity and COVID-19 disease severity has been found.[163]

Whole-exome and -genome sequencing of 659 patients with life-threatening COVID-19 pneumonia found genetic variants predicted to be loss-of-function at 13 loci previously associated with other life-threatening viral illness (e.g. influenza pneumonia). Genetic variants associated with poor clinical outcomes in acute COVID-19 patients occurred in genes participating in Type I IFN immunity, suggesting that impaired Type I IFN production might underlie life-threatening COVID-19 pneumonia.[164,165] Considering that inflammation and immunological alterations have been indicated as potential mechanisms of the cardiovascular sequelae of long COVID,[166] the results of these genetic studies might implicate IFN family members as critical molecules involved in the persistent myocardial inflammatory response after SARS-CoV-2 infection.[18] Despite this, recent data evaluating circulating levels of IFN and COVID-19 severity have concluded that IFNs levels do not reflect the clinical status of COVID-19 patients and are not recommended as a marker of disease severity.[167]

A genome-wide association study involving 1980 patients with COVID-19-induced respiratory failure, found a single-nucleotide polymorphism (SNP) at ABO blood group genetic locus to be associated with COVID-19 severity.[168] Despite the association between ABO blood groups and long-term cardiovascular outcomes[169] and the presence of cardiometabolic alterations observed in long-term SARS-CoV-1 survivors,[170] the role of ABO locus genetic variants in the determinism of long-term cardiovascular alterations after SARS-CoV-(1/2) infection is still unknown. However, considering that the ABO locus has been associated with genetic susceptibility for many different diseases (e.g. cancer, cardiovascular diseases, infections, haematologic disorders etc.[171]), it would be hard to pin-point any specific mechanisms involving ABO groups and long-COVID sequalae.

Recently, international, large scale, genetic consortia such as the COVID Human Genetic Effort[172] have been formed, with the aim of defining the genetic determinants of long COVID and its cardiovascular features.[173]

Clinical implication: Considering the variability of presentations and the differences in individual susceptibility to long COVID, genetic research in this field may hold promise. Genetic research in COVID-19, including GWAS studies in COVID-19 and long-COVID populations, focused on host genetic variants associated with specific sub-phenotypes, should be pursued in order to identify mechanistic targets for therapeutic intervention.[174–176]

4.6 Current and future strategies for investigating the mechanism of long COVID

Several animal models expressing human ACE2 have been developed to permit investigation of the acute effects on SARS-CoV-2 infection.[177] This approach was used to demonstrate that SARS-CoV-2-induced senescence, a putative mechanism of long COVID as discussed above, could be eliminated using senolytics in hamster and mouse models of acute COVID-19.[141,142] Cardiomyocytes derived from iPSC (iCM) have been used to investigate acute infection by SARS-CoV-2,[151] although important caveats arise regarding their maturity. 3D cellular models such as human cardiospheres and engineered cardiac tissue may be better models of the myocardium,[140,150] even if their utility in investigating long COVID remains to be established. The use of mouse-adapted SARS-CoV-2 provides the opportunity to study both acute and long-term effects of infection.[178]

4.7 Outstanding questions related to long COVID

As can be seen from the discussion above, many aspects about the causes and cardiovascular consequences of long COVID remain to be understood. Some of the key immediate questions are:

(1) Is long COVID a continuation of the active COVID-19 disease in a milder form, or a new multiorgan disease based on the virus-induced morphological and functional changes?
(2) To what extent is long COVID different from the sequelae of infection with other post-respiratory viruses?
(3) What are the long-term (>1 year) cardiovascular consequences of long COVID?
(4) What are the long-term consequences of the subclinical findings, such as haemodynamic non-significant perimyocarditis or pericardial effusion detected after COVID-19 infection?
(5) What are the long-term consequences of the haemodynamic compromise of the patients with POTS or autonomic dysfunction or COVID-induced hypertension?
(6) What are the long-term consequences of the viral load of cardiomyocytes inducing subclinical or clinical myocarditis?
(7) What are the long-term consequences of the activated EBV viremia during active infection; regarding chronic active infection or autoimmune diseases or increased incidence of malignancies?
(8) Does COVID-19 induce dyslipidaemia similar to the previous MERS coronavirus variants, and will it lead to accelerated atherosclerosis processes?
(9) How can long COVID be prevented?
(10) Is there any specific biomarker with high diagnostic value for cardiovascular effects of long COVID?

5. Approaches for further development of diagnostic procedures and therapeutic options for cardiovascular long-COVID manifestations

5.1 Diagnostic procedure

The ESC Council for Cardiology Practice has published a position paper on the evaluation and management of long-COVID patients with new

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cardiovascular symptoms.[36] Management guidelines apply to people with both suspected or confirmed prior acute COVID-19, irrespective of whether they had a positive or negative SARS-CoV-2 PCR test, but proven infection by the presence of nucleocapsid antibody.[23] The cardiovascular symptoms of long COVID are difficult to distinguish from the cardiac fatigue syndrome caused by other organ diseases, such as lung fibrosis, chronic thromboembolic, or gastroenteric or peripheral muscle or joint diseases.

Here, we focus on the general diagnostics of cardiovascular symptoms and findings, that have been suggested for long-COVID patients at primary, secondary, and tertiary levels, as discussed in more detail in specific guidelines.[21–23,30,33,36]

5.2 Cardiovascular diagnostics that are suggested for long-COVID patients

(1) Routine measurements of troponin T or I in all COVID patients shortly after the first negative PCR test. Hospitalized patients with elevated troponin during acute COVID-19 infection have a substantial higher mortality than patients without troponin elevation.[19,179–181] Since troponin is not measured in non-hospitalized patients with no, mild, or moderate symptoms, the subclinical cardiac complications are severely underestimated. However, this option is still of clinical relevance.
(2) Routine laboratory measurements of inflammatory (CRP), coagulation (D-dimer), and organ (kidney, musculoskeletal, rheumatic, haematologic) disease parameter, ECG, and chest X-ray for all long-COVID patients.
(3) Cardiology screening of *symptomatic patients with previous heart disease or hospitalized* during COVID-19 infection 1 month after the infection with ECG, laboratory investigations, echocardiography, Holter-ECG, chest X-ray, and spirometry/spiroergometry.
(4) Cardiology screening of *asymptomatic patients with previous heart disease* 3 month after COVID infection with ECG, laboratory investigations, echocardiography. Further specific investigations (e.g. stress testing, Holter-ECG) should be considered if necessary.
(5) Cardiovascular screening of *symptomatic, non-hospitalized long-COVID patients without history of pre-existing cardiovascular disease* with mild–moderate COVID disease at the primary care with ECG and laboratory investigation. Option to admit the patients to (i) secondary care for echocardiography, Holter-ECG, chest X-ray and spirometry or spiroergometry or (ii) specific long-COVID outpatient clinics.
(6) Cardiac MRI for *athletes* before starting the active sport.
(7) Cardiovascular rehabilitation to (i) all COVID-19-hospitalized patients; (ii) all patients with the history of cardiovascular diseases; (iii) all long-COVID patients with cardiovascular symptoms of any origin.
(8) Cardiac MRI for all patients with new onset of cardiovascular disease developed after COVID-19 infection.

Clinical implication: Targeted cardiovascular investigations should be performed in long-COVID patients with a history of cardiac or cardiovascular diseases or who were hospitalized during the acute infection, with an individualized diagnostic plan. Symptom-oriented cardiovascular diagnostic screening procedures are useful for patients with a mild or moderate disease course to verify or exclude SARS-CoV-2-induced long-lasting organ disorders.

5.3 Therapeutic options for long-COVID patients with cardiovascular symptoms

5.3.1 Symptomatic treatment

To date, no pharmaceutical agents have been shown to ameliorate all symptoms, or improve imaging and biomarker abnormalities caused by long COVID.[94] In most cases, the therapy of cardiac manifestations is limited to symptomatic treatment, for example anti-vasospastic drugs in patients with atypical angina or beta-blockers for palpitations. Medicinal treatment strategies for POTS include alpha-1 agonists, steroids, compression garments, fluid, and salt intake, whereas those for CFS include Toll-like receptor-3 agonists, analgesics, and mitochondrial modulators including Coenzyme Q10. Therapy options for mast cell activation syndromes include anti-histamines, mast cell stabilators, or leucotriene antagonist.[94] Non-steroidal anti-inflammatory drugs may be used to manage specific symptoms such as fever and pain.

5.3.2 Dietary supplements or other non-specific treatments

Several dietary supplements with putative antioxidant, anti-inflammatory, immunomodulatory, cardio- or neuroprotective effects have been recommended, such as high-dose Vitamin C or different Vitamin complexes, iron, selenium, zinc, etc., beside antihistamines, H2-receptor blockers, or low-dose beta-blockers.[182,183] Several patients report some symptom improvement, with individual reactions to these substances. Anecdotical case reports have been published on hyperbaric oxygen therapy[184,185] or Aptamer BC007[186] though without a strong scientific basis.

There are currently more than 300 interventional studies of 'long COVID' or 'post COVID' registered on clinicaltrials.gov. The NIH has recently provided $470 million to fund the 'Researching COVID to Enhance Recovery (RECOVER) Initiative' (https://www.nih.gov/news-events/news-releases/nih-builds-large-nationwide-study-population-tens-thousands-support-research-long-term-effects-covid-19).

Clinical implication: There is currently no evidence-based data for therapy of long COVID, and a lack of randomized clinical trials. Until the precise cause of long COVID and its cardiovascular manifestations become clear, it is difficult to predict which interventions are likely to be effective. However, given the increasingly intense investigation in this area, the situation is likely to improve.

5.3.3 Rehabilitation programmes

A personalized multi-disciplinary rehabilitation approach involving breathing, mobilization, 'paced' training (pacing), and psychological interventions have improved lung function and physical capacity in post-COVID patients.[187,188] Therefore, light aerobic exercise paced according to individual capacity may be effective in treating post-COVID in some patients. However, certain long-COVID conditions such as POTS or CFS with post-exertional malaise do not always respond favourably to physical rehabilitation.[94] It is important to emphasize the role of the patient in developing 'coping' strategies to fight against long-COVID. There are several e-cardiology programmes or on-line training available (e.g. brain training, fatigue-training, yoga, breathing-training), and also recommendations for home training for patients with POTS[189] and wearable smartwatch measuring heart rate, blood pressure, ECG, and some other physiological parameters.[38,190] It is important that patients do regular check-ups and maintain their cardiovascular health.

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Clinical implication: Individual rehabilitation programmes including 'pacing' and 'coping', as well as on-line training programmes are important therapeutic strategies for long-COVID patients.

5.3.4 Vaccination

The Office for National Statistics UK study published a 41% decrease in self-reported long-COVID symptoms if the vaccine was applied at least 2 weeks before the infection in more than 1 million infected patients.[191] Two doses of vaccination before infection with SARS-CoV-2 was also associated with substantial decrease in PASC in a smaller Israel study published in pre-print.[192] Vaccination was associated with improved symptoms in 56.7% of patients in a large ($n = 900$ patients) cohort but also in small case series of 163 patients with long COVID even if some patients reported unchanged symptoms.[193]

Clinical implication: Vaccination before COVID-19 infection significantly prevents the occurrence of long COVID after infection, but also reduces long-COVID symptoms if the patient was previously infected. An undoubted advantage of vaccination is the decrease in new infection and alleviation of the disease course of new infections, thereby reducing the incidence and severity of long COVID.

6. Conclusion

Emerging evidence points to increasing numbers of patients suffering from long COVID in the future. Many patients with severe COVID-19 illness will exhibit cardiac symptoms and some will show evidence of possible myocarditis. While in some cases these symptoms are likely to revert over time, long-term prognoses are difficult to estimate, and there may be instances where damage to the cardiovascular system is long-lasting. Current therapeutic options for long COVID are limited to symptom-management, rehabilitation programmes, and non-specific dietary interventions. Given the number of potential long-COVID patients, and the likelihood that SARS-CoV-2 and its variants becoming endemic, it is imperative that we gain a better understanding of the cellular and molecular mechanisms of long COVID. Future investigative and interventional studies will necessitate more accurate and specific diagnosis of long COVID in accordance with established practise. It will be important to determine the precise similarities and differences with other types of post-viral syndromes.

Conflict of interest: F.W.A., P.A., B.J.J.M.B., S.M.D., M.F., M.G., S.V.L., R.M., C.P., M.P., G.G.S., S.S., C.G.-T., T.K.: no conflicts to disclose. G.G.C. is coinventors on the International Patent WO/2020/226993 filed in April 2020. The patent relates to the use of antibodies which specifically bind IL-1α to reduce various sequelae of ischaemia-reperfusion injury to the central nervous system. G.G.C. is a consultant to Sovida solutions limited. P.F. is the founder and CEO of Pharmahungary Group, a group of R&D companies. C.T. has received speaker fees and/or contributions to congresses from Abbott, Abiomed, Astra Zeneca, Bayer, Böhringer-Ingelheim, Novartis, Pfizer, and Servier; all outside the submitted work.

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