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 & Pericardial Diseases

Mariann Gyöngyösi[1], Pilar Alcaide[2], Folkert W. Asselbergs[3,4], Bianca J.J.M. Brundel[5], Giovanni G. Camici[6,7], Paula da Costa Martins[8,9], Péter Ferdinandy[10,11], Marianna Fontana[12], Henrique Girao[13], Massimiliano Gnecchi[14,15], Can Gollmann-Tepeköylü[16], Petra Kleinbongard[17], Thomas Krieg[18], Rosalinda Madonna[19], Melanie Paillard[20], Antonis Pantazis[21], Cinzia Perrino[22], Maurizio Pesce[23], Gabriele G. Schiattarella[24-27], Joost P.G. Sluijter[28,29], Sabine Steffens[30,31], Carsten Tschöpe[32], Sophie Van Linthout[32], Sean M. Davidson[33]

Division of Cardiology, 2nd Department of Internal Medicine, Medical University of Vienna, Vienna, Austria
Department of Immunology, Tufts University School of Medicine, Boston, MA, USA
Department of Cardiology, Division Heart & Lungs, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
Health Data Research UK and Institute of Health Informatics, University College London, London, United Kingdom
Department of Physiology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, Vrije Universiteit Amsterdam, The Netherlands
Center for Molecular Cardiology, University of Zurich, Schlieren, Switzerland
University Heart Center, Department of Cardiology, University Hospital, Zurich, Switzerland
Department of Cardiology, CARIM School for Cardiovascular Diseases, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, Netherlands
Department of Molecular Genetics, Faculty of Sciences and Engineering, Maastricht University, Maastricht, The Netherlands
Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary
Pharmahungary Group, Szeged, Hungary
Royal Free Hospital London, Division of Medicine, University College London, London, UK
Center for Innovative Biomedicine and Biotechnology (CIBB), Clinical Academic Centre of Coimbra (CACC), Faculty of Medicine, Univ Coimbra, Institute for Clinical and Biomedical Research (iCBR), Coimbra, Portugal

Department of Molecular Medicine, Unit of Cardiology, University of Pavia
Unit of Translational Cardiology, Division of Cardiology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
Department of Cardiac Surgery, Medical University of Innsbruck, Austria
Institut für Pathophysiologie, Westdeutsches Herz- und Gefäßzentrum, Universitätsklinikum Essen, Essen, Germany
Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
Department of Pathology, Institute of Cardiology, University of Pisa, Pisa, Italy
Laboratoire CarMeN-équipe IRIS, INSERM, INRA, Université Claude Bernard Lyon-1, INSA-Lyon, Univ-Lyon, 69500 Bron, France
National Heart and Lung Institute, Imperial College London, London, United Kingdom; Cardiovascular Research Centre at Royal Brompton and Harefield Hospitals, London, United Kingdom
Department of Advanced Biomedical Sciences, Federico II University, Via Pansini 5, 80131 Naples
Unità di Ingegneria Tissutale cardiovascolare, Centro Cardiologico Monzino, IRCCS
Division of Cardiology, Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy
Center for Cardiovascular Research (CCR), Department of Cardiology, Charité - Universitätsmedizin Berlin, Berlin, Germany
DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany;
Translational Approaches in Heart Failure and Cardiometabolic Disease, Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany
Laboratory of Experimental Cardiology, Cardiology, UMC Utrecht Regenerative Medicine Center
Circulatory Health Laboratory, Utrecht University, University Medical Center Utrecht, Utrecht, The Netherlands
Institute for Cardiovascular Prevention (IPEK), Ludwig-Maximilians-Universität, Munich
Germany and Munich Heart Alliance, DZHK partner site Munich, Germany
Berlin Institute of Health (BIH) at Charité, - Universitätmedizin Berlin, BIH Center for Regenerative Therapies (BCRT), German Center for Cardiovascular Research (DZHK), Partner site Berlin and Dept Cardiology (CVK), Charité, Berlin; Germany
The Hatter Cardiovascular Institute, University College London, 67 Chenies Mews, WC1E 6HX, London, United Kingdom

Corresponding Author: Mariann Gyöngyösi

Division of Cardiology, 2nd Department of Internal Medicine, Medical University of Vienna,

Waehringer Guertel 18-20, 1090 Vienna, Austria

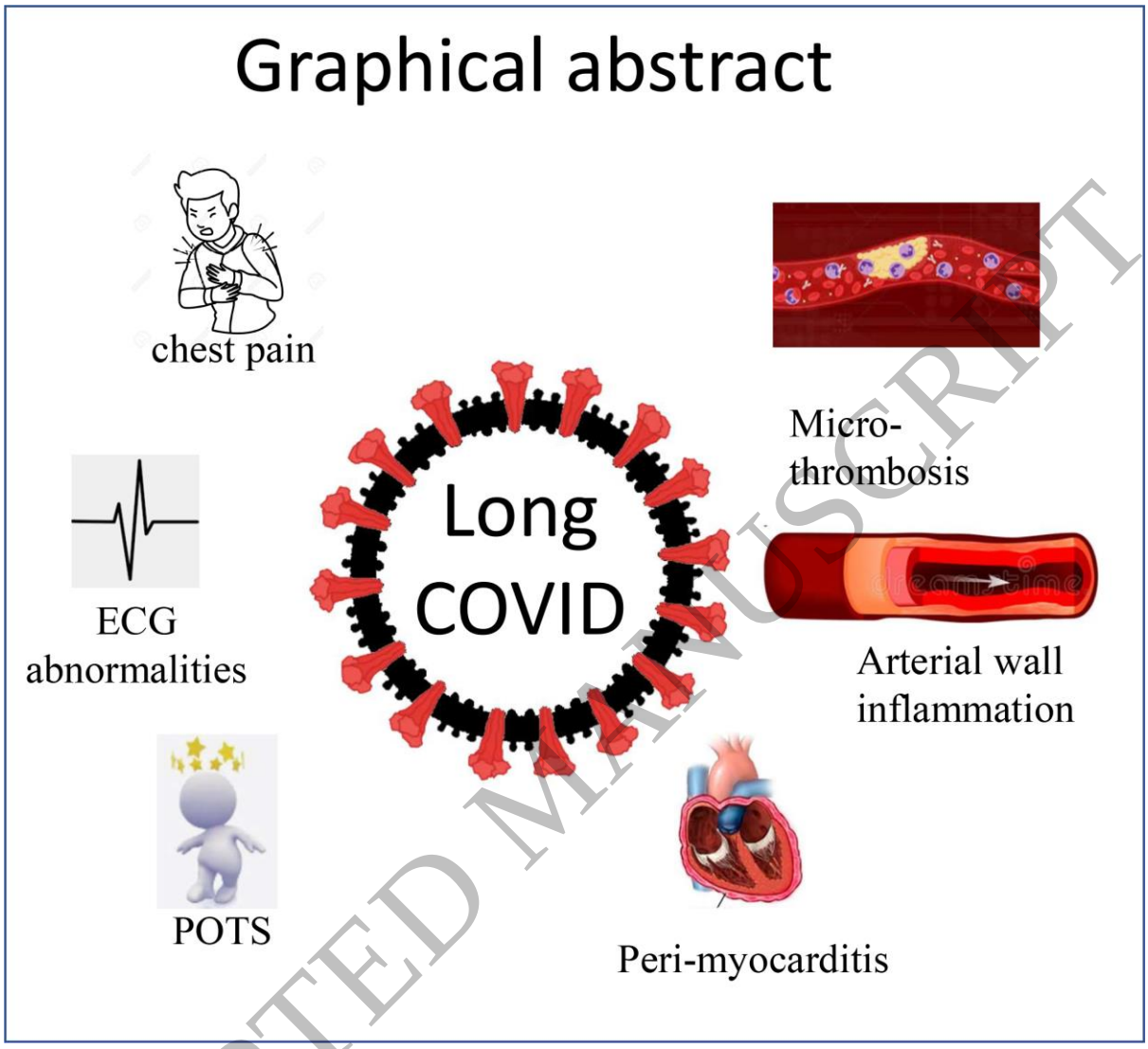
Tel: +43-1-40400-46140, Fax: +43-1-40400-42160

Email: mariann.gyongyosi@meduniwien.ac.at

Abstract

Long COVID has become a world-wide, non-communicable epidemic, caused by long-lasting multi-organ 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 peri-myocarditis with consequent left or right ventricular failure, arterial wall inflammation or micro-thrombosis 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, micro-thrombotic 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.

Keywords: COVID-19, long COVID, post COVID, virus, cardiovascular, cardiac



Graphical Abstract

Long-COVID syndrome

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% to 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 9 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 is 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 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.

2.2. 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 to 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 previous infection with SARS-CoV-2, either with evidence of prior positivity for PCR or nucleocapsid antigen.

2.3. 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, multi-organ 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 (eg: 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 40-60y.[12, 29] Other predictors of long COVID include: a greater body-mass index, older age, presence of combined symptoms from 5 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 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 approximately 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: 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, re-activation 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]

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.

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 ischemia, 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 echocardiographic findings may remain, including adverse left and right ventricular remodelling, diastolic and systolic dysfunction, pulmonary hypertension, pericardial effusions, or reduced LV or 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 depend 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 to healthy controls.[66] The cMRI abnormalities seen in patients recovered from acute COVID-19 are not always associated with pre-existing co-morbidities, 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 versus 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.

To complement cMRI information, functional PET/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 to 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 5 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 hemodynamic 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 pediatric 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 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.

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.

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 interleukin-6, show inconsistent association with long-COVID symptoms [13, 95-103] It is important to note that most published biomarker studies that have examined association with patient outcome (eg: 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., in which inflammatory markers in long-COVID patients were compared with matching populations of individuals recovered from COVID-19, unexposed controls and individuals infected with other coronaviruses.[106] Time-dependent elevations of inflammatory biomarkers were detected, and combinations of the plasma levels of IFN-β, PTX3 (pentraxin-3), IFN-γ, IFN-λ2/3 and IL-6 characterized long COVID with 78.5–81.6% accuracy. Finally, among 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]

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 3 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]

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. Upregulation 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.

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] 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.

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*. found increased expression of Programmed Cell Death protein (PD1) in convalescent individuals lasting up to 45 days,[119] while Yao *et al*. detected SARS-CoV-2-specific memory B cells and interferon-γ-secreting T cells in 70% of patients up to 9 months.[120] Lack of naïve T and B-cells expressing CD127 and TIM-3, as well as 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 (eg. 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 release of auto-antigens by activated or dying neutrophils, elevation of neutrophils to lymphocytes ratio (NLR) and neutrophil extracellular traps (NETs), 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 hematopoietic 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 leukocytes.[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.

Molecular pathomechanisms and cellular senescence

The majority of long-COVID patients suffer from chronic fatigue syndrome, 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 pro-inflammatory status in organs susceptible to aging. Most cardiomyocytes are terminally differentiated and, with aging, 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" aging, 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 aging (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 lack of respective cell culture or animal models.

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 (CMV) 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 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.

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 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.

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 indicates 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 (pLOF) 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 interferon (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 1,980 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, hematologic 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]

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]

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 hemodynamic non-significant perimyocarditis or pericardial effusion detected after COVID-19 infection?
5. What are the long-term consequences of the hemodynamic 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 dyslipidemia 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?

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

Diagnostic procedure

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

Cardiovascular diagnostics that are suggested for long-COVID patients

1. Routine measurements of troponin T or I in all COVID patients shortly after 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, hematologic) 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/spiro-ergometry;
4. Cardiology screening of *asymptomatic patients with previous heart disease* 3 month after COVID infection with ECG, laboratory investigations, echocardiography. Further specific investigations (eg. 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 a) secondary care for

echocardiography, Holter-ECG, chest X-ray and spirometry or spiroergometry or b) specific Long-COVID outpatient clinics;

6. Cardiac -MRI for *athletes* before starting the active sport;
7. Cardiovascular rehabilitation to a) all COVID-19-hospitalized patients; b) all patients with history of cardiovascular diseases; c) 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 individualised 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.

Therapeutic options for long COVID patients with cardiovascular symptoms

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 leukotriene antagonist.[94] Non-steroidal anti-inflammatory drugs may be used to manage specific symptoms such as fever and pain.

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.

Rehabilitation programs

A personalized multi-disciplinary rehabilitation approach involving breathing, mobilisation, "paced" training (pacing) and psychological interventions has 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 programs 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.

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

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 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 prior to 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.

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 programs 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.

Funding

This work was supported by:

UCL Hospitals NIHR Biomedical Research Center to FA. National Institutes of Health, Tufts University COVID19 seed funding [NIH-HL-144477] to PA. Medizinisch-Wissenschaftlichen Fonds des Bürgermeisters der Bundeshauptstadt Wien, Project Nr: 21176, MUW AP21176BGM and KP21176BGM) and Austrian Scientific Fund (FWF) Project Nr: KLI 1064-B to MG. The British Heart Foundation [PG/19/51/34493 and PG/16/85/32471] to SMD. Regione Lombardia [POR FESR 2014-2020-LINEA 2A COVID-grant no. 1850333] and CARDIO-COV project to MP. Incyte s.r.l. and funds from Ministero dell'Istruzione, Università e Ricerca Scientifica [549901_2020_Madonna:Ateneo] to RM. Swiss Heart Foundation and Swiss National Science Foundation [310030_175546] to GGC, Alfred and Annemarie von Sick Grants for Translational and Clinical Research Cardiology and Oncology to GGC. H.H. Sheikh Khalifa bin Hamad Al Thani Foundation Assistant Professorship at the Faculty of Medicine, University of Zurich to GGC. The European Research Council [Project EVICARE (No. 725229)]to JPS. The National Research, Development and Innovation Office of Hungary (Research Excellence Program TKP within the framework of the Therapeutic Development thematic program of the Semmelweis University; National Heart Laboratory; and 2020-1.1.6-JÖVŐ-2021-00013 – investment into the future) to PF, and the EU Horizon 2020 project COVIRNA [101016072] to PF. PF is a vice chair of the COST

Cardioprotection action (CA16225) and an MC member of the COST CardioRNA project (CA17129). DZHK (German Centre for Cardiovascular Research) JRG to GGS. Dutch CardioVascular Alliance (DCVA) awarded to the Phaedra consortium as well as the Impulse Grant 2018 awarded to the Phaedra IMPACT consortium [2012-08, 2014-11] to PDCM and by a Dutch Heart Foundation grant [NHS2015T066] to PDCM. DHF and DZKH (DnAFix project 2020B003).

Data Availability Statement

No new data were generated or analysed in support of this article.

Acknowledgements

n/a

Disclosures/CoI

FWA, PA, BJJMB, SMD, MF, MG, SVL, RM, CP, MP, GGS, SS, CGT, TK: no conflicts to disclose. GGC 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 ischemia-reperfusion injury to the central nervous system. GGC is a consultant to Sovida solutions limited. PF is the founder and CEO of Pharmahungary Group, a group of R&D companies. CT 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.

Tables

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 JE 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 SARSCoV-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 two and six weeks (four weeks on average) after COVID-19 infection.	195, 196

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, 198
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 5 symptoms from different organs during acute infections (fatigue, headache, dyspnea, hoarse voice, myalgia, but also loss of smell in pts age >70y)	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>70y	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;

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, 199-202,205	5-30%	120-1733	10, 25, 46, 120, 203-208
Palpitation, tachycardia, atrial fibrillation	10-32%	51-2113	54, 200, 202, ,205, 209	0.3-20%	92-1733	10,25,203, 205,210,211-213
Dyspnea	13.1-92.1%	33-3290	13, 20, 24,97,193 201, 202,,205, 209,, 214-216,217	4.1-70%	66-2649	10, 25, 31,204, 205,206-208,210, 213,218, 219,220-222
Cough	9-42.3%	110-3290	13, 97, 199, 205, 214, 217	4.2-16.7%	120-958	31, 204, 208, 213
Exercise-induced dyspnea, exercise-induced ventilatory inefficiency	51%	51	54	14.6%-29%	28-55	112, 223
Dysautonomia				15.2-25%	92-205	213, 224
Postural tachycardia syndrome, orthostatic intolerance, inappropriate sinus tachycardia				11-41%	27-1890	49, 213, 225-227

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

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, 228-231
Chronic pericarditis	1.9-27%	26-105	74, 232
Myocardial oedema	15.4 %	26	232
Myocardial fibrosis or scar	4%	26	232
Systolic or diastolic LV Dysfunction	0.06-35%	51-8983	54, 59, 66, 79, 200, 205, 208, 229, 211, 233-236
RV systolic dysfunction	7-22.6%	50-1414	59, 66, 205, 208, 211, 231
LV thrombus	2%	51	57
Coronary artery disease	8%	51	57
Acute myocardial infarction	1.5-8%	51-47780	46, 57, 83
Persistent systemic endothelial dysfunction	2.5-6.1%	72-133	237, 238
Coronary microvascular disease	18%	22	239
Heart failure	0.1-2%	543-8983	46, 79
Pulmonary hypertension	10-50%	102-145	21, 234, 240

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

LV: left ventricular; RV: right ventricular

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	203, 241
Diabetes mellitus	0.64-2.4%	287-512	24, 241
Stroke	0.1-6.7%	30-8983	79, 80
Venous Thromboembolism	0.2-12.5%	1062-8983	79, 82, 233
Hospitalization	4.5-29.4%	1062-47780	82, 83
Pediatric 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.

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 labor measurements; 57-71 d	63, 205, 233
N-terminal pro-Brain Natriuretic Peptide (proBNP)	9.6 mo	233
Inflammatory biomarkers		
C-reactive protein (CRP)	30 d -3 mo	93, 94, 99, 101, 104, 242
Interleukins general (IL)	15 d – 3 mo	93, 94, 242, 243
IL-6	inconsistent association with Long-COVID symptoms; over 3 mo	13, 84, 96-99, 101-103
Ferritin	associated with patient outcome in small cohort; over 3 mo	101, 105
IFN-β, IFN-λ1,	Combination of inflammatory markers are predictive for long COVID; 8 mo	106
CXCL9 and CXCL10	was also elevated in asymptomatic post-COVID patients; 8 mo	106
IL-8	was also elevated in asymptomatic post-COVID patients; 8 mo	106
TIM-3	was also elevated in asymptomatic post-COVID patients; 8 mo	106
Plasma ACE2 activity	was also elevated in asymptomatic post-COVID patients; 3-8 mo	106, 244
PTX3	8 mo	106
Procalcitonin	Correlated with microvessel disease, 3 mo	99
Coagulation biomarkers		
D-dimer	2 mo – 3 mo	98, 101, 109, 113
Factor VIII, vWF, Thrombomodulin	Returned to normal in >90% patients in convalescent phase; 68 d – 81 d	98, 109, 113
Novel biomarkers		
Taurin	3 mo	113
Reduced glutamine/glutamate ratio	3 mo	113
Lower nitrit, nitrite/nitrate	4 mo	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; vVF: von Willebrand Factor;

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 mo	120
Interferon-γ-secreting T cells, elevated INF-beta, INF-delta1	9 mo	120
CD8+ T-cell activation expressing PD-1 and TIM3	45 days, 8 mo	119, 106, 243
Lack of B and T cells expressing CD127 and TIM-3	8 mo	106
T-cell exhaustion with reduced cytokine production	Starts during acute infection	245, 246
Epigenetic reprogramming of hematopoietic progenitors	8 mo	127
Elevated level of activated CD38+HLA-DR+ myeloid cells	8 mo	106
Activated CD14+CD16+ monocytes	8 mo	106,155
Persistent activation of cardiac-resident fibroblasts	n.r.	151
Higher number of plasmacytoid dendritic cells (pDCs) expressing CD86 and CD38	8 mo	106
Mast cell activation	n.r.	126
Increased levels of circulating endothelial cells (CD45□ /CD31+ /CD133□ /DNA+)	27-46 days	243
Elevation of neutrophils to lymphocytes ratio (NLR)	n.r.	124
Development of NET	n.r.	124, 247
Release of autoantigens by neutrophils	n.r.	124
Persistent antibodies	9 mo	120
Protracted immunospuppression (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

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; 68d - 4 mo	98, 109, 156, 158, 159, 248
Reduced oxygen extraction	In spite of normal resting lung function and imaging	159, 249
Vascular dysfunction		
Capillary flow disturbance, heterogeneity of capillary transit time, deterioration of capillary integrity	Blood-flow limiting conditions, reduced oxygen exchange; 4 mo	156-159
Vasculitis	In several organs	72, 250
Coagulopathies, thrombosis		
Coagulopathy	With elevated D-dimer, mostly in hospitalized patients; 68 d – 80 d	98, 109
Microthrombosis	In several organs; 80 d	159
Activation of Neutrophil extracellular traps (NETs)	Circulating markers were elevated in acute COVID but returned to baseline by 4 mo.	125

Figure legends

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

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); Hematopoietic 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 (IFN) 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.

Graphical abstract

References

1. Worldometers.info. Worldometers. Dover, Delaware, U.S.A., 2021.
2. Ahmad FB, Anderson RN. The Leading Causes of Death in the US for 2020. *JAMA* 2021;**325**:1829-1830.
3. Karlinsky A, Kobak D. Tracking excess mortality across countries during the COVID-19 pandemic with the World Mortality Dataset. *Elife* 2021;**10**.
4. Troeger C. Just How Do Deaths Due to COVID-19 Stack Up? : Think Gloval Health, 2021.
5. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, Pujol JC, Klaser K, Antonelli M, Canas LS, Molteni E, Modat M, Jorge Cardoso M, May A, Ganesh S, Davies R, Nguyen LH, Drew DA, Astley CM, Joshi AD, Merino J, Tsereteli N, Fall T, Gomez MF, Duncan EL, Menni C, Williams FMK, Franks PW, Chan AT, Wolf J, Ourselin S, Spector T, Steves CJ. Attributes and predictors of long COVID. *Nat Med* 2021;**27**:626-631.
6. Blomberg B, Mohn KG, Brokstad KA, Zhou F, Linchausen DW, Hansen BA, Lartey S, Onyango TB, Kuwelker K, Saevik M, Bartsch H, Tondel C, Kittang BR, Bergen C-RG, Cox RJ, Langeland N. Long COVID in a prospective cohort of home-isolated patients. *Nat Med* 2021;**27**:1607-1613.
7. Stefano GB. Historical Insight into Infections and Disorders Associated with Neurological and Psychiatric Sequelae Similar to Long COVID. *Med Sci Monit* 2021;**27**:e931447.
8. Honigsbaum M, Krishnan L. Taking pandemic sequelae seriously: from the Russian influenza to COVID-19 long-haulers. *Lancet* 2020;**396**:1389-1391.
9. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry* 2021;**8**:416-427.
10. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, Kang L, Guo L, Liu M, Zhou X, Luo J, Huang Z, Tu S, Zhao Y, Chen L, Xu D, Li Y, Li C, Peng L, Li Y, Xie W, Cui D, Shang L, Fan G, Xu J, Wang G, Wang Y, Zhong J, Wang C, Wang J, Zhang D, Cao B. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021;**397**:220-232.
11. Ghosn J, Piroth L, Epaulard O, Le Turnier P, Mentre F, Bachelet D, Laouenan C, French Ccs, investigators g. Persistent COVID-19 symptoms are highly prevalent 6 months after hospitalization: results from a large prospective cohort. *Clin Microbiol Infect* 2021;**27**:1041 e1041-1041 e1044.
12. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLoS Med* 2021;**18**:e1003773.
13. Mandal S, Barnett J, Brill SE, Brown JS, Denneny EK, Hare SS, Heightman M, Hillman TE, Jacob J, Jarvis HC, Lipman MCI, Naidu SB, Nair A, Porter JC, Tomlinson GS, Hurst JR, Group ARCS. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax* 2021;**76**:396-398.
14. Heesakkers H, van der Hoeven JG, Corsten S, Janssen I, Ewalds E, Simons KS, Westerhof B, Rettig TCD, Jacobs C, van Santen S, Slooter AJC, van der Woude MCE, van den Boogaard M, Zegers M. Clinical Outcomes Among Patients With 1-Year Survival Following Intensive Care Unit Treatment for COVID-19. *JAMA* 2022;**327**:559-565.
15. Moore JP, Offit PA. SARS-CoV-2 Vaccines and the Growing Threat of Viral Variants. *JAMA* 2021;**325**:821-822.
16. statista. 7-day incidence of corona infections (COVID-19) in Germany by age group in 2021.
17. Khoury J, Najjar-Debbiny R, Hanna A, Jabbour A, Abu Ahmad Y, Saffuri A, Abu-Sinni M, Shkeiri R, Elemy A, Hakim F. COVID-19 vaccine - Long term immune decline and breakthrough infections. *Vaccine* 2021;**39**:6984-6989.

18. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022;**28**:583-590.
19. Satterfield BA, Bhatt DL, Gersh BJ. Cardiac involvement in the long-term implications of COVID-19. *Nat Rev Cardiol* 2021.
20. Tenforde MW, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Files DC, Gibbs KW, Erickson HL, Steingrub JS, Smithline HA, Gong MN, Aboodi MS, Exline MC, Henning DJ, Wilson JG, Khan A, Qadir N, Brown SM, Peltan ID, Rice TW, Hager DN, Ginde AA, Stubblefield WB, Patel MM, Self WH, Feldstein LR, Investigators IVYN, Team CC-R, Investigators IVYN. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**:993-998.
21. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ* 2020;**370**:m3026.
22. Herrera JE, Niehaus WN, Whiteson J, Azola A, Baratta JM, Fleming TK, Kim SY, Naqvi H, Sampsel S, Silver JK, Gutierrez MV, Maley J, Herman E, Abramoff B. Multidisciplinary collaborative consensus guidance statement on the assessment and treatment of fatigue in postacute sequelae of SARS-CoV-2 infection (PASC) patients. *PM R* 2021;**13**:1027-1043.
23. (UK) NIfHaCE. COVID-19 rapid guideline: managing the long-term effects of COVID-19. COVID-19 rapid guideline: managing the long-term effects of COVID-19. London, 2020.
24. Kamal M, Abo Omirah M, Hussein A, Saeed H. Assessment and characterisation of post-COVID-19 manifestations. *Int J Clin Pract* 2021;**75**:e13746.
25. Kayaaslan B, Eser F, Kalem AK, Kaya G, Kaplan B, Kacar D, Hasanoglu I, Coskun B, Guner R. Post-COVID syndrome: A single-center questionnaire study on 1007 participants recovered from COVID-19. *J Med Virol* 2021.
26. Jones R, Davis A, Stanley B, Julious S, Ryan D, Jackson DJ, Halpin DMG, Hickman K, Pinnock H, Quint JK, Khunti K, Heaney LG, Oliver P, Siddiqui S, Pavord I, Jones DHM, Hyland M, Ritchie L, Young P, Megaw T, Davis S, Walker S, Holgate S, Beecroft S, Kemppinen A, Appiagyei F, Roberts EJ, Preston M, Hardjojo A, Carter V, van Melle M, Price D. Risk Predictors and Symptom Features of Long COVID Within a Broad Primary Care Patient Population Including Both Tested and Untested Patients. *Pragmat Obs Res* 2021;**12**:93-104.
27. Kotecha T, Knight DS, Razvi Y, Kumar K, Vimalesvaran K, Thornton G, Patel R, Chacko L, Brown JT, Coyle C, Leith D, Shetye A, Ariff B, Bell R, Captur G, Coleman M, Goldring J, Gopalan D, Heightman M, Hillman T, Howard L, Jacobs M, Jeetley PS, Kanagaratnam P, Kon OM, Lamb LE, Manisty CH, Mathurdas P, Mayet J, Negus R, Patel N, Pierce I, Russell G, Wolff A, Xue H, Kellman P, Moon JC, Treibel TA, Cole GD, Fontana M. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. *Eur Heart J* 2021;**42**:1866-1878.
28. Jesuthasan A, Massey F, Manji H, Zandi MS, Wiethoff S. Emerging potential mechanisms and predispositions to the neurological manifestations of COVID-19. *J Neurol Sci* 2021;**428**:117608.
29. Torjesen I. Covid-19: Middle aged women face greater risk of debilitating long term symptoms. *BMJ* 2021;**372**:n829.
30. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. *BMJ* 2021;**374**:n1648.
31. Augustin M, Schommers P, Stecher M, Dewald F, Gieselmann L, Gruell H, Horn C, Vanshylla K, Cristanziano VD, Osebold L, Roventa M, Riaz T, Tschernoster N, Altmueller J, Rose L, Salomon S, Priesner V, Luers JC, Albus C, Rosenkranz S, Gathof B, Fätkenheuer G, Hallek M, Klein F, Suárez I, Lehmann C. Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. *Lancet Reg Health Eur* 2021;**6**:100122.

32. Cervia C, Zurbuchen Y, Taeschler P, Ballouz T, Menges D, Hasler S, Adamo S, Raeber ME, Bächli E, Rudiger A, Stüssi-Helbling M, Huber LC, Nilsson J, Held U, Puhan MA, Boyman O. Immunoglobulin signature predicts risk of post-acute COVID-19 syndrome. *Nat Commun* 2022;**13**:446.
33. Paterson I, Ramanathan K, Aurora R, Bewick D, Chow CM, Clarke B, Cowan S, Ducharme A, Gin K, Graham M, Gupta A, Jassal DS, Kazmi M, Krahn A, Lamarche Y, Marelli A, Roifman I, Ruel M, Singh G, Sterns L, Turgeon R, Virani S, Wong KK, Zieroth S. Long COVID-19: A Primer for Cardiovascular Health Professionals, on Behalf of the CCS Rapid Response Team. *Can J Cardiol* 2021;**37**:1260-1262.
34. Siso-Almirall A, Brito-Zeron P, Conangla Ferrin L, Kostov B, Moragas Moreno A, Mestres J, Sellares J, Galindo G, Morera R, Basora J, Trilla A, Ramos-Casals M, On Behalf Of The CLC-SG. Long Covid-19: Proposed Primary Care Clinical Guidelines for Diagnosis and Disease Management. *Int J Environ Res Public Health* 2021;**18**.
35. Sarfraz Z, Sarfraz A, Barrios A, Garimella R, Dominari A, Kc M, Pandav K, Pantoja JC, Retnakumar V, Cherrez-Ojeda I. Cardio-Pulmonary Sequelae in Recovered COVID-19 Patients: Considerations for Primary Care. *J Prim Care Community Health* 2021;**12**:21501327211023726.
36. Richter D, Guasti L, Koehler F, Squizzato A, Nistri S, Christodorescu R, Dievart F, Gaudio G, Asteggiano R, Ferrini M. Late phase of COVID-19 pandemic in General Cardiology. A position paper of the ESC Council for Cardiology Practice. *ESC Heart Fail* 2021;**8**:3483-3494.
37. Cau R, Faa G, Nardi V, Balestrieri A, Puig J, Suri JS, SanFilippo R, Saba L. Long-COVID diagnosis: From diagnostic to advanced AI-driven models. *Eur J Radiol* 2022;**148**:110164.
38. Ghram A, Ayadi H, Knechtle B, Ben Saad H. What should a family physician know about nutrition and physical exercise rehabilitation' advices to communicate to 'long-term COVID-19' patients? *Postgrad Med* 2022;**134**:143-147.
39. Gupta A, Jain V, Singh A. Stacking Ensemble-Based Intelligent Machine Learning Model for Predicting Post-COVID-19 Complications. *New Gener Comput* 2021:1-21.
40. Hossain MA, Hossain KMA, Saunders K, Uddin Z, Walton LM, Raigangar V, Sakel M, Shafin R, Hossain MS, Kabir MF, Faruqui R, Rana MS, Ahmed MS, Chakrovorty SK, Hossain MA, Jahid IK. Prevalence of Long COVID symptoms in Bangladesh: a prospective Inception Cohort Study of COVID-19 survivors. *BMJ Glob Health* 2021;**6**.
41. Fine JS, Ambrose AF, Didehbani N, Fleming TK, Glashan L, Longo M, Merlino A, Ng R, Nora GJ, Rolin S, Silver JK, Terzic CM, Verduzco-Gutierrez M, Sampsel S. Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of cognitive symptoms in patients with post-acute sequelae of SARS-CoV-2 infection (PASC). *PM R* 2022;**14**:96-111.
42. Narula N, Singh HS. Cardiology Practice and Training Post-COVID-19: Achieving "Normalcy" After Disruption. *J Am Coll Cardiol* 2020;**76**:476-479.
43. Dweck MR, Bularga A, Hahn RT, Bing R, Lee KK, Chapman AR, White A, Salvo GD, Sade LE, Pearce K, Newby DE, Popescu BA, Donal E, Cosyns B, Edvardsen T, Mills NL, Haugaa K. Global evaluation of echocardiography in patients with COVID-19. *Eur Heart J Cardiovasc Imaging* 2020;**21**:949-958.
44. Cenko E, Badimon L, Bugiardini R, Claeys MJ, De Luca G, de Wit C, Derumeaux G, Dorobantu M, Duncker DJ, Eringa EC, Gorog DA, Hassager C, Heinzel FR, Huber K, Manfrini O, Milicic D, Oikonomou E, Padro T, Trifunovic-Zamaklar D, Vasiljevic-Pokrajcic Z, Vavlukis M, Vilahur G, Tousoulis D. Cardiovascular disease and COVID-19: a consensus paper from the ESC Working Group on Coronary Pathophysiology & Microcirculation, ESC Working Group on Thrombosis and the Association for Acute CardioVascular Care (ACVC), in collaboration with the European Heart Rhythm Association (EHRA). *Cardiovasc Res* 2021.
45. Di Toro A, Bozzani A, Tavazzi G, Urtis M, Giuliani L, Pizzoccheri R, Aliberti F, Fergnani V, Arbustini E. Long COVID: long-term effects? *Eur Heart J Suppl* 2021;**23**:E1-E5.

46. Maestre-Muniz MM, Arias A, Mata-Vazquez E, Martin-Toledano M, Lopez-Larramona G, Ruiz-Chicote AM, Nieto-Sandoval B, Lucendo AJ. Long-Term Outcomes of Patients with Coronavirus Disease 2019 at One Year after Hospital Discharge. *J Clin Med* 2021;**10**.
47. Szekely Y, Lichter Y, Sadon S, Lupu L, Taieb P, Banai A, Sapir O, Granot Y, Hochstadt A, Friedman S, Laufer-Perl M, Banai S, Topilsky Y. Cardiorespiratory Abnormalities in Patients Recovering from COVID-19. *J Am Soc Echocardiogr* 2021.
48. Oronsky B, Larson C, Hammond TC, Oronsky A, Kesari S, Lybeck M, Reid TR. A Review of Persistent Post-COVID Syndrome (PPCS). *Clin Rev Allergy Immunol* 2021.
49. Asarcikli LD, Hayiroglu MI, Osken A, Keskin K, Kolak Z, Aksu T. Heart rate variability and cardiac autonomic functions in post-COVID period. *J Interv Card Electrophysiol* 2022.
50. Ramadan MS, Bertolino L, Zampino R, Durante-Mangoni E, Monaldi Hospital Cardiovascular Infection Study G. Cardiac sequelae after coronavirus disease 2019 recovery: a systematic review. *Clin Microbiol Infect* 2021;**27**:1250-1261.
51. Fan BE, Umapathi T, Chua K, Chia YW, Wong SW, Tan GWL, Chandrasekar S, Lum YH, Vasoo S, Dalan R. Delayed catastrophic thrombotic events in young and asymptomatic post COVID-19 patients. *J Thromb Thrombolysis* 2021;**51**:971-977.
52. Hall J, Myall K, Lam JL, Mason T, Mukherjee B, West A, Dewar A. Identifying patients at risk of post-discharge complications related to COVID-19 infection. *Thorax* 2021;**76**:408-411.
53. Weber B, Siddiqi H, Zhou G, Vieira J, Kim A, Rutherford H, Mitre X, Feeley M, Oganezova K, Varshney AS, Bhatt AS, Nauffal V, Atri DS, Blankstein R, Karlson EW, Di Carli M, Baden LR, Bhatt DL, Woolley AE. Relationship Between Myocardial Injury During Index Hospitalization for SARS-CoV-2 Infection and Longer-Term Outcomes. *J Am Heart Assoc* 2022;**11**:e022010.
54. Lewek J, Jatczak-Pawlik I, Maciejewski M, Jankowski P, Banach M. COVID-19 and cardiovascular complications - preliminary results of the LATE-COVID study. *Arch Med Sci* 2021;**17**:818-822.
55. Moulson N, Petek BJ, Drezner JA, Harmon KG, Kliethermes SA, Patel MR, Baggish AL, Outcomes Registry for Cardiac Conditions in Athletes I. SARS-CoV-2 Cardiac Involvement in Young Competitive Athletes. *Circulation* 2021;**144**:256-266.
56. Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton R, Lim PB. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. *Clin Med (Lond)* 2021;**21**:e63-e67.
57. Moody WE, Liu B, Mahmoud-Elsayed HM, Senior J, Lalla SS, Khan-Kheil AM, Brown S, Saif A, Moss A, Bradlow WM, Khoo J, Ahamed M, McAloon C, Hothi SS, Steeds RP. Persisting Adverse Ventricular Remodeling in COVID-19 Survivors: A Longitudinal Echocardiographic Study. *J Am Soc Echocardiogr* 2021;**34**:562-566.
58. Sechi LA, Colussi G, Bulfone L, Brosolo G, Da Porto A, Peghin M, Patruno V, Tascini C, Catena C. Short-term cardiac outcome in survivors of COVID-19: a systematic study after hospital discharge. *Clin Res Cardiol* 2021;**110**:1063-1072.
59. Lassen MCH, Skaarup KG, Lind JN, Alhakak AS, Sengelov M, Nielsen AB, Simonsen JO, Johansen ND, Davidovski FS, Christensen J, Bundgaard H, Hassager C, Jabbari R, Carlsen J, Kirk O, Lindholm MG, Kristiansen OP, Nielsen OW, Ulrik CS, Sivapalan P, Gislason G, Mogelvang R, Jensen GB, Schnohr P, Sogaard P, Solomon SD, Iversen K, Jensen JUS, Schou M, Biering-Sorensen T. Recovery of cardiac function following COVID-19 - ECHOVID-19: a prospective longitudinal cohort study. *Eur J Heart Fail* 2021.
60. Tudoran C, Tudoran M, Pop GN, Giurgi-Oncu C, Cut TG, Lazureanu VE, Oancea C, Parv F, Ciocarlie T, Bende F. Associations between the Severity of the Post-Acute COVID-19 Syndrome and Echocardiographic Abnormalities in Previously Healthy Outpatients Following Infection with SARS-CoV-2. *Biology (Basel)* 2021;**10**.

61. Ghugre NR, Orbach A, Biswas L, Connelly KA, Chan A, Strauss BH, Wright GA, Roifman I. Suspected subclinical myocarditis detected by cardiac magnetic resonance imaging late post COVID-19 recovery. *J Cardiol Cases* 2021.
62. Huang L, Zhao P, Tang D, Zhu T, Han R, Zhan C, Liu W, Zeng H, Tao Q, Xia L. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. *JACC Cardiovasc Imaging* 2020;**13**:2330-2339.
63. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, Vasa-Nicotera M, Zeiher AM, Vehreschild M, Nagel E. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020;**5**:1265-1273.
64. Urmeneta Ulloa J, Martinez de Vega V, Salvador Montanes O, Alvarez Vazquez A, Sanchez-Enrique C, Hernandez Jimenez S, Sancho Garcia FD, Lopez Ruiz L, Recio Rodriguez M, Pizarro G, Carnevali Ruiz D, Angel Cabrera J. Cardiac magnetic resonance in recovering COVID-19 patients. Feature tracking and mapping analysis to detect persistent myocardial involvement. *Int J Cardiol Heart Vasc* 2021;**36**:100854.
65. Kravchenko D, Isaak A, Zimmer S, Mesropyan N, Reinert M, Faron A, Pieper CC, Heine A, Velten M, Nattermann J, Kuetting D, Duerr GD, Attenberger UI, Luetkens JA. Cardiac MRI in Patients with Prolonged Cardiorespiratory Symptoms after Mild to Moderate COVID-19 Infection. *Radiology* 2021:211162.
66. Kato S, Azuma M, Fukui K, Kodama S, Nakayama N, Kitamura H, Hagiwara E, Ogura T, Horita N, Namkoong H, Kimura K, Tamura K, Utsunomiya D. Cardiac involvement in coronavirus disease 2019 assessed by cardiac magnetic resonance imaging: a meta-analysis. *Heart Vessels* 2022.
67. Friedrich MG, Cooper LT. What we (don't) know about myocardial injury after COVID-19. *Eur Heart J* 2021;**42**:1879-1882.
68. Joy G, Artico J, Kurdi H, Seraphim A, Lau C, Thornton GD, Oliveira MF, Adam RD, Aziminia N, Menacho K, Chacko L, Brown JT, Patel RK, Shiwani H, Bhuva A, Augusto JB, Andiapen M, McKnight A, Noursadeghi M, Pierce I, Evain T, Captur G, Davies RH, Greenwood JP, Fontana M, Kellman P, Schelbert EB, Treibel TA, Manisty C, Moon JC, Investigators CO. Prospective Case-Control Study of Cardiovascular Abnormalities 6 Months Following Mild COVID-19 in Healthcare Workers. *JACC Cardiovasc Imaging* 2021.
69. Kirkbride RR, Rawal B, Mirsadraee S, Galperin-Aizenberg M, Wechalekar K, Ridge CA, Litmanovich DE. Imaging of Cardiac Infections: A Comprehensive Review and Investigation Flowchart for Diagnostic Workup. *J Thorac Imaging* 2021;**36**:W70-W88.
70. Kadkhodayan A, Chareonthaitawee P, Raman SV, Cooper LT. Imaging of Inflammation in Unexplained Cardiomyopathy. *JACC Cardiovasc Imaging* 2016;**9**:603-617.
71. Satapathy S, Kumar R, Kavanal AJ, Krishnaraju VS, Ramachandran A, Deo P, Dhir V, Mittal BR. COVID-19 related multisystem inflammatory syndrome in children (MIS-C): Role of (18)F-FDG PET/CT to assess myocardial involvement. *J Nucl Cardiol* 2021.
72. Sollini M, Ciccarelli M, Cecconi M, Aghemo A, Morelli P, Gelardi F, Chiti A. Vasculitis changes in COVID-19 survivors with persistent symptoms: an [(18)F]FDG-PET/CT study. *Eur J Nucl Med Mol Imaging* 2021;**48**:1460-1466.
73. Sollini M, Morbelli S, Ciccarelli M, Cecconi M, Aghemo A, Morelli P, Chiola S, Gelardi F, Chiti A. Long COVID hallmarks on [18F]FDG-PET/CT: a case-control study. *Eur J Nucl Med Mol Imaging* 2021;**48**:3187-3197.
74. Saricam E, Dursun AD, Turkmen Sariyildiz G, Can N, Bozkurt E, Gonullu U, Basay N, Turkmen M, Denli A, Unlu M. Laboratory and Imaging Evaluation of Cardiac Involvement in Patients with Post-Acute COVID-19. *Int J Gen Med* 2021;**14**:4977-4985.

75. Strohbehn IA, Zhao S, Seethapathy H, Lee M, Rusibamayila N, Allegretti AS, Parada XV, Sise ME. Acute Kidney Injury Incidence, Recovery, and Long-term Kidney Outcomes Among Hospitalized Patients With COVID-19 and Influenza. *Kidney Int Rep* 2021;**6**:2565-2574.
76. Yende S, Parikh CR. Long COVID and kidney disease. *Nat Rev Nephrol* 2021.
77. Stevens JS, King KL, Robbins-Juarez SY, Khairallah P, Toma K, Alvarado Verduzco H, Daniel E, Douglas D, Moses AA, Peleg Y, Starakiewicz P, Li MT, Kim DW, Yu K, Qian L, Shah VH, O'Donnell MR, Cummings MJ, Zucker J, Natarajan K, Perotte A, Tsapepas D, Krzysztof K, Dube G, Siddall E, Shirazian S, Nickolas TL, Rao MK, Barasch JM, Valeri AM, Radhakrishnan J, Gharavi AG, Husain SA, Mohan S. High rate of renal recovery in survivors of COVID-19 associated acute renal failure requiring renal replacement therapy. *PLoS One* 2020;**15**:e0244131.
78. Gaebler C, Wang Z, Lorenzi JCC, Muecksch F, Finkin S, Tokuyama M, Cho A, Jankovic M, Schaefer-Babajew D, Oliveira TY, Cipolla M, Viant C, Barnes CO, Bram Y, Breton G, Hagglof T, Mendoza P, Hurley A, Turroja M, Gordon K, Millard KG, Ramos V, Schmidt F, Weisblum Y, Jha D, Tankelevich M, Martinez-Delgado G, Yee J, Patel R, Dizon J, Unson-O'Brien C, Shimeliovich I, Robbiani DF, Zhao Z, Gazumyan A, Schwartz RE, Hatziioannou T, Bjorkman PJ, Mehandru S, Bieniasz PD, Caskey M, Nussenzweig MC. Evolution of antibody immunity to SARS-CoV-2. *Nature* 2021;**591**:639-644.
79. Lund LC, Hallas J, Nielsen H, Koch A, Mogensen SH, Brun NC, Christiansen CF, Thomsen RW, Pottegard A. Post-acute effects of SARS-CoV-2 infection in individuals not requiring hospital admission: a Danish population-based cohort study. *Lancet Infect Dis* 2021;**21**:1373-1382.
80. Albu S, Zozaya NR, Murillo N, Garcia-Molina A, Chacon CAF, Kumru H. What's going on following acute covid-19? Clinical characteristics of patients in an out-patient rehabilitation program. *NeuroRehabilitation* 2021;**48**:469-480.
81. Mehta P, Bunker CB, Ciurtin C, Porter JC, Chambers RC, Papdopoulou C, Garthwaite H, Hillman T, Heightman M, Howell KJ, Eleftheriou D, Denton CP. Chilblain-like acral lesions in long COVID-19: management and implications for understanding microangiopathy. *Lancet Infect Dis* 2021;**21**:912.
82. Yeo I, Baek S, Kim J, Elshakh H, Voronina A, Lou MS, Vapnik J, Kaler R, Dai X, Goldbarg S. Assessment of thirty-day readmission rate, timing, causes and predictors after hospitalization with COVID-19. *J Intern Med* 2021;**290**:157-165.
83. Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, Banerjee A. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. *BMJ* 2021;**372**:n693.
84. Nicol M, Cacoub L, Baudet M, Nahmani Y, Cacoub P, Cohen-Solal A, Henry P, Adle-Biassette H, Logeart D. Delayed acute myocarditis and COVID-19-related multisystem inflammatory syndrome. *ESC Heart Fail* 2020.
85. Al-Falahi Z, Al-Harthi S, Farhan H, Al Busaidi I, Al Alawi AM. Late-Onset COVID-19-Related Multi-System Inflammatory Syndrome in a Middle-Aged Man. *Cureus* 2021;**13**:e15855.
86. Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, Klein JD, Bhutta ZA. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis* 2020;**20**:e276-e288.
87. Belay ED, Abrams J, Oster ME, Giovanni J, Pierce T, Meng L, Prezzato E, Balachandran N, Openshaw JJ, Rosen HE, Kim M, Richardson G, Hand J, Tobin-D'Angelo M, Wilson S, Hartley A, Jones C, Kolsin J, Mohamed H, Colles Z, Hammett T, Patel P, Stierman B, Campbell AP, Godfred-Cato S. Trends in Geographic and Temporal Distribution of US Children With Multisystem Inflammatory Syndrome During the COVID-19 Pandemic. *JAMA Pediatr* 2021;**175**:837-845.
88. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, Ramnarayan P, Fraisse A, Miller O, Davies P, Kucera F, Brierley J, McDougall M, Carter M, Tremoulet A, Shimizu C, Herberg J, Burns JC, Lyall H, Levin M, Group P-TS, Euclids, Consortia P. Clinical Characteristics of 58 Children

With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. *JAMA* 2020;**324**:259-269.
89. Syrimi E, Fennell E, Richter A, Vrljicak P, Stark R, Ott S, Murray PG, Al-Abadi E, Chikermane A, Dawson P, Hackett S, Jyothish D, Kanthimathinathan HK, Monaghan S, Nagakumar P, Scholefield BR, Welch S, Khan N, Faustini S, Davies K, Zelek WM, Kearns P, Taylor GS. The immune landscape of SARS-CoV-2-associated Multisystem Inflammatory Syndrome in Children (MIS-C) from acute disease to recovery. *iScience* 2021;**24**:103215.
90. Sigfrid L, Cevik M, Jesudason E, Lim WS, Rello J, Amuasi J, Bozza F, Palmieri C, Munblit D, Holter JC, Kildal AB, Reyes LF, Russell CD, Ho A, Turtle L, Drake TM, Beltrame A, Hann K, Bangura IR, Fowler R, Lakoh S, Berry C, Lowe DJ, McPeake J, Hashmi M, Dyrhol-Riise AM, Donohue C, Plotkin D, Hardwick H, Elkheir N, Lone NI, Docherty A, Harrison E, Baille JK, Carson G, Semple MG, Scott JT. What is the recovery rate and risk of long-term consequences following a diagnosis of COVID-19? A harmonised, global longitudinal observational study protocol. *BMJ Open* 2021;**11**:e043887.
91. Horn A, Krist L, Lieb W, Montellano FA, Kohls M, Haas K, Gelbrich G, Bolay-Gehrig SJ, Morbach C, Reese JP, Stork S, Fricke J, Zoller T, Schmidt S, Triller P, Kretzler L, Ronnefarth M, Von Kalle C, Willich SN, Kurth F, Steinbeis F, Witzenrath M, Bahmer T, Hermes A, Krawczak M, Reinke L, Maetzler C, Franzenburg J, Enderle J, Flinspach A, Vehreschild J, Schons M, Illig T, Anton G, Ungethum K, Finkenberg BC, Gehrig MT, Savaskan N, Heuschmann PU, Keil T, Schreiber S. Long-term health sequelae and quality of life at least 6 months after infection with SARS-CoV-2: design and rationale of the COVIDOM-study as part of the NAPKON population-based cohort platform (POP). *Infection* 2021;**49**:1277-1287.
92. Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, Rodrigues NB, Subramaniapillai M, Di Vincenzo JD, Cao B, Lin K, Mansur RB, Ho RC, Rosenblat JD, Miskowiak KW, Vinberg M, Maletic V, McIntyre RS. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. *Brain Behav Immun* 2022;**101**:93-135.
93. Laing AG, Lorenc A, Del Molino Del Barrio I, Das A, Fish M, Monin L, Munoz-Ruiz M, McKenzie DR, Hayday TS, Francos-Quijorna I, Kamdar S, Joseph M, Davies D, Davis R, Jennings A, Zlatareva I, Vantourout P, Wu Y, Sofra V, Cano F, Greco M, Theodoridis E, Freedman JD, Gee S, Chan JNE, Ryan S, Bugallo-Blanco E, Peterson P, Kisand K, Haljasmagi L, Chadli L, Moingeon P, Martinez L, Merrick B, Bisnauthsing K, Brooks K, Ibrahim MAA, Mason J, Lopez Gomez F, Babalola K, Abdul-Jawad S, Cason J, Mant C, Seow J, Graham C, Doores KJ, Di Rosa F, Edgeworth J, Shankar-Hari M, Hayday AC. A dynamic COVID-19 immune signature includes associations with poor prognosis. *Nat Med* 2020;**26**:1623-1635.
94. Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. *Infect Dis (Lond)* 2021;**53**:737-754.
95. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, Villapol S. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep* 2021;**11**:16144.
96. Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, O'Connor L, Leavy D, O'Brien K, Dowds J, Sugrue JA, Hopkins D, Martin-Loeches I, Ni Cheallaigh C, Nadarajan P, McLaughlin AM, Bourke NM, Bergin C, O'Farrelly C, Bannan C, Conlon N. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One* 2020;**15**:e0240784.
97. Moreno-Perez O, Merino E, Leon-Ramirez JM, Andres M, Ramos JM, Arenas-Jimenez J, Asensio S, Sanchez R, Ruiz-Torregrosa P, Galan I, Scholz A, Amo A, Gonzalez-delaAleja P, Boix V, Gil J, group CAr. Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. *J Infect* 2021;**82**:378-383.

98. Townsend L, Fogarty H, Dyer A, Martin-Loeches I, Bannan C, Nadarajan P, Bergin C, O'Farrelly C, Conlon N, Bourke NM, Ward SE, Byrne M, Ryan K, O'Connell N, O'Sullivan JM, Ni Cheallaigh C, O'Donnell JS. Prolonged elevation of D-dimer levels in convalescent COVID-19 patients is independent of the acute phase response. *J Thromb Haemost* 2021;**19**:1064-1070.
99. Qin Y, Wu J, Chen T, Li J, Zhang G, Wu D, Zhou Y, Zheng N, Cai A, Ning Q, Manyande A, Xu F, Wang J, Zhu W. Long-term microstructure and cerebral blood flow changes in patients recovered from COVID-19 without neurological manifestations. *J Clin Invest* 2021;**131**.
100. Paneroni M, Pasini E, Vitacca M, Scalvini S, Comini L, Pedrinolla A, Venturelli M. Altered Vascular Endothelium-Dependent Responsiveness in Frail Elderly Patients Recovering from COVID-19 Pneumonia: Preliminary Evidence. *J Clin Med* 2021;**10**.
101. Pasini E, Corsetti G, Romano C, Scarabelli TM, Chen-Scarabelli C, Saravolatz L, Dioguardi FS. Serum Metabolic Profile in Patients With Long-Covid (PASC) Syndrome: Clinical Implications. *Front Med (Lausanne)* 2021;**8**:714426.
102. Salmon-Ceron D, Slama D, De Broucker T, Karmochkine M, Pavie J, Sorbets E, Etienne N, Batisse D, Spiridon G, Baut VL, Meritet JF, Pichard E, Canoui-Poitrine F, collaboration AC-r. Clinical, virological and imaging profile in patients with prolonged forms of COVID-19: A cross-sectional study. *J Infect* 2021;**82**:e1-e4.
103. Venturelli S, Benatti SV, Casati M, Binda F, Zuglian G, Imeri G, Conti C, Biffi AM, Spada MS, Bondi E, Camera G, Severgnini R, Giammarresi A, Marinaro C, Rossini A, Bonaffini PA, Guerra G, Bellasi A, Cesa S, Rizzi M. Surviving COVID-19 in Bergamo province: a post-acute outpatient re-evaluation. *Epidemiol Infect* 2021;**149**:e32.
104. Raman B, Cassar MP, Tunnicliffe EM, Filippini N, Griffanti L, Alfaro-Almagro F, Okell T, Sheerin F, Xie C, Mahmod M, Mozes FE, Lewandowski AJ, Ohuma EO, Holdsworth D, Lamlum H, Woodman MJ, Krasopoulos C, Mills R, McConnell FAK, Wang C, Arthofer C, Lange FJ, Andersson J, Jenkinson M, Antoniades C, Channon KM, Shanmuganathan M, Ferreira VM, Piechnik SK, Klenerman P, Brightling C, Talbot NP, Petousi N, Rahman NM, Ho LP, Saunders K, Geddes JR, Harrison PJ, Pattinson K, Rowland MJ, Angus BJ, Gleeson F, Pavlides M, Koychev I, Miller KL, Mackay C, Jezzard P, Smith SM, Neubauer S. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *EClinicalMedicine* 2021;**31**:100683.
105. Sonnweber T, Boehm A, Sahanic S, Pizzini A, Aichner M, Sonnweber B, Kurz K, Koppelstatter S, Haschka D, Petzer V, Hilbe R, Theurl M, Lehner D, Nairz M, Puchner B, Luger A, Schwabl C, Bellmann-Weiler R, Woll E, Widmann G, Tancevski I, Judith Loffler R, Weiss G. Persisting alterations of iron homeostasis in COVID-19 are associated with non-resolving lung pathologies and poor patients' performance: a prospective observational cohort study. *Respir Res* 2020;**21**:276.
106. Phetsouphanh C, Darley DR, Wilson DB, Howe A, Munier CML, Patel SK, Juno JA, Burrell LM, Kent SJ, Dore GJ, Kelleher AD, Matthews GV. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nat Immunol* 2022;**23**:210-216.
107. Doykov I, Hallqvist J, Gilmour KC, Grandjean L, Mills K, Heywood WE. 'The long tail of Covid-19' - The detection of a prolonged inflammatory response after a SARS-CoV-2 infection in asymptomatic and mildly affected patients. *F1000Res* 2020;**9**:1349.
108. Patterson BK, Guevara-Coto J, Yogendra R, Francisco EB, Long E, Pise A, Rodrigues H, Parikh P, Mora J, Mora-Rodriguez RA. Immune-Based Prediction of COVID-19 Severity and Chronicity Decoded Using Machine Learning. *Front Immunol* 2021;**12**:700782.
109. Fogarty H, Townsend L, Morrin H, Ahmad A, Comerford C, Karampini E, Englert H, Byrne M, Bergin C, O'Sullivan JM, Martin-Loeches I, Nadarajan P, Bannan C, Mallon PW, Curley GF, Preston RJS, Rehill AM, McGonagle D, Ni Cheallaigh C, Baker RI, Renne T, Ward SE, JS OD, Irish C-VSi.

Persistent Endotheliopathy in the Pathogenesis of Long COVID Syndrome. *J Thromb Haemost* 2021.
110. Thomas T, Stefanoni D, Dzieciatkowska M, Issaian A, Nemkov T, Hill RC, Francis RO, Hudson KE, Buehler PW, Zimring JC, Hod EA, Hansen KC, Spitalnik SL, D'Alessandro A. Evidence of Structural Protein Damage and Membrane Lipid Remodeling in Red Blood Cells from COVID-19 Patients. *J Proteome Res* 2020;**19**:4455-4469.
111. Wong SW, Fan BE, Huang W, Chia YW. ST-segment elevation myocardial infarction in post-COVID-19 patients: A case series. *Ann Acad Med Singap* 2021;**50**:425-430.
112. Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, Jia JL, Li LM, Mao HL, Zhou XM, Luo H, Gao YF, Xu AG. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine* 2020;**25**:100463.
113. Holmes E, Wist J, Masuda R, Lodge S, Nitschke P, Kimhofer T, Loo RL, Begum S, Boughton B, Yang R, Morillon AC, Chin ST, Hall D, Ryan M, Bong SH, Gay M, Edgar DW, Lindon JC, Richards T, Yeap BB, Pettersson S, Spraul M, Schaefer H, Lawler NG, Gray N, Whiley L, Nicholson JK. Incomplete Systemic Recovery and Metabolic Phenoreversion in Post-Acute-Phase Nonhospitalized COVID-19 Patients: Implications for Assessment of Post-Acute COVID-19 Syndrome. *J Proteome Res* 2021;**20**:3315-3329.
114. Wang J, Mei F, Bai L, Zhou S, Liu D, Yao L, Ahluwalia A, Ghiladi RA, Su L, Shu T, Gong M, Wang X, Zhu L, Cai K, Zhang X. Serum nitrite and nitrate: A potential biomarker for post-covid-19 complications? *Free Radic Biol Med* 2021.
115. Garg A, Seeliger B, Derda AA, Xiao K, Gietz A, Scherf K, Sonnenschein K, Pink I, Hoeper MM, Welte T, Bauersachs J, David S, Bar C, Thum T. Circulating cardiovascular microRNAs in critically ill COVID-19 patients. *Eur J Heart Fail* 2021;**23**:468-475.
116. Fu Z, Wang J, Wang Z, Sun Y, Wu J, Zhang Y, Liu X, Zhou Z, Zhou L, Zhang CY, Yi Y, Xia X, Wang L, Chen X. A virus-derived microRNA-like small RNA serves as a serum biomarker to prioritize the COVID-19 patients at high risk of developing severe disease. *Cell Discov* 2021;**7**:48.
117. Badimon L, Robinson EL, Jusic A, Carpusca I, deWindt LJ, Emanueli C, Ferdinandy P, Gu W, Gyongyosi M, Hackl M, Karaduzovic-Hadziabdic K, Lustrek M, Martelli F, Nham E, Potocnjak I, Satagopam V, Schneider R, Thum T, Devaux Y. Cardiovascular RNA markers and artificial intelligence may improve COVID-19 outcome: a position paper from the EU-CardioRNA COST Action CA17129. *Cardiovasc Res* 2021;**117**:1823-1840.
118. Hachim MY, Al Heialy S, Senok A, Hamid Q, Alsheikh-Ali A. Molecular Basis of Cardiac and Vascular Injuries Associated With COVID-19. *Front Cardiovasc Med* 2020;**7**:582399.
119. Files JK, Sarkar S, Fram TR, Boppana S, Sterrett S, Qin K, Bansal A, Long DM, Sabbaj S, Kobie JJ, Goepfert PA, Erdmann N. Duration of post-COVID-19 symptoms is associated with sustained SARS-CoV-2-specific immune responses. *JCI Insight* 2021;**6**.
120. Yao L, Wang GL, Shen Y, Wang ZY, Zhan BD, Duan LJ, Lu B, Shi C, Gao YM, Peng HH, Wang GQ, Wang DM, Jiang MD, Cao GP, Ma MJ. Persistence of Antibody and Cellular Immune Responses in Coronavirus Disease 2019 Patients Over Nine Months After Infection. *J Infect Dis* 2021;**224**:586-594.
121. Chang SE, Feng A, Meng W, Apostolidis SA, Mack E, Artandi M, Barman L, Bennett K, Chakraborty S, Chang I, Cheung P, Chinthrajah S, Dhingra S, Do E, Finck A, Gaano A, Gessner R, Giannini HM, Gonzalez J, Greib S, Gundisch M, Hsu AR, Kuo A, Manohar M, Mao R, Neeli I, Neubauer A, Oniyide O, Powell AE, Puri R, Renz H, Schapiro J, Weidenbacher PA, Wittman R, Ahuja N, Chung HR, Jagannathan P, James JA, Kim PS, Meyer NJ, Nadeau KC, Radic M, Robinson WH, Singh U, Wang TT, Wherry EJ, Skevaki C, Luning Prak ET, Utz PJ. New-onset IgG autoantibodies in hospitalized patients with COVID-19. *Nat Commun* 2021;**12**:5417.
122. Richter AG, Shields AM, Karim A, Birch D, Faustini SE, Steadman L, Ward K, Plant T, Reynolds G, Veenith T, Cunningham AF, Drayson MT, Wraith DC. Establishing the prevalence of common

tissue-specific autoantibodies following severe acute respiratory syndrome coronavirus 2 infection. *Clin Exp Immunol* 2021;**205**:99-105.
123. Schultheiss HP, Baumeier C, Pietsch H, Bock CT, Poller W, Escher F. Cardiovascular consequences of viral infections: from COVID to other viral diseases. *Cardiovasc Res* 2021.
124. Sawadogo SA, Dighero-Kemp B, Ouedraogo DD, Hensley L, Sakande J. How NETosis could drive "Post-COVID-19 syndrome" among survivors. *Immunol Lett* 2020;**228**:35-37.
125. Ng H, Havervall S, Rosell A, Aguilera K, Parv K, von Meijenfeldt FA, Lisman T, Mackman N, Thalin C, Phillipson M. Circulating Markers of Neutrophil Extracellular Traps Are of Prognostic Value in Patients With COVID-19. *Arterioscler Thromb Vasc Biol* 2021;**41**:988-994.
126. Afrin LB, Weinstock LB, Molderings GJ. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. *Int J Infect Dis* 2020;**100**:327-332.
127. Kubankova M, Hohberger B, Hoffmanns J, Furst J, Herrmann M, Guck J, Krater M. Physical phenotype of blood cells is altered in COVID-19. *Biophys J* 2021;**120**:2838-2847.
128. Wood E, Hall KH, Tate W. Role of mitochondria, oxidative stress and the response to antioxidants in myalgic encephalomyelitis/chronic fatigue syndrome: A possible approach to SARS-CoV-2 'long-haulers'? *Chronic Dis Transl Med* 2021;**7**:14-26.
129. De Biasi S, Meschiari M, Gibellini L, Bellinazzi C, Borella R, Fidanza L, Gozzi L, Iannone A, Lo Tartaro D, Mattioli M, Paolini A, Menozzi M, Milic J, Franceschi G, Fantini R, Tonelli R, Sita M, Sarti M, Trenti T, Brugioni L, Cicchetti L, Facchinetti F, Pietrangelo A, Clini E, Girardis M, Guaraldi G, Mussini C, Cossarizza A. Marked T cell activation, senescence, exhaustion and skewing towards TH17 in patients with COVID-19 pneumonia. *Nat Commun* 2020;**11**:3434.
130. Nehme J, Borghesan M, Mackedenski S, Bird TG, Demaria M. Cellular senescence as a potential mediator of COVID-19 severity in the elderly. *Aging Cell* 2020;**19**:e13237.
131. Blagosklonny MV. From causes of aging to death from COVID-19. *Aging (Albany NY)* 2020;**12**:10004-10021.
132. Hohn A, Weber D, Jung T, Ott C, Hugo M, Kochlik B, Kehm R, Konig J, Grune T, Castro JP. Happily (n)ever after: Aging in the context of oxidative stress, proteostasis loss and cellular senescence. *Redox Biol* 2017;**11**:482-501.
133. Froidure A, Mahieu M, Hoton D, Laterre PF, Yombi JC, Koenig S, Ghaye B, Defour JP, Decottignies A. Short telomeres increase the risk of severe COVID-19. *Aging (Albany NY)* 2020;**12**:19911-19922.
134. Sanchez-Vazquez R, Guio-Carrion A, Zapatero-Gaviria A, Martinez P, Blasco MA. Shorter telomere lengths in patients with severe COVID-19 disease. *Aging (Albany NY)* 2021;**13**:1-15.
135. Horvath S, Raj K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. *Nat Rev Genet* 2018;**19**:371-384.
136. Mongelli A, Barbi V, Gottardi Zamperla M, Atlante S, Forleo L, Nesta M, Massetti M, Pontecorvi A, Nanni S, Farsetti A, Catalano O, Bussotti M, Dalla Vecchia LA, Bachetti T, Martelli F, La Rovere MT, Gaetano C. Evidence for Biological Age Acceleration and Telomere Shortening in COVID-19 Survivors. *Int J Mol Sci* 2021;**22**.
137. Singh M, Bansal V, Feschotte C. A Single-Cell RNA Expression Map of Human Coronavirus Entry Factors. *Cell Rep* 2020;**32**:108175.
138. Duarte C, Akkaoui J, Ho A, Garcia C, Yamada C, Movila A. Age-dependent effects of the recombinant spike protein/SARS-CoV-2 on the M-CSF- and IL-34-differentiated macrophages in vitro. *Biochem Biophys Res Commun* 2021;**546**:97-102.
139. Meyer K, Patra T, Vijayamahantesh, Ray R. SARS-CoV-2 Spike Protein Induces Paracrine Senescence and Leukocyte Adhesion in Endothelial Cells. *J Virol* 2021;**95**:e0079421.
140. Amendola A, Garoffolo G, Songia P, Nardacci R, Ferrari S, Bernava G, Canzano P, Myasoedova V, Colavita F, Castilletti C, Sberna G, Capobianchi MR, Piacentini M, Agrifoglio M, Colombo GI, Poggio P, Pesce M. Human cardiosphere-derived stromal cells exposed to SARS-CoV-2 evolve

into hyper-inflammatory/pro-fibrotic phenotype and produce infective viral particles depending on the levels of ACE2 receptor expression. *Cardiovasc Res* 2021;**117**:1557-1566.
141. Camell CD, Yousefzadeh MJ, Zhu Y, Prata L, Huggins MA, Pierson M, Zhang L, O'Kelly RD, Pirtskhalava T, Xun P, Ejima K, Xue A, Tripathi U, Espindola-Netto JM, Giorgadze N, Atkinson EJ, Inman CL, Johnson KO, Cholensky SH, Carlson TW, LeBrasseur NK, Khosla S, O'Sullivan MG, Allison DB, Jameson SC, Meves A, Li M, Prakash YS, Chiarella SE, Hamilton SE, Tchkonia T, Niedernhofer LJ, Kirkland JL, Robbins PD. Senolytics reduce coronavirus-related mortality in old mice. *Science* 2021;**373**.
142. Lee S, Yu Y, Trimpert J, Benthani F, Mairhofer M, Richter-Pechanska P, Wyler E, Belenki D, Kaltenbrunner S, Pammer M, Kausche L, Firsching TC, Dietert K, Schotsaert M, Martinez-Romero C, Singh G, Kunz S, Niemeyer D, Ghanem R, Salzer HJF, Paar C, Mulleder M, Uccellini M, Michaelis EG, Khan A, Lau A, Schonlein M, Habringer A, Tomasits J, Adler JM, Kimeswenger S, Gruber AD, Hoetzenecker W, Steinkellner H, Purfurst B, Motz R, Di Pierro F, Lamprecht B, Osterrieder N, Landthaler M, Drosten C, Garcia-Sastre A, Langer R, Ralser M, Eils R, Reimann M, Fan DNY, Schmitt CA. Virus-induced senescence is a driver and therapeutic target in COVID-19. *Nature* 2021.
143. Lindner D, Fitzek A, Brauninger H, Aleshcheva G, Edler C, Meissner K, Scherschel K, Kirchhof P, Escher F, Schultheiss HP, Blankenberg S, Puschel K, Westermann D. Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases. *JAMA Cardiol* 2020;**5**:1281-1285.
144. Natarajan A, Zlitni S, Brooks EF, Vance SE, Dahlen A, Hedlin H, Park RM, Han A, Schmidtke DT, Verma R, Jacobson KB, Parsonnet J, Bonilla HF, Singh U, Pinsky BA, Andrews JR, Jagannathan P, Bhatt AS. Gastrointestinal symptoms and fecal shedding of SARS-CoV-2 RNA suggest prolonged gastrointestinal infection. *Med (N Y)* 2022.
145. Zollner A, Koch R, Jukic A, Pfister A, Meyer M, Rossler A, Kimpel J, Adolph TE, Tilg H. Post-acute COVID-19 is characterized by gut viral antigen persistence in inflammatory bowel diseases. *Gastroenterology* 2022.
146. Roe K. A role for T-cell exhaustion in Long COVID-19 and severe outcomes for several categories of COVID-19 patients. *J Neurosci Res* 2021;**99**:2367-2376.
147. Cheng MH, Zhang S, Porritt RA, Noval Rivas M, Paschold L, Willscher E, Binder M, Arditi M, Bahar I. Superantigenic character of an insert unique to SARS-CoV-2 spike supported by skewed TCR repertoire in patients with hyperinflammation. *Proc Natl Acad Sci U S A* 2020;**117**:25254-25262.
148. Su Y, Yuan D, Chen DG, Ng RH, Wang K, Choi J, Li S, Hong S, Zhang R, Xie J, Kornilov SA, Scherler K, Pavlovitch-Bedzyk AJ, Dong S, Lausted C, Lee I, Fallen S, Dai CL, Baloni P, Smith B, Duvvuri VR, Anderson KG, Li J, Yang F, Duncombe CJ, McCulloch DJ, Rostomily C, Troisch P, Zhou J, Mackay S, DeGottardi Q, May DH, Taniguchi R, Gittelman RM, Klinger M, Snyder TM, Roper R, Wojciechowska G, Murray K, Edmark R, Evans S, Jones L, Zhou Y, Rowen L, Liu R, Chour W, Algren HA, Berrington WR, Wallick JA, Cochran RA, Micikas ME, Wrin T, Petropoulos CJ, Cole HR, Fischer TD, Wei W, Hoon DSB, Price ND, Subramanian N, Hill JA, Hadlock J, Magis AT, Ribas A, Lanier LL, Boyd SD, Bluestone JA, Chu H, Hood L, Gottardo R, Greenberg PD, Davis MM, Goldman JD, Heath JR. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell* 2022;**185**:881-895.e820.
149. Pesce M, Agostoni P, Botker HE, Brundel B, Davidson SM, Caterina R, Ferdinandy P, Girao H, Gyongyosi M, Hulot JS, Lecour S, Perrino C, Schulz R, Sluijter JP, Steffens S, Tancevski I, Gollmann-Tepekoylu C, Tschope C, Linthout SV, Madonna R. COVID-19-related cardiac complications from clinical evidences to basic mechanisms: opinion paper of the ESC Working Group on Cellular Biology of the Heart. *Cardiovasc Res* 2021;**117**:2148-2160.
150. Bailey AL, Dmytrenko O, Greenberg L, Bredemeyer AL, Ma P, Liu J, Penna V, Winkler ES, Sviben S, Brooks E, Nair AP, Heck KA, Rali AS, Simpson L, Saririan M, Hobohm D, Stump WT, Fitzpatrick JA,

Xie X, Zhang X, Shi PY, Hinson JT, Gi WT, Schmidt C, Leuschner F, Lin CY, Diamond MS, Greenberg MJ, Lavine KJ. SARS-CoV-2 Infects Human Engineered Heart Tissues and Models COVID-19 Myocarditis. *JACC Basic Transl Sci* 2021;**6**:331-345.

151. Bojkova D, Wagner JUG, Shumliakivska M, Aslan GS, Saleem U, Hansen A, Luxan G, Gunther S, Pham MD, Krishnan J, Harter PN, Ermel UH, Frangakis AS, Milting H, Zeiher AM, Klingel K, Cinatl J, Dendorfer A, Eschenhagen T, Tschope C, Ciesek S, Dimmeler S. SARS-CoV-2 infects and induces cytotoxic effects in human cardiomyocytes. *Cardiovasc Res* 2020;**116**:2207-2215.

152. Bernard I, Limonta D, Mahal LK, Hobman TC. Endothelium Infection and Dysregulation by SARS-CoV-2: Evidence and Caveats in COVID-19. *Viruses* 2020;**13**.

153. Tanacli R, Doeblin P, Gotze C, Zieschang V, Faragli A, Stehning C, Korosoglou G, Erley J, Weiss J, Berger A, Propper F, Steinbeis F, Kuhne T, Seidel F, Geisel D, Cannon Walter-Rittel T, Stawowy P, Witzenrath M, Klingel K, Van Linthout S, Pieske B, Tschope C, Kelle S. COVID-19 vs. Classical Myocarditis Associated Myocardial Injury Evaluated by Cardiac Magnetic Resonance and Endomyocardial Biopsy. *Front Cardiovasc Med* 2021;**8**:737257.

154. Grant RA, Morales-Nebreda L, Markov NS, Swaminathan S, Querrey M, Guzman ER, Abbott DA, Donnelly HK, Donayre A, Goldberg IA, Klug ZM, Borkowski N, Lu Z, Kihshen H, Politanska Y, Sichizya L, Kang M, Shilatifard A, Qi C, Lomasney JW, Argento AC, Kruser JM, Malsin ES, Pickens CO, Smith SB, Walter JM, Pawlowski AE, Schneider D, Nannapaneni P, Abdala-Valencia H, Bharat A, Gottardi CJ, Budinger GRS, Misharin AV, Singer BD, Wunderink RG, Investigators NSS. Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia. *Nature* 2021;**590**:635-641.

155. Fox SE, Falgout L, Vander Heide RS. COVID-19 myocarditis: quantitative analysis of the inflammatory infiltrate and a proposed mechanism. *Cardiovasc Pathol* 2021;**54**:107361.

156. Evans PC, Rainger GE, Mason JC, Guzik TJ, Osto E, Stamataki Z, Neil D, Hoefer IE, Fragiadaki M, Waltenberger J, Weber C, Bochaton-Piallat ML, Back M. Endothelial dysfunction in COVID-19: a position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science. *Cardiovasc Res* 2020;**116**:2177-2184.

157. Castro P, Palomo M, Moreno-Castano AB, Fernandez S, Torramade-Moix S, Pascual G, Martinez-Sanchez J, Richardson E, Tellez A, Nicolas JM, Carreras E, Richardson PG, Badimon JJ, Escolar G, Diaz-Ricart M. Is the Endothelium the Missing Link in the Pathophysiology and Treatment of COVID-19 Complications? *Cardiovasc Drugs Ther* 2021.

158. Lambadiari V, Mitrakou A, Kountouri A, Thymis J, Katogiannis K, Korakas E, Varlamos C, Andreadou I, Tsoumani M, Triantafyllidi H, Bamias A, Thomas K, Kazakou P, Grigoropoulou S, Kavatha D, Antoniadou A, Dimopoulos MA, Ikonomidis I. Association of COVID-19 with impaired endothelial glycocalyx, vascular function and myocardial deformation 4 months after infection. *Eur J Heart Fail* 2021.

159. Ostergaard L. SARS CoV-2 related microvascular damage and symptoms during and after COVID-19: Consequences of capillary transit-time changes, tissue hypoxia and inflammation. *Physiol Rep* 2021;**9**:e14726.

160. Bienvenu LA, Noonan J, Wang X, Peter K. Higher mortality of COVID-19 in males: sex differences in immune response and cardiovascular comorbidities. *Cardiovasc Res* 2020;**116**:2197-2206.

161. Bucciarelli V, Nasi M, Bianco F, Seferovic J, Ivkovic V, Gallina S, Mattioli AV. Depression pandemic and cardiovascular risk in the COVID-19 era and long COVID syndrome: Gender makes a difference. *Trends Cardiovasc Med* 2022;**32**:12-17.

162. Zhang Q. Human genetics of life-threatening influenza pneumonitis. *Hum Genet* 2020;**139**:941-948.

163. Avanoglu Guler A, Tombul N, Aysert Yildiz P, Ozger HS, Hizel K, Gulbahar O, Tufan A, Erbas G, Aygencel G, Guzel Tunccan O, Dizbay M, Ozturk MA. The assessment of serum ACE activity in

COVID-19 and its association with clinical features and severity of the disease. *Scand J Clin Lab Invest* 2021;**81**:160-165.

164. Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J, Ogishi M, Sabli IKD, Hodeib S, Korol C, Rosain J, Bilguvar K, Ye J, Bolze A, Bigio B, Yang R, Arias AA, Zhou Q, Zhang Y, Onodi F, Korniotis S, Karpf L, Philippot Q, Chbihi M, Bonnet-Madin L, Dorgham K, Smith N, Schneider WM, Razooky BS, Hoffmann HH, Michailidis E, Moens L, Han JE, Lorenzo L, Bizien L, Meade P, Neehus AL, Ugurbil AC, Corneau A, Kerner G, Zhang P, Rapaport F, Seeleuthner Y, Manry J, Masson C, Schmitt Y, Schluter A, Le Voyer T, Khan T, Li J, Fellay J, Roussel L, Shahrooei M, Alosaimi MF, Mansouri D, Al-Saud H, Al-Mulla F, Almourfi F, Al-Muhsen SZ, Alsohime F, Al Turki S, Hasanato R, van de Beek D, Biondi A, Bettini LR, D'Angio M, Bonfanti P, Imberti L, Sottini A, Paghera S, Quiros-Roldan E, Rossi C, Oler AJ, Tompkins MF, Alba C, Vandernoot I, Goffard JC, Smits G, Migeotte I, Haerynck F, Soler-Palacin P, Martin-Nalda A, Colobran R, Morange PE, Keles S, Colkesen F, Ozcelik T, Yasar KK, Senoglu S, Karabela SN, Rodriguez-Gallego C, Novelli G, Hraiech S, Tandjaoui-Lambiotte Y, Duval X, Laouenan C, Clinicians C-S, Clinicians C, Imagine CG, French CCSG, Co VCC, Amsterdam UMCC-B, Effort CHG, Group N-UTCI, Snow AL, Dalgard CL, Milner JD, Vinh DC, Mogensen TH, Marr N, Spaan AN, Boisson B, Boisson-Dupuis S, Bustamante J, Puel A, Ciancanelli MJ, Meyts I, Maniatis T, Soumelis V, Amara A, Nussenzweig M, Garcia-Sastre A, Krammer F, Pujol A, Duffy D, Lifton RP, Zhang SY, Gorochov G, Beziat V, Jouanguy E, Sancho-Shimizu V, Rice CM, Abel L, Notarangelo LD, Cobat A, Su HC, Casanova JL. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science* 2020;**370**.

165. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, Dorgham K, Philippot Q, Rosain J, Beziat V, Manry J, Shaw E, Haljasmagi L, Peterson P, Lorenzo L, Bizien L, Trouillet-Assant S, Dobbs K, de Jesus AA, Belot A, Kallaste A, Catherinot E, Tandjaoui-Lambiotte Y, Le Pen J, Kerner G, Bigio B, Seeleuthner Y, Yang R, Bolze A, Spaan AN, Delmonte OM, Abers MS, Aiuti A, Casari G, Lampasona V, Piemonti L, Ciceri F, Bilguvar K, Lifton RP, Vasse M, Smadja DM, Migaud M, Hadjadj J, Terrier B, Duffy D, Quintana-Murci L, van de Beek D, Roussel L, Vinh DC, Tangye SG, Haerynck F, Dalmau D, Martinez-Picado J, Brodin P, Nussenzweig MC, Boisson-Dupuis S, Rodriguez-Gallego C, Vogt G, Mogensen TH, Oler AJ, Gu J, Burbelo PD, Cohen JI, Biondi A, Bettini LR, D'Angio M, Bonfanti P, Rossignol P, Mayaux J, Rieux-Laucat F, Husebye ES, Fusco F, Ursini MV, Imberti L, Sottini A, Paghera S, Quiros-Roldan E, Rossi C, Castagnoli R, Montagna D, Licari A, Marseglia GL, Duval X, Ghosn J, Lab H, Group N-UIRtC, Clinicians C, Clinicians C-S, Imagine CG, French CCSG, Milieu Interieur C, Co VCC, Amsterdam UMCC-B, Effort CHG, Tsang JS, Goldbach-Mansky R, Kisand K, Lionakis MS, Puel A, Zhang SY, Holland SM, Gorochov G, Jouanguy E, Rice CM, Cobat A, Notarangelo LD, Abel L, Su HC, Casanova JL. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 2020;**370**.

166. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, Cook JR, Nordvig AS, Shalev D, Sehrawat TS, Ahluwalia N, Bikdeli B, Dietz D, Der-Nigoghossian C, Liyanage-Don N, Rosner GF, Bernstein EJ, Mohan S, Beckley AA, Seres DS, Choueiri TK, Uriel N, Ausiello JC, Accili D, Freedberg DE, Baldwin M, Schwartz A, Brodie D, Garcia CK, Elkind MSV, Connors JM, Bilezikian JP, Landry DW, Wan EY. Post-acute COVID-19 syndrome. *Nat Med* 2021;**27**:601-615.

167. da Silva RP, Goncalves JIB, Zanin RF, Schuch FB, de Souza APD. Circulating Type I Interferon Levels and COVID-19 Severity: A Systematic Review and Meta-Analysis. *Front Immunol* 2021;**12**:657363.

168. Severe Covid GG, Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, Fernandez J, Prati D, Baselli G, Asselta R, Grimsrud MM, Milani C, Aziz F, Kassens J, May S, Wendorff M, Wienbrandt L, Uellendahl-Werth F, Zheng T, Yi X, de Pablo R, Chercoles AG, Palom A, Garcia-Fernandez AE, Rodriguez-Frias F, Zanella A, Bandera A, Protti A, Aghemo A, Lleo A, Biondi A, Caballero-Garralda A, Gori A, Tanck A, Carreras Nolla A, Latiano A, Fracanzani AL, Peschuck A, Julia A, Pesenti A, Voza A, Jimenez D, Mateos B, Nafria Jimenez B, Quereda C,

Paccapelo C, Gassner C, Angelini C, Cea C, Solier A, Pestana D, Muniz-Diaz E, Sandoval E, Paraboschi EM, Navas E, Garcia Sanchez F, Ceriotti F, Martinelli-Boneschi F, Peyvandi F, Blasi F, Tellez L, Blanco-Grau A, Hemmrich-Stanisak G, Grasselli G, Costantino G, Cardamone G, Foti G, Aneli S, Kurihara H, ElAbd H, My I, Galvan-Femenia I, Martin J, Erdmann J, Ferrusquia-Acosta J, Garcia-Etxebarria K, Izquierdo-Sanchez L, Bettini LR, Sumoy L, Terranova L, Moreira L, Santoro L, Scudeller L, Mesonero F, Roade L, Ruhlemann MC, Schaefer M, Carrabba M, Riveiro-Barciela M, Figuera Basso ME, Valsecchi MG, Hernandez-Tejero M, Acosta-Herrera M, D'Angio M, Baldini M, Cazzaniga M, Schulzky M, Cecconi M, Wittig M, Ciccarelli M, Rodriguez-Gandia M, Bocciolone M, Miozzo M, Montano N, Braun N, Sacchi N, Martinez N, Ozer O, Palmieri O, Faverio P, Preatoni P, Bonfanti P, Omodei P, Tentorio P, Castro P, Rodrigues PM, Blandino Ortiz A, de Cid R, Ferrer R, Gualtierotti R, Nieto R, Goerg S, Badalamenti S, Marsal S, Matullo G, Pelusi S, Juzenas S, Aliberti S, Monzani V, Moreno V, Wesse T, Lenz TL, Pumarola T, Rimoldi V, Bosari S, Albrecht W, Peter W, Romero-Gomez M, D'Amato M, Duga S, Banales JM, Hov JR, Folseraas T, Valenti L, Franke A, Karlsen TH. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. *N Engl J Med* 2020;**383**:1522-1534.

169. Groot HE, Villegas Sierra LE, Said MA, Lipsic E, Karper JC, van der Harst P. Genetically Determined ABO Blood Group and its Associations With Health and Disease. *Arterioscler Thromb Vasc Biol* 2020;**40**:830-838.

170. Wu Q, Zhou L, Sun X, Yan Z, Hu C, Wu J, Xu L, Li X, Liu H, Yin P, Li K, Zhao J, Li Y, Wang X, Li Y, Zhang Q, Xu G, Chen H. Altered Lipid Metabolism in Recovered SARS Patients Twelve Years after Infection. *Sci Rep* 2017;**7**:9110.

171. Abegaz SB. Human ABO Blood Groups and Their Associations with Different Diseases. *BioMed research international* 2021;**2021**:6629060.

172. COVID Human Genetic Effort.

173. Marx V. Scientists set out to connect the dots on long COVID. *Nat Methods* 2021;**18**:449-453.

174. Pairo-Castineira E, Clohisey S, Klaric L, Bretherick AD, Rawlik K, Pasko D, Walker S, Parkinson N, Fourman MH, Russell CD, Furniss J, Richmond A, Gountouna E, Wrobel N, Harrison D, Wang B, Wu Y, Meynert A, Griffiths F, Oosthuyzen W, Kousathanas A, Moutsianas L, Yang Z, Zhai R, Zheng C, Grimes G, Beale R, Millar J, Shih B, Keating S, Zechner M, Haley C, Porteous DJ, Hayward C, Yang J, Knight J, Summers C, Shankar-Hari M, Klenerman P, Turtle L, Ho A, Moore SC, Hinds C, Horby P, Nichol A, Maslove D, Ling L, McAuley D, Montgomery H, Walsh T, Pereira AC, Renieri A, Gen OI, Investigators IC, Initiative C-HG, andMe I, Investigators B, Gen CI, Shen X, Ponting CP, Fawkes A, Tenesa A, Caulfield M, Scott R, Rowan K, Murphy L, Openshaw PJM, Semple MG, Law A, Vitart V, Wilson JF, Baillie JK. Genetic mechanisms of critical illness in COVID-19. *Nature* 2021;**591**:92-98.

175. Initiative C-HG. Mapping the human genetic architecture of COVID-19. *Nature* 2021;**600**:472-477.

176. Downes DJ, Cross AR, Hua P, Roberts N, Schwessinger R, Cutler AJ, Munis AM, Brown J, Mielczarek O, de Andrea CE, Melero I, Consortium CO-M-oBA, Gill DR, Hyde SC, Knight JC, Todd JA, Sansom SN, Issa F, Davies JOJ, Hughes JR. Identification of LZTFL1 as a candidate effector gene at a COVID-19 risk locus. *Nat Genet* 2021;**53**:1606-1615.

177. Cleary SJ, Pitchford SC, Amison RT, Carrington R, Robaina Cabrera CL, Magnen M, Looney MR, Gray E, Page CP. Animal models of mechanisms of SARS-CoV-2 infection and COVID-19 pathology. *Br J Pharmacol* 2020;**177**:4851-4865.

178. Dinnon KH, Leist SR, Okuda K, Dang H, Fritch EJ, Gully KL, De la Cruz G, Evangelista MD, Asakura T, Gilmore RC, Hawkins P, Nakano S, West A, Schafer A, Gralinski LE, Everman JL, Sajuthi SP, Zweigart MR, Dong S, McBride J, Cooley MR, Hines JB, Love MK, Groshong SD, VanSchoiack A, Phelan SJ, Liang Y, Hether T, Leon M, Zumwalt RE, Barton LM, Duval EJ, Mukhopadhyay S, Stroberg E, Borczuk A, Thorne LB, Sakthivel MK, Lee YZ, Hagood JS, Mock JR, Seibold MA, O'Neal

WK, Montgomery SA, Boucher RC, Baric RS. A model of persistent post SARS-CoV-2 induced lung disease for target identification and testing of therapeutic strategies. *bioRxiv* 2022.
179. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020;**5**:811-818.
180. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis treated with glucocorticoid and human immunoglobulin. *Eur Heart J* 2021;**42**:206.
181. Kini A, Cao D, Nardin M, Sartori S, Zhang Z, Pivato CA, Chiarito M, Nicolas J, Vengrenyuk Y, Krishnamoorthy P, Sharma SK, Dangas G, Fuster V, Mehran R. Types of myocardial injury and mid-term outcomes in patients with COVID-19. *Eur Heart J Qual Care Clin Outcomes* 2021;**7**:438-446.
182. Vollbracht C, Kraft K. Feasibility of Vitamin C in the Treatment of Post Viral Fatigue with Focus on Long COVID, Based on a Systematic Review of IV Vitamin C on Fatigue. *Nutrients* 2021;**13**.
183. Schomburg L. Selenium Deficiency Due to Diet, Pregnancy, Severe Illness, or COVID-19-A Preventable Trigger for Autoimmune Disease. *Int J Mol Sci* 2021;**22**.
184. Bhaiyat AM, Sasson E, Wang Z, Khairy S, Ginzarly M, Qureshi U, Fikree M, Efrati S. Hyperbaric oxygen treatment for long coronavirus disease-19: a case report. *J Med Case Rep* 2022;**16**:80.
185. Robbins T, Gonevski M, Clark C, Baitule S, Sharma K, Magar A, Patel K, Sankar S, Kyrou I, Ali A, Randeva HS. Hyperbaric oxygen therapy for the treatment of long COVID: early evaluation of a highly promising intervention. *Clin Med (Lond)* 2021;**21**:e629-e632.
186. Weisshoff H, Krylova O, Nikolenko H, Dungen HD, Dallmann A, Becker S, Gottel P, Muller J, Haberland A. Aptamer BC 007 - Efficient binder of spreading-crucial SARS-CoV-2 proteins. *Heliyon* 2020;**6**:e05421.
187. Jimeno-Almazan A, Pallares JG, Buendia-Romero A, Martinez-Cava A, Franco-Lopez F, Sanchez-Alcaraz Martinez BJ, Bernal-Morel E, Courel-Ibanez J. Post-COVID-19 Syndrome and the Potential Benefits of Exercise. *Int J Environ Res Public Health* 2021;**18**.
188. Scheiber B, Spiegl C, Wiederin C, Schifferegger E, Schiefermeier-Mach N. Post-COVID-19 Rehabilitation: Perception and Experience of Austrian Physiotherapists and Physiotherapy Students. *Int J Environ Res Public Health* 2021;**18**.
189. Benzarti W, Toulgui E, Prefaut C, Chamari K, Ben Saad H. General practitioners should provide the cardiorespiratory rehabilitation' 'minimum advice' for long COVID-19 patients. *Libyan J Med* 2022;**17**:2009101.
190. Calabrese M, Garofano M, Palumbo R, Di Pietro P, Izzo C, Damato A, Venturini E, Iesu S, Virtuoso N, Strianese A, Ciccarelli M, Galasso G, Vecchione C. Exercise Training and Cardiac Rehabilitation in COVID-19 Patients with Cardiovascular Complications: State of Art. *Life (Basel)* 2021;**11**.
191. Ayoubkhani D, Bosworth M, King S. Self-reported long COVID after two doses of a coronavirus (COVID-19) vaccine in the UK: 26 January 2022. 2022.
192. Kuodi P, Gorelik Y, Zayyad H, Wertheim O, Wiegler KB, Jabal KA, Dror AA, Nazzal S, Glikman D, Edelstein M. Association between vaccination status and reported incidence of post-acute COVID-19 symptoms in Israel: a cross-sectional study of patients tested between March 2020 and November 2021. *medRxiv* 2022:2022.2001.2005.22268800.
193. Arnold DT, Milne A, Samms E, Stadon L, Maskell NA, Hamilton FW. Symptoms After COVID-19 Vaccination in Patients With Persistent Symptoms After Acute Infection: A Case Series. *Ann Intern Med* 2021;**174**:1334-1336.
194. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV, Condition WHOCCDWGoP-C-. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis* 2022;**22**:e102-e107.
195. Network TCHA. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). 2020.

196. WHO. Multisystem inflammatory syndrome in children and adolescents with COVID-19.
197. Ram-Mohan N, Kim D, Rogers AJ, Blish CA, Nadeau KC, Blomkalns AL, Yang S. Association Between SARS-CoV-2 RNAemia and Post-Acute Sequelae of COVID-19. *medRxiv* 2021.
198. Ram-Mohan N, Kim D, Rogers AJ, Blish CA, Nadeau KC, Blomkalns AL, Yang S. Association Between SARS-CoV-2 RNAemia and Postacute Sequelae of COVID-19. *Open Forum Infect Dis* 2022;**9**:ofab646.
199. Arnold DT, Hamilton FW, Milne A, Morley AJ, Viner J, Attwood M, Noel A, Gunning S, Hatrick J, Hamilton S, Elvers KT, Hyams C, Bibby A, Moran E, Adamali HI, Dodd JW, Maskell NA, Barratt SL. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax* 2021;**76**:399-401.
200. de Graaf MA, Antoni ML, Ter Kuile MM, Arbous MS, Duinisveld AJF, Feltkamp MCW, Groeneveld GH, Hinnen SCH, Janssen VR, Lijfering WM, Omara S, Postmus PE, Ramai SRS, Rius-Ottenheim N, Schalij MJ, Schiemanck SK, Smid L, Stoger JL, Visser LG, de Vries JJC, Wijngaarden MA, Geelhoed JJM, Roukens AHE. Short-term outpatient follow-up of COVID-19 patients: A multidisciplinary approach. *EClinicalMedicine* 2021;**32**:100731.
201. Carfi A, Bernabei R, Landi F, Gemelli Against C-P-ACSG. Persistent Symptoms in Patients After Acute COVID-19. *JAMA* 2020;**324**:603-605.
202. Carvalho-Schneider C, Laurent E, Lemaignen A, Beaufils E, Bourbao-Tournois C, Laribi S, Flament T, Ferreira-Maldent N, Bruyere F, Stefic K, Gaudy-Graffin C, Grammatico-Guillon L, Bernard L. Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect* 2021;**27**:258-263.
203. Xiong Q, Xu M, Li J, Liu Y, Zhang J, Xu Y, Dong W. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. *Clin Microbiol Infect* 2021;**27**:89-95.
204. Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, Doucet L, Berkani S, Oliosi E, Mallart E, Corre F, Zarrouk V, Moyer JD, Galy A, Honsel V, Fantin B, Nguyen Y. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect* 2020;**81**:e4-e6.
205. Shimoni O, Korenfeld R, Goland S, Meledin V, Haberman D, George J, Shimoni S. Subclinical Myocardial Dysfunction in Patients Recovered from COVID-19 Disease: Correlation with Exercise Capacity. *Biology (Basel)* 2021;**10**.
206. Kersten J, Baumhardt M, Hartveg P, Hoyo L, Hüll E, Imhof A, Kropf-Sanchen C, Nita N, Mörike J, Rattka M, Andreß S, Scharnbeck D, Schmidtke-Schrezenmeier G, Tadic M, Wolf A, Rottbauer W, Buckert D. Long COVID: Distinction between Organ Damage and Deconditioning. *J Clin Med* 2021;**10**.
207. Charfeddine S, Ibn Hadj Amor H, Jdidi J, Torjmen S, Kraiem S, Hammami R, Bahloul A, Kallel N, Moussa N, Touil I, Ghrab A, Elghoul J, Meddeb Z, Thabet Y, Kammoun S, Bouslama K, Milouchi S, Abdessalem S, Abid L. Long COVID 19 Syndrome: Is It Related to Microcirculation and Endothelial Dysfunction? Insights From TUN-EndCOV Study. *Front Cardiovasc Med* 2021;**8**:745758.
208. Pelà G, Goldoni M, Cavalli C, Perrino F, Tagliaferri S, Frizzelli A, Mori PA, Majori M, Aiello M, Sverzellati N, Corradi M, Chetta A. Long-Term Cardiac Sequelae in Patients Referred into a Diagnostic Post-COVID-19 Pathway: The Different Impacts on the Right and Left Ventricles. *Diagnostics (Basel)* 2021;**11**.
209. Goertz YMJ, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FVC, Houben-Wilke S, Burtin C, Posthuma R, Franssen FME, van Loon N, Hajian B, Spies Y, Vijlbrief H, van 't Hul AJ, Janssen DJA, Spruit MA. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? *ERJ Open Res* 2020;**6**.

210. Havervall S, Rosell A, Phillipson M, Mangsbo SM, Nilsson P, Hober S, Thalin C. Symptoms and Functional Impairment Assessed 8 Months After Mild COVID-19 Among Health Care Workers. *JAMA* 2021;**325**:2015-2016.
211. Ingul CB, Grimsmo J, Mecinaj A, Trebinjac D, Berger Nossen M, Andrup S, Grenne B, Dalen H, Einvik G, Stavem K, Follestad T, Josefsen T, Omland T, Jensen T. Cardiac Dysfunction and Arrhythmias 3 Months After Hospitalization for COVID-19. *J Am Heart Assoc* 2022;**11**:e023473.
212. Aranyó J, Bazan V, Lladós G, Dominguez MJ, Bisbal F, Massanella M, Sarrias A, Adeliño R, Riverola A, Paredes R, Clotet B, Bayés-Genís A, Mateu L, Villuendas R. Inappropriate sinus tachycardia in post-COVID-19 syndrome. *Sci Rep* 2022;**12**:298.
213. Shah B, Kunal S, Bansal A, Jain J, Poundrik S, Shetty MK, Batra V, Chaturvedi V, Yusuf J, Mukhopadhyay S, Tyagi S, Meenahalli Palleda G, Gupta A, Gupta MD. Heart rate variability as a marker of cardiovascular dysautonomia in post-COVID-19 syndrome using artificial intelligence. *Indian Pacing Electrophysiol J* 2022;**22**:70-76.
214. Chopra V, Flanders SA, O'Malley M, Malani AN, Prescott HC. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. *Ann Intern Med* 2021;**174**:576-578.
215. Daher A, Balfanz P, Cornelissen C, Muller A, Bergs I, Marx N, Muller-Wieland D, Hartmann B, Dreher M, Muller T. Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae. *Respir Med* 2020;**174**:106197.
216. Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, Walshaw C, Kemp S, Corrado J, Singh R, Collins T, O'Connor RJ, Sivan M. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol* 2021;**93**:1013-1022.
217. Buttery S, Philip KEJ, Williams P, Fallas A, West B, Cumella A, Cheung C, Walker S, Quint JK, Polkey MI, Hopkinson NS. Patient symptoms and experience following COVID-19: results from a UK-wide survey. *BMJ Open Respir Res* 2021;**8**.
218. Sigfrid L, Drake TM, Pauley E, Jesudason EC, Olliaro P, Lim WS, Gillesen A, Berry C, Lowe DJ, McPeake J, Lone N, Munblit D, Cevik M, Casey A, Bannister P, Russell CD, Goodwin L, Ho A, Turtle L, O'Hara ME, Hastie C, Donohue C, Spencer RG, Donegan C, Gummery A, Harrison J, Hardwick HE, Hastie CE, Carson G, Merson L, Baillie JK, Openshaw P, Harrison EM, Docherty AB, Semple MG, Scott JT, investigators IC. Long Covid in adults discharged from UK hospitals after Covid-19: A prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol. *Lancet Reg Health Eur* 2021;**8**:100186.
219. Kerget B, Çelik E, Kerget F, Aksakal A, Uçar EY, Araz Ö, Akgün M. Evaluation of 3-month follow-up of patients with postacute COVID-19 syndrome. *J Med Virol* 2022;**94**:2026-2034.
220. Duggal P, Penson T, Manley HN, Vergara C, Munday RM, Duchen D, Linton EA, Zurn A, Keruly JC, Mehta SH, Thomas DL. Post-sequelae symptoms and comorbidities after COVID-19. *J Med Virol* 2022;**94**:2060-2066.
221. Munblit D, Bobkova P, Spiridonova E, Shikhaleva A, Gamirova A, Blyuss O, Nekliudov N, Bugaeva P, Andreeva M, DunnGalvin A, Comberiati P, Apfelbacher C, Genuneit J, Avdeev S, Kapustina V, Guekht A, Fomin V, Svistunov AA, Timashev P, Subbot VS, Royuk VV, Drake TM, Hanson SW, Merson L, Carson G, Horby P, Sigfrid L, Scott JT, Semple MG, Warner JO, Vos T, Olliaro P, Glybochko P, Butnaru D. Incidence and risk factors for persistent symptoms in adults previously hospitalized for COVID-19. *Clin Exp Allergy* 2021;**51**:1107-1120.
222. Luchian ML, Motoc A, Lochy S, Magne J, Belsack D, De Mey J, Roosens B, Van den Bussche K, Boeckstaens S, Chameleva H, Geers J, Houard L, De Potter T, Allard S, Weytjens C, Droogmans S, Cosyns B. Subclinical Myocardial Dysfunction in Patients with Persistent Dyspnea One Year after COVID-19. *Diagnostics (Basel)* 2021;**12**.
223. Dorelli G, Braggio M, Gabbiani D, Busti F, Caminati M, Senna G, Girelli D, Laveneziana P, Ferrari M, Sartori G, Dalle Carbonare L, Crisafulli E, On Behalf Of The Respicovid Study I. Importance of

Cardiopulmonary Exercise Testing amongst Subjects Recovering from COVID-19. *Diagnostics (Basel)* 2021;**11**.
224. Ladlow P, O'Sullivan O, Houston A, Barker-Davies R, May S, Mills D, Dewson D, Chamley R, Naylor J, Mulae J, Bennett AN, Nicol ED, Holdsworth DA. Dysautonomia following COVID-19 is not associated with subjective limitations or symptoms but is associated with objective functional limitations. *Heart Rhythm* 2022;**19**:613-620.
225. Buoite Stella A, Furlanis G, Frezza NA, Valentinotti R, Ajcevic M, Manganotti P. Autonomic dysfunction in post-COVID patients with and witfhout neurological symptoms: a prospective multidomain observational study. *J Neurol* 2021.
226. Shouman K, Vanichkachorn G, Cheshire WP, Suarez MD, Shelly S, Lamotte GJ, Sandroni P, Benarroch EE, Berini SE, Cutsforth-Gregory JK, Coon EA, Mauermann ML, Low PA, Singer W. Autonomic dysfunction following COVID-19 infection: an early experience. *Clin Auton Res* 2021;**31**:385-394.
227. Bisaccia G, Ricci F, Recce V, Serio A, Iannetti G, Chahal AA, Ståhlberg M, Khanji MY, Fedorowski A, Gallina S. Post-Acute Sequelae of COVID-19 and Cardiovascular Autonomic Dysfunction: What Do We Know? *J Cardiovasc Dev Dis* 2021;**8**.
228. Breitbart P, Koch A, Schmidt M, Magedanz A, Lindhoff-Last E, Voigtlander T, Schmermund A, Mehta RH, Eggebrecht H. Clinical and cardiac magnetic resonance findings in post-COVID patients referred for suspected myocarditis. *Clin Res Cardiol* 2021.
229. Dennis A, Wamil M, Alberts J, Oben J, Cuthbertson DJ, Wootton D, Crooks M, Gabbay M, Brady M, Hishmeh L, Attree E, Heightman M, Banerjee R, Banerjee A, investigators Cs. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open* 2021;**11**:e048391.
230. Patel P, Thompson PD. Diagnosing COVID-19 myocarditis in athletes using cMRI. *Trends Cardiovasc Med* 2022;**32**:146-150.
231. Clark DE, Dendy JM, Li DL, Crum K, Dixon D, George-Durrett K, Parikh AP, Wassenaar JW, Hughes SG, Soslow JH. Cardiovascular magnetic resonance evaluation of soldiers after recovery from symptomatic SARS-CoV-2 infection: a case-control study of cardiovascular post-acute sequelae of SARS-CoV-2 infection (CV PASC). *J Cardiovasc Magn Reson* 2021;**23**:106.
232. Malek LA, Marczak M, Milosz-Wieczorek B, Konopka M, Braksator W, Drygas W, Krzywanski J. Cardiac involvement in consecutive elite athletes recovered from Covid-19: A magnetic resonance study. *J Magn Reson Imaging* 2021;**53**:1723-1729.
233. Petersen EL, Goßling A, Adam G, Aepfelbacher M, Behrendt CA, Cavus E, Cheng B, Fischer N, Gallinat J, Kühn S, Gerloff C, Koch-Gromus U, Härter M, Hanning U, Huber TB, Kluge S, Knobloch JK, Kuta P, Schmidt-Lauber C, Lütgehetmann M, Magnussen C, Mayer C, Muellerleile K, Münch J, Nägele FL, Petersen M, Renné T, Riedl KA, Rimmele DL, Schäfer I, Schulz H, Tahir E, Waschki B, Wenzel JP, Zeller T, Ziegler A, Thomalla G, Twerenbold R, Blankenberg S. Multi-organ assessment in mainly non-hospitalized individuals after SARS-CoV-2 infection: The Hamburg City Health Study COVID programme. *Eur Heart J* 2022;**43**:1124-1137.
234. Tudoran C, Tudoran M, Cut TG, Lazureanu VE, Oancea C, Marinescu AR, Pescariu SA, Pop GN, Bende F. Evolution of Echocardiographic Abnormalities Identified in Previously Healthy Individuals Recovering from COVID-19. *J Pers Med* 2022;**12**.
235. Cassar MP, Tunnicliffe EM, Petousi N, Lewandowski AJ, Xie C, Mahmod M, Samat AHA, Evans RA, Brightling CE, Ho LP, Piechnik SK, Talbot NP, Holdsworth D, Ferreira VM, Neubauer S, Raman B. Symptom Persistence Despite Improvement in Cardiopulmonary Health - Insights from longitudinal CMR, CPET and lung function testing post-COVID-19. *EClinicalMedicine* 2021;**41**:101159.
236. Lakatos BK, Tokodi M, Fábián A, Ladányi Z, Vágó H, Szabó L, Sydó N, Csulak E, Kiss O, Babity M, Kiss AR, Gregor Z, Szűcs A, Merkely B, Kovács A. Frequent Constriction-Like Echocardiographic

Findings in Elite Athletes Following Mild COVID-19: A Propensity Score-Matched Analysis. *Front Cardiovasc Med* 2021;**8**:760651.
237. Ambrosino P, Calcaterra I, Molino A, Moretta P, Lupoli R, Spedicato GA, Papa A, Motta A, Maniscalco M, Di Minno MND. Persistent Endothelial Dysfunction in Post-Acute COVID-19 Syndrome: A Case-Control Study. *Biomedicines* 2021;**9**.
238. Mejia-Renteria H, Travieso A, Sagir A, Martínez-Gómez E, Carrascosa-Granada A, Toya T, Núñez-Gil IJ, Estrada V, Lerman A, Escaned J. In-vivo evidence of systemic endothelial vascular dysfunction in COVID-19. *Int J Cardiol* 2021;**345**:153-155.
239. Drakos S, Chatzantonis G, Bietenbeck M, Evers G, Schulze AB, Mohr M, Fonfara H, Meier C, Yilmaz A. A cardiovascular magnetic resonance imaging-based pilot study to assess coronary microvascular disease in COVID-19 patients. *Sci Rep* 2021;**11**:15667.
240. Sonnweber T, Sahanic S, Pizzini A, Luger A, Schwabl C, Sonnweber B, Kurz K, Koppelstatter S, Haschka D, Petzer V, Boehm A, Aichner M, Tymoszuk P, Lener D, Theurl M, Lorsbach-Kohler A, Tancevski A, Schapfl A, Schaber M, Hilbe R, Nairz M, Puchner B, Huttenberger D, Tschurtschenthaler C, Asshoff M, Peer A, Hartig F, Bellmann R, Joannidis M, Gollmann-Tepekoylu C, Holfeld J, Feuchtner G, Egger A, Hoermann G, Schroll A, Fritsche G, Wildner S, Bellmann-Weiler R, Kirchmair R, Helbok R, Prosch H, Rieder D, Trajanoski Z, Kronenberg F, Woll E, Weiss G, Widmann G, Loffler-Ragg J, Tancevski I. Cardiopulmonary recovery after COVID-19: an observational prospective multicentre trial. *Eur Respir J* 2021;**57**.
241. Mohiuddin Chowdhury ATM, Karim MR, Ali MA, Islam J, Li Y, He S. Clinical Characteristics and the Long-Term Post-recovery Manifestations of the COVID-19 Patients-A Prospective Multicenter Cross-Sectional Study. *Front Med (Lausanne)* 2021;**8**:663670.
242. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, Villapol S. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. *medRxiv* 2021.
243. Chioh FW, Fong SW, Young BE, Wu KX, Siau A, Krishnan S, Chan YH, Carissimo G, Teo LL, Gao F, Tan RS, Zhong L, Koh AS, Tan SY, Tambyah PA, Renia L, Ng LF, Lye DC, Cheung C. Convalescent COVID-19 patients are susceptible to endothelial dysfunction due to persistent immune activation. *Elife* 2021;**10**.
244. Patel SK, Juno JA, Lee WS, Wragg KM, Hogarth PM, Kent SJ, Burrell LM. Plasma ACE2 activity is persistently elevated following SARS-CoV-2 infection: implications for COVID-19 pathogenesis and consequences. *Eur Respir J* 2021;**57**.
245. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, Xu Y, Tian Z. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol* 2020;**17**:533-535.
246. Zheng HY, Zhang M, Yang CX, Zhang N, Wang XC, Yang XP, Dong XQ, Zheng YT. Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. *Cell Mol Immunol* 2020;**17**:541-543.
247. Paul BD, Lemle MD, Komaroff AL, Snyder SH. Redox imbalance links COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome. *Proc Natl Acad Sci U S A* 2021;**118**.
248. Vollenberg R, Tepasse PR, Ochs K, Floer M, Strauss M, Rennebaum F, Kabar I, Rovas A, Nowacki T. Indications of Persistent Glycocalyx Damage in Convalescent COVID-19 Patients: A Prospective Multicenter Study and Hypothesis. *Viruses* 2021;**13**.
249. Heerdt PM, Shelley B, Singh I. Impaired systemic oxygen extraction long after mild COVID-19: potential perioperative implications. *Br J Anaesth* 2022;**128**:e246-e249.
250. Kiatkittikul P, Promteangtrong C, Kunawudhi A, Siripongsatian D, Siripongboonsitti T, Ruckpanich P, Thongdonpua S, Jantarato A, Piboonvorawong C, Fonghoi N, Chotipanich C. Abnormality Pattern of F-18 FDG PET Whole Body with Functional MRI Brain in Post-Acute COVID-19. *Nucl Med Mol Imaging* 2022:1-13.

Figure 1

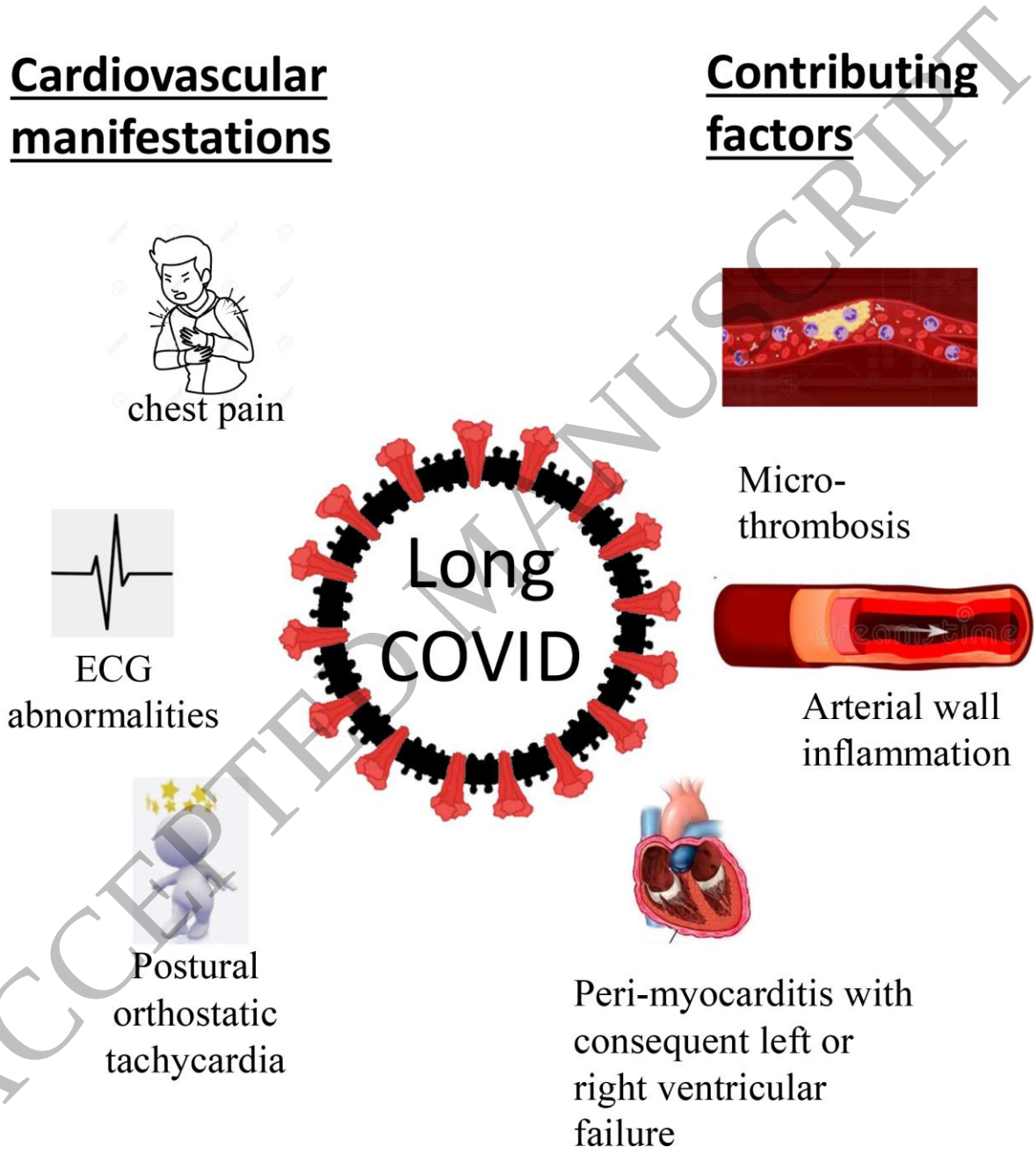


Figure 1
159x196 mm (.29 x DPI)

Figure 2

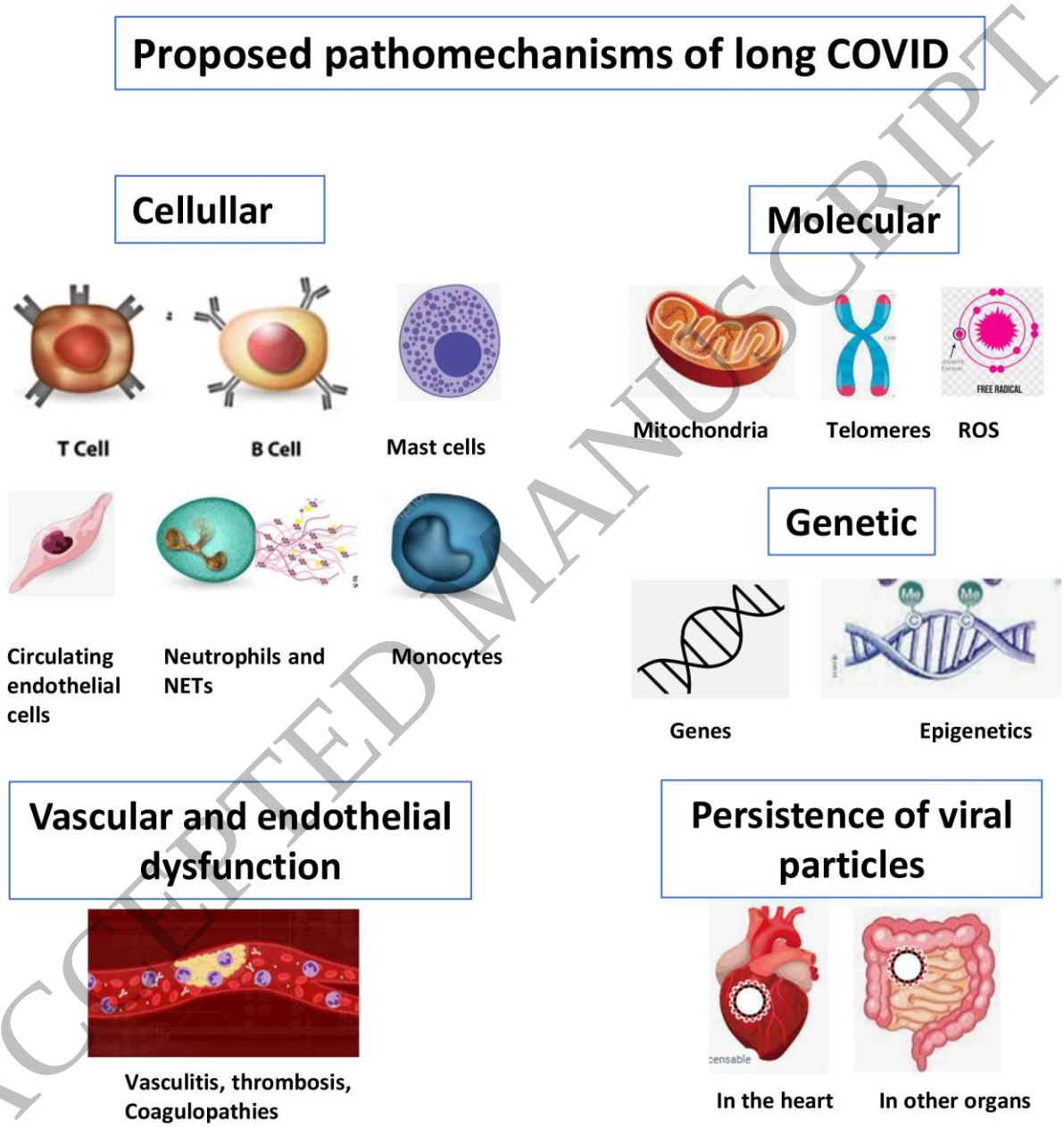


Figure 2
159x190 mm (.29 x DPI)