Long-COVID

Post-Acute Sequelae of COVID (PASC)

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EXECUTIVE SUMMARY

1. Definition of a New Disease:

At the start of the COVID-19 pandemic, medical concern was focused on prevention and treatment of the acute effects of this novel pneumonia. It was soon apparent that this was a multi-organ infection, not just respiratory. Persons complaining of ongoing symptoms, like tiredness, months after infection were a low priority for most medical practices. Now, several years into the ongoing pandemic, there is acceptance of Long-COVID as a separate, but related, entity with its own ICD-10 code, but the incidence, prevalence, symptomatology, and medical management remain uncertain. Concern about the long-term effects of COVID-19 led the US government to establish a new office, the Office of Long COVID Research and Practice, under Admiral Rachel Levine (Abbasi 2022). Long-COVID was defined as direct and indirect long-term effects of the SARS-CoV-2 infection (Levine 2022). Long-COVID consists of some 200 signs and symptoms and 50 conditions (Levine 2022), so the definition is flexible and defined loosely by time after the initial infection. While the timeframe of onset to be called Long-COVID varies, the UK guidance defined acute COVID-19 as lasting up to 4 weeks, ongoing COVID-19 as lasting 4 to 12 weeks and Long-COVID as signs and symptoms beyond 12 weeks (NICE, RCGP, and SIGN 2020).

2. Risk Factors:

Risk factors for Long-COVID include female gender, high age, previous morbidity, prior hospitalization for COVID-19, and a requirement for ventilation. While subjects with mild symptoms can get Long-COVID, those with severe infections are at higher risk.

3. Pathophysiology:

Multiorgan viral invasion and immune system overreactions may play a role in Long-COVID. As in COVID-19, cytokines such as IL-6 are increased in many patients (X. Chen et al. 2020), although the extent of the cytokine storm in the pathology of infections remains unclear. Only in severe disease would one expect circulating cytokine levels to be elevated while local levels could be high and influencing local cellular damage. Cellular injury may lead to vascular damage and thrombi formation in the microcirculation in affected organs. Circulating microthrombi from e.g., the heart may contribute to heterogenous symptoms of Long-COVID. Our knowledge is limited, as deaths and autopsy studies are rare in the post-acute phase. Involvement of the olfactory tract may lead to loss of taste and smell and may also be a pathway for viral entry into the CNS. It is also possible that inflammatory changes of the Blood Brain Barrier may open up tight junctions and facilitate viral entry into the CNS and lead to inflammatory changes affecting central functions.

4. Natural Course and Clinical Signs and Symptoms:

Signs and symptoms may be general or reflect the extent of organ involvement. Severity and incidence or prevalence may reflect type of study population ((hospitalization needed or not), length of follow up, type of dominant viral variant, and the design of study (pro- or retro-spective), and data collection (self- or investigator reported). To evaluate symptoms and signs during natural course, the summary below focuses on studies with 1-2 years follow-up.

Pre-Omicron Surge - Hospitalized Discharged Patients:

The largest prospective longitudinal study is from UK (2320 subjects, (Evans et al. 2022)). At 12 months follow-up after discharge 50-60% of subjects had fatigue, muscle ache, physical slowing

down, poor sleep, breathlessness, and 40-50% had joint pain / swelling, slowing down, and short term memory loss. Full recovery was noted in only 25-30% at 5 and 12 months.

Of note, patients with moderate or severe symptoms had increased level of IL-6 and other immune mediators compared to patients with mild symptoms. This supports the hypothesis that hyper-inflammation in the acute phase may lead to dysregulated immunity and multi organ dysfunction.

PRE-OMICRON SURGE - SYMPTOM PROFILES BASED SELF/REPORTED SYMPTOMS:

A large general population study in UK (n= 336,752, (Canas et al. 2022)) used a National Registry to identify COVID positive patients and smart phones to identify subjects with new symptoms lasting longer than 28 days and analyzed those with symptoms lasting >12 weeks, thus meeting the criteria for Long-COVID. They reported clusters of symptoms for different variants and vaccination status. Four symptom clusters were described (Cardio-respiratory; Neurological; Systemic-inflammatory; Abdominal).

There appeared to be a heterogenous profile for post COVID syndrome based on the type of variant (Delta or Omicron), with the most severe and debilitating cluster of symptoms reported for patients considered to have systemic / multi-organ inflammatory disease.

OMICRON SURGE:

A prospective longitudinal study in more than 97,000 COVID cases in the general population from the first 6 months of 2022 showed that the rate of Long COVID was only 5% among subjects with prior Omicron infection compared to 11% in Delta cases (Antonelli et al. 2022).

NEUROLOGICAL & PSYCHIATRIC SYMPTOMS – NATURAL COURSE DURING 2 - YEAR FOLLOW UP:

In the Prospective study in UK (Evans et al. 2022) with 1 year follow up of 2320 previously hospitalized patients, the rate of slowing down of thinking and short term memory loss was about 45%.

A similar prospective study from Wuhan, China (n= 3233; (Liu et al. 2022b)) found at 1 year follow up using questionnaires, the incidence of cognitive impairment was higher with no difference for early or late onset or progressive disease. Severe COVID-19 resulted in a higher incidence of cognitive impairment.

The largest study so far reported was a retrospective review of healthcare record from an international network (TriNetx including about 89 million patients from hospitals, outpatient or private clinics in US, UK, Australia, Spain Bulgaria, India, Malaysia and Taiwan. Close to 1.3 million patients (including children, adults and elderly) with a previous diagnosis of COVID-19 during a two year period January 20, 2020 to April 13, 2022 were selected and matched 1:1 with patients with another respiratory disease. For the overall population, common psychiatric symptoms such as mood and anxiety disorders. after an initial increase, returned to base line after 1-2 months. By contrast, cognitive deficit (known as “brain fog”), dementia, psychotic disorders, and epilepsy/ seizures kept increasing during the 2-year follow up (Taquet et al. 2022).

A prospective study (Becker JH et al, JAMA 2021) using cognitive testing in 740 patients reported cognitive impairment at average 7.6 months follow up where most prominent findings were reduced memory encoding and memory recall in 23-24% in the overall population and 37-39% in previously hospitalized patients. There was also evidence of reduced executive functioning in 13% and 27% in the two groups, respectively (Becker et al. 2021).

PEDIATRIC PATIENTS – SIGNS AND SYMPTOMS

In children (n = 185,748) there was no apparent risk for mood or anxiety disorder, whereas they had an increased risk for cognitive deficit, insomnia, intracranial hemorrhage, ischemic stroke, nerve, nerve root /plexus disorders and psychotic disorders. As well as epilepsy/seizure disorders. However, by contrast to adults, cognitive symptoms had a finite risk horizon (75 days) and time to equal incidence compared to control group (491 days).

CDC used medical reports to assess 9 potential post-COVID signs and symptoms (symptoms) and 15 potential post-COVID conditions among 781,419 U.S. children and adolescents aged 0–17 years with COVID-19 compared with 2,344,257 U.S. children and adolescents without recognized COVID-19 during March 1, 2020–January 31, 2022 (Kompaniyets et al. 2022).

- The highest hazard ratios were recorded for acute pulmonary embolism (aHR = 2.01), myocarditis and cardiomyopathy (1.99), venous thromboembolic event (1.87), acute and unspecified renal failure (1.32), and type 1 diabetes (1.23), all of which were rare or uncommon in this study population.
- Compared to subjects without COVID-19, patients with COVID-19 were less likely to experience respiratory signs and symptoms, symptoms of mental conditions, muscle disorders, neurological conditions, anxiety and fear-related disorders, mood disorders, and sleeping disorders, possibly related to how subjects without COVID were selected (visit to healthcare provider for treatment). Differences were noted among age groups of children for COVID subjects vs. COVID-negative:
    - Children aged 2–4 years had higher rates of asthma diagnosis (1.12) and respiratory signs and symptoms (1.07) after COVID-19.
    - Among children aged 5–11 years, the highest aHRs for patients with COVID-19 were for myocarditis and cardiomyopathy (2.84), venous thromboembolic event (2.69), and acute and unspecified renal failure (1.38).
    - Among patients aged 12–17 years, the highest aHRs for those with COVID-19 were for acute pulmonary embolism (2.03), myocarditis and cardiomyopathy (1.66), and venous thromboembolic event (1.52).

5. INCIDENCE AND PREVALENCE:

Although Omicron variants are less likely to cause Long-COVID, the incidence and prevalence may still be high or increased as these variants spread more rapidly and thus increase the number of infected persons in the general population.

6. SOCIOECONOMIC IMPACT:

In May 2022 CDC estimated a cumulative number of 81 million COVID cases and 995,000 deaths. The tentative Guidelines are being drafted by Health authorities and preliminary Guidelines have been issued in UK number of Long COVID is roughly 9.6 million or 10 times higher than the number of deaths, as only about 25% of the patients recovered at 12 months follow up. Thus, there may be long term impact on health, which may increase cost of health care and reduce hours worked and income earned.

7. MANAGEMENT OF LONG-COVID:

Preliminary Guidelines have been issued in UK and are being considered by other Health Authorities. To date no antiviral or immunomodulatory drug has proven effective for the treatment of Long-COVID in clinical trials. The presence of long-lasting systemic inflammation in some patients with long COVID would suggest that anti-inflammatory agents might have potential not only during the acute phase of infection, but also during the post-acute phase.

A clinical trial of the efficacy of vaccination in the treatment of Long-COVID symptoms was proposed and designed by clinicians. A case-control study of 1.2 million users of a COVID symptom tracker app in the UK showed that there were lower odds of symptoms lasting ≥28 days in individuals who had received 2 vaccine doses (OR 0.51 [0.32–0.82]; p=0.0060)—i.e., the risk of developing Long-COVID was reduced by around 50% in those who were double vaccinated.

The US government allocated $1.2 B for Long COVID research and support in the form of a 40,000 patient RECOVER study conducted at 30 centers in the US to define the long term effects of COVID. The Recover study aims to complete enrollment of more than 17,000 adults by September and 20,000 children by the end of the year 2022; as of 8 September 2022, 8225 adults were enrolled. The NIH has issued a Research Opportunity Announcement (ROA) for Clinical Trials for the Prevention and/or Treatment of Post-Acute Sequelae of SARS-CoV-2 infection (PASC) as part of the NIH RECOVER initiative in the form of an emergency competitive revision to existing NIH awards. Considering the magnitude and emergency of the problem, it seems important to make additional funding available for trials evaluating new treatment paradigms to prevent long-term potentially debilitating effects of Long COVID.

BACKGROUND

START OF A PANDEMIC

From a few cases of an unexplained pneumonia in Wuhan China in late 2019, the SARS-CoV-2 virus circumnavigated the globe and was quickly declared a pandemic. Early on in the COVID-19 pandemic, it was thought that the virus would wreak havoc for some months, a vaccine would become available, and herd immunity would be established in the US. Several months later, the first vaccines became available, but the pandemic did not disappear and vaccine efficacy faded, while anti-vaccine efforts increased in some areas of the US. Other medications including some antivirals were developed, some with little or no demonstrated efficacy, yet backed by internet proponents of questionable merit. Slowly, the approved vaccines were distributed to Western and developed countries and then slowly to additional poorer nations, although the distribution was uneven and flawed.

SARS-CoV-2 is the third coronavirus that has caused severe disease in humans to spread globally in the past 2 decades. The first was severe acute respiratory syndrome (SARS), which was thought to originate in Foshan, China, and resulted in the 2002-2003 SARS-CoV pandemic and the second was Middle East respiratory syndrome (MERS),which originated from the Arabian peninsula in 2012 (Wiersinga et al. 2020). SARS-CoV-2, or the novel coronavirus, has a diameter of 60-140 nm and distinctive spikes, ranging from 9 nm to 12 nm, giving the virions the appearance of a solar corona. The spikes are important for allowing the virus entry into cells. The genomic structure of the 29.3 kilobase novel coronavirus gene and the domain structure of the 1273-amino acid spike glycoprotein S were described (Pillay 2020). It consists of the envelope protein gene, a membrane protein gene, a nucleocapsid protein gene, a receptor-binding motif (RBM), an RNA-dependent RNA polymerase, and a spike (S) glycoprotein gene.

PATHOPHYSIOLOGY OF COVID-19

COVID-19 Not Just a Pneumonia

Since COVID-19 was initially identified as an unusual type of pneumonia. it was not unexpected that the early pathology reports focused on the respiratory tract. The primary mechanism of infection by the novel coronavirus appears to be respiratory, as the virus likely is spread through airborne methods (Klompas, Baker, and Rhee 2020; Wiersinga et al. 2020). The virus also was shown to remain viable on surfaces for days (Suman et al. 2020; van Doremalen et al. 2020) and might spread by this mechanism after touching the face with contaminated hands. As newer variants of the virus arose and spread globally, characteristics of the virus in addition to infectivity and pathogenesis also changed. COVID-19 was initially identified as a type of severe pneumonia that easily spread among individuals. However, COVID-19 has multiple extrapulmonary clinical manifestations that may be related to COVID-19-associated widespread vascular pathology. Some of these manifestations are common to all critical illness states (e.g., renal dysfunction) or are reminiscent of the complications of other viral pneumonias (Osuchowski et al. 2021). However, COVID-19 includes some complications that seem to be specific to SARS-CoV-2 infection. The pathology of acute and chronic COVID-19 and the extent of involvement of lungs and other organ systems are becoming clearer, although the presentation can be heterogenous, as discussed below. Severe disease caused by SARS-CoV-2 has clinical and pathophysiological features unlike those of respiratory failure due to other causes, and acute disease remains a priority for research as COVID-19-associated morbidity and mortality continue to pose a huge burden globally (Editor

2021). Post-acute symptoms might reflect immune-mediated or inflammatory changes commonly associated with acute infection or might be specific to SARS-CoV-2 (Editor 2021).

Phases of SARS-CoV-2 Infection

In addition to an acute phase, at least 2 other periods of illness appear to be temporally associated with SARS-CoV-2 infection: a rare post-acute hyperinflammatory illness and late inflammatory and virological sequelae (Datta, Talwar, and Lee 2020). These 3 illness periods define the temporal course of SARS-CoV-2 infection at the population level and also capture distinct phases of host-viral interaction. However, any temporal definition of phases is artificial and not all patients will fit neatly into a phase. Based on an international survey of subjects with COVID-19, it was decided that the acute phase of infection could be differentiated from the post-acute phase which began with symptoms after 3 weeks from initial onset and a chronic phase with symptoms extending beyond 12 weeks (del Rio, Collins, and Malani 2020). Symptoms in the acute phase are variable and even absent in some patients. The most commonly reported symptoms after acute COVID-19 are fatigue and dyspnea. Other common symptoms include joint pain and chest pain. In addition to these general symptoms, specific organ dysfunction has been reported, involving primarily the heart, lungs, kidneys, and brain. These likely are related to direct viral invasion of these organs. Two other phases of disease have been defined: chronic disease, seen only (or mostly) in immunosuppressed individuals, and long-COVID, as discussed below.

Blood Clotting Dysfunction and Microthrombi

Viral invasion and inflammation in multiple organs are likely to lead to microthrombi in the circulation, which can lead to ischemia if they block the microcirculation as well as additional organ damage. A recent hypothesis was presented that some of the array of symptoms of Long-COVID might be due to micro-clots circulating in the blood and affecting various tissues and organs (Willyard 2022). Patients typically are not dying of Long-COVID so autopsy findings are not available. However, thrombotic complications of SARS-CoV-2 infection were recognized early in the pandemic, when infected patients often presented with abnormal coagulation findings and acute macrovascular obstruction, and evidence of pulmonary microvascular thrombosis was identified on autopsy (Connors and Ridker 2022; McFadyen, Stevens, and Peter 2020). The main causes of death in COVID-19 were disseminated intravascular coagulation (DIC) and diffuse alveolar damage (W. Chen and Pan 2021). Microthrombosis is a prominent clinical feature of COVID-19, and 91.3% of dead patients had microthrombi (W. Chen and Pan 2021). In a review of 151 autopsies of patients who died of COVID-19, microthrombi were found in 91 cases in the lungs (73%), heart (11%), kidney (24%), and liver (16%) (Parra-Medina, Herrera, and Mejia 2021). Myocyte necrosis, primarily of the left ventricle, was found in 35% of 40 hearts of patients who died of COVID-19 (Pellegrini et al. 2021). Anticoagulation is a vital component of COVID-19 treatment protocols in hospitals. Several recent clinical trials that addressed the potential utility of aspirin or P2Y12 inhibitors among COVID-19 inpatients (Horby, Landray, and RECOVERY_Collaborative_Group 2022; Berger et al. 2022; Bradbury and Investigators 2022) as well as 1 trial of COVID-19 outpatients (Connors et al. 2021) do not support adding anti-platelet therapy to anticoagulation. Acute COVID-19-associated coagulopathy mimics other systemic coagulopathies that are regularly seen in severe infections, most notably disseminated intravascular coagulation (DIC) (Levi and Coppens 2021). Coagulation abnormalities in severe COVID-19 are associated with a high risk of thrombotic vascular complications, in particular venous thromboembolism (Di Minno et al. 2020; Obi et al. 2021). In severe COVID-19, fulminant activation of coagulation and consumption of clotting factors occur (Wiersinga et al. 2020).

Inflamed lung tissues and pulmonary endothelial cells may result in microthrombi formation and contribute to the high incidence of thrombotic complications, such as deep venous thrombosis, pulmonary embolism, and thrombotic arterial complications (e.g., limb ischemia, ischemic stroke, myocardial infarction) in critically ill patients (Wiersinga et al. 2020). Between 21% and 69% of critically ill patients with COVID-19 present with venous thromboembolism (Obi et al. 2021), far exceeding the 7.5% occurrence reported in surgical patients in the intensive care unit (Osuchowski et al. 2021).

LONG-COVID

A few months into the pandemic, some patients who had confirmed COVID-19 started to complain on social media about having symptoms months later, mostly chronic fatigue. These individuals, if and when they were tested, were negative for viral RNA. Since lockdowns were still the norm, these subjects often were not able to be examined by medical personnel, not that there was any treatment for their symptoms. Speculation was that these were malingerers unwilling to return to work in a changed world of masking, distancing, and isolation. The number of voices complaining about the persistent symptoms appeared to be increasing months later leading to additional interest in the lay press and finally in medical circles, which were still occupied with dealing with new primary infection patients and how best to manage COVID-19. After vaccines were released and other medications were approved for emergency use, more medical attention was focused on Long-COVID.

Perhaps the first term to be applied to subjects with persistent symptoms following COVID-19 infection was long haulers, although this nonmedical term stayed mostly in the press reports. As the pandemic wore on and increasing medical attention was directed to the syndrome, various other terms were applied in medical reports, including long-term effects of COVID-19 infection and Long-COVID. A recent attempt was PASC, which stood for post-acute sequelae of SARS-CoV-2, a term less likely to gain broad usage. PASC was recently clarified to refer to direct effects of the virus long after infection while Long-COVID was taken to include direct and indirect effects of the virus (Levine 2022). The concept of so-called long-COVID gained prominence in 2021, with both WHO and the US NIH requesting additional study of the phenomenon (see NIH NIAID on-line workshop: NIH October 29-30, 2020 (https://www.niaid.nih.gov/research/covid-19-sig-workshop). WHO used a Delphi method to develop a clinical definition of post-COVID-19 condition, their accepted terminology, as a range of symptoms occurring 3 or more months after probable or confirmed SARS-CoV-2 infection that last for at least 2 months, cannot be explained by an alternative diagnosis, generally have an impact on daily functioning, and may fluctuate or relapse over time (Ward et al. 2021). The absence of specific diagnostic criteria complicates the clinical picture. In the UK, NICE developed a clinical protocol for long COVID (Ward et al. 2021), but this was lacking practical guidance for general practitioners, so a Delphi study was initiated to come up with recommendations for recognition, diagnosis, and management of long COVID (Nurek et al. 2021). Characteristic symptoms include post-exertional symptom exacerbation, severe fatigue, breathlessness, tachycardia, cognitive deficits, and dysautonomia (Ward et al. 2021). Another definition used by the CDC is post-COVID-19 symptoms and conditions described as those occurring 30 days or more after infection (Kompaniyets et al. 2022). Others, especially early in the pandemic, referred to these as late inflammatory and virological sequelae, although often these included testing positive for SARS-CoV-2, whereas Long-COVID does not include positive testing.

Behind the Pathophysiology of Long-COVID

Three main theories are posed for the pathophysiology of Long-COVID: abnormal blood clotting, long-term survival of the virus in the body, and an immune system which had an abnormal response to the infection and has not recovered (Couzin-Frankel 2022b). It is quite likely that all three causes are involved. The virus could survive in some selected organs or perhaps in privileged sites like neurons.

Shared Features with Chronic Fatigue Syndrome

Long Covid shares certain features with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), another condition thought to follow an infection (Couzin-Frankel 2022a). Lower levels of cortisol were found in the blood of 99 subjects with Long-COVID compared with controls (Klein et al. 2022). Elevated humoral responses directed against SARS-CoV-2 were found among participants with Long-COVID, as well as in antibody responses directed against non-SARS-CoV-2 viral pathogens, particularly the Epstein-Barr virus, which is implicated in ME/CFS (Klein et al. 2022).

In one study of 37 subjects (30 females) with Long-COVID, a single molecule array assay detected either S1 protein subunit, spike protein, or N (nucleocapsid) protein in 65% of the patients with blood samples collected up to 5 months after a diagnosis of PASC (Swank et al. 2022). The most common was spike protein in 60% of PASC patients but in none of the 26 subjects who did not have PASC after COVID-19. N protein was detected in only 1 subject at numerous times, suggesting intact virus might not be present. Extracellular vesicles released from spike-expressing cells could carry spike in the blood and serve as decoys for anti-spike neutralizing antibodies, promoting viral infection (Troyer et al. 2021). While a number of circulating cytokines were assayed for (IFN-γ, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-22, and TNF-α), no differences were noted between groups and most levels remained in normal range (Swank et al. 2022).

Clinical Symptoms

Patient-reported symptoms of long-haul COVID-19 such as fatigue, insomnia, anxiety and depression, autonomic disturbances, cognitive difficulties, pain, and others are difficult to quantify and might be dismissed by some medical personnel. About 88% of patients employed prior to COVID-19 had returned to work by 1 year (L. Huang et al. 2021). The health status of COVID-19 survivors at 1 year was lower than that of matched controls (L. Huang et al. 2021). Other symptoms reported in reviews of Long-COVID are summarized in the table below and its references.

Several groups have conducted reviews of the literature (some limited to English language publications) on Long-COVID, as summarized in Table 1. These studies are difficult to integrate because of heterogeneous methods and the lack of a standard for denoting the many phenotypic manifestations or clusters. Patient-led studies are of particular importance for understanding the natural history of COVID-19, but integration is hampered because they often use different terms to describe the same symptom or condition (Deer et al. 2021). Reporting of conditions does not establish causality by COVID-19, as some symptoms could be due to post-intensive care syndrome, normal (or abnormal) aging, treatments for COVID-19, or other reasons.

Table 1: Reviews of Long-COVID

Author	Year	Number of Studies		Results
		Identified	Used	
(Groff et al. 2021)		2100 pubs and databases	57 pubs, 250,351 patients	54% of COVID-19 survivors reported ≥1 PASC at 1 mo, 55% at 2-5 mo, and 54% at ≥6 mo. Most prevalent were pulmonary sequelae, neurologic disorders, mental health disorders, functional mobility impairments, and general and constitutional symptoms. Other frequently reported symptoms included cardiac, dermatologic, digestive, and ear, nose, and throat disorders.
(Deer et al. 2021)	Apr 29, 2021	303	59 pubs (81 cohorts)	Across at least 10 cohorts, authors reported 31 unique clinical features; most common was fatigue (median 45.1%) and the least common was nausea (median 3.9%).
(Ahmad et al. 2021)	May 2021	249	20	persistent fatigue and dyspnea were seen in almost all of the studies. Other common symptoms included: shortness of breath, cough, joint pain, chest pain or tightness, headache, loss of smell/taste, sore throat, diarrhea, loss of memory, depression, anxiety. Cardio-respiratory, neurological, and mental issues were common, as were GI symptoms.
(Raveendran, Jayadevan, and Sashidharan 2021)	Pre-Mar 2021		44 refs	Fatigue, cough, chest tightness, breathlessness, palpitations, myalgia, and difficulty to focus are symptoms reported in long COVID. These could be related to organ damage, post viral syndrome, post-critical care syndrome and others.
(Michelen et al. 2021)	17 Mar 2021		39 studies	>60 physical & psychological symptoms with wide prevalence were reported, most commonly weakness (41%; 95% CI 25% to 59%), general malaise (33%; 15% to 57%), fatigue (31%; 24% to 39%), concentration impairment (26%; 21% to 32%) and breathlessness (25%; 18% to 34%). 37% (18% to 60%) of patients reported reduced quality of life; 26% (10/39) of studies presented evidence of reduced pulmonary function.
(Fainardi et al. 2022)	Dec 2021		14 studies	In children, long COVID might be a relevant clinical problem; prognosis usually good but some develop long-term symptoms with negative QOL issues. Issues were cardiovascular, respiratory, neurological, dermatological gastrointestinal, fatigue, fever, myalgia or arthralgia.

Recent clinical cohort studies of Long-COVID are summarized in Table 2. Not included is the ongoing NIH prospective cohort study, "Researching COVID to Enhance Recovery" (RECOVER) initiative in tens of thousands of patients funded with a 470 M USD grant from the American

Rescue Plan at 30 study centers administered by NYU (https://www.nih.gov/news-events/news-releases/nih-builds-large-nationwide-study-population-tens-thousands-support-research-long-term-effects-covid-19).

Table 2: Cohort Studies of Long-COVID

Study	Type	Time Period	Variant	Number of Subjects	Findings
US & UK					
US, (Cohen et al. 2022)	Medicare plan survey, historical control, age ≥65 years	1 Jan to 31 Dec 2020	Wild type	87,337 w/ Covid; 88,070 historical, 73,490 w/ viral LRI	32% Covid ≥1 symptom (vs. 21% controls); respiratory failure, fatigue, dementia worse Covid vs. viral LRI
US, (Sneller et al. 2022)	Longitudinal cohort	30 Jun 2020 to 1 July 2021		189 120 control	symptoms were reported by 55% of the COVID-19 cohort and 13% of control participants; no evidence of persistent viral infection, autoimmunity, or abnormal immune activation
US, UK, (Davis et al. 2020)	Online survey	6 Sep to 25 Nov 2020		3762	most frequent symptoms after month 6 were fatigue, post-exertional malaise, and cognitive dysfunction; 3 symptom clusters; 88% cognitive dysfunction or memory issues.
US, (Ali et al. 2022)	Neurologic clinic follow-up of non-hospitalized	May to Nov 2020 initial neuro clinic assessments; study completed 11-18 mo after infection		100 (50+ 50-)	no significant change in 1st and 6-9 mo follow-up evaluations: brain fog (81 vs. 71%), numbness/tingling (69 vs. 65%), headache (67 vs. 54%), dizziness (50 vs. 54%), blurred vision (34 vs. 44%), tinnitus (33 vs. 42%), and fatigue (87 vs. 81%). QOL remained lower.
UK, (Taquet et al. 2022)	Retrospective cohort	20 Jan 2020 to 13 Apr 2022		1,284,437	mood and anxiety disorders increase was transient; increased risk of psychotic disorder, cognitive deficit, dementia, and epilepsy or seizures persisted for 2 years
UK (Canas et al. 2022)	Prospective, longitudinal, phone app	Mar 20-Nov 20 Jan 21-Apr 21 May 21-Dec 21	Wild type Alpha Delta	336,652	distinct profiles of symptoms for post-COVID syndrome within and across variants: cardio-respiratory, neurological, & multi-organ
UK, US, other (Sudre et al. 2021)	Prospective app based	24 Mar 2020 to 2 Sep 2020		4,223,955 registered; 4182 cases of COVID	13.3% reported symptoms lasting ≥28 days, 4.5% for ≥8 weeks and 2.3% for ≥12 weeks

Study	Type	Time Period	Variant	Number of Subjects	Findings
US & UK (Contin.)					
UK (Thompson et al. 2022)	Survey of 10 UK longitudinal studies & databases			6907 self-reported, 1.1 million HER	any symptoms for 12+ weeks ranged from 7.8% and 17%
UK (Evans et al. 2022)	Prospective, longitudinal, cohort	7 Mar 2020 to 18 Apr 2021 discharge	Wild type Alpha Delta	2320 (807 assessed 5 & 12 mo)	Substantial sequelae at 1 year in majority of patients
CHINA					
China, (Liu et al. 2022a)	Cohort hospitalized	10 Feb to 10 Apr 2020	Wild type	3233 pts age ≥60	increase in risk of longitudinal cognitive decline at 1 yr
China (C. Huang et al. 2021; L. Huang et al. 2021)	Ambidirectional cohort; Prospective cohort 1-year follow-up	Jan 7 to 29 May 2020 discharge	Wild type	2469 initial, 1276 1 yr	At 6 mo, main issues were fatigue, muscle weakness, anxiety, depression, sleep issues; 49% ≥1 sequelae at 12 months; dyspnea @ 39%
EU					
Spain (Fernández-de-las-Peñas et al. 2021)	Cohort study hospitalized	1 Mar to 1 May, 2020	Wild type	1950	Prevalence of cough 2.5% at 1 year
Spain, (Maestre-Muñiz et al. 2021)	Cross sectional hospitalized	1 Mar to 1 Jun 2020	Wild type	587	Significant portion had ongoing symptoms at 1 year
France, (Morin et al. 2021)	Prospective cohort hospitalized	1 Mar to 21 May 2020	Wild type	834	51% report ≥1 new symptom at 4 months, fibrotic lung lesion 19%
Italy, (Carfì et al. 2020)	Prospective	21 Apr to 29 May 2020	Wild type	179	At a mean of 60 days, only 12.5 were free of symptoms, 32% had 1-2, and 55% had ≥3; fatigue (53.1%), dyspnea (43.4%), joint pain, (27.3%) and chest pain (21.7%)
Italy, (Latronico et al. 2022)	Prospective longitudinal	23 Feb to 30 Jun 2020	Wild type	114	depression, anxiety & PTSD at 12 mo
Italy, (Boscolo-Rizzo et al. 2022)	Cohort	29-22 Mar 2020		202	≥1 symptom at 2 years in 28%, smell/taste not recovered in 12%
Denmark, (Sørensen et al. 2022)	nationwide cross-sectional questionnaire	Sep 2020 to Apr 2021		152,880	At 6-12 months, 18 of 21 symptoms elevated in Covid compared to negative control; dysosmia, dysgeusia, fatigue, dyspnea, reduced arm leg strength most at

Study	Type	Time Period	Variant	Number of Subjects	Findings
					risk. 53.1% had concentration or, memory issues, sleep problems, mental/physical exhaustion, anxiety or depression
EU (Contin.)					
Norway, (Blomberg et al. 2021)	Prospective cohort			312	52% symptoms at 6 mo: loss taste/smell 28%, fatigue 21%, dyspnea 13%, impaired concentration 13%, memory problem 11%
Netherlands, (Wynberg et al. 2022)	Prospective cohort	11 May 2020 to 1 May 2021		342	Symptoms persisted (41%) for >1 year even in mild disease, greater with severe disease (87%)
Netherlands, (Ballering et al. 2022)	Prospective cohort	31 Mar 2020 to 2 Aug 2021		76,422 (4231 Covid)	12.7% had persistent symptoms 90-150 days due to Covid; respiratory issues, fatigue, myalgia, sensory
England, (Whitaker et al. 2021)	Community survey	15 Spe 2020 to 8 Feb 2021		508,707	30% of subjects had persistent symptoms >12 weeks, little decline thereafter. 2 clusters: tiredness and respiratory

A prospective, longitudinal study of 336,652 subjects in the UK using a smartphone app identified 9323 subjects (2.8%) with Long-COVID (defined as symptoms lasting >28 days) and 1459 (0.4%) with post-COVID syndrome, defined as lasting >12 weeks of symptoms (Canas et al. 2022). These definitions add another layer of complexity to the definition of the syndrome. Distinct profiles of symptoms (clusters) were identified for the post-COVID syndrome, with 4 endotypes for the wild-type SARS-CoV-2 viral variant, 7 for the Alpha variant, and 5 for the Delta variant. A cardiorespiratory cluster of symptoms (dyspnea and chest pain) occurred across the 3 variants, with a second cluster of central neurological symptoms (anosmia/dysosmia, fatigue, brain-fog, depression, delirium and headache) and a third systemic/inflammatory cluster with the most severe and debilitating multi-organ symptoms. Abdominal symptoms were often predominantly isolated within a single (smallest) cluster, evident across the 3 viral variants. There appears to be a heterogenous profile for post-COVID syndrome based on the different SARS-CoV-2 variant, although some groups of symptoms appear to cluster consistently across variants.

Another prospective, longitudinal study was conducted in the UK of 1-year follow-up of patients following hospitalization for COVID-19 (Evans et al. 2022). 2320 subjects discharged from hospital between March 7, 2020, and April 18, 2021, were assessed at 5 months after discharge and 807 (32.7%) participants completed both the 5- and 12-month visits. Full recovery was reported by 25.5% at 5 months and 28.9% at 1 year, with less recovery associated with female sex (OR 0.68), obesity (0.50), and invasive mechanical ventilation (0.42). Four clusters were seen: very severe, severe, moderate with cognitive impairment, and mild. The ten most common persistent symptoms at 1 year after discharge were fatigue (60.1%), aching muscles (54.6%), physically slowing down (52.9%, poor sleep (52.3%), breathlessness (51.4%), joint pain or swelling (47.6%), slowing down in thinking (46.7%, pain (46.6%), short-term memory loss (44.6%), and limb weakness (41.9%). Increased inflammatory mediators of tissue damage and repair were found in both the very severe and the moderate with cognitive impairment clusters compared with the mild cluster, including IL-6 concentration, which was increased in both comparisons (n=626 participants). Patient-perceived health-related quality of life was reduced at 1 year compared with before hospital admission. These findings are consistent with a hypothesis that the hyperinflammation associated with acute COVID-19 leads to a persistent inflammatory state following COVID-19, associated with dysregulated immunity and multiorgan dysfunction. This study demonstrated the persistence of at least one symptom from SARS)CoV-2 infection at 1 year in the majority of hospitalized patients.

Long-COVID is defined by the symptoms and the timeframe examined. One study from the Netherlands examined symptoms in patients with COVID-19 and corrected for baseline symptoms prior to infection as well as using a control group of noninfected subjects (Ballering et al. 2022). 4231 participants with COVID-19 were matched to 8462 controls out of a population of 76,422 subjects. Persistent symptoms in COVID-19-positive participants at 90–150 days after COVID-19 compared with before COVID-19 and compared with matched controls included chest pain, difficulties with breathing, pain when breathing, painful muscles, ageusia or anosmia, tingling extremities, lump in throat, feeling hot and cold alternately, heavy arms or legs, and general tiredness. At least one of these symptoms was increased to at least moderate severity in 21.4% of COVID-19 subjects compared with 8.7% of control subjects, a difference of 12.7%. Female COVID-19-positive subjects showed a longer persistence of increased symptom severity after COVID-19 than male COVID-19-positive subjects.

Omicron Variants and Long-COVID

One of the missing pieces in the long-COVID story was whether the viral variant affected the incidence or severity of the disease. Since the Omicron surge was relatively recent, a publication in June 2022 (6 months into the surge) answered part of the question, demonstrating that people with Omicron infection were less likely than those with Delta infections to experience long-COVID (Antonelli et al. 2022). In the study, 2501 (4.5%) of 56,003 people with Omicron infections experienced long-COVID and, among prior Delta cases, 4469 (10.8%) of 41,361 people experienced Long-COVID. The OR of long-COVID was lower for Omicron whether the individual was vaccinated within 3 months (RR= 0.50) , 3-6 months (0.24), or >6 months prior (0.26). Given the large number of people who experienced Omicron infections, an increase in the incidence of long-COVID is to be expected from the Omicron surge. Numerous subvariants of Omicron are present currently at various levels of predominance and prior infection with other variants or the original Omicron variant appear to offer little protection. Whether infection with such a subvariant carries the same or even a greater risk of Long-COVID is unknown.

Estimating the Incidence or Prevalence of Long-COVID

It is difficult to estimate the number of subjects with long-COVID in any country or in the world. Since the diagnosis is by exclusion of other etiologies in patients who have recovered from COVID-19, some studies provide an incidence rate at various times after infection. General estimates initially were that 37% to 50% of patients recovering from COVID-19 get long-COVID, but the current incidence may be lower. Some of the reported difference in incidence may be related to whether patients were hospitalized with severe COVID-19 or not. The incidence of Long-COVID may decrease with time after onset of COVID-19, although this perception is based on the symptoms being followed as comprising long-COVID. It appears that even patients with asymptomatic infections may get long-COVID. In a study from the Netherlands (31 March 2020 to 2 August 2021; pre-Omicron), post-COVID-19 condition might occur in about 1 out of 8 people with COVID-19 in the general population (Ballering et al. 2022). However, some of the same core symptoms were present in COVID-negative subjects as well as at baseline prior to infection. Current evidence supports the view that long COVID is common and can persist for at least 2 years after SARS-CoV-2 infection, although severe debilitating disease is present in a minority of subjects and vaccination lowers the risk of the syndrome and the symptom burden (Brightling and Evans 2022).

In late summer of 2021, the American Society of Physical Medicine and Rehabilitation calculated that some 11 million persons in the US had long-COVID (Mazer 2022). The number grew to 25 million as of June 2022 with the Omicron surge in the US, based on an estimate of 30% of cases developing lasting symptoms, and on an estimate of 85 million confirmed cases. The number of confirmed cases is probably a gross underestimate for the US given that most of the Omicron cases were probably mild to moderate, did not require hospitalization, and home testing results are rarely reported. The 30% estimate might be high (Mazer 2022) and could be 10-15% (Antonelli et al. 2022) or even 2% (Sudre et al. 2021), but still would involve millions of patients in the US and other nations with symptoms like chronic fatigue, difficulty breathing, or deadly blood clots. The low estimate of 2% came from a study which used an app and surveyed over 4 million registered adult patients primarily in the UK of which 4182 incident cases of COVID-19 between March and September 2020 were analyzed (Sudre et al. 2021). The incidence of Long-COVID from the Omicron variant may be in the range of 4-5% of COVID-19 patients (Antonelli et al. 2022). Given

the huge surge in cases globally due to the Omicron variant, the incidence of Long-COVID is expected to increase and potentially be a huge medical burden for years.

The US CDC estimated that as of May 5, 2022, the US has had roughly 81 million cases of COVID-19 and 994,187 COVID deaths. Even the lower-end estimate of 12% of people with 3 or more symptoms of long-COVID implies that 9.6 million people in the US may have developed long COVID—roughly 10 times the number of COVID-19 deaths (Cutler 2022). It is not known how long people with long-COVID will be symptomatic, but recovery in the first year of long-COVID for affected individuals may be very slow. Reduced health is one consequence of long-COVID, but reduced hours worked and reduced salary are another. Increased medical costs are a third effect. People out of the workforce because of long-COVID disproportionately worked in service jobs, including health care, social care, and retail. The shortage of workers in these fields is driving up wages and prices, feeding the ongoing inflation in the US. An expected surge in applications for Social Security Disability insurance has not manifested, possibly related to closure of such centers during the pandemic and requirements to apply online (Cutler 2022). From a review of about electronic patient records, the US CDC reported that COVID-19 survivors (n=353,164 compared with 1,640,776 controls) have twice the risk for developing pulmonary embolism or respiratory conditions; 20% of COVID-19 survivors aged 18–64 years and 25% of survivors aged ≥65 years experienced at least one incident condition that might be attributable to previous COVID-19 (Bull-Otterson et al. 2022).

The current prevalence estimates in September 2021 for Long-COVID suggested that 1–2 million people in the UK are affected (Siddiqui and Brightling 2021). The UK Office for National Statistics highlighted that breathlessness is the second most common symptom after tiredness in people at least 12 weeks after infection. The burden of both respiratory and non-respiratory symptoms appears to be even greater in patients who were hospitalized with acute COVID-19 than in those who were not, with failure to fully recover being reported in 30-50% of patients who were hospitalized. Damage to the alveolar–capillary interface might be a hallmark of the longer-term pathogenesis of COVID-19 lung disease. Pulmonary fibrosis might be a complication of COVID-19 (Rai, Sharma, and Kumar 2021; Spagnolo et al. 2020), although some studies do not show radiologic proof of fibrosis after recovery from the infection. On Mar 3, 2022, the UK Government's Office of National Statistics published their latest report on the prevalence of Long-COVID in the UK from a representative survey; as of 31 Jan 2022, around 1.5 million people living in the UK had self-reported Long-COVID (95% CI 1.228–1.304; 2.4% of the total population) (Office for National Statistics 2022). Of these individuals, 1.1 million (71%) had confirmed or suspected COVID-19 at least 12 weeks previously. Fatigue continued to be the most common symptom reported (51% of those with self-reported long-COVID), followed by shortness of breath (35%), loss of smell (34%), and loss of taste and difficulty concentrating (both 25%) .

In a systematic review of 57 studies comprising 250,351 survivors of COVID-19, most sequelae (PASC) included mental health, pulmonary, and neurologic disorders, were prevalent >6 months after SARS-CoV-2 exposure (Groff et al. 2021). Other frequently reported symptoms included cardiac, dermatologic, digestive, and ear, nose, and throat disorders. The mean (SD) age of survivors was 54.4 (8.9) years, 140,196 (56%) were male, and 197,777 (79%) were hospitalized during acute COVID-19. High-income countries contributed 45 studies (79%). The median (IQR) proportion of COVID-19 survivors experiencing at least 1 PASC was:

- 54.0% (45.0%-69.0%; 13 studies) at 1 month (short-term),
- 55.0% (34.8%-65.5%; 38 studies) at 2 to 5 months (intermediate-term), and

- 54.0% (31.0%-67.0%; 9 studies) at 6 or more months (long-term).

SYMPTOMS OF LONG-COVID

Long-COVID presents as a constellation of debilitating symptoms most commonly including unremitting fatigue, post-exertional malaise, cognitive impairment, and autonomic dysfunction among many others. Perhaps the first observation of this disease was the presence of ongoing cough or breathing difficulties. Long-COVID consists of some 200 signs and symptoms and 50 conditions (Levine 2022), so the definition is flexible and defined loosely by time after the initial infection. Four symptom clusters were described in a large survey (Cardio-respiratory; Neurological; Systemic-inflammatory; Abdominal) (Canas et al. 2022). More such clusters might exist.

The editors of a medical journal remarked that Long-COVID symptoms such as persistent fatigue, breathlessness, brain fog, and depression could debilitate many millions of people globally, yet very little is known about Long-COVID (Editors 2021a). It was suggested recently that the emergence of Long-COVID would best be understood as a "mass disabling event" of historic proportions, with the health-care system struggling to absorb an influx of infirmity, and economic growth blunted for years to come (Mazer 2022). See also Huang C et al., 2021 and Huang L et al., 2021 for a discussion of 6-month (C. Huang et al. 2021) and 12-month follow-up (L. Huang et al. 2021) of COVID-19 survivors in China. Accepted common symptoms of Long-COVID-19 in the UK guideline include the following (NICE, RCGP, and SIGN 2020) (Table 3).

Table 3: Symptoms of Long-COVID-19

Organ System	Symptom
Respiratory	Breathlessness
	Cough
Cardiovascular	Chest tightness
	Chest pain
	Palpitations
Generalized	Fatigue
	Fever
	Pain
Neurological	Cognitive impairment ("brain fog")
	Headache
	Sleep disturbances
	Peripheral neuropathy
	Dizziness
	Delirium
Gastrointestinal	Abdominal pain
	Nausea
	Diarrhea
	Anorexia or reduced appetite
Musculoskeletal	Joint pain
	Muscle pain
Psychological/Psychiatric	Depression (mental)
	Anxiety
Ear, Nose, and Throat	Tinnitus
	Earache

Organ System	Symptom
	Sore throat
	Loss of taste or smell
Dermatological	Skin rashes

(NICE, RCGP, and SIGN 2020)

The temporal trends in respiratory outcomes in patients hospitalized for severe COVID-19 in Wuhan China was assessed in a prospective, longitudinal, cohort study at 3, 6, 9, and 12 months after discharge (Wu et al. 2021). A total 83 (61%) of 135 eligible patients (median age 60 years) were enrolled in this study between 1 Feb and 31 Mar 2020. Temporal improvement in pulmonary physiology and exercise capacity was observed in most patients; however, persistent physiological and radiographic abnormalities remained in 24% of patients (n=20) at 12 months after discharge. Radiological abnormalities were associated with peak HRCT pneumonia scores during hospitalization (1.36 [1.13–1.62]; p=0.0009). Lung damage from COVID-19 can be long lasting. This study, however, assessed a limited patient population infected early in the pandemic, presumably by the original variant, and may not be reflective of results in currently infected populations with different variants (Olliaro 2021).

In a retrospective cohort study based on linked electronic health records, data from 81 million patients including 273,618 COVID-19 survivors in the UK were examined (Taquet et al. 2021). Among COVID-19 survivors (mean [SD] age: 46.3 [19.8], 55.6% female), 57.0% had one or more Long-COVID feature recorded during the whole 6-month period (i.e., including the acute infection phase), and 36.6% between 3 and 6 months. The incidence of each symptom decreased with time (days 1-180; days 90-180):

- abnormal breathing (18.7%; 7.9%),
- fatigue/malaise (12.8%; 5.9%),
- chest/throat pain (12.6%; 5.7%),
- headache (8.7%; 4.6%),
- other pain (11.6%; 7.2%),
- abdominal symptoms (15.6%; 8.3%),
- myalgia (3.2%; 1.5%),
- cognitive symptoms (7.9%; 3.9%),
- anxiety/depression (22.8%; 15.5%).

All 9 symptoms were more frequently reported after COVID-19 than after historical cases of influenza (with an overall excess incidence of 16.6% and hazard ratios between 1.44 and 2.04, all $p < 0.001$), co-occurred more commonly, and formed a more interconnected network. Significant differences in incidence and co-occurrence were associated with sex, age, and illness severity (Taquet et al. 2021).

In a study using a health app, Long-COVID was characterized by symptoms of fatigue, headache, dyspnea and anosmia and was more likely with increasing age and body mass index and female sex (Sudre et al. 2021). Experiencing more than 5 symptoms during the first week of illness was associated with a higher risk of getting Long-COVID (OR 3.53 (2.76–4.50)).

In a long-term follow-up report of COVID-19 cases from Italy (Carfì et al. 2020), 143 patients were included with a mean age of 56.5 (± 14.6) years, and 53 (37%) were women. During hospitalization, 72.7% of participants had evidence of interstitial pneumonia. The mean length of

hospital stay was 13.5 (± 9.7) days; 21 patients (15%) received noninvasive ventilation and 7 patients (5%) received invasive ventilation. Patients were assessed a mean of 60.3 (± 13.6) days after onset of the first COVID-19 symptom; at the time of the evaluation, only 18 (12.6%) were completely free of any COVID-19–related symptom, while 32% had 1 or 2 symptoms and 55% had 3 or more. None of the patients had fever or any signs or symptoms of acute illness. Worsened quality of life was observed among 44.1% of patients. A high proportion of individuals still reported fatigue (53.1%), dyspnea (43.4%), joint pain, (27.3%) and chest pain (21.7%) about 2 months after the first symptoms.

Since follow-up of COVID-19 cases was incomplete early in the pandemic as physicians were occupied with new cases, one group decided to conduct a preliminary characterization of post-COVID-19 symptoms using social media data from Twitter in 2020. A combination of natural language processing (#longcovid, #chroniccovid) and clinician reviews was used to identify long term self-reported symptoms on a set of Twitter users (Banda et al. 2020). A total of 7,781 unique tweets were identified from 4,607 users. After annotation, 2,603 tweets were manually reviewed, resulting in 150 eligible tweets from 107 users. A total of 192 reports including 34 distinct ICD-10 codes were identified. The 10 most commonly mentioned symptoms were: malaise and fatigue (62%), dyspnea (19%), tachycardia/palpitations (13%), chest pain (13%), insomnia/sleep disorders (10%), cough (9%), headache (7%), and joint pain, fever, and unspecified pain by 6% each. Less common symptoms included ear-nose-throat (tinnitus, anosmia, chronic sinusitis, parageusia, aphonia), neuro-psychological (amnesia, neuralgia/neuropathy, disautonomia, visual disturbance, cognitive impairment, and disorientation), myalgia, and skin pruritus/rash. The validity of such self-reporting can be questioned, but taken together with some clinical reports it appears symptoms may persist long after release from the hospital.

An April 2021 published report from Sweden examined symptoms and functional impairment at 8 months after mild COVID-19 among healthcare workers (Havervall et al. 2021). A considerable portion of low-risk individuals with mild COVID-19 reported a diversity of long-term symptoms, and these symptoms disrupted work, social, and home life. A total of 323 seropositive and 1072 seronegative participants completed the 8-month assessment. Comparing seropositive vs seronegative participants, 26% vs 9% reported at least 1 moderate to severe symptom lasting for at least 2 months (RR, 2.9 [95% CI, 2.2-3.8]) and 15% vs 3% reported at least 1 moderate to severe symptom lasting for at least 8 months (RR, 4.4 [2.9-6.7]). The most common moderate to severe symptoms lasting for at least 2 months in the seropositive group were anosmia (15%), fatigue (8%), ageusia (8%), and dyspnea (4%). These were reported at 8 months by 15%, 8%, 4%, and 4% of subjects, respectively. Less common adverse events included sleeping disorders, headache, palpitations, impaired concentration, muscle or joint pain, and memory impairment.

In February of 2021, Dr. Fauci, a leading infectious diseases expert in the US, revealed a scientific name for the new syndrome previously termed COVID long-haulers – Post Acute Sequelae of SARS-CoV-2 (PASC). His comments followed publication of a report on post-COVID symptoms at 6 months after infection (Logue et al. 2021). A total of 177 of 234 participants (75.6%; mean age, 48.0 [18-94] years; 57% women) with COVID-19 completed the survey between 3 and 9 months after illness onset. Overall, 11 (6.2%) were asymptomatic, 150 (84.7%) were outpatients with mild illness, and 16 (9.0%) had moderate or severe disease requiring hospitalization. The follow-up survey was completed a median (range) of 169 (31-300) days after illness onset among participants with COVID-19 and 87 (71-144) days after enrollment among 21 patients in the control group. Among participants with COVID-19, persistent symptoms were reported by:

- 17 of 64 patients (26.6%) aged 18 to 39 years,
- 25 of 83 patients (30.1%) aged 40 to 64 years, and
- 13 of 30 patients (43.3%) aged 65 years and older.

Overall, 49 of 150 outpatients (32.7%), 5 of 16 hospitalized patients (31.3%), and 1 of 21 healthy participants (4.8%) in the control group reported at least 1 persistent symptom (Logue et al. 2021). Of 31 patients with hypertension or diabetes, 11 (35.5%) experienced ongoing symptoms. The most common persistent symptoms were fatigue (13.6%) and loss of sense of smell or taste (13.6%). Overall, 23 patients (13.0%) reported other symptoms, including brain fog (4 [2.3%]). A total of 51 outpatients and hospitalized patients (30.7%) reported worse quality of life compared with baseline vs 4 healthy participants and asymptomatic patients (12.5%); 14 patients (7.9%) reported negative impacts on at least 1 activity of daily living (ADL), the most common being household chores.

The 4-month status of a cohort of patients following hospitalization in France for COVID-19 was reported (Morin et al. 2021). Among 834 eligible patients, 478 were evaluated by telephone (mean age, 61 years [±16 years]; 201 men, 277 women). During the telephone interview, 244 patients (51%) declared at least 1 symptom that did not exist before COVID-19: fatigue in 31%, cognitive symptoms in 21%, and new-onset dyspnea in 16%. There was further evaluation in 177 patients (37%), including 97 of 142 former ICU patients. Multidimensional Fatigue Inventory score (n = 130) was 4.5 for reduced motivation and 3.7 for mental fatigue (1 [best] to 5). The median 36-Item Short-Form Health Survey score (n = 145) was 25 for the subscale "role limited owing to physical problems" (0 [best] to 100). Computed tomographic lung-scan abnormalities were found in 108 of 171 patients (63%), mainly subtle ground-glass opacities. Fibrotic lesions were observed in 33 of 171 patients (19%), involving less than 25% of parenchyma in all but 1 patient. Fibrotic lesions were observed in 19 of 49 survivors (39%) with acute respiratory distress syndrome. Among 94 former ICU patients, anxiety, depression, and posttraumatic symptoms were observed in 23%, 18%, and 7%, respectively. The left ventricular ejection fraction was less than 50% in 8 of 83 ICU patients (10%). New-onset chronic kidney disease was observed in 2 ICU patients. Serology was positive in 172 of 177 outpatients (97%). Thus, 4 months after hospitalization for COVID-19, a cohort of patients frequently reported symptoms not previously present, and lung-scan abnormalities were common among those who were tested.

Neurological Symptoms

Numerous reports have some patients reporting persistent neurological manifestations, from milder symptoms such as headaches, hyposmia, hypogeusia, and fatigue to more severe conditions including sleep disorders, pain, cognitive impairment, and (in very rare cases) Guillain-Barré syndrome (Editors 2021b; Liu et al. 2022b). In a cohort study of 3233 subjects in Wuhan, China, COVID-19 survival was associated with an increase in risk of longitudinal cognitive decline (Liu et al. 2022b). Severe COVID-19 was associated with a higher risk of early-onset cognitive decline (OR 4.87; 95% CI, 3.30-7.20), late-onset cognitive decline (7.58; 3.58-16.03), and progressive cognitive decline (19.00; 9.14-39.51), while nonsevere COVID-19 was associated with a higher risk of early-onset cognitive decline (1.71; 1.30-2.27) when adjusting for age, sex, education level, body mass index, and comorbidities (Liu et al. 2022b). Survivors of SARS-CoV-2 infection frequently experience lingering neurological symptoms, including impairment in attention, concentration, speed of information processing, and memory, features shared with the syndrome of cancer therapy-related cognitive impairment (CRCI) associated with neuroinflammation, particularly microglial reactivity and consequent dysregulation of hippocampal neurogenesis and

oligodendrocyte lineage cells (Fernández-Castañeda et al. 2022). In a mouse model of mild respiratory SARS-CoV-2 infection induced by intranasal SARS-CoV-2 delivery, white matter-selective microglial reactivity, a pattern observed in CRCI, was noted. Human brain tissue from 9 individuals with COVID-19 infection exhibited the same pattern of prominent white matter-selective microglial reactivity. Impaired hippocampal neurogenesis, decreased oligodendrocytes, and myelin loss in subcortical white matter were evident at 1 week, and persisted until at least 7 weeks, following mild respiratory SARS-CoV-2 infection in mice. Humans experiencing long-COVID with cognitive symptoms (48 subjects) similarly demonstrated elevated levels of CCL11, a pro-inflammatory cytokine, compared to those with Long-COVID who lack cognitive symptoms (15 subjects). These findings illustrate similarities between the neuropathophysiology after cancer therapy and after SARS-CoV-2 infection, and elucidate cellular deficits that may contribute to lasting neurological symptoms following even mild SARS-CoV-2 infection.

Physical, mental, or cognitive symptoms were frequently reported in an exploratory study of patients in 11 Dutch hospitals who survived 1 year following ICU treatment for COVID-19 (Heesakkers et al. 2022). Patients (N = 452) with COVID-19, aged ≥16 years and alive after hospital discharge following admission to 1 of the 11 ICUs during the first COVID-19 surge (March 1 to July 1, 2020) were eligible for inclusion. Patients were followed up for 1 year, and the date of final follow-up was June 16, 2021. At 1 year, physical symptoms were reported by 74.3% (95% CI, 68.3%-79.6%), mental symptoms were reported by 26.2% (20.8%-32.2%), and cognitive symptoms were reported by 16.2% (11.8%-21.5%). The most frequently reported new physical problems were:

- weakened condition (38.9%),
- joint stiffness (26.3%)
- joint pain (25.5%),
- muscle weakness (24.8%) and
- myalgia (21.3%).

Fatigue is a common complaint in long-COVID with a substantial impact on daily life, but the neural mechanisms behind post-COVID fatigue remain unclear (Baker et al. 2022). German volunteers (n=37) with self-reported fatigue after a mild COVID infection were examined in a battery of behavioral and neurophysiological tests assessing the central, peripheral and autonomic nervous systems. Underactivity in specific cortical circuits, dysregulation of autonomic function, and myopathic change in skeletal muscles were seen in the post-COVID subjects compared with matched controls without fatigue. Cluster analysis revealed no sub-groupings, suggesting post-COVID fatigue is a single entity with individual variation, rather than a small number of distinct syndromes. Larger studies have reported some clusters of symptoms and differences among patients (see above).

Loss of Taste or Smell

A substantial proportion of patients with COVID-19 might develop long lasting change in their sense of smell or taste, contributing to the growing burden of Long-COVID (Tan et al. 2022; Boscolo-Rizzo et al. 2022). In a meta-analysis of 18 studies including 3699 patients, persistent self-reported smell and taste dysfunction could develop in an estimated 5.6% (95% CI 2.7%-11.0%) and 4.4% (1.2%-4.6%) of patients with COVID-19, respectively (potential underestimates) (33). At 30, 60, 90, and 180 days, respectively, 74.1% (64.0%-81.3%), 85.8% (77.6%-90.9%), 90.0% (83.3%-94.0%), and 95.7% (89.5%-98.3%) of patients recovered their

sense of smell and 78.8% (70.5%-84.7%), 87.7% (82.0%-91.6%), 90.3% (83.5%-94.3%), and 98.0% (92.2%-95.5%) recovered their sense of taste. Women were less likely than men to recover their sense of smell as were those with greater initial severity of dysfunction or nasal congestion. In studies from Italy, about 7% of subjects remained anosmic at 1 year, but 88.2% of 202 subjects recovered from their smell or taste dysfunction by 2 years (Boscolo-Rizzo et al. 2022). At 2-year follow-up, the most frequent non-chemosensory symptoms were fatigue (n = 31; 18.5%; 95% CI, 12.9%-25.2%), followed by shortness of breath (n = 18; 10.7%; 6.5%-16.4%). Overall, the persistence of at least 1 symptom at 2-year follow-up was reported by 47 patients (28.0%; 21.3%-35.4%).

In a single case-control study from Japan, a COVID-19-positive woman presented with chronic (6-month) bilateral dacryoadenitis with SARS-CoV-2–positive inflammatory cells with glandular damage (Kase and Ishida 2022). Expression of ACE2 in the lacrimal glands might be a target for SARS-CoV-2 to adhere to resulting in COVID-19 aftereffects.

Pediatric Post-COVID Signs and Symptoms

CDC used medical reports to assess 9 potential post-COVID signs and symptoms (symptoms) and 15 potential post-COVID conditions among 781,419 U.S. children and adolescents aged 0–17 years with COVID-19 compared with 2,344,257 U.S. children and adolescents without recognized COVID-19 during March 1, 2020–January 31, 2022 (Kompaniyets et al. 2022). The highest hazard ratios were recorded for acute pulmonary embolism (aHR = 2.01), myocarditis and cardiomyopathy (1.99), venous thromboembolic event (1.87), acute and unspecified renal failure (1.32), and type 1 diabetes (1.23), all of which were rare or uncommon in this study population. Patients with COVID-19 were less likely to experience respiratory signs and symptoms, symptoms of mental conditions, muscle disorders, neurological conditions, anxiety and fear-related disorders, mood disorders, and sleeping disorders than subjects without COVID, possibly related to how subjects without COVID were selected (visit to healthcare provider). Differences were noted among age groups of children for COVID subjects vs. COVID-negative. Children aged 2–4 years had higher rates of asthma diagnosis (1.12) and respiratory signs and symptoms (1.07) after COVID-19. Among children aged 5–11 years, the highest aHRs for patients with COVID-19 were for myocarditis and cardiomyopathy (2.84), venous thromboembolic event (2.69), and acute and unspecified renal failure (1.38). Among patients aged 12–17 years, the highest aHRs for those with COVID-19 were for acute pulmonary embolism (2.03), myocarditis and cardiomyopathy (1.66), and venous thromboembolic event (1.52).

In a review of Long-COVID in pediatric subjects, the main issues were cardiovascular, respiratory, neurological, dermatological gastrointestinal, fatigue, fever, and myalgia or arthralgia, similar to those symptoms reported in adults (Fainardi et al. 2022). The incidence of Long-COVID in children and adolescents appeared to be low.

Management of Long-COVID

The heterogeneity of symptom profiles suggests that a single approach to follow-up and management of long-COVID will not be effective (Prescott 2021). In addition, long-term adverse effects were described for the lungs and other organs (Boland 2020; Spagnolo et al. 2020; Fraser 2020; Davis et al. 2020; del Rio, Malani, and Omer 2021; Banda et al. 2020). Even milder cases of COVID-19, which do not require the use of a respirator to enable breathing, are now known to cause damage to numerous organs. While people worldwide have recovered from COVID-19, there remains concern that some organs, including the lungs, might have long-term impairment

following infection (Spagnolo et al. 2020). Identifying the long-term effects of COVID-19 can feel a little bit like predicting the future, but parallels to cases of ARDS could guide expectations in severe COVID-19 cases (Boland 2020). Long-lasting systemic inflammation was present in people with more severe symptoms of long COVID (Evans et al. 2022), which could provide biological plausibility for the presence of severe impairments in people with persistent symptoms after acute COVID-19 and allow new therapeutic strategies to be applied in these patients via a personalized medicine approach (Florencio and Fernández-de-las-Peñas 2022). The presence of long-lasting systemic inflammation in some patients with long COVID would suggest that anti-inflammatory agents might have potential not only during the acute phase of infection, but also during the post-acute phase (Venkatesan 2022). The safety profile and efficacy of such agents would dictate the stage of disease at which their use in treatment is optimal, as would the patient and disease characteristics.

An interesting phenomenon was reported in the press in March 2021 with respect to vaccination in subjects with Long-COVID. In an informal survey of nearly 600 people who self-reported lingering symptoms after COVID-19, 47% saw no difference after vaccination, 39% improved after getting a vaccine. and 14% felt worse. Two hypotheses were proposed for this effect. First, the long-COVID subject's body might still harbor particles or pieces of the virus that causes COVID-19. The vaccine could theoretically stimulate their immune system to hunt down these remaining bits and clear them away so they can no longer cause inflammation. Second, the virus might cause a kind of autoimmune reaction and the vaccine might reset the immune system. A clinical trial of the efficacy of vaccination in the treatment of Long-COVID symptoms was proposed and designed by clinicians. A case-control study of 1.2 million users of a COVID symptom tracker app in the UK showed that there were lower odds of symptoms lasting ≥28 days in individuals who had received 2 vaccine doses (OR 0.51 [0.32–0.82]; p=0.0060)—i.e., the risk of developing Long-COVID was reduced by around 50% in those who were double vaccinated (Sabel et al. 2021).

To date (March 2022) no antiviral or immunomodulatory drug has proven effective for the treatment of Long-COVID in clinical trials (Ward et al. 2021). As was pointed out, much of the focus has been on higher income countries and long-COVID, but the pandemic was global and treatments for long-COVID should include patients in poor nations. In one small study, non-invasive brain stimulation using microcurrent (NIBS), which is known to enhance blood flow and neuronal synchronization, improved the visual and cognitive deficits in two confirmed SARS-COV-2 patients (Sabel et al. 2021).

DISCUSSION

The individuals with long-COVID present an unusual dilemma as it is not known how long such an individual is contagious and how long the symptoms will last. Such patients will continue to challenge the healthcare industry far into 2022 and probably beyond. This is especially disconcerting as children may get Long-COVID of undetermined duration and younger adults with the syndrome already are requiring increased medical attention while being unable to work or work as effectively as prior to infection. While the incidence rate for Long-COVID is lower with Omicron variants than prior VOC, the number of subjects infected is higher leading to an increased incidence. At least the feared long-term neurological effects of SARS-CoV-2 infection do not appear to be as significant as was feared by parallel with other infections. However, the common symptoms of Long-COVID, especially fatigue and mental dysfunction, can lead to serious adverse

effects on the quality of life for the individual. Potential treatments could be aimed at preventing the syndrome in the first place, stopping the cascading events that lead to increasing damage to multiple organs, and restoring the balance in organs to allow them to heal. Since the likely avenues of infection are respiratory, mainly, gastrointestinal, or ocular, treatments aimed at these sites are most likely to slow the progress of the infection and its consequences.

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