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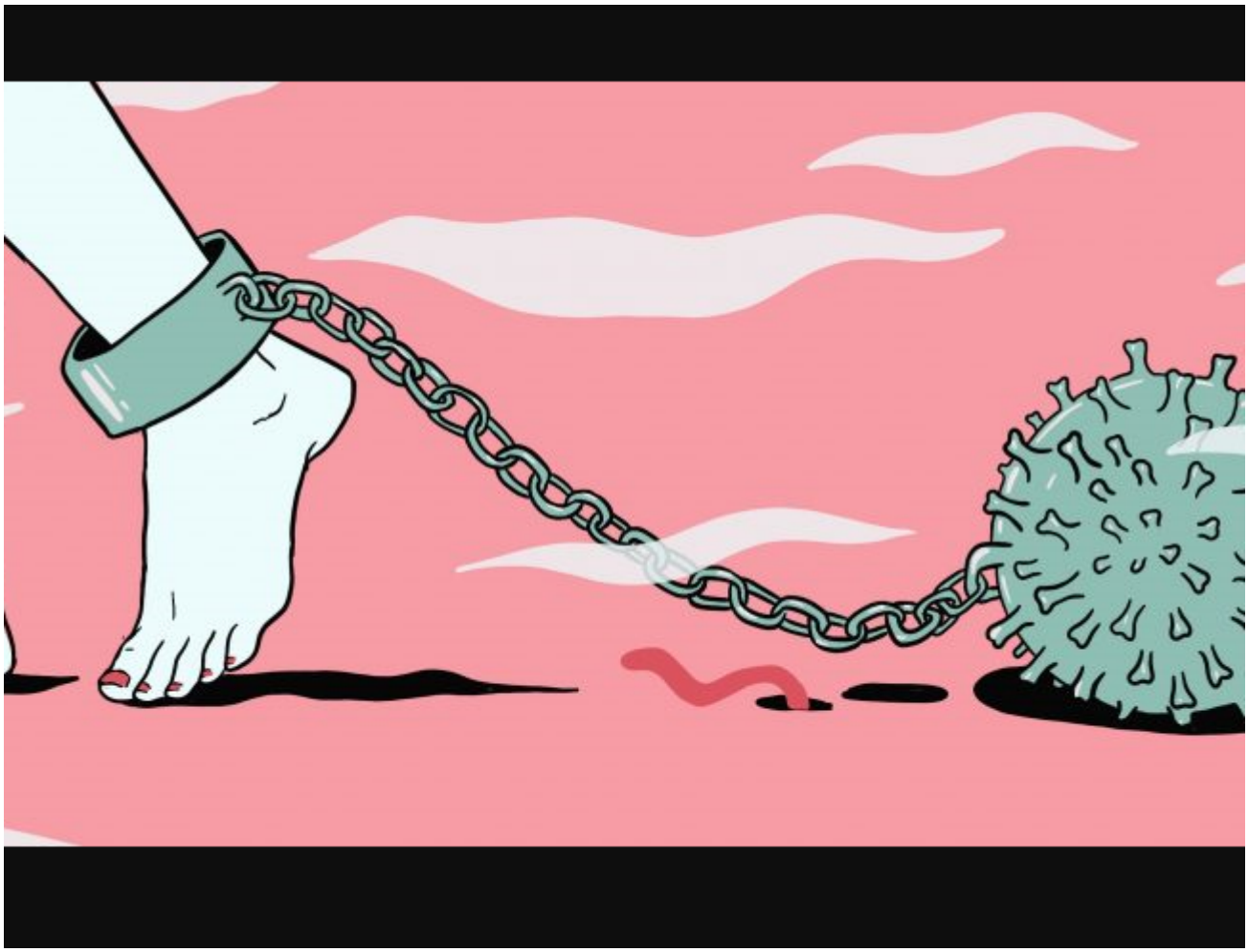

Update on Long-COVID

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This blog post updates an earlier post on Long-COVID and reports that estimates of prevalence are still wide at about 15 to 65% of those initially infected with the pandemic virus, SARS-CoV-2. As things stand now across the world, we do not yet have systems in place to diagnose and manage the massive burden of the disease that is Long-COVID. An elimination strategy that includes, but is not limited to, widespread vaccination is not only crucial to reduce the acute case load and high mortality associated with infection with SARS-CoV-2 but is also key to minimising the damage that Long-COVID is otherwise certain to create for individuals, whanau, communities, and nations. This is a "long-read" post – and so readers short on time are welcome to jump to the Conclusions Section.

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Long-COVID may be unique in the annals of medicine inasmuch as it was first described by sufferers rather than physicians or biomedical scientists. Social media also played a part, as noted by Callard and Perego[1], the syndrome acquired its name as a result of sufferers finding each other on Twitter.

What is Long-COVID? That proves to be a question without an easy answer. When we first discussed this topic on this blog in September 2020 we said, “Some are beginning to call it “long-COVID”[2] and refer to the misery of “the long haulers”[3]… [T]here is enough coherence to the current evidence to establish that long-COVID is a real phenomenon and that, for many, the burden of infection with SARS-CoV-2 does not end with discharge from hospital, with the disappearance of the virus, or with the fading of acute symptoms.”

We noted that the earliest reports were the result of good non-specialist reporting. For instance, in June 2020, the *Washington Post* had described multiple individuals who had spent more than 60 days with serious symptoms[4].

We also noted, at that time, that what was available in the literature was largely anecdotal reports and collections of cases; that prevalence was not easy to determine because, in most reports, there were no denominators providing numbers of cases; and, again, that it was those with the disorder who were contributing extensively to what we know. They were not only providing data to investigators but also establishing observatories to continue the dialogue among themselves. At that time, too, it was clear that the manifestations were so widespread that defining it as a single syndrome was difficult.

What have we learned in the ensuing eight months? Firstly, it is clear that this really is a

spectrum of disorders and that, although the name, Long-COVID, captures perfectly the persistence of symptoms after the acute infection with SARS-CoV-2 has subsided, there are symptoms and signs across multiple organ systems. This diversity and the difficulty of defining the disease process is made abundantly clear by the number of research groups — at least seven[5-11] — who have attempted definitions but with little agreement about typology. The simplest classification may be that of Sudre et al[9] who noted two broad patterns — those reporting “exclusively fatigue, headache and upper respiratory complaints (shortness of breath, sore throat, persistent cough and loss of [sense of] smell)” and those with additional complaints across multiple organ systems, “including fever and gastroenterological symptoms”[9].

Secondly, there is also evidence that some individuals experienced symptoms that began at the time of the initial infection and that, for others, symptoms arose at some time after the initial infection had resolved[12].

Thirdly and relatedly perhaps, one of the key features is a picture of remitting/relapsing symptoms also referred to by some as an undulating pattern[13-15].

Fourthly, understanding the nature of the long-term consequences of infection with SARS-CoV-2 is made difficult by the fact that there is nothing consistent about the populations that have been studied[14]. Recruitment has: a) in most cases, been through volunteer or convenience sampling; b) involved groups with very different initial presentations as evidenced by history of hospitalisation varying from none to all; and c) by the timing of measurement or reporting of symptoms and signs. There are almost no studies with sequential observations on the same individuals and, finally, most studies involved fewer than 500 individuals.

Nonetheless, the studies collectively have some key findings that advance our understanding of the nature of Long-COVID and the spectrum of organ systems that are involved.

Studies of Prevalence

The largest and probably the most careful study to date was conducted in the US by Daugherty et al[16]. They undertook a retrospective cohort analysis using data sources within the UnitedHealth Group Clinical Discovery Database that covered claims, laboratory results for SARS-CoV-2, and hospital admissions for COVID-19. The primary group consisted of individuals aged 18-65 with continuous enrolment in the health plan from 1 January 2019 to the index date, defined as the date of the first occurrence of any of: diagnosis of COVID-19; claims for relevant diagnostic codes; documentation of a PCR test; or hospitalisation. They identified three “comparator groups”: from 2020 (no COVID-19 diagnosis, positive PCR, or hospital admission); from 2019 (“to account for possible ascertainment bias” resulting from reduced use of healthcare services during the 2020 pandemic); and enrolled members with viral lower respiratory tract illness (“because many serious viral illnesses have a risk of morbidity after the acute illness”). They did not analyse the entire population of almost 10 million but created propensity-score-matched sets.

Fourteen percent of individuals aged ≤65 who were infected with SARS-CoV-2 (27,074 of 193,113) developed at least one new clinical manifestation that required medical care after the acute phase of COVID-19; this was 4.95% higher than the 2020 comparator group and 1.65% higher than among individuals diagnosed as having viral lower respiratory tract illness. The researchers interpreted these findings as suggesting that the SARS-CoV-2 virus

is not unique in causing sequelae after acute infection. Increased risk was noted across a range of organ systems, including cardiovascular, neurologic, renal, and respiratory systems, as well as mental-health complications.

Diagnoses, including chronic respiratory failure, cardiac arrhythmia, hypercoagulability, encephalopathy, peripheral neuropathy, memory problems, diabetes, liver-test abnormalities, myocarditis, anxiety, and fatigue were all statistically significantly ($p<0.001$) more common in those who had been infected with SARS-CoV-2 than in the three comparator groups. The risk was greatest in individuals aged >50 but the absolute risk in young adults aged 18-34 was statistically significantly elevated ($p<0.001$), albeit modestly, for some conditions. Risk of sequelae increased with age, pre-existing conditions, and admission to hospital for COVID-19 but, in adults aged ≤50 and those with no pre-existing conditions or not hospitalised, risk for some clinical sequelae was still elevated.

In England, Ayoubkhani et al[6] undertook to "quantify rates of organ specific dysfunction in individuals with COVID-19 after discharge from hospital". A cohort of 47,780 individuals (average age 65, 55% men) hospitalised with COVID-19 and discharged alive by 31 August 2020, were exactly matched to controls from a pool of about 50 million people on personal and clinical characteristics from 10 years of electronic health records.

Over an average follow-up of 140 days, 29.4% (14,060 of 47,780) of those discharged from hospital after a diagnosis of acute COVID-19 were readmitted and 12.3% (5875) died after discharge; this is four and eight times greater, respectively, than in the matched controls. Rates of respiratory disease, diabetes, and cardiovascular disease were also statistically significantly raised (all $p<0.001$) in patients with COVID-19. Rate ratios were greater for individuals <70 than for those aged ≥70 years, and in ethnic minority groups compared with the white population.

Using data from the national Coronavirus (COVID-19) Infection Survey (CIS) – a nationally representative sample of the UK community population – the UK Office of National Statistics estimated that about 20% of respondents who had tested positive for COVID-19 exhibited symptoms for ≥5 weeks and about 10% for ≥12 weeks[17]. They subsequently estimated that the 5-week prevalence of any symptom among CIS respondents who had tested positive for COVID-19 was 22.1% (20.7% of males; 23.6% of females), ranging from 12.9% among those aged 2-11 years to 26.8% among those aged 35-49 years. They estimated that, in the week ending 27 December 2020, 301,000 individuals in the UK were experiencing post-COVID symptoms for 5 to 12 weeks[18].

Munblit et al[19] undertook a longitudinal cohort study of adults (≥18 years of age) with clinically diagnosed or laboratory-confirmed COVID-19 admitted to Sechenov University Hospital Network in Moscow. Data were collected from patients discharged between April 8 and July 10, 2020. Participants were interviewed via telephone for Post COVID conditions. Overall, 2,649 of 4,755 patients discharged from the hospitals were available for follow-up. The median age of the patients was 56 years and 51.1% were women. The median follow-up time post-discharge was 217.5 (200.4-235.5) days. At the time of follow-up, 1247 (47.1%) participants reported long-standing symptoms, with the most common being fatigue (21.2%), shortness of breath (14.5%) and forgetfulness (9.1%). Multi-system involvement was less common (11.3%).

Cirulli et al[8] reported on an adult population cohort derived from two existing US studies. It included 357 SARS-CoV-2-positive cases, 5,497 SARS-CoV-2-negative controls, and 19,095 who had not been tested. The majority of COVID-19 cases were mild, with only 9 of the 357

having been hospitalised and were thought to be representative of the general population. After 30, 60, and 90 days, respondents identified their persistent symptoms from a list of 32 thought to be associated with COVID-19 or Long-COVID. The initially SARS-C0V-2-positive patients had a higher prevalence of persistent symptoms at each of the three time points than the other two groups. Over a third (36.1%) of the SARS-C0V-2-positive individuals had symptoms lasting > 30 days, and 14.8% at least one symptom >90 days. These proportions were higher among those who were initially more ill: 44.9% at 30 days and 20.8% at 90 days. However, even for very mild and initially asymptomatic individuals, 21.3% had complications for ≥30 days. The most common long-term symptoms were anosmia (loss of a sense of smell), loss of a sense of taste, difficulty concentrating, shortness of breath, memory loss, confusion, chest pain, and pain on deep breaths. Individuals with shortness of breath were statistically significantly more likely to develop long-term symptoms.

Huang et al[20] undertook a cohort study of patients with confirmed COVID-19 who had been discharged from Jin Yin-tan Hospital (Wuhan, China) between January 7, 2020, and May 29, 2020. 736 patients were excluded but the remaining 1733 patients of 2469 discharged patients (median age 57·0 years and 52% were men) provided data. Median follow-up time after symptom onset was 186 days. Fatigue or muscle weakness (63%, 1038 of 1655) and sleep difficulties (26%, 437 of 1655) were the most common symptoms. Anxiety or depression was reported among 23% (367 of 1617) of patients. Patients who were more severely ill during their hospital stay had more severely impaired lung function.

In the USA, Logue et al[21] studied a small number of people (n=234) with confirmed COVID-19 infection, only 15% of whom had been hospitalised. A third (33%) of the non-hospitalised patients and 31% of those who were hospitalised reported at least one persistent symptom six months after diagnosis. This six-month prevalence is a lower estimate than that of Huang et al[20], but confirms that, for a substantial proportion of those with an initial diagnosis of COVID-19, symptoms persist over a prolonged period.

These studies above give a still quite imprecise (15-65%) estimate of prevalence of Long-COVID among those initially diagnosed with acute disease. The variation may be related to hospitalisation: as the second NIHR report notes[14], for those not admitted to hospital, it appears that at least 20-30% experience at least one enduring symptom around one month later and at least 10% three months later but for those who were hospitalised, between 50% and 89% have at least one enduring symptom after two months and more than half may still be experiencing symptoms after six months. A very recent paper using the national healthcare databases of the US Department of Veterans Affairs confirms the important role of initial severity of COVID-19. Al-Aly et al[22] reported that their analysis of a series of prespecified outcomes among those who survived 30 days after an initial diagnosis showed a risk gradient that increased across: those who were infected but not hospitalized; those hospitalized; and those admitted to intensive care.

Studies of Individuals with Self-Reported Persistent Symptoms

There are also studies that focus specifically on individuals with symptoms of Long-COVID, without a sense of the population from which they were drawn. What these studies do is improve our understanding of the spectrum of symptoms and signs that emerge among those whose disorder persists, re-emerges, or remits and relapses. They reinforce and expand on the data that were available when we first discussed Long-COVID in September 2020, especially as there are now studies reporting on larger numbers.

The COVID Symptom Study is a mobile app launched in response to the COVID-19 pandemic. Contributors are prompted to provide daily information on health status and symptoms, as well as results of any available COVID-19 test. Between 24 March 2020 (launch date in the UK) and 2 September 2020, more than four million adults registered (average age 46 years; 57% female), with the majority from the UK (88.2%), as well as the US and Sweden. Sudre et al[9] selected 4,182 individuals to investigate the duration of persistent symptoms in those with a diagnosis of COVID-19. A total of 558 (13.3%) participants reported symptoms lasting ≥28 days, 189 (4.5%) for ≥8 weeks, and 95 (2.3%) for ≥12 weeks. Long-COVID was characterised by symptoms of fatigue, headache, shortness of breath, and loss of a sense of smell, and was more likely with increasing age and body mass index and female sex. Experiencing more than five symptoms during the first week of illness was associated with risk of Long-COVID (odds ratio = 3.5 (2.8–4.5)). It is notable that among >2.8 million users of the Covid Symptom Study app, only 40% with COVID-19 symptoms had had a PCR test[23].

Davis et al[15] analysed responses from an international survey – distributed via online COVID-19 support groups and social media – of 3,762 individuals, from 56 countries, who had confirmed (1,020) or suspected (2,742) COVID-19 with an illness duration of at least 28 days. 3608 (96%) reported symptoms beyond 90 days. A collective prevalence of 205 different symptoms in 10 different organ systems was estimated in this cohort, with 66 symptoms traced over seven months. Respondents experienced an average of 14.5 symptoms in an average of 9 organ systems. Except for loss of smell and taste, the prevalence and trajectory of all symptoms were similar between groups with confirmed and suspected COVID-19. The most likely early symptoms were fatigue, dry cough, shortness of breath, headaches, muscle aches, chest tightness, and sore throat. The most frequent symptoms reported after month 6 were: fatigue (77.7%) post-exertional malaise (72.2%), and cognitive dysfunction (including “brain fog”) (55.4%). These symptoms were also the most commonly reported overall. The majority (>85%) experienced relapses, with exercise, physical or mental activity, and stress as the main triggers. Nearly half (1,700; 45.2%) reported requiring a reduced work schedule compared to pre-illness and 839 (22.3%) were not working at the time of survey due to their health conditions. Although this study relied on a convenience sample, it does provide some important longitudinal data and emphasises just how persistent symptoms can be.

Many of the other studies of individuals with Long-COVID are small. They provide additional evidence for the severity and persistence of symptoms, with, in most cases, 30-50% describing prolonged symptoms or an inability to return to work[24-28]. Most of them, however, involve self-reported symptoms among selected respondents and do not add greatly to understanding of mechanisms or provide additional input on the spectrum of manifestations.

Studies of Individuals Who Reported Persistent Symptoms and Were Examined

Imaging Studies

Arnold et al[29] prospectively recruited consecutive patients admitted with confirmed COVID-19 in Bristol, UK, and invited them to a systematic clinical follow-up. Most (110 of 131) people attended 8-12 weeks after acute infection. Examination included chest X-ray. They noted that 74% of participants, including those originally admitted with mild disease, reported at least one persistent symptom (particularly breathlessness and excessive

fatigue) or physical limitations. Clinically significant abnormalities on chest X-ray, exercise tests, blood tests, and lung function tests were less frequent (35%), particularly among those who had not required supplementary oxygen (7%).

Informatively, but in some contrast, D'Cruz et al[30] noted that, among patients hospitalised with severe COVID-19 pneumonia and who had undergone face-to-face assessment 4-6 weeks post-discharge, breathlessness scores were above pre-COVID baseline in 46% despite resolution on X-ray of COVID-19 pneumonitis in 87%. They also reported persistent fatigue (68%) and sleep disturbance (57%).

Mandal et al[31] followed 384 patients (average age 59.9 years; 62% male) after discharge from any of three London hospitals for a median 54 days. Over half (53%) reported persistent breathlessness, 34% cough, and 69% fatigue. Over a tenth (14.6%) had depression. Of the people who attended for repeat imaging and blood tests because investigations on discharge had been abnormal, 9% had a deteriorating chest X-ray appearances suggestive of pulmonary fibrosis and 30.1% and 9.5% had persistently elevated D-dimer (evidence of blood clotting) and C reactive protein (a marker of inflammation) concentrations respectively.

In a prospective observational cohort study, 100 patients recently recovered from COVID-19 were identified from the University Hospital Frankfurt COVID-19 Registry between April and June 2020 (median age 49; 53% male)[32]. The participants underwent cardiac magnetic resonance imaging (CMR) with a median time interval between diagnosis and CMR of 71 days. Over three quarters (78; 78%) showed cardiac involvement and 60 (60%) continuing inflammation of the heart muscle, independent of pre-existing conditions.

The Coverscan study is "an ongoing, prospective, longitudinal COVID-19 recovery study with biochemical and imaging characterisation of organ function, starting in April 2020 before recognition of 'long-COVID', proper testing availability, and prospective COVID-19-related research." It aims to recruit around 500 individuals ≥18 years from two UK centres, specifically, a real-world population at lower risk of COVID-19 severity and mortality but with persistent symptoms following recovery from acute SARS-CoV-2 infection and age-matched healthy controls. The aim is to map the prevalence and impact of COVID-19 on multiple organs using magnetic resonance imaging (MRI), blood DNA tests, and online questionnaires. In an interim report, Dennis et al[33] reported that the 201 participants to date had an average age of 45 years were 71% female, 88% white, and 32% healthcare workers. They had relatively few pre-existing conditions (obesity 20%, hypertension 7%, type 2 diabetes 2%, heart disease 5%). Only 19% had been hospitalised during their acute illness. 42% of individuals had 10 or more symptoms and 60% had severe post-COVID-19 syndrome. Fatigue (98%), muscle aches (87%), breathlessness (88%) and headaches (83%) were the most frequently reported symptoms. MRI scans revealed mild organ impairment in the heart (26%), lungs (11%), kidneys (4%), liver (28%), pancreas (40%) and spleen (4%), with single-organ and multiorgan impairment in 70% and 29%, respectively. Severe Long-COVID was statistically significantly associated ($p<0.05$) with MRI evidence of damage to heart muscle.

Two to three months after onset of symptoms, 58 patients who had been hospitalised with COVID-19 in the UK were compared with age, sex, body mass index, comorbidity-matched controls[34]. They underwent multiorgan (brain, lungs, heart, liver and kidneys) MRI scans, lung function tests, and assessments of cardiopulmonary and cognitive function and mental health. Around two thirds (64%) of patients experienced breathlessness and 55% reported fatigue. On MRI, abnormalities were seen in lungs (60%), heart (26%), liver (10%) and

kidneys (29%). Patients exhibited changes in multiple parts of the brain on MRI scans and demonstrated impaired cognitive function. Exercise tolerance and six-minute walk distance were statistically significantly reduced. The extent of MRI abnormalities outside of the lungs and exercise intolerance correlated with serum markers of inflammation and acute illness severity. Patients had a higher burden of self-reported symptoms of depression and experienced significant impairment in all domains of quality of life compared to controls.

Guedj et al[35] reported on Positron Emission Tomography (PET) scans in patients with biologically confirmed SARS-CoV-2 and persistent functional complaints more than 3 weeks after the initial infection. These showed reduced metabolic activity in multiple parts of the brain – including those that might plausibly explain the patients' symptoms and functional complaints. In this study group, more functional complaints correlated with a longer duration of symptoms. Both memory/cognitive impairment and a higher number of functional complaints correlated with younger age.

Cognitive Function

In a large cross-sectional study (n=84,285), members of the general public – largely within the UK – were invited to take part in the Great British Intelligence Test. Among those in this population who had recovered from confirmed or suspected COVID-19, 60 reported having been on a ventilator; a further 147 were hospitalised without a ventilator; 176 required medical assistance at home for respiratory difficulties; 3466 had respiratory difficulties and received no medical assistance; and 9201 reported being ill without respiratory symptoms. Hampshire et al[36] found that the COVID-19 group, including those no longer reporting symptoms, exhibited significantly more cognitive deficits when controlling for age, sex, education level, income, racial-ethnic group, and pre-existing conditions. The deficits were more marked among people who had been hospitalised but were also found among those with mild, but biologically confirmed, disease who reported no breathing difficulty.

Studies of blood clotting (thrombosis)

Bergamo province in Italy experienced the pandemic early and intensely. Venturelli et al[10] organised a follow-up programme for COVID-19 patients discharged from the emergency department or the inpatient wards of the largest public hospital in the area. The first 767 patients completed a post-discharge multidisciplinary assessment at a median time of 81 days after discharge. Around half (51.4%) still complained of symptoms, most commonly fatigue and exertional shortness of breath, and 30.5% were still experiencing psychological consequences. Impaired lung function was found in 19%. Some (17%) had excessive blood clotting with D-dimer values over 1000 ng/ml (the threshold for diagnosis of a clot in the lung (pulmonary embolism) being 500 ng/ml).

Vlachou et al[37] evaluated the prevalence of clots in the lung (pulmonary thrombosis) and heart dysfunction associated with COVID-19 at the Royal Free Hospital in London, a tertiary referral COVID-19 centre. Of 370 SARS-CoV-2-positive patients, 39 (average age 62; 56% male) underwent computed tomography pulmonary angiography because of increased oxygen requirements and very elevated D-dimer levels. Clots (thrombosis) in the lung were found in 18 (46.2%) patients. Such clots were observed even after recovery from acute COVID-19. Four patients were re-admitted after having recovered from COVID-19 pneumonia and been discharged, having tested COVID-19 positive at first review but negative at the time of clot in the lung diagnosis at their later second admission. The researchers note that "pulmonary thrombosis is common in association with COVID-19" and that "the thrombotic risk in the pulmonary vasculature is present before and during hospital

admission and continues at least up to four weeks after discharge".

Kommoss et al[38] completed autopsies on 13 people who had died of COVID-19. The cause of death in most patients was lung damage caused by blood clots in the small blood vessels that supply the tiny air sacks in the lung (alveoli). They speculate that this may be a mechanism in people who survive COVID-19 with lung tissue scarring (pulmonary fibrosis) that leads to impairment of lung function.

Immune System

Doykov et al[39] reported that immune profiles of the 10 non-hospitalised people who had tested positive for COVID-19 were clearly disrupted even 40 days after infection, when compared 10 people who had tested negative. The significantly altered biomarker proteins were either anti-inflammatory or associated with a stress response.

Bergamaschi et al[40], in their study of 207 SARS-CoV2-infected individuals note that "immune recovery is complex, with profound persistent cellular abnormalities correlating with a change in the nature of the inflammatory response." What they reported was that signatures characteristic of increased oxidative phosphorylation and reactive-oxygen species-associated inflammation replaced those driven by cytokines. They suggested that these changes in the nature of the inflammatory response along with unresolved immune cell defects, may contribute to Long-COVID.

Diabetes

A recent commentary in Nature Metabolism[41] questioned whether a separate entity of post-COVID-19 diabetes exists. It is clear, however, that diabetes is associated with COVID-19 disease severity and mortality[42-44] and that pancreas abnormalities have been reported on MRI in a population with low pre-COVID diabetes[33].

Intestinal micro-organisms

The significance of the finding of Yeoh et al[45] – namely that there is a relationship between COVID-19 severity and an imbalance of gut bacteria up to 30 days after clearance of the SARS-CoV-2 virus – remains to be replicated and understood. As gastrointestinal symptoms are common in COVID-19 and as these researchers found that concentrations of inflammatory markers in the blood were associated with disruption of digestive system micro-organisms, this may represent yet another disease mechanism but also, perhaps, a target for prevention or treatments in Long-COVID.

Studies on Children

There are only a handful of studies on children in the context of Long-COVID. Indeed, Ludvigsson[46] planned a systematic review and found no papers that reported on children. He described case reports on five children in Sweden whose parents described symptoms similar to those seen in adults more than six months after diagnosis. A larger study of Italian children is consistent with this observation[47]. Although multisystem inflammatory syndrome has been identified in children, typically presenting three or four weeks after initial infection with SARS-COV-2, to date, there seem to be no data on long-term impacts[48].

Mechanisms

As we discussed in September 2020, the specific manifestations of Long-COVID may result from: tissue damage consequent upon invasion, virus replication and tissue destruction (*e.g.,* encephalitis; myocarditis; diabetes); the immune response involving extensive systemic release of inflammatory cytokines with resulting microvascular damage from thrombosis (*e.g.,* stroke; heart attacks). Recently, Yong et al have made similar observations[11].

There are also data on the persistence of the virus itself. Anecdotal reports[49,50] have been supported by a studies in the Netherlands[51] and Italy[52]. Overall, in the Netherlands study, the probability of detecting infectious virus dropped below 5% after 15 days after onset of symptoms; in one patient, however, infectious virus was detected up to 20 days after onset of symptoms. In Italy, of 131 patients who underwent a follow-up nasopharyngeal PCR test approximately two months after recovery from an initial proven disease, 17% tested positive again. There are known to be individuals who shed late and asymptomatically and these are acknowledged in New Zealand but rather poorly described as “historic cases”. They may be important to our understanding of Long-COVID and even of its remitting/relapsing nature.

The cause of the neurocognitive symptoms remains to be determined but as the data discussed above suggest and the fact that loss of a sense of smell is a very common presenting symptom reinforces, SARS-CoV-2 is almost certainly a neurotropic virus[53,54]. Whether blood clotting processes are also involved is queried by some because these were not thought to continue beyond the acute infection; however, the studies of post-COVID thrombosis above suggest otherwise[10,31,37], although the detection of clots at autopsy are uncommon[55].

Others have suggested other causes, including reinfection by the same or a different strain and, perhaps, post-traumatic stress[12].

Conclusions

The real prevalence of Long-COVID remains unclear. The studies that rely on self-report suggest that it is at least 15-20% of survivors of the acute infection. However, the studies that have explored evidence of tissue damage in multiple organ systems may point to wider organ damage without obvious symptoms (*e.g.,* lung scarring [fibrosis], and heart muscle inflammation [myocarditis]) that is not detected in many now – because it is not looked for – but may emerge later in life or following some other disorder.

Many health workers who clinically manage Long-COVID rightfully point to the wide spectrum of presentations and needs. They also note that we do not know how, why, or if this chronic disorder resolves. Finally we have no clear understanding of what support and treatment needs are essential for the management of the massive number of Long-COVID patients who are still accumulating across the world (note, again, that the Office of National Statistics estimated that, at the end of 2020, there were over 300,000 sufferers in the UK alone[18]).

Clinical management is facing the problem that Long-COVID is clearly a set of different syndromes with different manifestations presenting as a result of different disease processes and that, therefore, the need is for a multi-focused treatment playbook. This playbook has not yet been drafted.

Across the whole of humanity, over and above the huge case load and death toll associated with infection with SARS-CoV-2, we need to remain focused on the fact that the long-term disease burden will continue to grow and will remain with us, probably for decades. To characterise this as “a relatively mild pathogen” as a New Zealand economist did very recently is complete nonsense and, quite frankly, monstrous.

Finally, what all this tells us – still in the dark as we are about the exact burden and the appropriate management strategies – is that we have to rely extensively on prevention as the vital first step. That means persisting with our Elimination strategy[56] in Aotearoa New Zealand even as we vaccinate as widely as possible. This is not Eradication, rather we need to maintain our current approach to:

- Border management, including exclusion and quarantine, facilities for which need to be purpose-built soon
- Case identification, contact tracing including using digital technology, and outbreak management, including case isolation and quarantine
- Disease surveillance, including widespread testing and surveillance of those without disease – sentinel surveillance and wastewater surveillance
- Physical distancing and movement restriction at various levels (up to and including full lockdown)
- Public communication to improve hand washing, cough and sneeze etiquette, mask wearing, and physical distancing
- Protecting vulnerable populations
- Improving health-system capacity, e.g., expanding ICU and ventilator capacity as well as updating quarantine facilities
- Protecting healthcare workers

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