Review Article

Post-Acute COVID-19 Sequelae – 'COVID Long Hauler'

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ABSTRACT

Severe acute respiratory syndrome coronavirus-2 infection manifests with an acute illness of varying severity and unpredictable mortality. Those who survive may develop a more prolonged disease process called post-acute COVID-19 sequelae which causes considerable disability regardless of the severity of the acute disease.

Two phenotypes have been described. First, those with persistent organ dysfunction related to the degree of the inflammatory response and second those with less well defined, but no less troublesome symptoms, that considerably impact the quality of life.

This review discusses both phenotypes and the proposed mechanisms and also explores possible therapies for this condition.

Keywords: COVID 19; Long Haulers; debility

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first detected in Wuhan, China, and is responsible for the current 'Covid-19 (COVID)' pandemic. The disease associated with this virus manifests with many symptoms predominantly, but not exclusively, respiratory. These may include cough, shortness of breath or difficulty in breathing, fatigue, muscle or body aches, headache, loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhoea and occasionally fever.(1)

This symptom constellation can progress to more severe disease most often related to hypoxaemia from COVID pneumonia but may also be associated *inter alia* with cardiac, neurological, haematological and thrombotic manifestations. More severe disease has substantial mortality despite intensive support and is usually related to a dysregulated inflammatory response that results in respiratory failure. Other causes of mortality, not primarily related to viral pneumonia, include veno-thromboembolism, cerebrovascular accidents (CVA), myocardial infarction, a macrophage activation/cytokine release syndrome and diabetic ketoacidosis.(2)

The diagnosis of COVID is confirmed by a positive result for SARS-CoV-2 using a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay. Antigen tests can be used for a more rapid diagnosis but, while they are as specific as the nucleic acid amplification test, they are less sensitive meaning that false positives are rare but false negatives do occur.(3) With the burden of emerging new viral strains, a confirmatory PCR is advisable for patients having symptoms, to allow for accurate epidemiological tracking of disease.

CHRONIC MANIFESTATIONS

A distinct syndrome of a more chronic disease is being defined and is colloquially referred to as 'long COVID'. It has been described as the persistence of symptoms for a prolonged period of time after a patient has experienced 'the illusion of recovery'.(4) This condition manifests with a constellation of symptoms where a patient suffers from post-acute COVID-19 sequelae (PACS). There are a wide range of recurring symptoms regardless of whether or not the acute disease required hospitalisation. These symptoms may manifest in the respiratory system, brain, cardiovascular system, kidneys, gut, liver and skin. Symptoms range in intensity, duration and are non-sequential. Although patients who required ventilatory support may be expected to have symptoms that take longer to recover, many patients with PACS may have had 'mild' disease not requiring hospitalisation at all.(5)

COVID patients who develop chronic symptoms (not related to intensive care complications) are often physically fit, younger people who had relatively mild disease. They may have persistent exercise intolerance, breathlessness, cough, anxiety, palpitations, poor concentration, intense fatigue, mood swings, muscle and joint pains, headaches and a poorly defined cerebral sensation known as 'brain fog'.(6,7)

A study amongst health-care workers in Sweden compared participants with no or mild symptoms with a seronegative group who had not had COVID.(8) Twenty-six per cent of the former vs 9% of the latter reported ≥1 moderate-to-severe symptoms that had been present for ≥2 months (risk ratio (RR) 2.9 [95% confidence interval (CI), 2.2–3.8]) and 15% vs 3% had ≥1 symptoms for ≥8 months (RR 4.4 [95% CI, 2.9–6.7]). The symptoms that had been present for ≥2 months were most commonly anosmia, fatigue, ageusia and dyspnoea and, compared with seronegative participants, the seropositive participants felt that these had moderately to markedly disrupted work life (8% vs 4%; RR 1.8 [95% CI, 1.2–2.9]); social life (15% vs 6%; RR 2.5 [95% CI, 1.8–3.6]) and home life (12% vs 5%; RR, 2.3 [95% CI, 1.6–3.4]). In addition, 11% of seropositive participants felt that they had moderate to marked disruption in any of the Sheehan Disability Scale categories as well having ≥1 moderate-to-severe symptoms lasting for ≥8 months compared to 2% of seronegative participants (RR 4.5 [95% CI, 2.7–7.3]).(8)

In another study, 292 patients were interviewed and of 94% with ≥1 symptom at diagnosis, 35% had not recovered at a median of 16 days post testing.(9) Symptoms were present in 26% aged 18–34 years, 32% aged 35–49 years and 47% aged ≥50 years. Forty-three per cent of those who had a cough as an initial symptom, 35% with fatigue and 29% with a shortness of breath still had these symptoms at follow-up. Factors associated with the persistence of symptoms were age ≥50 vs 18–34 years (adjusted odds ratio (aOR) 2.29 [95% CI, 1.14–4.58]); ≥3 comorbidities vs no comorbidities (aOR 2.29 [95% CI, 1.07–4.90]); body mass index (BMI) ≥30 (aOR 2.31 [95% CI, 1.21–4.42]) and an underlying psychiatric condition (aOR 2.32 [95% CI, 1.17–4.58]).(9)

A more recent publication found that prolonged symptoms were less common but still affected a considerable number of patients.(10) The study recorded self-reported symptoms on a cell phone app for 4182 COVID cases. Of these, 558 (13.3%) had symptoms for ≥28 days, 189 (4.5%) for ≥8 weeks and 95 (2.3%) for ≥12 weeks. The major symptoms were the same as for other studies: fatigue, headache, dyspnoea and anosmia with predisposing factors being age, BMI and female sex. In addition, the number of symptoms originally experienced was related to the likelihood of on-going symptoms (OR 3.53 [95% CI, 2.76–4.50]).(10)

A recent single hospital Chinese cohort study of 1733 COVID positive patients was followed post symptom onset for a median of 186 (175–199) days.(11) Their median and interquartile range age was 57.0 (47.0–65.0) years and 52% were male. In these patients the severity of their initial illness was categorised according to whether they required supplemental oxygen, need for other delivery modes such as high flow nasal or CPAP or if they required intubation and mechanical ventilation (MV). Questionnaires were administered evaluating symptoms and health-related quality of life (HRQoL) and a physical examination, a 6-min walk test and blood tests were performed. At 6-month follow-up, 76% had at least one symptom. These included fatigue or muscle weakness (63%), insomnia (26%), hair loss (22%), anosmia or ageusia (11% and 9%) and relative immobility (7%). With regard to mobility, the reduction in the 6-min walk test was in the region of 20%–30% below the lower limit of the normal range. There were also significant increases in anxiety and depression.(11)

Neurological Dysfunction

Cognitive dysfunction is perhaps one of the most troublesome manifestations and is described as 'brain fog' by many. Of 84,285 Great British Intelligence Test participants, those who recovered from COVID were selected and tested for cognitive dysfunction.(12) There were 60 who reported being MV, 147 hospitalised but not ventilated, 176 required medical assistance at home for respiratory difficulties, 3466 had respiratory difficulties but received no medical assistance and 9201 who reported being ill but not having respiratory symptoms. Amongst these patients, the investigators found that there were significant cognitive deficits when controlling for age, gender, education level, income, racial-ethnic group and pre-existing medical disorders. The effect size was greatest for those who were hospitalised, but also significant for mild confirmed cases that had not had respiratory symptoms. The 0.57 standard deviation (SD) global composite score reduction for the MV group was equivalent to the average global performance of 10-year decline between ages 20 and 70 and was larger than the mean deficit in 512 people who had previously had a CVA. Of interest, a 0.57 SD decline is equivalent to an 8.5-point difference in IQ.(12)

Another recently published study followed a large cohort of patients discharged from hospital and who were identified by telephonic interview as having at least one persistent symptom compatible with 'long COVID' or having been admitted to intensive care.(13) Four hundred and seventy-eight patients thereafter underwent a full history and examination which included the recording of any symptoms and also quality of life scores. Of the symptoms that were elicited via a telephonic interview, fatigue was present in 31%, cognitive dysfunction in 21% and dyspnoea in 16%. Of 177 patients who had an in-person assessment, quality-of-life scores were lowest for activities relating to daily living (physical impairments), with a median score of 25 on a scale of 0 (worst) to 100, and for reduced motivation related to fatigue, with a median score of 4.5 on a scale of 1 (best) to 5.(13) In terms of specific symptoms,

sleep disturbance (54%) and cognitive impairment (38%) were frequent and in 94 patients who had been admitted to intensive care unit (ICU), anxiety (23%), depression (18%) and posttraumatic stress disorder (7%) were the most frequent. Muscular weakness occurred in 27.5% of those who had undergone MV.

Many of the complications experienced by patients are similar to post ICU syndrome (PICS) which describes health problems that persist after any critical illness.(14) These symptoms may be present in the ICU and persists after discharge. For instance, weakness is present in >50% who are admitted to the ICU for ≥1 week and may take more than 1 year to recover from. Many factors contribute to the weakness, including the use of neuromuscular blockers, deep sedation, glucose control and severity of illness.(14,15) Most studies of PICS report persistent anxiety and depression at 12 months, but some report post-traumatic stress disorder for up to 8 years and there is a 3-fold increase in the odds of moderate/severe cognitive impairment.(14)

Pulmonary Complications

Perhaps the most easily recognisable and measurable symptom post COVID is persistent respiratory disability. Respiratory manifestations generally include dyspnoea and a chronic cough which may be as a result of lung fibrosis, traction bronchiectasis and pulmonary embolic disease. Of note, 30% of survivors of SARS-CoV-1 or Middle East Respiratory Syndrome coronavirus infections also had persistent lung abnormalities; however, this was mostly mild with a reduction in gas transfer, i.e. diffusing capacity for carbon monoxide (DLCO) in the region of 70%–80%.(16)

Pulmonary fibrosis occurs in patients who have had the most severe disease and interestingly the risk factors for severe COVID are similar to those of idiopathic pulmonary fibrosis (male sex and older age), in which a viral stimulus such as the herpesvirus that targets the endothelial cell has been implicated.(16) Essentially, fibrosis occurs in response to a defective repair process following inflammation or oxidant-induced endothelial injury, with a proliferation of fibroblasts and myofibroblasts and a deposition of collagen in the extracellular matrix.(17)

These patients may have severe restriction with a reduction in DLCO that persists for months or potentially may be permanent. Some patients who have severe fibrosis and appear unlikely to recover may have some improvement over time. Corticosteroids may hasten recovery to some extent although it is too early to be certain of the overall impact on long-term respiratory disability.(18)

Dyspnoea is the most common persistent pulmonary symptom of 'long COVID', ranging from a 42%–66% prevalence at 60–100 days of follow-up and in one study the need for CPAP or supplemental oxygen was 6.6 and 6.9%, respectively, at 60 days.(13) A reduction in DLCO is the most common measurable manifestation of PACS, particularly in those who have required oxygen and especially in those who have been mechanically ventilated. This is frequently accompanied by restrictive lung disease which has been documented to be present for at least 3–6 months.(11,19–21)

In a study by Huang et al., in which patients were categorised according to oxygen requirement and mode of delivery, and thereafter categorised on a 7-point severity scale where 7 was the most severe category achieved during their admission, diffusion impairment occurred in 22% for severity scale 3, 29% for scale 4 and 56% for scale 5–6.(11) Median-computerised tomography (CT) scan scores for fibrosis and the DLCO deficit increased in relation to severity of initial illness as well.

It is becoming increasingly recognised locally and internationally that a syndrome that clinically resembles cryptogenic organising pneumonia (COP), in which bilateral ground glass infiltrates are seen on chest X-ray, occurs weeks or months after the acute COVID infection and may be steroid responsive. This syndrome was recently described in a study from the United Kingdom.(22) Of 837 patients followed up 4 weeks after discharge, 39% ($n = 325$) had on-going symptoms. At 6 weeks, 4.8% ($n = 35$) had evidence of interstitial lung disease with bilateral ground glass opacities (mostly COP). Of these, 30 received 0.5 -mg/kg prednisolone weaned over 3 weeks with resultant improvement in DLCO by 31.6% ($P < 0.001$) and forced vital capacity by 9.6% ($P = 0.014$). The syndrome affected mostly males (71.5%) who had a mean BMI of 28.3 (26% were obese) and had ≥1 comorbidity, most commonly diabetes and asthma (22.9%).(22)

Thus it is essential that COVID patients who have new onset or worsening shortness of breaths after discharge be investigated. This should include full lung function tests and a high-resolution CT scan, with or without pulmonary angiography, to exclude organising pneumonia and pulmonary embolism.

Cardiac Complications

Myocardial injury with potential for myocardial dysfunction remains a concern with PACS. In an autopsy study of COVID patients, in which pneumonia was listed as the cause of death in 89.7%, although histopathology did not meet the criteria for acute myocarditis, actively replicating virus was present in the interstitial cells and macrophages of the myocardium in 61.5% (16 of 24 patients). This was associated with an increased activity of pro-inflammatory genes as well.(23,24)

In another study, 20%–35% of hospitalised patients with COVID infection had elevated troponin and natriuretic peptides and these findings were associated with higher mortality.(25) Echocardiography during hospitalisation demonstrated right ventricular dilatation in 39% and left ventricular (LV) diastolic dysfunction in 16%.(26) Similar findings have been shown in 105 hospitalised patients from New York.(27)

A German study comparing mild-to-moderate COVID cases with healthy and risk factor–matched controls, evaluated at a mean of 71 days after recovery, found 78% had demonstrable cardiac involvement on cardiac magnetic resonance (CMR) imaging, 76% had detectable high-sensitivity troponin, and 60% had evidence of myocardial injury and inflammation on CMR.(28) LV ejection fraction was lower and LV volumes higher and 32% manifested late gadolinium enhancement and 22% pericardial involvement.(28) Although there was potentially selection bias, and as such generalisability was uncertain and not all may have recovered, this still remains a concern. Notably an Ohio State University study showed CMR changes suggestive of myocarditis in 15% of athletes after asymptomatic/mild disease.(29)

A more recent study performed CMR imaging (including adenosine stress perfusion if indicated) at a median of 68 days after discharge in 148 COVID patients (all of whom had required hospital admission and 42% had required MV), which had elevated troponin levels during their admission. LV function was normal in 89% with a mean ejection fraction of 67% ± 11%. Late gadolinium enhancement and/or ischaemia was found in 54% comprising myocarditis-like scars in 26%, infarction and/or ischaemia in 22% and both in 6%.(30) Myocarditis-like injury without LV dysfunction which was limited to ≤3 myocardial segments was present in 88% of patients, 30% of whom had active myocarditis. Of particular concern, myocardial infarction was found in 19% and inducible ischaemia in 26%. Of those patients with ischaemic changes, 66% had no past history of coronary disease.(30)

It is currently unknown whether the cardiac injury will persist in PACS patients and it is also not clear if the ischaemic events were virally mediated or were related to pre-existing coronary vascular disease. However, in those with the most severe disease and in particular if the troponin levels were elevated, cardiac function should be evaluated and monitored.

PATHOGENESIS OF PACS

The aetiology of PACS features is unknown, and investigations are on-going to elucidate the problem. There may be an association with the extent of the inflammatory response, cytokine-mediated cellular injury and cellular energy depletion, which may account for some of the symptoms; however, not all patients who develop this syndrome experience severe symptoms during the acute phase.(31) A deficiency of nicotinamide adenine dinucleotide (NAD+) (the primary building block being nicotinic acid), which along with zinc is essential for the activation of the silent information regulator (SIRT 1), an immunomodulatory molecule suppressing the production of pro-inflammatory cytokines, may be a factor involved in acute COVID infection and also in its chronic manifestations.(32–34) NAD+ deficiency is present in most of the comorbid conditions associated with severe disease and mortality, and COVID-19 itself further decreases NAD+ by increasing its utilisation as an energy source through inflammation and through the activation of the DNA repair enzyme poly [ADP-ribose] polymerase 1 (PARP1).(35,36) This deficiency may persist following the acute illness and be enhanced by low grade on-going inflammation, particularly in those with the comorbidities described earlier.(37) Where NAD+ is depleted and exogenous sources are not available, tryptophan is utilised via the kynurenine pathway to enhance production which, in addition to its role in SIRT activation, is an essential cofactor for cell survival and even more so in metabolically active tissues (Figure 1).(38)

NAD+ levels are maintained by three pathways. The most common is the Preiss–Handler pathway in which nicotinic acid is the substrate. If nicotinic acid is insufficient, NAD+ is synthesised from tryptophan with an excessive accumulation of the metabolites kynurenine and quinolinic acid. The NAD+ salvage pathway recycles the nicotinamide generated as a by-product of the enzymatic activities of NAD+-consuming enzymes.(39)

NAD+ BIOSYNTHETIC PATHWAYS

The resultant depletion of tryptophan is exacerbated by the genetic upregulation of the kynurenine pathway in COVID infection and by the increase in proinflammatory cytokines such as TNFα and γ-interferon.(36,38) This decreases the availability of serotonin and melatonin, which are important for control of mood, temperature regulation, sleep cycle, sensory stimulation, nociception and nerve regulation.(40–42) Metabolites of tryptophan catabolism so produced are implicated in many disease processes and may explain various symptoms of PACS, including autonomic dysfunction.(43–46) Similarly, quinolinic acid, a precursor of nicotinic acid mononucleotide, is increased by an upregulation of the kynurenine pathway and increased levels have been implicated in the clinical manifestations of many diseases.(44,47–49) Quinolinic acid also activates NMDA receptors with the release of glutamate and the resultant calcium influx increases protein kinases, phospholipases, nitric oxide synthetase and proteases which may contribute to the neurological manifestations.(50) Finally, autopsy studies have shown changes in brain parenchyma and blood vessels, and these may affect the integrity of the blood–brain/cerebrospinal fluid barriers which may promote neurological inflammation.(31,51,52)

DIAGNOSIS

Clear clinical syndromes of PACS may be recognisable, but they may also overlap. They can be due to organ dysfunction related to the acute illness or to a post viral condition where the diagnosis may be vague and the social impact more difficult to quantify as most studies have focused on symptoms alone and not the impact of these symptoms on patients' lives. One of the most troubling aspects of PACS is that symptoms

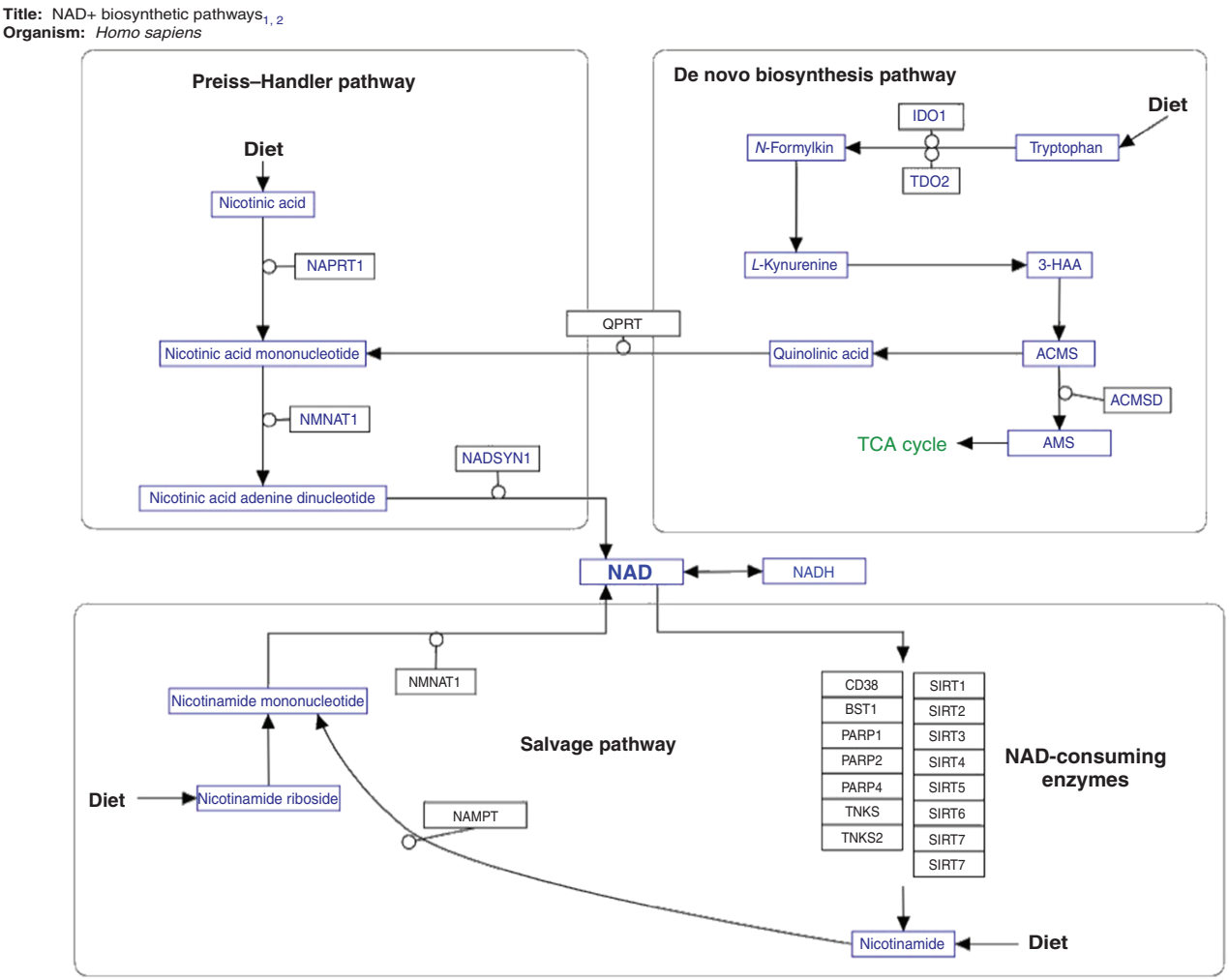

Fig 1: The Preiss–Handler, de novo synthesis and salvage pathways of NAD+.(39) NAPRT, nicotinic acid phosphoribosyltransferase; NAMN, nicotinamide adenine mononucleotide; NAAD, nicotinic acid adenine dinucleotide; NMNAT, NAMN transferase; NADS, NAD+ synthase; *N*-formylkin, *N*-formylkynurenine; IDO, indoleamine-pyrrole 2,3-dioxygenase; TDO, tryptophan 2,3-dioxygenase; ACMS, amino-3-carboxymuconate semialdehyde; PARPS, poly-ADP ribose polymerases; SIRT, sirtuins

frequently manifest in the young and may occur following mild or moderate disease. There are furthermore no specific diagnostic criteria or biological tests that would facilitate its identification, and as a consequence there are no proven therapies available. Health-care services are generally not geared to manage these patients and few dedicated clinics exist, leaving the patient feeling helpless, without support and feeling unable to return to work. The latter has been the subject of intense study and certain tools have been developed that can measure the impact on HRQoL such as the effects on mobility, the sensation of fatigue and cognitive/neurological function.(53) The WHO form to assess PACS consists of 45 criteria and includes questions on patient functionality. A similar tool has recently been published as a preprint from France which has been validated for their circumstance.(54) This type of tool is essential in that it can measure symptoms and their impact on quality of life and functioning as well as document severity, record recovery and evaluate therapeutic modalities.

TREATMENT

Prevention of fibrosis in COVID patients involves lung protective ventilation and corticosteroids as per the RECOVERY trial. However, if oxygenation continues to deteriorate and interleukin-6 and CRP continue to rise, larger doses of steroids and potentially administration of Tocilizumab may be needed to dampen the inflammatory process.(55,56) It is possible that other anti-inflammatory agents such as colchicine may reduce the propensity to form mature collagen; however, there are no clinical studies to confirm this treatment as yet.(57)

Pirfenidone is an antifibrotic and anti-inflammatory agent used in the treatment of idiopathic pulmonary fibrosis and there are a few case reports emerging suggesting some efficacy in patients with 'COVID-associated pulmonary fibrosis'. The drug, however, remains very expensive in most settings and would be used as an off-label indication.(58–60) Other on-going studies are assessing

several antifibrotic agents to potentially decrease the progression of fibrosis or as potential therapy for established fibrosis.(31)

We have recently described significant improvement in oxygenation in some patients following the removal of fibrinous, tenacious plugs by fiberoptic bronchoscopy.(61) It is possible that if fibrinous plugs are present, and removed by bronchoscopy, and ventilator time is reduced, the potential for fibrosis to occur would also be reduced. However, this technique is limited by the availability of expertise and it can cause significant hypoxaemia during the procedure. It is possible that these plugs may also be prevented prior to their development by the use of mucolytics or heparin nebulisation.(62–64) Whether primary prevention in this manner would improve outcome and reduce fibrosis is not proven and requires further study.

In terms of the proposed aetiological mechanism of PACS, it is possible that where the symptomatology is not related to specific organ dysfunction, combinations of supplements inclusive of nicotinic acid, zinc and vitamin D may be of benefit but at this point no randomised trials have been performed.

CONCLUSION

PACS is real, but not always easy to define. It may affect multiple organ systems and considerably impact HRQoL. More detailed studies are needed so that effective, evidence-based therapies are found. Where specific organ dysfunction occurs, preventative strategies should be developed and tested and response to these interventions documented. 'Long COVID' clinics are being established in resource-rich countries, but this may not always be possible in low- or middle-income countries. Physicians should however be aware of the problem, support patients and collaborate amongst with each other to promote a return to health.

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