A clinical review of long-COVID with a focus on the respiratory system

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ABSTRACT

Purpose of review

Persistence of symptoms after acute COVID-19, often described as long-COVID, is common and debilitating. In this article, we review the epidemiology, clinical features, and research priorities for long-COVID focusing on the respiratory system.

Recent findings

Breathlessness, cough and chest pain were the most commonly reported respiratory symptoms associated with long-COVID. In hospitalised patients, abnormalities on lung function testing or chest imaging were observed less commonly at 12 months compared to six months since discharge. Clinical assessment of patients with persisting symptoms after acute COVID-19 requires a comprehensive evaluation to exclude other possible causes for symptoms. With no robust current evidence for interventions to treat long-COVID respiratory symptoms, symptomatic treatment, supported self-management and pulmonary rehabilitation should be considered to help individuals with respiratory symptoms associated with long-COVID.

Summary

Long-COVID is a debilitating syndrome which often includes persisting respiratory symptoms and to a lesser degree, abnormalities in lung physiology or imaging. Respiratory features of long-COVID may reduce over time, yet resolution is not seen in all cases. Future research is needed to understand the natural history of long-COVID, identify factors associated with spontaneous improvement/persistence, investigate mechanisms for persisting symptoms, and test interventions to prevent and treat long-COVID.

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Keywords: COVID-19; long-COVID; respiratory; breathlessness

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has had a devastating impact worldwide, with over 270 million confirmed cases and more than 5.3 million deaths reported by the end of 2021.[1] Whilst many individuals experience Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection as an acute illness, approximately 1 in 10 people report persisting illness beyond 12 weeks, which is referred to variably as post-acute COVID-19 syndrome, the post-COVID-19 condition, or most commonly long-COVID.[2] In this article we review the epidemiological and clinical evidence for long-COVID with a focus on the respiratory system and outline priorities for future research.

Definition of long-COVID

According to clinical case definitions, symptoms or signs continuing over 12 weeks after the onset of confirmed or probable SARS-CoV-2 infection which are not explained by an alternative diagnosis can be described as the post-COVID-19 syndrome.[3,4] In addition to the case definition, long-COVID is a term used by affected people to describe ongoing symptoms after acute COVID-19. In this review we use the term long-COVID as defined by the National Institute of Health and Care Excellence (NICE) as being both ongoing symptomatic COVID-19 (symptoms between four and 12 weeks) and post-COVID syndrome (12 weeks or more).[3]

Epidemiology

Prevalence estimates for long-COVID vary due to the definition, sample, and method of data collection used. In the UK, the population prevalence of self-reported long-COVID has been estimated between 2%[2] and 6%[5]. In individuals taking part in community-based studies, who had confirmed or suspected SARS-CoV-2 infection, the prevalence of symptoms after 12 weeks has been estimated between 2%[6] and 38%.[5] Individuals requiring hospital treatment for acute COVID-19 tend to report higher levels of debilitating symptoms; at six months since discharge,

93% of patients completing a symptom questionnaire in the post-hospitalisation COVID-19 (PHOSP-COVID) cohort reported at least one persistent symptom.[7] In addition to hospitalisation, the (population) prevalence of self-reported long-COVID also varies by age, sex and pre-existing health status, with older age groups, females and individuals whose activity is limited by another health condition more likely to report long-COVID.[2,8] Different variants of SARS-CoV-2 (i.e. alpha, delta, omicron) may also influence the degree to which long-COVID is experienced.

Clinical manifestations

Long-COVID symptoms may be persistent following acute infection, may fluctuate or relapse over time, or be new in onset following a perceived recovery from the acute phase.[3,4] Individuals with long-COVID describe a wide range of debilitating symptoms including fatigue, breathlessness, muscle ache, joint pain, headache, cough, chest tightness, loss of smell/taste, anxiety, poor concentration and diarrhoea.[8]

Phenotypes of long-COVID

A study of 4,182 community based respondents who were predominantly female and below the age of 70 years, reported two main symptom clusters 28 days after COVID-19 infection: firstly fatigue, headache and respiratory symptoms (breathlessness, sore throat, cough, loss of smell); secondly multi-system features including persistent fever and gastrointestinal symptoms.[6] In a smaller cohort of 327 patients who required hospitalisation for COVID-19 and responded to a follow up questionnaire at least 90 days after discharge, two major symptom clusters were identified.[9] Fatigue, muscle ache, and sensorineural deficits were described in one cluster, and loss of smell/taste, reduced appetite, weight loss, and difficulty passing urine in a second cluster.[9]

Using data from a symptom questionnaire, physical performance testing and cognitive assessment, the PHOSP-COVID consortium conducted a cluster analysis based on 1,077

patients (36% female, mean age 58 years, 69% White ethnicity) who were followed up for a median of 5.9 months after discharge from hospital.[7] Using measures of breathlessness, fatigue, anxiety, depression, post-traumatic stress disorder, physical performance, and cognition, four cluster phenotypes were identified: i) very severe mental or physical impairment; ii) severe mental or physical impairment; iii) moderate mental or physical impairment and poor cognition; and iv) mild impairment. In the very severe cluster, 38% of individuals required the highest level of respiratory support, 54% were male, 68% were obese and co-morbidities were common.[7] Only 3% of those in the severe cluster considered themselves fully recovered, with breathlessness, fatigue, and very severe disability noted.[7] In comparison, individuals in the mild cluster reported fewest symptoms and mild disability with 43% of individuals feeling fully recovered.[7] The mild cluster had fewer (28%) individuals requiring the highest level of respiratory support during acute admission, a greater proportion of males (72%) and fewer co-morbidities.[7]

Respiratory symptom cluster

The most commonly reported respiratory symptoms associated with long-COVID include breathlessness, cough and chest pain or tightness. In a meta-analysis, breathlessness was estimated to affect 32% (95% CI 18 to 47; 16 studies, n=4,283) of individuals with long-COVID.[8] The experience of breathlessness is likely to be more common in those who required hospitalisation for COVID-19,[10] for instance, in the PHOSP-COVID cohort, 51% of individuals reported breathlessness 12 months following discharge.[11] Estimates for the prevalence of other respiratory symptoms following COVID-19 also vary depending on if patients required hospitalisation and the duration of follow-up. At 30 days after the onset or admission for COVID-19, the prevalence of cough was estimated as 18.6% (95% CI 10.6 to 30.7; 9 studies, n= 1,829), decreasing to 8.6% (95% CI 5.3 to 13.7; 8 studies, n=8,219) after 90 days.[12] The prevalence of chest pain at 30 days since COVID-19 was estimated as 6.6% (95% CI 1.5 to 25.2; 5 studies, n=832) increasing to 9.4% (95% CI 6.7 to 13.1; 13 studies, n=8,945) at 90 days.[12] The estimated

prevalence of cough was higher in hospitalised compared to non-hospitalised populations at 30 (25.6% vs 13.9%) and 90 days (10.4% vs 6.7%) from the onset of COVID-19.[12] In contrast, the prevalence of chest pain was lower in individuals who had been hospitalised compared to those not requiring hospital care at 30 (1.1% vs 10.9%) and 90 days (7.7% vs 14.9%).[12]

Objective evidence of lung damage after COVID-19

Abnormalities on lung function testing or chest imaging have been reported in several cohorts of individuals who required hospitalisation for COVID-19, but many studies are limited in that there was selective use of further investigation, in part due to pandemic limitations. In the PHOSP-COVID study, approximately one-third of individuals who underwent lung function testing six months following discharge had an abnormal Forced Expiratory Volume in 1 second (FEV_1), Forced Vital Capacity (FVC) or Transfer Capacity of the Lung for Carbon Monoxide (TLCO), though it was not possible to identify if the changes preceded hospitalisation for COVID-19.[7] A further UK study of 384 patients hospitalised for COVID-19 reported that compared to baseline, chest x-ray images were normal or improved in 88% of those who had a repeat x-ray two months after hospital discharge.[13] In a Chinese cohort of 1,276 individuals hospitalised for COVID-19, the proportion of individuals with an abnormal findings on chest Computerised Tomography (CT) at 12 months since onset of symptoms was significantly reduced compared to six months.[14] In the 243 individuals who completed pulmonary function testing, lung volume measurements were within the normal limits for most patients, though 87 (36%) individuals had lung diffusion impairment at 12 months.[14]

Comparison to other clinical syndromes

Initial estimates for the possible long-term consequences of COVID-19 were informed by prospective cohort studies of patients treated for severe acute respiratory syndrome (SARS).[15] One study of 55 patients who required hospitalisation for SARS in Hong Kong, found that 29

(53%) individuals had an impaired diffusing capacity of the Lung for Carbon Monoxide (DLCO) persisting for at least 24 months, though in most cases the impairment was mild.[16] Exercise capacity and health status were lower than the general population throughout the two year study period.[16] In a further study, 71 patients treated for hospital acquired SARS in Beijing, were followed up over 15 years.[17] Three years after acute illness, 46 (35%) patients had mild impairment in DLCO, with 10 (22%) having restrictive ventilation disorder.[17] Little change in lung function tests was found 15 years later.[17] Pulmonary CT scans identified ground glass opacities or cord-like consolidations in 27 (38%) of individuals after SARS, however, after 12 months many of the radiological changes had reduced or resolved.[17]

Whilst long-COVID may be the most obvious reason for persisting respiratory symptoms or lung damage after acute COVID-19, other factors should also be considered, particularly in those requiring hospital treatment. For instance, for patients treated in the Intensive Care Unit, barotrauma due to high pressure ventilation has been linked to the development of lung fibrosis.[15,18] Follow up studies of individuals treated for acute respiratory distress syndrome (ARDS) unrelated to COVID-19, have found that whilst there is recovery in lung function and only mild abnormalities seen on chest radiography, reduced quality of life with ongoing exercise limitations can persist for up to five years after treatment for critical illness.[19,20]

Diagnostic work-up

The following clinical recommendations are based on the joint guideline for managing the long-term effects of COVID-19, co-produced by NICE, the Scottish Intercollegiate Guidelines Network (SIGN) and Royal College of General Practitioners (RCGP).[3] Making a diagnosis of long-COVID requires holistic and multi-professional assessment, including a careful history, alongside appropriate examination, and investigation. Individuals may not have considered the possibility of long-COVID as an explanation for their symptoms, or might feel anxious that their experiences may not be taken seriously, so listening attentively and empathetically are important.[3] Having an understanding of the personal characteristics which make long-COVID more likely (e.g. female

sex, requiring hospital treatment, co-morbidities)[8] is important, but should not preclude long-COVID being considered in those without risk factors.[3] Similarly, the absence of a positive SARS-CoV-2 test should not exclude individuals from being assessed for long-COVID, as long as the case definition criteria are met.[3]

Physical examination and investigations should be conducted in accordance with the clinical history. For individuals presenting with respiratory long-COVID symptoms to primary care, consider blood tests (for example, a full blood count, renal and liver function, C-reactive protein, N-terminal pro B-type natriuretic peptide (NT-BNP) or BNP, HbA1c and thyroid function tests), the 1-minute sit-to-stand test[21] and a chest x-ray.[3] A normal chest x-ray does not necessarily exclude underlying lung disease.[3] In secondary care, additional bloods such as d-dimer and troponin and should be considered in addition to an exercise tolerance test (6 minute walking or incremental shuttle walking tests) which is more achievable in a secondary care setting and may offer advantages over the sit-to-stand test.[22,23] To investigate persisting respiratory complaints after COVID-19 in the hospital setting, lung function testing (including gas transfer), cardiac investigation and further chest imaging with a high resolution computed tomography (HRCT) scan or computed tomography pulmonary angiography (CTPA) should be organised as appropriate.[22,24] In some instances, CTPA may underestimate pulmonary vascular manifestations after COVID-19 (such as small vessel pulmonary thromboses) and therefore, ventilation perfusion (VQ) scintigraphy and VQ single-photon emission computed tomography (SPECT) may be considered to screen for ongoing lung perfusion complications.[25] In some instances, identifying lung abnormalities on imaging or physiology tests may not be fully explainable by long-COVID alone and should not exclude assessment for other treatable traits causing breathlessness and cough.

In addition to clinical investigations, patients referred to specialist long-COVID clinics should be screened for breathing pattern disorders. As part of a holistic assessment of respiratory symptoms, checking for co-existing anxiety and/or depression should be considered and addressed.[3]

Clinical management

Specific complications (such as pulmonary embolism, myocarditis) should be managed appropriately. For non-acute presentations when alternative diagnoses have been excluded, options for management should be discussed to facilitate shared decision making.[3] Depending on local availability, referral to a specialist, multi-professional long-COVID, respiratory or rehabilitation service may be considered.[3] Patients should be given advice on self-management, including how to monitor and respond to their symptoms and setting realistic goals. Some patients may value devices/applications to help them monitor heart rate, oxygen saturation, blood pressure or keep a record of their symptoms and progress over time.[3,26] For specific symptoms such as chest pain, cough or breathlessness, symptomatic treatment may be appropriate, though patients should be clear that there is a currently a lack of robust evidence for medications to treat long-COVID itself.[3] Pulmonary rehabilitation may also be considered for respiratory symptoms associated with long-COVID, and as many individuals will not have a prior chronic lung condition, the aim of rehabilitation is for full recovery.[27] The involvement of an occupational therapist, physiotherapist or psychologist is invaluable where post-viral fatigue syndrome, dysfunctional breathing, deconditioning or post-traumatic stress disorder are present.[27] It is important to recognise that there is a significant overlap in the experience of fatigue and breathlessness, with some patients finding it difficult to distinguish between the two symptoms. Rehabilitation programmes for patients with fatigue should be aware of the risk of developing post-exertional malaise in patients with long-COVID, and the importance of carefully pacing patients.[27]

Prognosis

Whilst early indications suggest that the prevalence of long-COVID decreases with time from the onset of acute SARS-CoV-2 infection, a substantial proportion of people continue to report

symptoms well beyond 12 months. In a Chinese cohort of 1,276 individuals hospitalised for COVID-19, 88% of those in full or part-time work had returned to their original work at 12 months after the onset of COVID-19 symptoms.[14] In contrast, in the PHOSP-COVID cohort, which had a higher proportion of individuals with more severe acute disease than the Chinese study, only 29% of individuals felt fully recovered 12 months since discharge.[11] Current evidence suggests that breathlessness, cough (though not chest pain) are reported less frequently as time since acute COVID-19 extends.[10,12] The proportion of individuals with abnormalities on lung function testing or chest imaging may also reduce over time, though further studies which include individuals in the community are required to verify these observations.[14]

Research priorities

Addressing the substantial burden of respiratory symptoms experienced as part of long-COVID will require more observational studies, mechanistic work, trials of interventions and further evaluation of COVID-19 specific pulmonary rehabilitation.[3,28,29,30] According to an international consensus on research priorities for long-COVID in patients with pre-existing and new onset airways disease ,the most important areas for research included: comprehensively mapping the incidence of long term sequelae of COVID-19 (e.g. cardiovascular, pulmonary, thrombo-embolic, complications) beyond 12 months since the onset of acute infection; investigating the value of prognostic scores or clinical features to predict who will develop long-COVID; developing and validating tools to improve self-monitoring of respiratory symptoms; assessing the value of bespoke nutritional and rehabilitation programmes to aid recovery from long-COVID; and investigating the potential benefit of existing medications (e.g. anticoagulants, inhaled corticosteroids) to reduce the burden of long-COVID.[28] In addition, understanding how the respiratory features of long-COVID present following infection with different variants of SARS-CoV-2, in different patient groups (including children, young people, pregnant women and different ethnic groups) and developing screening tools to identify long-COVID in the population will be important to inform clinical practice.[3] Early evidence suggests potential inequalities in

referral to long-COVID clinics in patients from minority ethnic groups.[31] Given that patients from minority groups have been disproportionately affected by the COVID-19 pandemic,[32] research is needed to study patient pathways and the measures needed to reduce inequalities in accessing long-COVID rehabilitation services.

Conclusions

Long-COVID is a diverse, debilitating syndrome which often includes persisting respiratory symptoms, and, to a lesser extent, can be associated with abnormalities in lung physiology or imaging. Current evidence suggests that respiratory features of long-COVID may reduce over time, yet resolution is not seen in all cases. Future research should evaluate the clinical characteristics of individuals with long-COVID beyond 12 months in hospitalised and community samples, investigate the mechanisms for persisting respiratory features, and evaluate therapeutic and rehabilitation interventions to prevent and treat long-COVID.

KEY POINTS

- Long-COVID is a term used to describe ongoing symptoms four weeks or more after acute COVID-19 infection.
- Breathlessness is the most common respiratory symptom associated with long-COVID, with cough and chest pain also reported frequently in people who have been hospitalised or treated in the community for the original infection.
- Based on current estimates, the prevalence of breathlessness and cough reduce with time since onset of acute COVID-19, yet in contrast, the prevalence of chest pain may increase over time.
- With no robust evidence-based treatments currently available, understanding the causal processes for the respiratory components of long-COVID and evaluating therapeutic and rehabilitation interventions to treat long-COVID are priorities for research.

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CONFLICTS OF INTEREST

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