Characteristics and impact of long COVID-19 in people with lung disease

A rapid review for Lung Foundation Australia

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Glossary of terms:

6MWD	6-minute walk distance
CPET	Cardiopulmonary exercise testing
DLCO	Diffusing capacity
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HRQoL	Health Related Quality of Life
PHQ	Patient Health Questionnaire
PCS	Post-COVID-19 Functional Status
TLC	Total lung capacity

Acknowledgement of country

The George Institute acknowledges the Gadigal people of the Eora Nation as the First Custodians of the land on which our Australian office is situated. We pay our respect to Elders past, present and emerging.

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Background:

The emergence and rapid spread of Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) has resulted in unprecedented rates of mortality and morbidity. The acute phase of COVID-19 results in clinical presentations ranging from asymptomatic infection to severe illness requiring hospital admission and intensive care. Increased risk of infection is related to factors such as age, gender, ethnicity, socioeconomic status and pre-existing comorbidities.[1] Risk of more severe disease and a worse outcome is increased in older people, those with inadequate vaccination and those with common comorbidities such as hypertension, diabetes, ischaemic heart disease and obesity.[2] As of 19th July 2022, there have been more than 561 million cases worldwide and over 6.3 million deaths reported to the World Health Organisation (WHO).[3]

Being a respiratory disease, the acute severe manifestations of COVID-19 are predominantly marked by development of severe pneumonia and acute respiratory distress syndrome (ARDS). Early in the pandemic, people living with existing chronic lung diseases were thought to be at high risk of having worse outcomes from this disease.[4] A systematic review and meta-analysis of 33 studies found that there was a higher prevalence of respiratory diseases in fatal cases in comparison to total cases.[5]

Recent evidence indicates that some effects of COVID-19 can persist or occur de novo in people beyond the period of acute presentation.[6] A study of 270,000 people conducted in USA reported that 36.55% of the group had one or more long COVID symptom between three and six months after the diagnosis of acute infection.[7] Another study conducted in China, which followed up 1200 people reported that COVID-19 survivors had a poorer self-reported health-related quality of life (HRQoL), 2 years after acute infection.[8]

People living with non-respiratory comorbidities have also been identified as high-risk groups and such conditions are being extensively studied and reviewed at present. Although, as yet not extensively reported, people with common lung diseases may also be at increased risk, which needs to be ascertained from available evidence, quantified and described.

In this rapid review, we aim to explore the impacts of COVID-19, as a new respiratory disease in patients who have survived from COVID-19, focussing on people who suffer from pre-existing lung disease or lung cancer. In addition, we use the term 'long COVID' in this review to define the spectrum of clinical signs and symptoms which people experience after recovering from acute phase of COVID-19. It is also worth mentioning that the term 'long COVID' was coined by patients and was used in social media for the first time. Later on the term gained popularity and has been used interchangeably with post-acute sequelae of COVID-19 (PASC) and post-COVID syndrome (PCS).[9]

Review questions:

What are the clinical and social impacts of COVID-19, as a new respiratory disease, on people with existing lung disease or lung cancer?

What are the clinical and social impacts of post-acute sequelae of COVID-19?

Methods:

A literature search was conducted of medical and health databases, including CINAHL, Embase, LitCovid and APA PsychInfo. A few articles were also obtained through hand searching. We identified literature published in English language between January 2019 and May 2022. The searches were conducted in May 2022.

Definition:

For the purpose of this review, we defined long COVID as a post-COVID-19 condition occurring in individuals with a history of confirmed COVID-19 where signs and symptoms of COVID-19 last for more than 4 weeks and cannot be explained by any other diagnosis.[9, 10, 11]

The time period which qualifies persisting post-COVID symptoms as "long COVID" rather than a slow recovery which finally resolves within an acceptable time period is still controversial. Many leading institutions suggest that long COVID occurs if symptoms persist for a minimum duration of 12 weeks after initial testing for COVID-19.[11] The WHO sought to define long COVID with patients, researchers and clinicians through Delphi methodology, and states "Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis".[12]

In relation to lung diseases, we extracted data related to conditions such as chronic obstructive pulmonary disease (COPD), asthma, pulmonary arterial hypertension (PAH), bronchiectasis, idiopathic pulmonary fibrosis (IPF) and lung cancer.

Inclusion/exclusion criteria:

We included:

1. Studies which followed up patients during the post-acute phase of COVID-19.
2. Studies which included people with COVID-19 confirmed either by RT-PCR or antigen testing.
3. Studies with a minimum follow up time of 4 weeks.
4. Studies which had an established baseline of pre-existing respiratory comorbidities.
5. Studies involving people aged 16 years and above.

We excluded:

1. Post-mortem or biopsy studies.
2. Animal studies.
3. Reviews or meta-analyses.
4. Abstracts.

Data collection:

The search was supported by a research librarian and selection of studies was conducted independently by one reviewer (AS) and verified by another reviewer (CJ). Data extraction was conducted using a Microsoft Excel spreadsheet by one reviewer (AS). The selection process was recorded and reported in the form of a PRISMA flow diagram.

Outcomes:

The main outcomes of interest included the duration and impact of residual symptoms such as disability, fatigue and breathlessness, the spectrum and impact of post-COVID-19 complications and the risk factors associated with the development of long COVID.

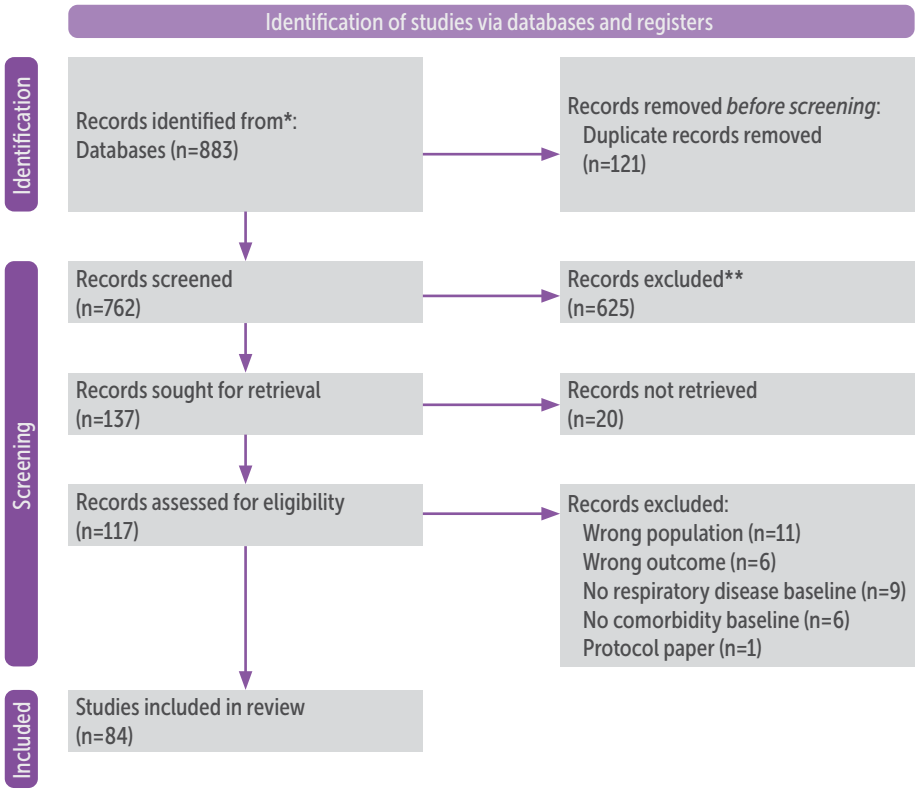
Additionally, psychosocial outcomes such as quality of life, anxiety, depression, post-traumatic stress, and other mental health outcomes were also collected where available.

Patient reported outcome measures such as the EuroQoL-5 Dimensions (EQ-5D-5L) questionnaire for change in health-related quality of life (HRQoL) and the modified Medical Research Council (mMRC) for change in breathlessness were collected. Outcome variables in lung function tests such as spirometry (FEV1/FVC % predicted, DLCO, % predicted, TLC, % predicted), CPET results and 6MWD outcomes were also collected.

Results:

A total of 883 records were identified. After removing duplicates, 762 records were screened and 137 underwent full text review. Finally, 84 studies were included in the review and selected for data extraction (Figure 1). Out of 84 studies which were included, 59 were cohort studies, 11 cross-sectional studies and four case series. Two were pre-post, one was a randomised controlled trial, four were database analyses and three were case-control studies. Most of the included studies were from European countries – 12 from Italy, 10 from the United Kingdom (UK), seven from Spain, five from Germany, four from Denmark, two from France, one from Austria and one from Finland. Among others, nine studies were conducted in the United States of America (USA), 10 in China, two in India and two in Bangladesh.

Figure 1: PRISMA diagram for identification of studies



Spectrum of physiological long COVID symptoms:

The most common symptoms experienced by people during long COVID were fatigue, myalgia, palpitations, muscle or joint pain, chest pain or tightness, dyspnoea at rest, dyspnoea on exertion, sleep difficulties, loss of smell and taste, gastrointestinal complaints (such as diarrhoea, abdominal pain, nausea), headache and hair loss.[6, 7, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27] Most people with long COVID rated their health poorly after COVID-19, when compared to before COVID-19. The majority of studies indicated that people who were hospitalised or had a more severe form of infection during the acute phase of COVID-19 were more likely to develop long COVID, as compared to non-hospitalised individuals and people with moderate/mild form of acute COVID-19.[7, 28] Additionally, people who had received mechanical ventilation during their acute COVID-19 phase were more likely to suffer from long COVID.[19, 21] However, 49 studies out of 84 in this review only included hospitalised patients, and so there is less certainty around the

likelihood of long COVID in non-hospitalised patients, particularly those who were minimally symptomatic and may not have sought to be tested.

In a retrospective cohort study based on linked electronic health record data from 273,618 COVID-19 survivors (predominantly USA), a comparison was made with a propensity score-matched cohort of patients diagnosed with influenza during the same time period. In relation to residual symptoms, the incidence of each and any long COVID symptom was significantly higher after COVID-19 than after influenza (overall HR – 1.65 [95% CI 1.62-1.67]).[7] Long COVID symptoms assessed were chest/throat pain, abnormal breathing, abdominal symptoms, fatigue/malaise, anxiety/depression, pain, headache, cognitive dysfunction, and myalgia. In the 6 months after COVID-19 diagnosis, 57% (95% CI 56.6 to 57.4) had at least one feature of long-COVID recorded.[7] This value includes the incidence of features recorded in the acute as well as the later phase of the illness.[7] In the 90- to 180-day "long" phase post-diagnosis, 36.6% (95%CI 36.2-36.9) had a long-COVID feature recorded.[7]

Fatigue

Out of 84 studies, 38 studies reported fatigue as the most prevalent symptom.

In a Chinese cohort study of older people, fatigue was reported by 32.4% of people who were followed up after hospital discharge. In another study conducted in Russia, out of 2599 people who were discharged from hospitals after acute covid, 551 reported persistent fatigue 6 months post hospital discharge.[26] In a study conducted in the UK which reported findings on the presence and duration of COVID-19 symptoms in the acute and post-acute phases, 83.3% of 3290 participants reported fatigue as a persistent symptom, 12 weeks since acute infection.[29]

A separate survey of 551 participants in the USA found that fatigue was cited as a main reason for delayed return to work by at least 5 weeks.[24] However, as this was a survey accessed through a telemedicine program in a single virtual clinic in USA, some selection bias is possible.[24]

A cohort study of 2649 participants in Russia reported that females and people with pre-existing COPD were at a higher risk of developing chronic fatigue, six months after hospital discharge (ORs 1.81 (1.40-2.34) and 1.66 (1.08-2.54) respectively).[26]

Another cohort study of 130 participants conducted in Mexico, reported older age (>40 years), female sex (OR 1.95 [0.94-40.6]), mechanical ventilation during acute phase and higher BMI (>25kgm2) as some of the risk factors associated with developing long COVID fatigue, of which only age (>40 years) had a statistical significance.[22]

Breathing problems

After fatigue, breathlessness was the most commonly reported symptom among people with long COVID. A single-centre, cross-sectional study conducted in Spain reported dyspnoea in 41.6% of the 266 hospitalised participants, one year after discharge.[30] These investigators also reported that people who were hospitalised experienced breathlessness significantly more than people who were discharged from the emergency room (53.9% vs 32.5%; $p < 0.001$).(30) Two

studies conducted in Italy and China mentioned that a significant proportion of hospitalised patients (30-35%) reported exertional dyspnoea after one year with a worsening trend compared to 6 month follow-up.[31, 32]

In an Italian cohort, it was found that 30.4% of the 251 participants had a residual respiratory dysfunction, 3 months after being discharged from the hospital. mMRC scores (≥2) at one-month follow-up emerged as a predictor for the for residual respiratory dysfunction (OR, 95% CI 1.49, 1.20-1.86).[33] In this study, it was also found that COPD was an independent predictor of residual respiratory dysfunction (defined by an mMRC score ≥2 or SpO2 ≤95% on room air) (OR, 95% CI: 4.13, 1.17-16.88, p=0.033).(33) In this cohort, history of COPD, increased length of stay, worsening SaO2, respiratory rate and health status at the one month visit emerged as predictors of residual respiratory dysfunction at three months, whereas transfer to ICU did not.[33] In their longitudinal cohort study, Munblit et al reported that over 61% of the cohort reported mMRC score of 1, 23.3% reported grade 2, 7.3% suffered from grade 3, 3.5% and 1.2% from grade 4 and 5, respectively, six months after being discharged from hospital.[26]

In the aforementioned study of an online survey conducted via a UK online post-COVID-19 support and information hub, Buttery et al found that people with pre-existing lung disease were more likely to report breathing problems after COVID-19 compared to those without. Although, the difference was small numerically, it was a statistically significant difference between the groups (88.4% vs 83.7%; $\chi 2$ 11.6, p=0.001).[29]

Spectrum of psychosocial long COVID symptoms:

Survivors of COVID-19 mostly reported that they suffered from anxiety and depression and self-rated their quality of life as worse than before COVID-19.[6, 27, 29, 32, 34, 35, 36] Some studies also reported that people experienced loss of concentration and loss of memory. [15, 22, 35, 37, 38, 39]

In a cohort study of 1276 participants hospitalised in Wuhan, China between January and May 2020, it was found that anxiety and depression increased from 23% to 26% between 6- and 12-months post hospital discharge.(32)

Poor sleep quality, cognitive impairment, lack of concentration and memory lapses were some of the other symptoms which were frequently reported. In a study which specifically evaluated higher burden of disease for women, it was found that women reported severe mood problems when compared to men (18.6% vs 3.8%, p=0.031).[19] A cross-sectional study in China reported that after adjusting for age and sex, COPD and stroke history were significantly associated with a higher risk of cognitive decline and impairment in a group of discharged people, aged 60 years and older.

Health related quality of life (HRQoL) was consistently rated as poor by COVID-19 survivors.[35] In the included studies, health-related quality of life was mostly assessed by validated instruments such as the EQ-5D-5L, Barthel Index and PHQ, followed by RAND and PCFS (Post Covid Functional Status). People with long COVID symptoms tend to have mild to moderate limitations in undertaking functional activities which range from inability to perform usual activities, experiencing pain and discomfort, and experiencing issues with mobility. In a follow-up of 128 patients, Vejen et al reported that participants frequently reported

pain and discomfort (61%), usual activities (54%) and mobility (51%) in the EQ-5D-5L questionnaire. Moreover, a mild to severe impairment was also reported by 59% of participants at follow-up compared to 32% before COVID-19. In another study of 456 hospitalised COVID-19 patients, it was reported that 2.4% of participants had a poorer self-perception of health and 31.7% reported their health status as excellent after 12 months of follow-up.[35] However, 55.5% rated self-perception of general health to be poorer post COVID-19 when compared with health status prior to COVID-19.[35]

A two-year longitudinal study in China which followed up COVID-19 survivors after hospitalisation found continuous improvements in HRQoL, exercise capacity and mental health.[40] However, about half still suffered from symptomatic sequelae at 2 years, which were mostly related to decreased quality of life, reduced exercise capacity, poor mental health, and increased use of health care after discharge. (40) The proportion of COVID-19 survivors with at least one sequelae symptom decreased significantly from 68% at 6 months to 55% at 2 years ($p<0{\cdot}0001$), with fatigue or muscle weakness always being the most frequent.[32]

A high number of studies reported that participants mostly had more than one long COVID symptom during follow-up. This high number of persistent symptoms would be likely to contribute to the poor health-related quality of life scores. A retrospective case series conducted in the USA reported that 20.7% of participants suffered from reduced mobility up to 6 months after hospitalisation.[13] It also mentioned that 19.3% had a reduced independence such as inability to live alone without support from a home health aide, nurse or family member.[13] These findings highlight the impact of ongoing burden of COVID-19 in the community.

Imaging and Diagnostics:

Pulmonary fibrosis was a common finding in studies which reported high resolution computed tomography (HRCT) and radiological findings.[6, 30, 39, 41, 42, 43] The proportion of patients with radiologic abnormalities consistent with fibrotic change varied depending on the population studied, from 0.01% amongst community-based patients to over 50% in patients followed up after hospital or ICU admission. Some of the higher estimates were in small populations of highly selected patients.[6, 30, 39, 41-43]

Radiological (CT/CXR) findings:

The most frequently occurring patterns in chest CT scans were ground glass opacities and consolidation. A prospective Spanish cohort study of 207 patients six months post-COVID-19 diagnosis and hospital admission reported that of 56.9% of participants who were found to have chest image abnormalities, 52% had bilateral pulmonary involvement, 28.5% showed a subpleural reticular pattern and 43.1% had a peripheral distribution and 45.4% exhibited ground glass opacity pattern.[27]

Lung function impairment

Many studies (15 out of 84) showed impaired diffusion capacity of the lung four weeks after COVID-19 infection.[25, 27, 31, 32, 39, 43, 44, 45, 46, 47, 48 49, 50, 51, 52]

People with moderate to severe COVID-19 showed improvements in lung function tests at six months, although persistent symptoms and lung function abnormalities

have been shown in a third to a half of hospitalised patients at 6 months.[32] A prospective multicentre study in Spain assessed adult patients after hospital admission with pneumonia due to COVID-19, at two months and six months with a wide range of tests including full respiratory function testing (RFTs), 6MWD, mMRC score, and Chest X-rays.[45] When chest X-rays or RFTs were abnormal, a thoracic HRCT was performed.[45] In this cohort, 47% of participants still had impaired DLCO (< 80% predicted) at six months and a third of the cohort suffered dyspnoea.[45] Statistical associations with diffusion impairment included female sex, increasing age, chest X-ray abnormality and elevated D-dimer.(45) The increased risk of reduced diffusion for females post-COVID-19 at six months has been demonstrated in several studies to date.[32, 49, 53] A critical clinical course (respiratory support by high flow oxygen or mechanical ventilation) was not a predictor of altered diffusion at follow-up.(45) Out of 313 patients, 226 underwent CT scan, of whom 66% had radiological sequelae of COVID-19.[45]

A pre-post study which evaluated the effect of multidisciplinary rehabilitation in a cohort of people with pre-existing cardiopulmonary comorbidities reported that FEV1 and diffusion capacity increased in people who underwent rehabilitation.[54] In addition, 6MWD results and dyspnoea were shown to improve after rehabilitation.[54] This suggests that multidisciplinary pulmonary rehabilitation is effective in people suffering from reduced pulmonary function and physical activity after COVID-19 infection.

Risk factors associated with long COVID:

Risk factors for long COVID were assessed by robust statistical methods in 60 studies where older age, female sex, increased BMI, severe COVID-19 and presence of pre-existing lung diseases were some of the common risk factors.

Age has been consistently identified as an independent risk factor for developing long COVID symptoms. Older people aged 40 years and above were at an increased risk of developing persistent symptoms such cognitive impairment, anxiety, decreased HRQoL, than other age groups.[17, 19, 20, 46, 55, 56, 57, 58] Abnormal radiological patterns in the lungs were most commonly seen in older patients.[46, 59, 60]

People with pre-existing comorbidities, previous or current smokers, females, people with higher BMI (>24 kg/m2) and people who received mechanical ventilation during the acute phase of COVID-19 infection were more likely to develop long COVID symptoms.[27, 35, 61]

Females had a higher risk of developing long COVID symptoms such as fatigue, poorer health-related quality of life and psychosocial symptoms such as anxiety and depression.[7, 20, 22, 23, 26, 35, 39, 49, 56, 61, 62, 63, 64] Interestingly, an Italian study which followed up both inpatients and outpatients for one year, reported that males seemed to have a protective effect against developing long COVID symptoms.[56] However, a retrospective cohort study which followed up 273,618 COVID-19 survivors reported that males had a higher risk of developing breathing difficulties and cognitive symptoms.[7]

A cross-sectional study in Germany which included 30,950 patients reported that females were more likely to take long-term sick leave after being diagnosed with COVID-19, as compared to males (OR 1.19).[65]

Mechanical ventilation was also a risk factor for incomplete radiological resolution after discharge from hospital.[43, 60] In addition, it has also been found to contribute to persistent pulmonary function impairment.[50] Han et al reported that non-invasive mechanical ventilation was an independent risk predictor of development of fibrotic changes in the lung (OR: 6.3; 95% CI: 1.3, 30; P = 0.02).[44, 48] A UK study which compared general practitioner (GP) consultation rates before and after COVID-19 in a cohort, found that people who were community managed during acute COVID-19 had higher consultation rates for lung fibrosis as compared to the hospitalised population.[6]

A few studies suggested that people with asthma and COPD are at an increased risk developing worse and prolonged long COVID symptoms.[23, 24, 26, 38, 63, 66, 67, 68] Maestre-Muñiz et al reported that in a Spanish cohort of 766 people who were followed up till a year after hospital discharge, 1.8% were newly diagnosed with COPD and 2 people were newly diagnosed with asthma.[30] Moreover, increased treatment was required in 7 people with pre-existing COPD and in 8 people with pre-existing asthma.[30] 39.3% of people with pre-existing COPD were diagnosed with COPD after recovery from COVID-19.[30] A Brazilian study reported that people living with asthma had an increased risk of developing persistent anxiety.[69] In a study of 287 hospitalised patients in Italy, it was reported that people with asthma had a three times higher risk of DLCO impairment compared to those without, 12 weeks after discharge.[31]

On the contrary, a study which prospectively collected data from 35 asthmatic and 76 non-asthmatic patients reported that the resolution of lower respiratory symptoms did not differ between the two groups, and the percentage of patients reporting persistent symptoms gradually declined over 8 months.[70] It also suggested that in an asthmatic cohort of 100 hospitalised patients and 498 out-patients, allergic asthma phenotype was significantly associated with a lower risk of hospitalisation, as compared to non-allergic asthma; (OR 0.54, 95% CI 0.28-0.91 p=0.026).[70] An Indian study which looked at post-COVID-19 sequelae in 100 patients, three weeks after discharge, did not find a significant difference in complete radiological resolution in patients with or without bronchial asthma.[71] These evidence might suggest that people living with pre-existing asthma might not be at significant risk of developing worse or prolonged long COVID symptoms when compared to non-asthmatic people.

People with other pre-existing comorbidities such as hypertension, diabetes mellitus, chronic kidney disease and neuropsychiatric disorders might also be at a higher risk of developing long COVID symptoms.[34] A Spanish study which included 1969 patients reported that an increased number of pre-existing comorbidities was independently associated with a higher number of long-term symptoms after COVID-19.[72] However, the authors also mentioned that no specific comorbidity was associated with a greater number of symptoms after COVID-19.[72] A cross-sectional analysis of 2334 COVID-19 patients in Ghana reported that patients with hypertension and diabetes mellitus were four times more likely to develop long COVID symptoms as compared to patients with other comorbidities, four weeks post discharge.[73] Similarly, an Italian cohort study of 456 patients found that cardiovascular comorbidities remained as independent predictors of health impairment. 12 months after hospital discharge.[35]

Another database analysis of 50,402 COVID-19 patients in Germany found that obesity and lipid metabolism disorders were strongly associated with the development of long COVID symptoms.(61) Pre-existing asthma (OR 1.67, 95% CI 1.39-2.00, p < 0.001) and patients aged 46 to 60 years (compared to age ≤ 30, (OR 1.81 95% CI 1.54-2.13, p < 0.001)), female sex (OR 1.33, 95% CI 1.20-1.47, p < 0.001), depression in women (OR 1.27, 95% CI 1.09-1.47, p = < 0.002) and cancer in men (OR 1.4, 95% CI 1.09-1.95, p = < 0.012) were associated with an increased likelihood of development of long COVID symptoms.[61] Although, not extensively studied in relation to long COVID, one study in Netherlands which followed up 351 cancer patients (51 with lung cancer) reported that people living with lung cancer had a risk of fatality or poorer health outcomes, 4 weeks post hospitalisation.[74]

Discussion

During the early periods of the pandemic, the term 'long COVID' emerged on social media platforms such Twitter and Facebook, where patients started a movement to demand recognition of what was happening to them.(75) Previously healthy and active people reported to have experienced debilitating symptoms which continue even after the acute phase of COVID-19. Some reported these symptoms to be relapsing and fluctuating in nature.[75]

This rapid review presents some of the most important and up to date findings related to long COVID. Till date, there have been only a few systematic reviews which have reviewed literature on long COVID, but none have specifically determined the impacts of long COVID on people with pre-existing lung disease. Our findings suggest that long COVID affects both hospitalised and non-hospitalised people and is characterised by fatigue, muscle or joint pain, loss of concentration, brain fog, breathlessness and difficulty sleeping. Psychosocial effects were also very common in COVID survivors, and anxiety and depression were the two most common features in addition to poorer self-related quality of life and PTSD. Ability to return to work was moderately affected if either of these were present. In an online survey of > 3000 people via a COVID-19 support and information hub in the UK, other common symptoms included sleep disturbances and cough, but symptoms did not appear to be related to the severity of the acute illness or to the presence of pre-existing medical conditions.[29]

In our review, older people (age >40 years), females, people with higher BMI, and people who were admitted to ICU due to COVID-19 had an increased risk of developing long COVID. Significantly, persistent post-COVID respiratory symptoms such as increased dyspnoea scores, poorer HRQoL, abnormalities in chest radiographs and CT scans, and reduced lung function were significantly associated with a history of COPD or asthma.

Our findings also suggest that people with pre-existing lung disease may be at a higher risk of developing long COVID symptoms. However, it should be mentioned that studies included in this review mostly had COPD and asthma as the most common lung conditions in their baseline characteristics, which means that the effect of long COVID on people with other lung diseases have been studied less frequently. This highlights the need for further studies to explore the effects of long COVID in people living with lung diseases such as bronchiectasis, IPF, PAH and lung cancer.

It should also be mentioned that COVID-19 vaccinations appear to be effective in reducing the likelihood of experiencing long COVID symptoms. In a community based study of 28,356 people, it was reported that activity-limiting symptoms of long COVID were reduced by 12.3% after administration of first dose of vaccine and by 9.1% after the second dose, followed by a decrease of 0.5% per week until the end of follow-up.[76] The authors also mentioned that symptoms such as fatigue, headache, loss of smell and taste, and sleeping difficulties decreased significantly after two doses of vaccination.[76]

Conclusion

Several definitions of long COVID are in common use, with varying thresholds for duration of post COVID-19 symptoms. Most often however long COVID is described as a syndrome characterised by ongoing symptoms after SARS-CoV-2 infection that persist for over 4 weeks, and definitions as in the UK[77] and WHO[12], for 12 weeks or longer. The commonest symptoms of long COVID are fatigue, lethargy, cognitive difficulty, and breathlessness. Between 3% and 12% people infected with SARS-CoV-2 experience long COVID, depending on the time interval at which these persistent symptoms are assessed. Prevalence estimates of long COVID have been affected by the different phases of the pandemic and changing variants of concern, regulatory requirements for testing, severity of the initial illness, and the availability of anti-viral therapies and vaccination.

Risk factors for long COVID vary according to the population studied, whether community based and tested with or without symptoms, acute healthcare presentations, or hospitalised. The pandemic phase in which the initial infection occurred also appears important, there being higher prevalence rates for people infected with Wuhan wild-type and Delta variants than subsequent omicron SARS-CoV-2 variants. These caused more severe COVID illness than the omicron variants and occurred at a time when vaccination was not available in most countries. Age has been consistently identified as an independent risk factor for developing long COVID symptoms, starting from age 40 years and above. Persistent symptoms such cognitive impairment, anxiety, decreased HRQoL are more likely in older adults than younger age groups.

Other consistently identified risk factors for developing long COVID include being female, having a higher BMI, and being admitted to ICU for COVID-19 illness. Although not consistently reported, having persistent symptoms such as increased dyspnoea scores, poorer HRQoL, abnormalities in chest radiographs and CT scans, and reduced lung function were significantly associated with a history of COPD or asthma. Whether this represents a true indication of increased risk of long COVID, or a propensity to persistent respiratory symptoms in people with pre-existing obstructive lung disease has not been fully elucidated and requires further research.

Implications of this review

While this review has identified risk factors for long COVID, the evidence that pre-existing chronic lung disease is a likely risk factor for developing long COVID is not as strong as for consistent features such as older age, female sex and higher BMI. However, patients with asthma and COPD appear to be more prone to persistent respiratory symptoms after COVID-19 illness, particularly dyspnoea and cough, along with poorer health-related quality of life. More research is needed to clarify whether these are part of a spectrum of long COVID symptoms to which people with asthma and COPD are susceptible for reasons independent of an exacerbation of their pre-existing airways disease.

People with chronic lung disease, especially asthma and COPD, should take every precaution to reduce their risk of acquiring COVID-19 and developing long COVID by

- *Minimising exposure to infection by mask wearing, social distancing and hand hygiene*
- *Maintaining optimal COVID-19 vaccination schedules as recommended by health authorities*
- *Seeking specialist or GP review of their underlying respiratory disease to ensure they are on the best treatment and updating their written Action Plans*
- *Maintaining their treatment if they develop COVID-19*
- *Seeking urgent health care review if their symptoms worsen*

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