NHS
Test and Trace

Joint Biosecurity Centre

Long COVID

Briefing note

Health Protection Directorate
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Introduction

Over 94 million people have been infected with SARS-CoV-2 causing COVID-19 and there have been 2.03 million deaths worldwide.[1] In the UK an estimated 3.47 million cases have been detected, and as of 19/01/2021 there have been 91,470 deaths.[2] Despite this high burden of mortality there is limited understanding of the morbidity of the disease beyond its acute phase.

Long COVID is a term used to describe the ongoing illness of those who have recovered from COVID-19 but are still reporting lasting effects of the infection or have experienced symptoms for far longer than would be expected. NICE has recently defined long COVID as: *'signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than four weeks and are not explained by an alternative diagnosis.'*[3]

Anecdotally, lived experiences of long COVID have been shared across different social and general media platforms; however, research is limited.

In order to review current research on Long COVID-19 electronic databases (Pubmed and Google Scholar) were searched, with 'Long COVID' as the search term (19/01/2021). Listings on the National Institute for Health Research website were also searched for ongoing studies. This brief reflects a rapid assessment, rather than a systematic literature review.

Long-term impacts of severe illness

A study in Italy retrospectively described the medical and psychological needs of people after hospitalisation with COVID-19. Out of 143 patients, 60 days from initial symptom onset, 125/143 (87%) were still experiencing symptoms. These were commonly fatigue (53%), dyspnoea (43%), joint pain (27%), and chest pain (22%).[4] These are similar to the findings from a cohort study in China which followed up 1,733 patients after hospitalisation with COVID-19, for a median of 186 days from initial symptom onset. Six months after acute infection the symptoms most commonly reported were fatigue or muscle weakness (63%), sleep difficulties (26%), and anxiety and depression (23%).[5] However, as observational studies, findings may be affected by selection and/or reporting bias, and there is no comparator group to assess how frequently these symptoms are reported in a comparable demographic group who have not had COVID-19.

A further retrospective cohort study led by ONS and the University of Leicester in the UK showed that of 47,780 participants who had been in hospital with COVID-19 and discharged, 29.4% were re-admitted and 12.3% died following discharge. These events occurred at a rate of 766 (753-799) and 320 (312-328) per 1,000 person-years respectively; 3.5 and 7.7 times greater than matched controls. Controls were matched on demographic and clinical factors; however, selection was made from the general public as opposed to people previously hospitalised with another condition of similar severity.[6]

The PHOSP-COVID study is an additional study currently being carried out prospectively by the University of Leicester to assess individuals after COVID-19

hospitalisation to study the short (0-3 months), medium (3-6 months) and long (6-12 months) term effects of the disease. Results are pending.[7]

Studies have also been carried out to understand the long-term effects of COVID-19 on multiple organ systems. In China, 55 patients were followed up (64 - 93 days) after hospital discharge. Of these, 35 were still experiencing infection related symptoms, 39 had differing degrees of radiological illness and 14 had abnormal lung function.[8] Again whilst these findings suggest substantial morbidity, the study is observational following up cases only, and may be subject to the same biases described above.

Although COVID-19 directly affects the lungs, cardiovascular complications have been shown to be important in the course of severe disease. A cohort study in Germany investigated long-term cardiac sequelae by using cardiac magnetic resonance imaging on 100 patients, two weeks after receiving a positive COVID-19 test result. Results showed abnormal cardiac MRI findings in 78/100 (78%) and ongoing myocardial inflammation in 60/100 (60%). These findings were independent of pre-existing health conditions, severity of illness, or time from symptom onset. [9] The COVID-HEART study, which is currently open and led by Leeds Teaching Hospital is investigating this further by using MRI scanning to look at prevalence of cardiac sequelae after COVID-19.[10] In addition, the C-MORE study (University of Oxford, UK) aims to follow up 616 participants with laboratory-confirmed COVID-19 to investigate sequelae affecting lung, heart, brain, liver and kidney function. In this study 62 patients who have not been infected with COVID-19 will also be recruited to act as a control group. [11]

Long-term impacts of mild illness

Ongoing illness post COVID-19 recovery or prolonged symptoms of disease have been reported after COVID-19 without hospitalisation. The ONS COVID-19 Infection Survey estimated that around 1 in 5 respondents testing positive for COVID-19 experience symptoms for 5 weeks or longer, and 1 in 10 experience symptoms for 12 weeks or longer. Based on this it was estimated that during the week commencing the 22 November, approximately 186,000 people in England were living with symptoms that had been persisting for between 5-12 weeks. A new question is being added to the ONS COVID-19 Infection Survey asking participants about symptoms and their impact on their daily lives.[12] The ONS COVID-19 findings are slightly higher than the findings from the ZOE symptom tracker App, which collects information on symptoms from over 4.5 million members of the public in the UK. Data were analysed from 4,182 cases of COVID-19 who prospectively logged their symptoms, to show 558 (13.3%) had symptoms lasting longer than 28 days, 189 (4.5%) for longer than 8 weeks and 95 (2.5%) for longer than 12 weeks. Factors associated with Long COVID were increasing age, BMI and female sex.[13]

In the United States, the Centre for Disease Control and Prevention (CDC) conducted a cross-sectional study (randomised telephone survey) of 292 adults who had tested positive for COVID-19. Of these around a third (35%) reported not returning to their prior levels of health two weeks or more after testing. Even among adults aged 18-34 years old with no previous medical conditions, 1 in 5 had not fully

recovered.[14] A more informal online survey conducted by a patient led research group showed that 91% of the 640 respondents, who were on average 40 days post symptom onset, had still not fully recovered. The symptoms most commonly reported included fatigue, chills and sweats, body aches, headaches, and gastrointestinal issues. However, just under a quarter of respondents (23%) had received a positive COVID-19 test, making it likely that individuals who were not infected with COVID-19 took part in this survey.[15] In addition, there may be reporting bias, with those having symptoms potentially more likely to respond to such a survey.

Conclusion

Data are limited on Long COVID, and more information is urgently needed to assess the burden of disease after illness. Whilst observational studies to date suggest the potential for considerable morbidity with COVID-19, as observational studies they are likely to be prone to reporting and selection bias. However, if even a small proportion of those with COVID-19 experience symptoms long term, given the numbers of people who have been, and will be, infected, this would still represent a considerable ongoing burden of disease.

References

1. World Health Organization. WHO coronavirus disease (covid-19) dashboard. https://covid19.who.int/ [Accessed 19 Jan. 2021].
2. Gov.uk (2020). Coronavirus (COVID-19) cases in the UK. [online] coronavirus.data.gov.uk. https://coronavirus.data.gov.uk/. [Accessed 19 Jan. 2021].
3. NICE. COVID-19 rapid guideline: managing the long-term effects of COVID-19. https://www.nice.org.uk/guidance/ng188.
4. Carfì, A., Bernabei, R. and Landi, F., 2020. Persistent Symptoms in Patients After Acute COVID-19. JAMA, 324(6), p.603.
5. Huang C, Huang L, Wang Y, Li X, Gu X et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet.* Vol 397: 10270. P220-232, 16 January 2021. DOI:https://doi.org/10.1016/S0140-6736(20)32656-8
6. Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I and Banerjee A. Epidemiology of post-COVID syndrome following hospitalisation with coronavirus: a retrospective cohort study. *medRxiv* doi: https://doi.org/10.1101/2021.01.15.21249885
7. NIHR. Post-hospitalisation COVID-19 study: a national consortium to understand and improve long-term health outcomes (PHOSP-COVID). [online] Available at: https://www.nihr.ac.uk/covid-studies/study-detail.htm?entryId=285439 [Accessed 20 Jan. 2021].
8. Zhao, Y., Shang, Y., Song, W., Li, Q., Xie, H., Xu, Q., Jia, J., Li, L., Mao, H., Zhou, X., Luo, H., Gao, Y. and Xu, A. (2020). Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine, 25, p.100463.
9. Puntmann, V.O., Carerj, M.L., Wieters, I., Fahim, M., Arendt, C., Hoffmann, J., Shchendrygina, A., Escher, F., Vasa-Nicotera, M., Zeiher, A.M., Vehreschild, M. and Nagel, E. (2020). Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiology. [online] Available at: https://jamanetwork.com/journals/jamacardiology/fullarticle/2768916.
10. NIHR. Demographic, multi-morbidity and genetic impact on myocardial involvement and its recovery from COVID-19: a UK national study (The COVID-HEART Study).

[online] Available at: https://www.nihr.ac.uk/covid-studies/study-detail.htm?entryId=285147 [Accessed 20 Jan. 2021].
11. NIHR. Assessing the effects of Coronavirus Disease (COVID-19) on multiple organ systems and impact on quality of life, functional capacity and mental health. [online] Available at: https://www.nihr.ac.uk/covid-studies/study-detail.htm?entryId=282608 [Accessed 20 Jan. 2021].
12. ONS. The prevalence of long COVID symptoms and COVID-19 complications - Office for National Statistics. [online] Available at: https://www.ons.gov.uk/news/statementsandletters/theprevalenceoflongcovidsymptomsandcovid19complications [Accessed 20 Jan. 2021].
13. Sudre C, Murray B, Varsavsky T, Graham M, Penfold S, Bowyer R et al. Attributes and predictors of Long-COVID: analysis of COVID cases and their symptoms collected by the Covid Symptoms Study App. *medRxiv* doi: https://doi.org/10.1101/2020.10.19.20214494
14. Tenforde, M.W. (2020). Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020. MMWR. Morbidity and Mortality Weekly Report, [online] 69. Available at: https://www.cdc.gov/mmwr/volumes/69/wr/mm6930e1.htm?s_cid=mm6930e1_w.
15. Patient Led Research. Report: What Does COVID-19 Recovery Actually Look Like? [online] Available at: https://patientresearchcovid19.com/research/report-1/ [Accessed 19 Jan. 2021]

Appendix

Reference	Date	Title	Country	Summary
4	11/08/2020	Persistent symptoms in patients after acute COVID-19.	Italy	A retrospective observational study in Italy recruited 143 participants from an outpatient service for individuals discharged from hospital with COVID-19. A standardised questionnaire was administered at enrolment asking patients to retrospectively state the presence or absence of different symptoms during the acute phase of their illness and whether each symptom persisted. 125/143 (87%) were still experiencing symptoms 60 days from symptom onset. Limitations of this study include a relatively small sample size and a lack of a control group of patients who were discharged for reasons other than COVID-19. Persistent symptoms are also associated with community acquired pneumonia, suggesting these findings may not be exclusive to COVID-19.
5	08/01/2021	6-month consequences of COVID-19 in patients discharged from hospital: a cohort study	China	A retrospective cohort study of patients with confirmed COVID-19 discharged from Yin-tan hospital between Jan 7 2020 and May 29 2020. All patients underwent physical examinations and were interviewed with a series of questionnaires to assess symptoms. Six months after acute infection the symptoms most commonly reported were fatigue or muscle weakness (63%), sleep difficulties (26%), and anxiety and depression (23%). Patients who were more severely ill during there hospital stay had more severely impaired pulmonary diffusion capacities and abnormal chest imaging. Findings may be affected by selection and/or reporting bias, and there is no comparator group.
6	15/01/2021 (pre-print, not peer reviewed)	Epidemiology of post-COVID syndrome following hospitalisation with coronavirus: a retrospective cohort study	UK	A retrospective matched cohort study which recruited 47,780 individuals who had been in hospital with COVID-19 and discharged. Participants were matched to controls on demographic and clinical characteristics. Of the individuals with COVID-19, 29.4% were re-admitted and 12.3% died following discharge. These events occurred at rates which were 3.5 and 7.7 times higher respectively than in matched controls. Rates of multi-organ dysfunction, particularly diabetes and MACE were also higher in those with COVID-19 compared to the control group. Limitations of this study include the general population being used as the control group as opposed to people previously hospitalised with another condition of similar severity.

7	Ongoing	Post-hospitalisation COVID-19 study: a national consortium to understand and improve long-term health outcomes (PHOSP-COVID)	UK	An ongoing observational study aiming to recruit 10,000 individuals with a COVID-19 diagnosis on hospital discharge in order to determine the short (0-3 months), medium (3-6 months) and long (6-12 months) term effects of the disease. Routine clinical data will be analysed and linked to retrospective and prospective health and social care data. Some participants will be followed up for at least 25 years. This will be the largest study to date investigating the long-term effects of COVID-19; however, this study does not include a comparable demographic group who have not been infected with COVID-19.
8	14/07/2020	Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery	China	A retrospective cohort study that recruited 55 recovered COVID-19 patients for high resolution computed tomography (HRCT), lung function and SARS-CoV-2 IgG antibody tests 3 months after discharge. Results showed that of these, 35 (63.6%) were still experiencing infection related symptoms, 39 (71.9%) had differing degrees of radiological illness and 14 (25.4%) had abnormal lung function. Critical patients were excluded from this study, further lung function testing and HRCT scanning in critical patients would need to be assessed. Findings may be affected by selection and/or reporting bias, and there is no comparator group.
9	27/07/2020	Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered from Coronavirus Disease 2019 (COVID-19)	Germany	A prospective observational cohort study where 100 patients were identified from a COVID-19 test centre, 64-92 days from original diagnosis. Cardiac magnetic resonance imaging and cardiac block markers were used to determine myocardial damage. Results showed abnormal MRI findings in 78 patients (78%) and ongoing myocardial inflammation in 60 patients (60%). Findings may be affected by selection and/or reporting bias, and there is no comparator group.
10	Ongoing	Demographic, multi-morbidity and genetic impact on myocardial involvement and its recovery from COVID-19: a UK national study	UK	This ongoing observational study will use MRI scanning to look at prevalence of cardiac sequelae after COVID-19. This study aims to follow up 5,000 patients up to 6 months after a hospital discharge of COVID-19. Recruitment will be linked to the PHOSP-COVID[5] study. It will look at how the heart muscle damage and how recovery is affected by age, sex, ethnic group and other medical conditions.

		(The COVID-HEART Study)		
11	Ongoing	Assessing the effects of Coronavirus Disease (COVID-19) on multiple organ systems and impact on quality of life, functional capacity and mental health	UK	This ongoing case-control study aims to investigate sequelae of COVID-19 affecting lung, heart, brain, liver and kidney function as well as to assess impact on quality of life and mental health. Researchers aim to recruit up to 616 patients who have been infected with COVID-19 and 62 individuals who have not to act as a control group. Follow-up will take place three, six and twelve months after infection and will include MRI imaging, and breathing, exercise capacity and mental health assessments.
12	Ongoing	ONS COVID-19 Infection Survey	UK	The ONS COVID-19 Infection Survey is a nationally representative sample of the UK community population and collects COVID-19 test results in addition to respondent-reported data on symptoms. More than two million swab tests have now been completed as part of the survey. It has been estimated that 1 in 5 respondents testing positive for COVID-19 exhibit symptoms for 5 weeks or longer, with 1 in 10 for 12 weeks or longer. Uncertainty may have been introduced to these estimates due to data being incorrect or missing as a result of participants accidentally missing or misinterpreting questions.
13	Ongoing	Attributes and predictors of Long-COVID: analysis of COVID cases and their symptoms collected by the Covid Symptoms Study App	UK	The Zoe Symptom Tracker app is currently collecting information on symptoms from over 4.5 million members of the public in the UK. Data was analysed from 4,182 incident cases of COVID-19 who prospectively logged their symptoms, to show 558 (13.3%) had symptoms lasting longer than 28 days, 189 (4.5%) for longer than 8 weeks and 95 (2.5%) for longer than 12 weeks. Experiencing more than 5 symptoms during the first week of illness, age, BMI and female gender were all found to be associated Long-COVID.As an opt in activity, those who participate in providing daily symptom information are likely to differ from those who do not.

14	24/07/2020	Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020	USA	A respective cross-sectional study conducted by the Centres for Disease Control and Prevention. Telephone interviews were carried out on a random sample of 292 adults who had received a positive COVID-19 test result 14-21 days prior to the interview date. Respondents were given a standardised survey including questions on symptoms at the time of testing, and whether they had persisted. Of these around a third (35%) reported not returning their prior levels of health two weeks or more after testing. Even among adults aged 18-34 years with no previous medical conditions, 1 in 5 had not fully recovered. This study will have been subject to responder bias, with those with more severe illness less likely to answer the phone. The study also relies on self-reporting symptoms at the time of testing which may have resulted in incorrect recall or responder bias.
15	11/05/2020	An Analysis of the Prolonged COVID-19 Symptoms Survey by Patient-Led Research Team	USA	A patient led research group known as The Body Politic COVID-19 Support Group conducted an online survey to quantify the experiences of patients suffering with prolonged symptoms of COVID-19. Of the 640 individuals who responded to the survey about a quarter (23%) had received a positive COVID-19 test result. This captures individuals with mild symptoms who were not able to get tested during the first wave of the pandemic due to lack of mass community testing. However, this does mean some individuals who were never infected will be included. Results showed that 91% of the respondents, who were on average 40 days post symptom onset, had still not fully recovered. The report for this study has not been published or undergone peer review.