Characteristics and risk factors for post-COVID breathlessness after hospitalisation for COVID-19

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Take home message: Socio-economic deprivation, pre-existing depression/anxiety, female sex, and longer admission duration were risk factors for persistent breathlessness in patients assessed 5 months after hospitalisation for COVID-19.

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Abstract

Background

Persistence of respiratory symptoms—particularly breathlessness—after acute COVID-19 infection has emerged as a significant clinical problem. We aimed to characterise and identify risk factors for patients with persistent breathlessness following COVID-19 hospitalisation.

Methods

PHOSP-COVID is a multi-centre prospective cohort study of UK adults hospitalised for COVID-19. Clinical data were collected during hospitalisation and at a follow-up visit. Breathlessness was measured by a numeric rating scale of 0-10. We defined post-COVID breathlessness as an increase in score of 1 or more compared to the pre-COVID-19 level. Multivariable logistic regression was used to identify risk factors, and to develop a prediction model for post-COVID breathlessness.

Results

We included 1,226 participants (37% female, median age 59 years, 22% mechanically ventilated). At a median five months after discharge, 50% reported post-COVID breathlessness. Risk factors for post-COVID breathlessness were socio-economic deprivation (adjusted odds ratio, 1.67; 95% confidence interval, 1.14–2.44), pre-existing depression/anxiety (1.58; 1.06–2.35), female sex (1.56; 1.21–2.00) and admission duration (1.01; 1.00–1.02). Black ethnicity (0.56; 0.35–0.89) and older age groups (0.31; 0.14–0.66) were less likely to report post-COVID breathlessness. Post-COVID breathlessness was associated with worse performance on the shuttle walk test and forced vital capacity, but not with obstructive airflow limitation. The prediction model had fair discrimination (concordance-statistic 0.66; 0.63–0.69), and good calibration (calibration slope 1.00; 0.80–1.21).

Conclusions

Post-COVID breathlessness was commonly reported in this national cohort of patients hospitalised for COVID-19 and is likely to be a multifactorial problem with physical and emotional components.

Abstract word count: 250/250

Introduction

Coronavirus disease (COVID-19) continues to have a huge impact internationally [1]. The post-acute COVID-19 syndrome (also known as long-COVID) usually occurs three months from the onset of COVID-19, with symptoms that last for at least two months and cannot be explained by an alternative diagnosis [2]. The term long-COVID may also be used to refer to ongoing symptomatic COVID-19 occurring between four and 12 weeks after acute COVID-19 infection [3]. With increasing understanding of the debilitating longer-term effects of COVID-19 [4,5,6,7], characterising and being able to predict which individuals will suffer from long-COVID is a policy priority [8].

Breathlessness is one of the most common and burdensome symptoms reported by individuals, forming part of a complex of respiratory symptoms observed in long-COVID [9]. The prevalence of persistent breathlessness in hospitalised and non-hospitalised patients after acute COVID-19 is estimated between 26-39% [10,11,12,13,14]. Breathlessness is understood as a multidimensional disease concept with different underlying physiological mechanisms including respiratory and cardiovascular diseases, deconditioning, being overweight, and emotional factors such as anxiety [15,16].

In a community-based sample investigating the persistence of symptoms 12-weeks after acute COVID-19, a respiratory-predominant symptom cluster, including breathlessness, chest tightness and chest pain was identified. [17] Within this respiratory cluster, a higher proportion of individuals were obese, cigarette smokers, had more co-morbidities and considered their acute COVID symptoms severe. [17] In a single-site study of 478 hospital survivors, new onset dyspnoea was more likely in younger patients, those treated in the Intensive Therapy Unit (ITU), and with pulmonary embolism; [18] yet another smaller study found no association with dyspnoea at three months and ITU admission [19]. A further single-site study of 119 adults hospitalised with severe COVID-19 pneumonia found that failure to return to pre-COVID breathlessness a median 61 days after discharge was associated with co-morbid obstructive lung disease, high scores on anxiety, depression or post-COVID-19 functional status screening, but not ITU admission or inpatient pulmonary embolism. [20]

In this study, we sought to estimate the frequency of and characterise risk factors for persisting breathlessness using a multi-centre cohort of patients who were discharged following hospitalisation for COVID-19. A secondary aim was to derive a prediction model to identify individuals most at risk of new or worsening breathlessness post-hospitalisation for COVID-19.

Methods

Study design, setting and population

PHOSP-COVID is a multi-centre prospective cohort study of adults discharged from one of 53 National Health Service (NHS) hospitals in the United Kingdom (UK) following admission for COVID-19. Data were collected during hospital admission and at a research visit, between 1-8 months after discharge (depending on participant and investigator availability), from clinical health records and supplemented by questionnaires, clinical and research samples, and additional clinical assessments. Participants aged ≥18 years who were discharged from hospital following inpatient treatment for COVID-19 based on a positive Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) test for SARS-CoV-2 or clinician diagnosis (if there was a high index of suspicion and testing was either unavailable or considered inaccurate) were included. Individuals were excluded if they attended the emergency department but were not admitted to hospital or had an existing condition with a life expectancy below six months. Recruitment occurred between August 2020 and November 2021. In this manuscript, we report on the patients who provided data for breathlessness both before COVID-19 and at their first research assessment, before January 2022.

Data collection and outcome

Patient characteristics prior to admission, during hospitalisation and at the research visit were considered. We included patient demographics, patient-reported past medical history, number of co-morbidities, body mass index (BMI) and smoking status. Hospital admission data included the level of respiratory support received (categorised based on the World Health Organization clinical progression scale; Table S1) [21], length of stay, treatments, and complications during hospitalisation. At the research visit, patient-reported outcomes were collected using the General Anxiety Disorder-7 Questionnaire (GAD-7) [22], Patient Health Questionnaire-9 (PHQ-9) [23] and Post Traumatic Stress Disorder Checklist (PCL-5) [24]. Results from clinical tests included full blood count, C-reactive protein (CRP), N-terminal pro B-type natriuretic peptide (NT-BNP) or BNP, lung function tests, and the incremental shuttle walk test (ISWT).

Lung function testing was limited in certain recruiting sites due to COVID-19 restrictions [25]. Forced Expired Volume in 1 second (FEV_1) and Forced Vital Capacity (FVC) were conducted in accordance with American Thoracic Society/European Respiratory Society criteria [26] and used to calculate the FEV_1/FVC ratio. Airflow obstruction was defined by an FEV_1/FVC ratio less than the lower limit of normal (LLN). Transfer Capacity of the Lung for the uptake of carbon monoxide (TLCO) and carbon monoxide transfer coefficient (KCO) were obtained using the best of two readings. Percent predicted and lower limit of normal values were calculated using Global Lung Initiative equations [27,28].

At the research visit, participants reported their perceived breathlessness at the time of the visit and recalled their level of breathlessness before developing COVID-19 using a Patient Symptom

Questionnaire (PSQ), a numeric rating scale between 0–10 (Figure S1). The availability of the PSQ breathlessness score at the time of the research visit and before COVID-19 allowed a new variable to be created, which we defined as "*post-COVID breathlessness*"; this was used as our primary outcome. In line with Johnson *et al.* (2013), we took the minimum clinically important difference for a change in breathlessness as one point on the 0-10 numeric rating scale [29] Thus, individuals who rated their breathlessness at the time of the research visit as at least one point greater than before developing COVID-19 (i.e., they reported new or worsening breathlessness compared to baseline), were categorised as having post-COVID breathlessness. Sensitivity analyses were performed using breathlessness reported at the time of the research visit based on i) PSQ and ii) Dyspnoea-12 (which was only reported at the research visit) [30].

Statistical analysis

We used descriptive statistics to describe participant characteristics. Continuous variables were presented as means and standard deviations, or medians and interquartile ranges, as appropriate. Binary and categorical variables were presented as counts and percentages.

For the primary outcome, we report univariable and multivariable logistic regression with and without imputed data. Continuous explanatory variables were checked for linearity compared with the dependent variable and included with a quadratic term when necessary. Explanatory variables were assessed for multicollinearity. Explanatory variables collected at the research visit were not included in the multivariable model for two reasons. First, the model was intended to make predictions for breathlessness using data available at hospital discharge. Second, due to the multi-site nature of the study, certain variables (such as lung function) were likely to be missing at specific sites in a systematic manner, making imputation of these variables inappropriate. Explanatory variables were added to the model manually following initial descriptive analysis (though not based on a p-value threshold) and in consultation with the expert clinical group. Final model selection was based on a criterion-based approach intending to minimise the Akaike Information Criteria (AIC) and maximise the concordance statistic (C-statistic). First order interactions were checked and included if influential. Under the assumption that missing values within variables were missing at random, we used multiple imputation by chained equations to create 20 datasets each with 10 iterations based on the following variables: sex at birth, age at admission (as a factor), ethnicity, socioeconomic status determined using the Index of Multiple Deprivation (IMD) expressed as quintiles, BMI, number of co-morbidities, pre-existing respiratory disease, pre-existing depression or anxiety, admission duration, level of respiratory support and post-COVID breathlessness. Apparent performance measures of the prediction model were evaluated using the C-statistic, Expected/Observed number of events (E/O), calibration slope (each calculated using the median from the 20 imputed datasets) and calibration plot (evaluated in the first imputed dataset). To investigate differences between individuals according to the severity of post-COVID breathlessness, multinomial

modelling was used in the imputed dataset (see Table S2 in the supplementary material). To assess the associations between clinical measures during the research visit and post-COVID breathlessness, separate multivariable logistic regression models were fitted, adjusting for age, sex, ethnicity and IMD.

We used R (version 3.6.3) for all statistical analysis.

Results

Participants

1,843 participants attended a research visit between 1 and 8 months, of whom 617 had no data for breathlessness and were excluded (Figure 1). There were no clear differences between included and excluded participants (Table S3). Of the 1,226 participants included in this analysis, 458 (37%) were female and the median age was 59 years (range 21–89 years). 873 (71%) were of White ethnicity (Table 1). Median admission duration was 8 days (interquartile range 4–17 days, Table 2). Of those with data for RT-PCR, 1,039 (85%) had a positive result. 270 (22%) patients required the highest level of respiratory support (i.e. invasive mechanical ventilation). 714 (58%) participants were discharged between March and July 2020 (Figure 2). There was a higher proportion of missingness for the clinical tests at the research visit (Table 3) compared with data collected during hospitalisation.

Main results

615 (50%) participants reported post-COVID breathlessness at the research visit compared to their pre-COVID baseline level, of whom 407 reported no breathlessness (a PSQ=0) at baseline (Table 1). Females were more likely to report post-COVID breathlessness than males (57% vs 46%; Table 1, Figure S2). There was little difference between individuals with and without post-COVID breathlessness in ethnicity (Figure S3), smoking status, or number of comorbidities including the pre-existence of respiratory or cardiovascular diseases. However, the prevalence of pre-existing depression or anxiety was higher in the group with post-COVID breathlessness (22% vs 11%), and those with post-COVID breathlessness had a slightly higher BMI (mean 32.7 vs 31.4). Individuals with post-COVID breathlessness had longer hospital admission (median 9 vs 7 days), with little or no difference in the level of respiratory support required, medications (including corticosteroids) received, or in-hospital complications (Table 2).

The multivariable logistic regression identified that post-COVID breathlessness was associated with the most deprived quintile (adjusted odds ratio, 1.67; 95% confidence interval, 1.14–2.44, Table 4 and Figure 3), pre-existing depression/anxiety (1.58; 1.06–2.35), female sex (1.56; 1.21–2.00) and admission duration (1.01; 1.00–1.02 per day). Individuals of Black ethnicity (0.56; 0.35–0.89) were less likely to report post-COVID breathlessness. Compared to 50–59-year-olds, participants aged 60–69 years (0.70; 0.51–0.96), 70-79 years (0.43; 0.28–0.64) and 80 years or older (0.31; 0.14–0.66) were less likely to report post-

COVID breathlessness. The level of respiratory support received, pre-existing respiratory disease, number of co-morbidities and BMI were not associated with post-COVID breathlessness.

Multinomial modelling

Of the 615 participants with post-COVID breathlessness, 213 (35%) had mild and 402 (65%) severe breathlessness. Compared to those with no post-COVID breathlessness, severe post-COVID breathlessness was associated with the two most deprived quintiles, female sex, pre-existing depression/anxiety, and admission duration (Table 5). Black ethnicity and older age groups were less likely to report severe post-COVID breathlessness. Mild post-COVID breathlessness was associated with having more co-morbidities and longer admission duration.

Prediction model

The multivariable model (Equation S1) had fair discriminative ability (C-statistic 0.66; 95% confidence interval 0.63–0.69, Figure S4) and good calibration (calibration slope 1.00; 95% confidence interval 0.80–1.21, E/O 1.00) though some under- and over-prediction at higher probabilities (Figure S5).

Clinical characteristics from the research visit

The period between discharge and research visit was a median 4.7 months (interquartile range 3.4 to 6.0). Fewer participants reviewed between six and eight months after discharge were treated with steroids or antibiotics, and had on average a longer admission duration, and required the highest level of respiratory support compared to individuals who attended a research visit within six months of hospitalisation (Table S4-S6 and Figure S6). Despite these differences, the period between discharge and research visit was not associated with post-COVID breathlessness (median 4.7 vs 4.7 months; OR 1.00 (95% CI 1.00 to 1.00), Table 3).

At the research visit, individuals with post-COVID breathlessness had higher scores on the PHQ-9 (median 8.0 vs 3.0), GAD-7 (median 5.0 vs 2.0) and PCL-5 (median 15.0 vs 6.0) than participants without post-COVID breathlessness. With differences in age, sex, ethnicity, and socioeconomic status accounted for, individuals with post-COVID breathlessness walked shorter ISWT distances (median 350 vs 440m) with greater leg fatigue afterward (median 3.0 vs 2.0), but no difference in oxygen saturations (median 96.0 vs 96.0).

748 (61%) participants completed spirometry at the research visit, with gas transfer available for up to 276 (23%) people. More individuals with post-COVID breathlessness had an FVC less than the LLN (28.0% vs 13.8%) and an FEV_1 less than the LLN (21.5% vs 14.6%). However, there was little difference in the presence of obstructive lung function (based on the LLN of FEV_1/FVC) between those with and without

post-COVID breathlessness (3.9% vs 6.9%). KCO % predicted values were lower in those with post-COVID breathlessness compared to those without (median 99.6% vs 103.5%), while little difference was observed for TLCO % predicted values (median 90.7% vs 90.1%).

The following measures from the research visit were associated with increased risk of post-COVID breathlessness (Table 3): higher total scores on the PHQ-9 (adjusted odds ratio 1.09; 95% confidence interval 1.07–1.12), GAD-7 (1.07; 1.05–1.09) and PCL-5 (1.03; 1.02–1.04), lower haemoglobin level (0.88; 0.79–0.98 per 1g/dL), shorter ISWT distance (0.91; 0.85–0.97 per 100m), higher leg fatigue (1.14; 1.06–1.23) and lower FVC % predicted value (0.98; 0.97–0.99).

Sensitivity analyses

Results from the sensitivity analyses were consistent with results from the primary outcome and are described in the supplementary material (Tables S7-S13, Figure S7)

Discussion

In this national cohort of 1,226 patients who required hospitalisation for COVID-19, half considered their breathlessness to be new or worsening at the research visit compared to before they had COVID-19. Post-COVID breathlessness was associated with the most deprived quintile, pre-existing depression or anxiety, female sex, and longer admission duration. Black ethnicity and individuals aged 60 years and over were less likely to report post-COVID breathlessness at follow-up. There was no association between severity of acute COVID-19 and post-COVID breathlessness. At the research visit, participants reporting post-COVID breathlessness had on average, worse mental health status, lower haemoglobin levels and walked shorter distances during- and greater leg fatigue after the ISWT. Individuals with post-COVID breathlessness were more likely to have an FEV1 and FVC below the LLN compared to those with no change or improvement in breathlessness. However, there was no clear association with TLCO or airflow obstruction. Sensitivity analyses supported the primary findings.

Our results have similarities with a French cohort of 478 adults evaluated 3 months after hospitalisation for COVID-19, who found that participants with new/worsening dyspnoea were on average younger, had a longer hospital admission and little or no difference in pulmonary function tests compared to those without new/worsening dyspnoea [18]. In addition, and in keeping with our findings, having a pre-existing respiratory condition was not associated with post-COVID breathlessness [18] which may be explained by individuals with chronic lung disease being used to a background level of breathlessness which was not considered worse following COVID-19.

In contrast to our study, Jutant *et al* (2022) found that individuals with new/worsening dyspnoea were more likely to have required ITU treatment and have a pulmonary embolism during the admission [18]. Participants in the study by Jutant *et al*., (2022) had similarities to participants in our cohort, in respect to median age (61 years), sex (58% male) and the proportion who were diagnosed with pulmonary embolism (9.1%), however, a much greater proportion were intubated (51%), compared to 22% of patients in our study. [18] Prior to COVID-19, Herridge *et al* (2011) found that patients (median age 44 years, 41% without co-morbidities) admitted to ITU with acute respiratory distress syndrome (ARDS) were likely to have ongoing limitations in exercise capacity due to ventilator induced lung injury, skeletal muscle wasting and deconditioning, therefore it might be anticipated that severity of COVID-19 be associated with post-COVID breathlessness. [31] Our cohort were older, with more co-morbidities than the sample studied by Herridge *et al* (2011) and fewer participants were intubated than the participants reported by Jutant *et al* (2022). [18,31] Therefore, a possible explanation for the lack of association observed between severity of acute COVID-19 and post-COVID breathlessness in our study may be that those not admitted to ITU had poor pre-morbid health and were more liable to suffer from acute deconditioning than those admitted to ITU.

Our analyses suggest that post-COVID breathlessness was not associated with objective measures of airflow obstruction and therefore less likely a consequence of new airways disease. Similarly, we did not see an excess of restrictive patterns in those with post-COVID breathlessness. Individuals with post-COVID breathlessness had, on average, a lower FVC which may suggest an element of interstitial disease. In the smaller number of individuals who underwent gas transfer tests, KCO % predicted values were lower in those with post-COVID breathlessness compared to those without, but when adjusted for age, sex, ethnicity and IMD, the association with post-COVID breathlessness was not statistically significant (i.e., the confidence intervals overlapped with the null value), making the possibility of fibrosis difficult to confirm. We consider it likely that several factors may have contributed to this observation. Firstly, pulmonary vascular involvement (e.g., pulmonary embolism and its sequelae) can contribute to ongoing breathless after acute COVID-19 in the absence of an ongoing clot burden. [32] One possibility is that some individuals with post-COVID breathlessness had sub clinical pulmonary emboli during admission. [32] The possible influence of selection bias should also be recognised. Although we aimed to have all patients undertaking all procedures as per protocol, access to more complex lung function tests such as gas transfer were limited and may have resulted in those with clinical features suggesting an interstitial process were more likely to have undergone these tests.

Post-COVID breathlessness was more likely in the most deprived socio-economic group. Physical activity levels are known to be lowest in the most deprived groups, [33] so deprivation may have led to a low exercise tolerance phenotype that was compounded by acute and chronic sequelae of COVID-19. Obesity is also associated with deprivation, as well as chronic breathlessness. [16,34] Whilst obesity was not

associated with post-COVID breathlessness, the mean BMI of this sample was 32.0 which may be an additional contributing factor to the experience of breathlessness. We speculate that post-COVID breathlessness is likely to be a multifactorial and therefore heterogeneous problem, which may consist of a decrement in lung function in combination with anxiety or depression, deconditioning, poor exercise tolerance, fatigue and lower haemoglobin. Post-COVID breathlessness may also be influenced by central nervous system perception [35] and whilst we did not collect data specifically to confirm or refute this hypothesis, Jutant *et al* (2022) found that a greater proportion of individuals reporting new/worsening breathlessness scored highly on the Nijmegen questionnaire suggesting a component of dysfunctional breathing [18,36].

Regarding interventions for post-COVID breathlessness, our findings suggest that screening for, and addressing both the physical and emotional components of breathlessness are likely to be important. In a randomised controlled trial of a 6-week online breathing and wellbeing programme, Philip *et al*. demonstrated improvements in mental health and aspects of breathlessness in people with ongoing symptoms after COVID-19 [37]. Interestingly, the intervention led to improvements in the affective, rather than the physical component of the dyspnoea-12 score which may suggest that changes in breathlessness experience were related to the emotional impact of the wellbeing programme. Other rehabilitation programmes, which have tended to focus on physical conditioning, have also been shown to improve breathlessness [35,38], walking distance, lower limb strength and health related quality of life in patients with persisting symptoms after COVID-19 [35,38,39], though corroboration of these results in larger trials would be valuable.

PHOSP-COVID is one of the largest cohorts of post-hospitalisation COVID-19 survivors in the world with comprehensive assessment of participants providing information on physical, psychological, and biochemical characteristics/exposures [6,7]. This analysis included participants discharged between March 2020 and 31 March 2021 meaning patients treated in hospital both before and after changes in clinical practice for COVID-19 patients (e.g., the use of oral steroids [40] or proning during mechanical ventilation [41]) were represented. Limitations include the lack of viral genomic sequencing, vaccination and lung imaging data which meant that we could not account for vaccination status, radiological abnormalities [18,19] or the influence that infection with different genetic strains of SARS-CoV-2 may have on post-COVID breathlessness [42]. Participants in this study represent a small proportion of the total number of patients discharged from hospital after treatment for COVID-19 in the UK which may affect the generalisability of the results. Furthermore, participants in this study were younger than a larger sample of hospitalised COVID-19 patients [43], and only included individuals able to attend the research visit. Predicting the influence of this potential selection bias is challenging, because whilst more severely affected individuals may be under-represented, it is conceivable that those with ongoing symptoms may have been more willing to participate.

We chose to use patient reported breathlessness from the PSQ as the primary outcome because it provided a measure of breathlessness both before and after admission for COVID-19. We wanted to account for pre-existing breathlessness in our analyses because being able to identify participants whose breathlessness was new or worsening after COVID-19 was most important to inform policymakers and health services. We acknowledge that as the PSQ breathlessness score before COVID-19 was recorded at the research visit, patient responses may be considered subjective and liable to recall bias. Nevertheless, as the sensitivity analyses supported the associations identified with the primary outcome, we feel that recall bias or subjectivity related to the PSQ breathlessness score has not unduly influenced the main findings. The model derived in this analysis has the potential to predict the probability that an individual discharged following treatment for COVID-19 will experience post-COVID breathlessness. However, a limitation of our work is the lack of model validation which should be addressed before the prediction model is used.

The multi-centre nature of the study and workload pressures on sites, meant the period between discharge and follow-up varied. The heterogeneity introduced by considering patient reported breathlessness from different periods is likely to influence how individuals reported breathlessness, with those reviewed later since hospital discharge having longer time to recover. Compared to individuals who attended a research visit within six months of discharge, a higher proportion of participants attending the research visit six months or more after discharge had a longer admission duration and required higher levels of respiratory support. A possible explanation for this observation is that the majority of participants attending six to eight months after hospitalisation were discharged before July 2020 (Figure S6), and were therefore treated earlier on in the pandemic, and before the use of oral steroids was widespread. [40] However, overall, there was no difference in the period between discharge and the research visit between those reporting post-COVID breathlessness and not.

In conclusion, post-COVID breathlessness was common in this national cohort of patients hospitalised for COVID-19. Our analysis indicates that individuals discharged following COVID-19 who are from deprived backgrounds, females, below 70 years of age, with pre-existing depression or anxiety and who had an admission of over a week, are at greatest risk of new or worsening breathlessness post-COVID-19.

Ethics approval, study registration and role of the funders

The PHOSP-COVID study received ethical approval from the Leeds West Research Ethics Committee (20/YH/0225) and was registered with the ISRCTN Registry (ISRCTN10980107). All participants provided written informed consent. The funders had no role in study design, data collection/analysis, or report writing.

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Author's Contributions

The manuscript was initially drafted by LD, BZ and AS and further developed by the writing group. RAE, AH, OMK, CJ, NH, MT, JB, NE, PEP, NDB, LPH, JDC, MM, HM, MS, AShi ASi, made substantial contributions to the acquisition of data. LD, BZ, AS, CEB, RAE, LVW, OE, HM, AShi, ADS, RGJ, LH, AH, MT, PEP, LPH, JDC, MM, EMH, ABD, AShi, NIL, LGH made substantial contributions to the conception and design of the work. All authors contributed to data interpretation and critical review and revision of the manuscript. LD, BZ and AS verified all the data in the study and had final responsibility for the decision to submit the article for publication.

Declaration of interests

CEB, AShi and MS report grants from UKRI -MRC/DHSC- NIHR during the conduct of the study. JC reports grants and personal fees from Astrazeneca, grants and personal fees from BI, personal fees from Chiesi, grants from Gilead Sciences, grants and personal fees from GSK, grants and personal fees from Insmed, personal fees from Janssen, grants and personal fees from Novartis, personal fees from Zambon outside the submitted work. ADS reports grants, personal fees and other from AZ, Bayer, BI, Chiesi, Forest labs, GSK, Grifols, Insmed, MedImmune, Novartis, Pfizer, 30T outside the submitted work. RAE reports grants from UKRI/MRC/NIHR, during the conduct of the study, speaker fees from BI. AH reports funding from NIHR Manchester Biomedical Research Centre, grants from the Cystic Fibrosis Foundation, JP Moulton Trust and NIHR, and personal fees from Vertex Pharmaceuticals and Mylan Healthcare, all outside the submitted work. LGH other from AZ, BI, Chiesi, GSK and Napp Pharmaceuticals, personal fees from Novartis, Hoffman la Roche/Genetech Inc, Sanofi, Evelo Biosciences, GSK, AZ, Teva,

Theravance, Circassia, grants from Medimmune, Novartis UK, Roche/Genetech Inc and GSK, Amgen, Genetech/Hoffman la Roche, AZ, Medimmune, GSK, Aerocrine and Vitalograph outside the submitted work. JRH reports grants, personal fees and non-financial support from pharmaceutical companies that make medicines to treat respiratory disease, outside the submitted work. RGJ reports grants from GSK, grants and personal fees from Pliant Therapeutics, grants from Biogen, during the conduct of the study; personal fees from Galapagos, other from Galecto, personal fees and other from GSK, personal fees and other from AZ, personal fees from Boehringer Ingelheim, personal fees from Pliant, personal fees from Bristol Myers Squibb, personal fees from Chiesi, personal fees from Roche/Promedior, personal fees and other from RedX, other from NuMedii, other from Nordic Biosciences, personal fees from Veracyte, personal fees from PatientMPower, personal fees from Resolution Therapeutics, personal fees from Vicore, outside the submitted work; and is supported by a National Institute of Health Research Professorship (NIHR ref: RP-2017-08-ST2-014) and trustee for Action for Pulmonary Fibrosis. JDC reports grants and personal fees from AZ and BI, and personal fees from GSK, Insmed, Novartis, Chiesi, and Zambon, outside the submitted work. PEP reports grants from NIHR, outside the submitted work. JKQ reports grants and personal fees from AZ, grants from Bayer, grants and personal fees from BI, grants and personal fees from Chiesi, grants and personal fees from GSK, grants from MRC, grants from The health foundation, grants from AUK/BLF, outside the submitted work. BR is supported by the British Heart Foundation Oxford Centre of Research Excellent (RE/18/3/34214). AS reports grants from HDRUK, grants from NIHR, grants from MRC, grants from ICSF, during the conduct of the study; and Member of Scottish Government's CMO COVID-19 Advisory Group and Standing Committee on Pandemics. ASi reports grants from MRC, during the conduct of the study. SS reports grants from NIHR Leicester Biomedical Research Centre, grants from NIHR PHOSP COVID, personal fees from AZ, personal fees from GSK, personal fees from CSL Behring, personal fees from Knopp Biosciences, from Owlstone Medical, personal fees from Chiesi, outside the submitted work; and has a patent pending for volatile breath biomarkers of breathlessness. MT reports personal fees from Actelion/J&J, personal fees from GSK, other from Morphogen-IX, outside the submitted work. LVW reports grants from GSK, grants from Orion, outside the submitted work. All other authors declare no competing interests.

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Data sharing statement

The protocol, consent form, definition and derivation of clinical characteristics and outcomes, training materials, regulatory documents, information about requests for data access, and other relevant study materials are available online. Please see https://phosp.org/ for more information.

494 **Table 1 Patient characteristics**

	Total N	Levels	Post-COVID breathlessness		Total
			No (%)	Yes (%)	
Total N (%)			611 (49.8)	615 (50.2)	1226
Age at admission (years)	1213 (98.9)	<30	10 (1.6)	15 (2.4)	25 (2.0)
		30-39	38 (6.2)	41 (6.7)	79 (6.4)
		40-49	87 (14.2)	103 (16.7)	190 (15.5)
		50-59	151 (24.7)	203 (33.0)	354 (28.9)
		60-69	183 (30.0)	174 (28.3)	357 (29.1)
		70-79	107 (17.5)	61 (9.9)	168 (13.7)
		80+	29 (4.7)	11 (1.8)	40 (3.3)
		(Missing)	6 (1.0)	7 (1.1)	13 (1.1)
Sex at birth	1226 (100.0)	Male	416 (68.1)	352 (57.2)	768 (62.6)
		Female	195 (31.9)	263 (42.8)	458 (37.4)
Ethnicity	1203 (98.1)	White	422 (69.1)	451 (73.3)	873 (71.2)
		South Asian	82 (13.4)	71 (11.5)	153 (12.5)
		Black	52 (8.5)	40 (6.5)	92 (7.5)
		Mixed	17 (2.8)	16 (2.6)	33 (2.7)
		Other	27 (4.4)	25 (4.1)	52 (4.2)
		(Missing)	11 (1.8)	12 (2.0)	23 (1.9)
Index of multiple deprivation	1204 (98.2)	1 - most deprived	112 (18.3)	154 (25.0)	266 (21.7)
		2	135 (22.1)	131 (21.3)	266 (21.7)
		3	116 (19.0)	112 (18.2)	228 (18.6)
		4	111 (18.2)	103 (16.7)	214 (17.5)
		5 - least deprived	127 (20.8)	103 (16.7)	230 (18.8)
		(Missing)	10 (1.6)	12 (2.0)	22 (1.8)
BMI	1090 (88.9)	Mean (SD)	31.4 (7.1)	32.7 (7.1)	32.0 (7.1)
Smoking	1213 (98.9)	Never	350 (57.3)	339 (55.1)	689 (56.2)
		Ex-smoker	246 (40.3)	260 (42.3)	506 (41.3)
		Current smoker	7 (1.1)	11 (1.8)	18 (1.5)
		(Missing)	8 (1.3)	5 (0.8)	13 (1.1)
Number of comorbidities	1226 (100.0)	Median (IQR)	2.0 (0.0 to 3.0)	2.0 (1.0 to 4.0)	2.0 (0.0 to 3.0)
Pre-existing cardiovascular condition	1226 (100.0)	No	329 (53.8)	350 (56.9)	679 (55.4)
		Yes	282 (46.2)	265 (43.1)	547 (44.6)
Pre-existing respiratory condition	1226 (100.0)	No	449 (73.5)	444 (72.2)	893 (72.8)
		Yes	162 (26.5)	171 (27.8)	333 (27.2)
Pre-existing depression or anxiety	1207 (98.5)	No	538 (88.1)	471 (76.6)	1009 (82.3)
		Yes	66 (10.8)	132 (21.5)	198 (16.2)

	Total N	Levels	Post-COVID breathlessness		Total
			No (%)	Yes (%)	
		(Missing)	7 (1.1)	12 (2.0)	19 (1.5)
Breathlessness before COVID-19 (PSQ)	1226 (100.0)	0	374 (61.2)	407 (66.2)	781 (63.7)
		1-2	103 (16.9)	128 (20.8)	231 (18.8)
		3 or more	134 (21.9)	80 (13.0)	214 (17.5)
BMI = Body Mass Index. PSQ = Patient Symptom Questionnaire					

495

496

497 **Table 2 Patient characteristics available during hospital admission**

	Total N	Levels	Post-COVID breathlessness		Total
			No (%)	Yes (%)	
Total N (%)			611 (49.8)	615 (50.2)	1226
Admission duration (days)	1225 (99.9)	Median (IQR)	7.0 (4.0 to 14.0)	9.0 (4.0 to 22.0)	8.0 (4.0 to 17.0)
SARS-CoV-2 PCR result	1142 (93.1)	Negative	47 (7.7)	51 (8.3)	98 (8.0)
		Positive	522 (85.4)	517 (84.1)	1039 (84.7)
		Missing	42 (6.9)	47 (7.3)	89 (7.3)
WHO clinical progression scale	1226 (100.0)	WHO – class 3-4	110 (18.0)	113 (18.4)	223 (18.2)
		WHO – class 5	252 (41.2)	225 (36.6)	477 (38.9)
		WHO – class 6	136 (22.3)	120 (19.5)	256 (20.9)
		WHO – class 7-9	113 (18.5)	157 (25.5)	270 (22.0)
Proning during mechanical ventilation	1102 (89.9)	No	466 (76.3)	426 (69.3)	892 (72.8)
		Yes	87 (14.2)	123 (20.0)	210 (17.1)
		(Missing)	58 (9.5)	66 (10.7)	124 (10.1)
Pulmonary Embolism	1146 (93.5)	No	518 (84.8)	507 (82.4)	1025 (83.6)
		Yes	56 (9.2)	65 (10.6)	121 (9.9)
		(Missing)	37 (6.1)	43 (7.0)	80 (6.5)
Coronary thrombosis	1140 (93.0)	No	570 (93.3)	565 (91.9)	1135 (92.6)
		Yes	<5 (-)	<5 (-)	5 (0.4)
		(Missing)	- (-)	- (-)	86 (7.0)
Antibiotic therapy	1187 (96.8)	No	115 (18.8)	121 (19.7)	236 (19.2)
		Yes	477 (78.1)	474 (77.1)	951 (77.6)
		(Missing)	19 (3.1)	20 (3.3)	39 (3.2)
Systemic steroids (Oral or IV)	1144 (93.3)	No	319 (52.2)	294 (47.8)	613 (50.0)
		Yes	250 (40.9)	281 (45.7)	531 (43.3)
		(Missing)	42 (6.9)	40 (6.5)	82 (6.7)
Therapeutic dose anti-coagulation	1150 (93.8)	No	352 (57.6)	333 (54.1)	685 (55.9)
		Yes	220 (36.0)	245 (39.8)	465 (37.9)
		(Missing)	39 (6.4)	37 (6.0)	76 (6.2)

IV = Intravenous. World Health Organisation (WHO) clinical progression scale: not requiring continuous supplemental oxygen (levels 3-4); continuous supplemental oxygen only (level 5); Continuous Positive Airway Pressure (CPAP) ventilation, Bi-Level Positive Airway Pressure or High Flow Nasal Oxygen (HFNO) (level 6); Invasive Mechanical Ventilation (IMV), Extra-Corporeal Membrane Oxygenation (ECMO) and acute Renal Replacement Therapy (RRT) (levels 7-9). Cell counts <5 and related sub-totals have been suppressed.

498 **Table 3 Patient characteristics available at the research visit**

	Total N	Levels	Post-COVID breathlessness		Total	OR (95% CI)
			No (%)	Yes (%)		
Total N (%)			611 (49.8)	615 (50.2)	1226	-
Discharge to review period (months)	1226 (100.0)	Median (IQR)	4.7 (3.4 to 6.0)	4.7 (3.3 to 6.0)	4.7 (3.4 to 6.0)	1.00 (1.00 to 1.00)
Breathlessness at research visit (PSQ)	1226 (100.0)	0	462 (75.6)	0 (0.0)	462 (37.7)	-
		1-2	70 (11.5)	143 (23.3)	213 (17.4)	-
		3 or more	79 (12.9)	472 (76.7)	551 (44.9)	-
PHQ-9 total score	1188 (96.9)	Median (IQR)	3.0 (1.0 to 8.0)	8.0 (3.0 to 13.0)	5.0 (2.0 to 11.0)	1.09 (1.07 to 1.12)
GAD-7 total score	1187 (96.8)	Median (IQR)	2.0 (0.0 to 6.0)	5.0 (1.0 to 11.0)	3.0 (0.0 to 8.0)	1.07 (1.05 to 1.09)
PCL-5 Total Severity Score	1184 (96.6)	Median (IQR)	6.0 (2.0 to 15.0)	15.0 (5.0 to 31.2)	9.0 (3.0 to 23.0)	1.03 (1.02 to 1.04)
CRP	800 (65.3)	Median (IQR)	4.0 (1.4 to 5.0)	4.0 (2.0 to 5.0)	4.0 (1.8 to 5.0)	1.01 (0.99 to 1.04)
BNP/NT-Pro-BNP ng/L >threshold	642 (52.4)	No	293 (48.0)	304 (49.4)	597 (48.7)	-
		Yes	29 (4.7)	16 (2.6)	45 (3.7)	0.65 (0.32 to 1.33)
Haemoglobin level All (g/dL)	861 (70.2)	Median (IQR)	14.4 (13.3 to 15.2)	14.0 (13.1 to 15.0)	14.2 (13.2 to 15.2)	0.88 (0.79 to 0.98)
Haemoglobin male (g/dL)	537 (43.8)	Median (IQR)	14.7 (13.9 to 15.6)	14.6 (13.6 to 15.5)	14.7 (13.8 to 15.5)	0.90 (0.79 to 1.03)
Haemoglobin female (g/dL)	324 (26.4)	Median (IQR)	13.5 (12.8 to 14.3)	13.4 (12.6 to 14.0)	13.4 (12.7 to 14.1)	0.80 (0.65 to 0.99)
ISWT distance (m)	737 (60.1)	Median (IQR)	440.0 (270.0 to 615.0)	350.0 (230.0 to 540.0)	380.0 (257.5 to 570.0)	0.91 (0.85 to 0.97)*
ISWT % predicted	658 (53.7)	Median (IQR)	60.5 (42.0 to 81.9)	52.5 (35.1 to 71.2)	56.3 (37.9 to 75.9)	0.99 (0.98 to 1.00)
Oxygen saturations post ISWT	727 (59.3)	Median (IQR)	96.0 (94.0 to 98.0)	96.0 (94.0 to 98.0)	96.0 (94.0 to 98.0)	0.98 (0.94 to 1.02)
Borg leg fatigue score post ISWT	722 (58.9)	Median (IQR)	2.0 (0.5 to 3.0)	3.0 (2.0 to 4.0)	3.0 (1.0 to 4.0)	1.14 (1.06 to 1.23)
FEV1 (L)	748 (61.0)	Median (IQR)	2.8 (2.3 to 3.4)	2.7 (2.2 to 3.3)	2.8 (2.2 to 3.3)	0.96 (0.81 to 1.15)
FEV1 % predicted	683 (55.7)	Median (IQR)	93.9 (83.4 to 105.7)	89.9 (77.9 to 101.3)	91.7 (79.7 to 103.7)	1.00 (0.99 to 1.00)
FEV1 < LLN	683 (55.7)	No	274 (85.4)	284 (78.5)	558 (81.7)	-
		Yes	47 (14.6)	78 (21.5)	125 (18.3)	1.61 (1.05 to 2.45)
FVC (L)	746 (60.8)	Median (IQR)	3.6 (2.9 to 4.3)	3.3 (2.6 to 4.0)	3.5 (2.8 to 4.2)	0.70 (0.57 to 0.86)
FVC % predicted	681 (55.5)	Median (IQR)	93.7 (83.0 to 105.4)	86.8 (74.5 to 98.5)	90.0 (78.2 to 102.4)	0.98 (0.97 to 0.99)
FVC < LLN	681 (55.5)	No	276 (86.2)	260 (72.0)	536 (78.7)	-
		Yes	44 (13.8)	101 (28.0)	145 (21.3)	2.43 (1.60 to 3.70)

FEV1/FVC ratio expressed as %	736 (60.0)	Median (IQR)	79.4 (73.9 to 84.0)	81.6 (77.3 to 86.0)	80.6 (76.0 to 85.5)	1.04 (1.02 to 1.06)
FEV1/FVC < LLN	673 (54.9)	No	295 (93.1)	342 (96.1)	637 (94.7)	-
		Yes	22 (6.9)	14 (3.9)	36 (5.3)	0.58 (0.28 to 1.19)
TLCO	272 (22.2)	Median (IQR)	7.6 (6.4 to 8.7)	6.8 (5.8 to 8.3)	7.3 (6.1 to 8.4)	0.94 (0.83 to 1.07)
TLCO % predicted	252 (20.6)	Median (IQR)	90.1 (78.6 to 102.7)	90.7 (74.2 to 104.2)	90.7 (76.8 to 103.2)	0.99 (0.99 to 1.00)
TLCO predicted <80%	252 (20.6)	No	86 (72.3)	90 (67.7)	176 (69.8)	
		Yes	33 (27.7)	43 (32.3)	76 (30.2)	1.48 (0.79 to 2.77)
KCO	276 (22.5)	Median (IQR)	1.5 (1.3 to 1.6)	1.5 (1.2 to 1.7)	1.5 (1.3 to 1.6)	0.49 (0.18 to 1.29)
KCO % predicted	259 (21.1)	Median (IQR)	103.5 (92.6 to 108.7)	99.6 (87.4 to 112.3)	101.8 (89.2 to 110.1)	0.99 (0.97 to 1.00)
KCO predicted <80%	259 (21.1)	No	112 (92.6)	127 (92.0)	239 (92.3)	
		Yes	9 (7.4)	11 (8.0)	20 (7.7)	1.43 (0.53 to 3.88)

PHQ-9 = Patient Health Questionnaire-9, GAD-7 = General Anxiety Disorder-7, PCL-5 = Posttraumatic Stress Disorder Checklist for DSM-5, CRP = C-reactive Protein, BNP = Brain Natriuretic Peptide, NT-Pro-BNP = N-terminal-pro hormone BNP, ISWT = Incremental Shuttle Walk Test, FEV1 = Forced Expiratory Volume in 1 second, LLN = Lower Limit of Normal, FVC = Forced Vital Capacity, TLCO = Transfer Capacity of the lung , KCO = Carbon monoxide transfer coefficient, PSQ = Patient Symptom Questionnaire. *The OR for ISWT refers to the risk of worsening breathlessness for each 100m achieved.

501 **Table 4 Multivariable logistic regression for post-COVID breathlessness**

Dependent: Post-COVID breathlessness		Post-COVID breathlessness		OR (univariable)	OR (multivariable)	OR (multiple imputation)
		No	Yes			
Sex at birth	Male	416 (54.2)	352 (45.8)	-	-	-
	Female	195 (42.6)	263 (57.4)	1.59 (1.26-2.01, p<0.001)	1.44 (1.10-1.90, p=0.009)	1.56 (1.21-2.00, p=0.001)
Age at admission (years)	50-59	151 (42.7)	203 (57.3)	-	-	-
	<30	10 (40.0)	15 (60.0)	1.12 (0.49-2.63, p=0.795)	1.20 (0.47-3.12, p=0.706)	1.35 (0.57-3.23, p=0.498)
	30-39	38 (48.1)	41 (51.9)	0.80 (0.49-1.31, p=0.378)	0.83 (0.48-1.44, p=0.511)	0.86 (0.51-1.44, p=0.568)
	40-49	87 (45.8)	103 (54.2)	0.88 (0.62-1.26, p=0.482)	0.96 (0.64-1.44, p=0.832)	0.96 (0.66-1.40, p=0.832)
	60-69	183 (51.3)	174 (48.7)	0.71 (0.53-0.95, p=0.022)	0.62 (0.44-0.88, p=0.007)	0.70 (0.51-0.96, p=0.025)
	70-79	107 (63.7)	61 (36.3)	0.42 (0.29-0.62, p<0.001)	0.41 (0.26-0.64, p<0.001)	0.43 (0.28-0.64, p<0.001)
	80+	29 (72.5)	11 (27.5)	0.28 (0.13-0.57, p=0.001)	0.27 (0.11-0.60, p=0.002)	0.31 (0.14-0.66, p=0.003)
Index of Multiple Deprivation	5 - least deprived	127 (55.2)	103 (44.8)	-	-	-
	4	111 (51.9)	103 (48.1)	1.14 (0.79-1.66, p=0.480)	1.30 (0.85-1.99, p=0.220)	1.22 (0.82-1.81, p=0.328)
	3	116 (50.9)	112 (49.1)	1.19 (0.82-1.72, p=0.352)	1.21 (0.80-1.84, p=0.365)	1.22 (0.82-1.79, p=0.327)
	2	135 (50.8)	131 (49.2)	1.20 (0.84-1.71, p=0.321)	1.31 (0.87-1.96, p=0.195)	1.20 (0.82-1.76, p=0.338)
	1 - most deprived	112 (42.1)	154 (57.9)	1.70 (1.19-2.42, p=0.004)	1.87 (1.24-2.84, p=0.003)	1.67 (1.14-2.44, p=0.009)
Ethnicity	White	422 (48.3)	451 (51.7)	-	-	-
	South Asian	82 (53.6)	71 (46.4)	0.81 (0.57-1.14, p=0.231)	0.83 (0.55-1.26, p=0.378)	0.80 (0.55-1.17, p=0.244)
	Black	52 (56.5)	40 (43.5)	0.72 (0.46-1.11, p=0.137)	0.57 (0.34-0.95, p=0.031)	0.56 (0.35-0.89, p=0.015)
	Mixed	17 (51.5)	16 (48.5)	0.88 (0.44-1.77, p=0.720)	0.98 (0.44-2.20, p=0.956)	0.85 (0.41-1.75, p=0.656)
	Other	27 (51.9)	25 (48.1)	0.87 (0.49-1.52, p=0.616)	0.84 (0.44-1.62, p=0.606)	0.80 (0.44-1.44, p=0.448)
BMI	Mean (SD)	31.4 (7.1)	32.7 (7.1)	1.03 (1.01-1.04, p=0.002)	1.08 (0.97-1.21, p=0.164)	1.08 (0.98-1.19, p=0.107)
Number of comorbidities	Mean (SD)	2.0 (2.0)	2.4 (2.3)	1.09 (1.03-1.15, p=0.002)	1.09 (1.00-1.18, p=0.049)	1.08 (1.00-1.17, p=0.049)

Dependent: Post-COVID breathlessness		Post-COVID breathlessness		OR (univariable)	OR (multivariable)	OR (multiple imputation)
		No	Yes			
Pre-existing respiratory condition	No	449 (50.3)	444 (49.7)	-	-	-
	Yes	162 (48.6)	171 (51.4)	1.07 (0.83-1.37, p=0.611)	0.85 (0.62-1.17, p=0.312)	0.82 (0.61-1.11, p=0.195)
Pre-existing depression or anxiety	No	538 (53.3)	471 (46.7)	-	-	-
	Yes	66 (33.3)	132 (66.7)	2.28 (1.66-3.16, p<0.001)	1.54 (1.00-2.38, p=0.050)	1.58 (1.06-2.35, p=0.026)
Admission duration (days)	Mean (SD)	13.2 (17.2)	17.2 (22.2)	1.01 (1.00-1.02, p=0.001)	1.01 (1.00-1.02, p=0.064)	1.01 (1.00-1.02, p=0.002)
WHO clinical progression scale	WHO – class 3-4	110 (49.3)	113 (50.7)	-	-	-
	WHO – class 5	252 (52.8)	225 (47.2)	0.87 (0.63-1.19, p=0.388)	0.88 (0.61-1.29, p=0.522)	0.84 (0.60-1.18, p=0.314)
	WHO – class 6	136 (53.1)	120 (46.9)	0.86 (0.60-1.23, p=0.407)	0.90 (0.58-1.38, p=0.619)	0.80 (0.54-1.18, p=0.260)
	WHO – class 7-9	113 (41.9)	157 (58.1)	1.35 (0.95-1.93, p=0.097)	1.17 (0.70-1.98, p=0.548)	0.92 (0.57-1.47, p=0.715)

BMI = Body Mass Index. World Health Organisation (WHO) clinical progression scale: not requiring continuous supplemental oxygen (levels 3-4); continuous supplemental oxygen only (level 5); Continuous Positive Airway Pressure (CPAP) ventilation, Bi-Level Positive Airway Pressure or High Flow Nasal Oxygen (HFNO) (level 6); Invasive Mechanical Ventilation (IMV), Extra-Corporeal Membrane Oxygenation (ECMO) and acute Renal Replacement Therapy (RRT) (levels 7-9). The logistic regression model also included BMI^2

504 **Table 5 Multinomial modelling for post-COVID breathlessness**

Dependent: Post-COVID breathlessness		Post-COVID breathlessness (OR 95% CI)	
		Mild	Severe
Sex at birth	Male	1.00	1.00
	Female	1.34 (0.95-1.88)	1.67 (1.26-2.22)
Age at admission (years)	50-59	1.00	1.00
	<30	2.22 (0.78-6.33)	0.95 (0.35-2.62)
	30-39	1.23 (0.62-2.43)	0.68 (0.38-1.22)
	40-49	1.38 (0.84-2.26)	0.78 (0.51-1.18)
	60-69	0.79 (0.51-1.23)	0.64 (0.46-0.91)
	70-79	0.44 (0.25-0.80)	0.39 (0.25-0.62)
	80+	0.58 (0.23-1.41)	0.13 (0.04-0.44)
Index of Multiple Deprivation	5 - least deprived	1.00	1.00
	4	1.14 (0.68-1.90)	1.26 (0.79-2.00)
	3	1.05 (0.63-1.74)	1.38 (0.88-2.18)
	2	0.82 (0.49-1.36)	1.52 (0.99-2.35)
	1 - most deprived	1.02 (0.61-1.71)	2.22 (1.44-3.44)
Ethnicity	White	1.00	1.00
	South Asian	0.80 (0.49-1.33)	0.74 (0.48-1.14)
	Black	1.02 (0.61-1.71)	0.46 (0.27-0.80)
	Mixed	0.76 (0.27-2.15)	0.88 (0.39-1.98)
	Other	0.88 (0.39-1.96)	0.77 (0.39-1.49)
BMI (kg/m^2)	-	0.99 (0.96-1.02)	1.01 (0.99-1.04)
Number of comorbidities	-	1.12 (1.02-1.24)	1.06 (0.98-1.16)
Pre-existing respiratory condition	No	1.00	1.00
	Yes	0.94 (0.64-1.39)	0.76 (0.55-1.07)
Pre-existing depression or anxiety	No	1.00	1.00
	Yes	1.41 (0.83-2.38)	1.64 (1.06-2.54)
Admission duration (days)	-	1.01 (1.00-1.02)	1.02 (1.01-1.02)
WHO clinical progression scale	WHO – class 3-4	1.00	1.00
	WHO – class 5	0.92 (0.59-1.45)	0.81 (0.55-1.20)
	WHO – class 6	0.76 (0.45-1.31)	0.83 (0.53-1.30)
	WHO – class 7-9	0.90 (0.48-1.69)	0.98 (0.58-1.65)
The reference group (not shown) were those with no post-COVID breathlessness (n=611). Mild post-COVID breathlessness (n=213), Severe post-COVID breathlessness (n=402).			

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References

1 World Health Organization. COVID-19 Weekly Epidemiological Update. 2021:67. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---1-june-2022 Date last updated: 1 June 2022. Date last accessed: 1 June 2022.

2 Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV, Group WC. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis*. 2021;22(4):E102-E107.

3 National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. NICE guideline [NG188] https://www.nice.org.uk/guidance/ng188 Date last updated: 11 November 2021. Date last accessed: 7 June 2022.

4 Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet.* 2021;397(10270):220-232.

5 Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, Hu P, Guo L, Liu M, Xu J, Zhang X. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet*. 2021;28;398(10302):747-58.

6 Evans RA, McAuley H, Harrison EM, et al. Physical, cognitive, and mental health impacts of COVID-19 following hospitalisation – a multi-centre prospective cohort study. *Lancet Respir Med*. 2021;9(11):1275-87.

7 Evans RA, Leavy OC, Richardson M, et al. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. *Lancet Respir Med*. 2022. DOI: https://doi.org/10.1016/S2213-2600(22)00127-8

8 Adeloye D, Elneima O, Daines L, et al. The long-term sequelae of COVID-19: an international consensus on research priorities for patients with pre-existing and new-onset airways disease. *Lancet Respir Med*. 2021;9(12):1467-78

9 Office for National Statistics. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 1 June 2022. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bullet

ins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/latest Date last updated: 1 June 2022. Date last accessed: 7 June 2022.

10 Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep* 2021;11:16144.

11 Fernandez-de-Las-Penas C, Palacios-Cena D, Gomez-Mayordomo V, et al. Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. *Eur J Intern Med* 2021;92:55-70.

12 Iqbal FM, Lam K, Sounderajah V, et al. Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis. *EClinicalMedicine*. 2021;36:100899. doi: 10.1016/j.eclinm.2021.100899.

13 Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R, et al. Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Chron Respir Dis* 2021;18:14799731211002240.

14 Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. *JAMA Netw Open.* 2021;4(5):e2111417. doi:10.1001/jamanetworkopen.2021.11417

15 Lansing RW, Gracely RH, Banzett RB. The multiple dimensions of dyspnea: review and hypotheses. *Respir Physiol Neurobiol*. 2009;167(1):53–60.

16 Bowden JA, To TH, Abernethy AP, et al. Predictors of chronic breathlessness: a large population study. *BMC public health*. 2011;11:33 doi: 10.1186/1471-2458-11-33.

17 Whitaker M, Elliott J, Chadeau-Hyam M, Riley S, Darzi A, Cooke G, Ward H, Elliott P. Persistent COVID-19 symptoms in a community study of 606,434 people in England. Nature communications. 2022;13(1):1-0.

18 Jutant EM, Meyrignac O, Beurnier A, et al. Respiratory symptoms and radiological findings in post-acute COVID-19 syndrome. *ERJ Open Res*. 2022;8:00479-2021; DOI: 10.1183/23120541.00479-2021

19 Lerum TV, Aaløkken TM, Brønstad E, Aarli B, Ikdahl E, Lund KM, Durheim MT, Rodriguez JR, Meltzer C, Tonby K, Stavem K. Dyspnoea, lung function and CT findings 3 months after hospital admission for COVID-19. *Eur Respir J*. 2021;57(4).

20 D'Cruz RF, Waller MD, Perrin F, Periselneris J, Norton S, Smith LJ, Patrick T, Walder D, Heitmann A, Lee K, Madula R. Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia. ERJ open research. 2021;7(1).

21 WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020;20(8):e192-197.

22 Johnson SU, Ulvenes PG, Øktedalen T, et al. Psychometric properties of the general anxiety disorder 7-item (GAD-7) scale in a heterogeneous psychiatric sample. *Front Psychol.* 2019;10:1713.

23 Levis B, Benedetti A, Thombs BD. Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. *BMJ.* 2019;365:l1476.

24 Blevins CA, Weathers FW, Davis MT, et al. The posttraumatic stress disorder checklist for DSM-5 (PCL-5): Development and initial psychometric evaluation. *J Trauma Stress*. 2015;28(6):489-98.

25 World Health Organization. Scientific brief. Transmission of SARS-CoV-2: implications for infection prevention precautions. 2020. https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions Date last updated: 9 July 2020. Date last accessed: 7 June 2022.

26 Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. *Am J Respir Crit Care Med.* 2019;200(8):e70-e88.

27 Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40:1324-1343

28 Stanojevic S, Graham BL, Cooper BG, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J*. 2017;50(3):1700010

29 Johnson MJ, Bland JM, Oxberry SG, et al. Clinically important differences in the intensity of chronic refractory breathlessness. *J Pain Symptom Manage*. 2013;46(6):957-963.

30 Yorke J, Moosavi SH, Shuldham C, et al. Quantification of dyspnoea using descriptors: development and initial testing of the Dyspnoea-12. *Thorax*. 2010;65(1):21-26

31 Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, Guest CB, Mazer CD, Mehta S, Stewart TE, Kudlow P. Functional disability 5 years after acute respiratory distress syndrome. New England Journal of Medicine. 2011;364(14):1293-304.

32 Dhawan RT, Gopalan D, Howard L, Vicente A, Park M, Manalan K, Wallner I, Marsden P, Dave S, Branley H, Russell G. Beyond the clot: perfusion imaging of the pulmonary vasculature after COVID-19. The Lancet Respiratory Medicine. 2021;9(1):107-16.

33 NHS Digital. Statistics on Obesity, Physical Activity and Diet. Part 5: Physical activity. 8 May 2019. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-obesity-physical-activity-and-diet/statistics-on-obesity-physical-activity-and-diet-england-2019/part-5-adult-physical-activity [Accessed 12 September 2022]

34 NHS Digital. Health survey for England 2018. Overweight and obesity. 3 December 2019. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2018/summary#overweight-and-obesity [Accessed 12 September 2022]

35 Bouteleux B, Henrot P, Ernst R, Grassion L, Raherison-Semjen C, Beaufils F, Zysman M, Delorme M. Respiratory rehabilitation for Covid-19 related persistent dyspnoea: A one-year experience. Respir Med. 2021;189:106648.

36 Van Dixhoorn J, Folgering H. The Nijmegen Questionnaire and dysfunctional breathing. *ERJ Open Res*. 2015;1(1).

37 Philip KE, Owles H, McVey S, et al. An online breathing and wellbeing programme (ENO Breathe) for people with persistent symptoms following COVID-19: a parallel-group, single-blind, randomised controlled trial. *Lancet Respir Med*. 2022 https://doi.org/10.1016/S2213-2600(22)00125-4

38 Curci C, Negrini F, Ferrillo M, et al. Functional outcome after inpatient rehabilitation in postintensive care unit COVID-19 patients: findings and clinical implications from a real-practice retrospective study. *Eur J Phys Rehabil Med*. 2021:443-50.

39 Li J, Xia W, Zhan C, et al. A telerehabilitation programme in post-discharge COVID-19 patients (TERECO): a randomised controlled trial. *Thorax.* 2021. doi: 10.1136/thoraxjnl-2021-217382

40 The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19—preliminary report. *N Engl J Med.* 2021;384:693-704

41 Koeckerling D, Barker J, Mudalige NL, et al. Awake prone positioning in COVID-19. *Thorax*. 2020;75(10):833-834.

42 Sheikh A, McMenamin J, Taylor B, et al. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet*. 2021; 26;397(10293):2461-2462.

43 Docherty AB, Harrison EM, Green CA, et al. Features of 20,133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020;369:m1985.