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Cohort Profile: Post-hospitalisation COVID-19 study (PHOSP-COVID)

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Key features

- PHOSP-COVID is a national UK multi-centre cohort study of patients who were hospitalised for COVID-19 and subsequently discharged.
- PHOSP-COVID was established to investigate the medium- and long-term sequelae of severe COVID-19 requiring hospitalisation, understand the underlying mechanisms of these sequelae, evaluate the medium- and long-term effects of COVID-19 treatments, and to serve as a platform to enable future studies, including clinical trials.
- Data collected covered a wide range of physical measures, biological samples, and Patient Reported Outcome Measures (PROMs).
- Participants could join the cohort either in Tier 1 only with remote data collection using hospital records, a PROMs app and postal saliva sample for DNA, or in Tier 2 where they were invited to attend two specific research visits for further data collection and biological research sampling. These research visits occurred at five (range 2-7) months and 12 (range 10-14) months post-discharge. Participants could also participate in specific nested studies (Tier 3) at selected sites.
- All participants were asked to consent to further follow-up for 25 years via linkage to their electronic healthcare records and to be re-contacted for further research.
- In total, 7935 participants were recruited from 83 UK sites: 5238 to Tier 1 and 2697 to Tier 2, between August 2020 and March 2022.
- Cohort data are held in a Trusted Research Environment and samples stored in a central biobank. Data and samples can be accessed upon request and subject to approvals.

Why was the cohort set up?

To date, there have been over 750 million reported cases of COVID-19 globally since the pandemic began in early 2020 (1). In the UK, there have been over one million patients hospitalised and 180,000 deaths due to COVID-19 (2). Previous viral epidemics and conditions causing acute respiratory distress syndrome (ARDS) caused long lasting heath impacts on the affected survivors (3, 4). At the time of conception of the PHOSP-COVID cohort in March 2020, the longer-term pulmonary and multisystem effects of COVID-19 and impact on health status were unknown (5). We identified a need to establish a cohort of hospitalised COVID-19 survivors to collect detailed information about the medium- and long–term effects of COVID-19 on physical and mental health, lifestyle, and occupation status.

Although the majority of individuals with COVID-19 were not hospitalised, we expected the consequences of COVID-19 might be most pronounced after severe illness. Furthermore, the pressures on health systems during the pandemic needed to be taken into consideration when establishing a new clinical cohort. Therefore, we designed the PHOSP-COVID study to align with clinical follow-up reviews of hospitalised patients, where possible.

PHOSP-COVID was designed to take a patient-centred, holistic approach to understand the medium- and long-term effects of COVID-19 recognising the need to consider physical and mental health, social support, and lifestyle. There were three main aims of PHOSP-COVID:

1. To determine the medium- and long-term health (and health economic) sequelae of COVID-19 in post-hospitalisation survivors; to define demographic, clinical and molecular biomarkers of susceptibility, including to severity of the acute illness and development, progression, and resolution of sequelae.
2. To understand the impact of in-patient and post-discharge, pharmacological and non-pharmacological interventions on long-term sequelae of COVID-19.
3. To build the foundation for in-depth studies of emergent conditions and worsening of premorbid disease to inform precision medicine in at-risk groups by directing new clinical trials and care for current and future patients with long COVID.

Who is in the cohort?

Individuals who were discharged from hospital between 1 February 2020 and 31 March 2021 were invited to participate in the PHOSP-COVID study if they were: aged 18 years or above, admitted to a participating UK hospital with confirmed or clinically suspected COVID-19, and were able to provide informed consent either personally or via a consultee or an appropriate representative. Exclusion criteria included: admission due to a diagnosis of a different pathogen with no indication or likelihood of co-infection with COVID-19, attendance to emergency department only, declined to provide informed consent or life-limiting illness with life expectancy less than six months such as disseminated malignancy. During recruitment period (August 2020 to March 2022), eligible patients were invited to participate in the study by research teams based at the participating sites up to one year after discharge. A total of 83 sites from England, Northern Ireland, Scotland, and Wales participated following the study advertisement in social media and research networks. Different methods were used to obtain consent including: face-to-face, telephone, postal and eConsent.

Participants could join as Tier 1 participants only with remote data collection, or could join as Tier 2 participants where they were invited to attend two research visits for further data collection and biological research sampling (**Figure 1**).

Participants in either Tier 1 or Tier 2 could additionally join Tier 3 sub-studies where they were either recalled for additional research procedures or undertook additional research procedures during their Tier 2 research visits. For example, a subset of 141 participants had an extended blood draw to enable additional sampling and advanced cellular studies (6) and another subset of 531 participants completed up to three whole body magnetic resonance imaging (MRI) scans to examine the effect of COVID-19 on multiple body organs (Capturing MultiORgan Effects of COVID-19, C-MORE sub study) (7, 8).

A total of 7935 participants were recruited into the PHOSP-COVID cohort, 5238 participants to Tier 1 and 2697 to Tier 2, between 10th August 2020 and 31st March 2022. The

participants' demographics, comorbidities, and admission characteristics are detailed in **Table 1** and **Table S1**. Over 1000 participants to date have also been included in Tier 3 studies.

Overall, the cohort has a mean age of 59.3 years, 40% of participants are female, 82% report white ethnicity and 23% are from the lowest quintile of the Index of Multiple Deprivation (IMD). The cohort was co-morbid with more than 55% of participants having two or more pre-existing comorbidities at the time of hospital admission. More than 93% had a positive SARS-CoV-2 RT-PCR test result on admission and 38% required non-invasive or invasive ventilation (Class 6 or above on the WHO clinical progression scale) (9) during their original hospital admission.

Given the pressures of the ongoing pandemic during recruitment, non-response to invitations to join the study was not recorded.

How often have they been followed up?

Data collection for Tier 1 participants was restricted to available clinical data from routine hospital follow-up plus the collection of PROMs via an app every three months for up to one year post discharge. Tier 2 participants were invited to two research visits: the first between 2-7 months, and the second between 10-14 months post hospital discharge. Of the 2570 Tier 2 participants who attended the first research visit (labelled as five-month visit due to median length of time between discharge and the visit), 1973 participants also attended a second research visit (labelled one-year visit). A further 127 Tier 2 participants attended the one-year visit only (**Figure 1**). The characteristics of the 597 participants who did not return for a one-year visit are listed in **Table S2**.

All participants provided consent for further data collection via linkage to retrospective and prospective health and social care records including primary care, hospital episode statistics, and specialist tertiary clinical databases for up to 25 years. Participants were also invited to provide consent to be re-contacted for further research, including Tier 3 sub-studies, such as mechanistic studies and clinical trials (10).

What has been measured?

A summary of the data collected for PHOSP-COVID participants is provided in **Table 2**. For all participants, information about their demographics, acute illness and hospital admission were obtained retrospectively from hospital notes by the research team once a consent form was signed. This included: comorbidities, presenting symptoms, length of stay, severity of acute illness, treatment received, complications and common clinical test results. Hospital records were also reviewed to collect clinical data obtained from any planned follow-up appointments organised by the local hospital team after discharge. These included: physiological tests and imaging, routine blood test results and clinical questionnaires (**Table SM1**). Further data were collected on post-discharge care accessed including mental health

interventions, rehabilitation programmes and details from any emergency hospital admission for up to one year post discharge. All the captured data measures were recorded in paper forms, transferred to a study-specific online database and subsequently to a national Data Safe Haven.

For participants in Tier 1, clinical data were obtained from medical records and no specific research visit was undertaken. However, a subset of Tier 1 participants used an online app to remotely complete PROM questionnaires and a bespoke study-specific Patient Symptom Questionnaire (PSQ) (11). The PSQ was used to collect information about ongoing symptoms, changes in occupation, and perceived recovery where the participant was asked to answer 'yes', 'no' or 'not sure' to the question "Do you feel fully recovered from COVID-19?". A total of 371 participants provided 519 entries using the online PROMs app (142 Tier 1 and 229 Tier 2) between April 2021 and April 2022. Another subset of Tier 1 participants provided a saliva sample for DNA analysis via a collection kit posted to their home (**Table S3**).

At Tier 2 research visits, clinical questionnaires, procedures and sampling were undertaken including completion of the PSQ. Physical performance was assessed using questionnaires and physical tests including: handgrip and quadriceps strength, Short Physical Performance Battery (SPPB) and Incremental Shuttle Walk Test (ISWT). All Tier 2 participants were additionally invited to undertake daily physical activity monitoring using a wearable GENEactive© accelerometer for 14 days. Lung function was assessed using spirometry and measurement of gas transfer when feasible given the COVID-19 restrictions on aerosol generating procedures (**Table 3**).

All assessments were performed as part of the two dedicated research visits except when relevant measures were already available from clinical follow-up appointments at the corresponding time points to reduce procedures burden and duplication.

All Tier 2 participants were invited to provide blood, urine, oral rinse, and sputum samples for research purposes. Six different blood sample tube types were used: plasma (EDTA, lithium heparin, citrate), serum, DNA and RNA (**Table S3**). All samples were minimally processed at the local site before being shipped at intervals for longer-term storage at a central laboratory. This centralisation of samples facilitated their use in multi-site studies. Participants were asked to consent to use of their samples by other researchers, including commercial parties, both in the UK and abroad. Participants were given an option to decline their consent for genetic studies.

The participants' consent to access healthcare records allowed access and acquisition of clinically indicated images including chest x-ray and thoracic CT scans from certain participating sites, which were transferred to a national imaging database (National COVID-19 Chest Imaging Database) for analysis and secure storage (**Table S4**).

Procedures for Tier 3 sub-studies were dependent on the specific criteria of the project e.g., whole body MRI imaging scans as part of C-MORE sub-study (**Table S5**), body composition measurements using Dual Energy X-ray Analysis (DXA) imaging or further cognitive assessment using the Cognitron (12) online test (**Table 2**).

What have we achieved?

Priority setting to identify 10 key research questions regarding the long-term sequelae of COVID-19

In order to ensure the patient voice was central to the research undertaken using the PHOSP-COVID cohort, a joint patient and clinician priority setting exercise was undertaken between December 2020 and March 2021 to determine 10 priority research questions (13). The priority setting incorporated views from adults with self-reported long COVID, carers, clinicians, clinical researchers and charities including the Long Covid Support and Asthma + Lung UK. A modified version of the James Lind Alliance (JLA) priority setting partnerships (PSP) process was used (14). A total of 119 initial questions were gathered prior to refining, rewording, and grouping into a shorter list of 24 questions which was shared through an online prioritisation survey receiving 882 responses. The final top 10 research questions were agreed at a dedicated prioritisation workshop mediated by independent JLA facilitators and hosted via videoconference. The final top 10 research questions are listed in **Table S6**.

What has it found

Significant burden of ongoing health impairment

Results from the first 1077 Tier 2 participants at five months post-discharge highlighted that only 29% of participants felt fully recovered, 20% reported a new disability assessed by the Washington Group Short Set on Functioning (WG-SS), and 18% were no longer working (11). The 10 most reported symptoms were: aching muscles, fatigue, physical slowing down, impaired sleep quality, joint pain or swelling, limb weakness, breathlessness, pain, short-term memory loss, and slowing down in thinking. These findings were consistent with reported symptoms from smaller cohorts or cohorts of patients with a less severe initial illness (15-17). Around one in four of the cohort had clinically relevant symptoms of anxiety and depression and nearly half of the participants had features of functional impairment measured using ISWT and SPPB at five months post-discharge. There was also evidence of specific organ impairment: 35% had prediabetes or diabetes, 31% had impaired lung function, 17% had at least mild cognitive impairment, 13% abnormal kidney function, and 7% raised brain natriuretic peptide (BNP). Further investigation of post-COVID residual lung abnormalities (RLA) using clinical thoracic imaging at a median of four months post discharge, revealed abnormalities affecting at least 10% of the lung were observed in 79.4% of a subset of 209 PHOSP-COVID participants (18). The prevalence of RLA was estimated between 8.5% and 11.7% and a proposed clinically applicable risk stratification suggested that 7.8% of the examined cohort had moderate- to very-high risk of RLA post-COVID hospitalisation.

A striking finding was the lack of a clear association between the severity of the acute illness and the ongoing symptoms, mental and physical health impairments with the exception of

pulmonary function tests and walking performance, which were worse in the group who received invasive mechanical ventilation (11).

At one-year after hospital discharge there was very little improvement from five-months in self-perceived recovery, ongoing symptoms, mental health, physical performance, cognitive and organs impairment (19). The top 10 most prevalent symptoms were also similar to those at five-months. Frailty and pre-frailty were present in more than two-thirds of participants at one year (20). A fall in the number of participants working at one-year was seen with 8.5% of those who were working before hospitalisation no longer working and 34.6% of participants reporting that COVID-19 had resulted in a change in their occupation (**Table S7**). Results from the complete Tier 2 cohort for the early and one year research visits are included in **Tables 3 and 4**.

Risk factors for lack of recovery

The risk factors associated with lack of recovery at one-year were: being female, being obese and having received invasive mechanical ventilation or other organ support during the acute illness (19). History of treatment with acute corticosteroids during the acute admission was not associated with any effect on patient perceived recovery at one-year despite the beneficial acute effects (21). Frailty was also positively associated with non-recovery and reduced health-related quality of life at one year following discharge (20).

We identified risk factors for new or worse breathlessness post-COVID at five months including socio-economic deprivation, pre-existing depression/anxiety, female sex and longer hospital stay (22). Further analysis has also revealed disrupted sleep, present in 62% of the cohort, associated with dyspnoea, anxiety, and muscle weakness revealing an intriguing potential therapeutic intervention (23).

Recovery trajectory clusters

We undertook unsupervised cluster modelling using validated objective measures of breathlessness, fatigue, anxiety, depression, post-traumatic stress disorder (PTSD), physical performance and cognitive impairments at five months and described four ‘recovery clusters’ (11). The severity of most of the health impairments largely tracked together in the ‘very severe’, ‘severe’ and ‘mild’ clusters whilst the ‘moderate’ cluster was dominated by cognitive impairment (**Figure 2**). The more severe clusters were associated with female sex, higher body-mass index (BMI), a higher number of symptoms, reduced physical function and elevated C-reactive protein levels. The ‘very severe’ recovery cluster was associated with fewer days/week containing continuous bouts of moderate-to-vigorous physical activity, longer total sleep time, and higher variability in sleep timing (24). Although these are associations for which causal directions of effect have not been determined, these data highlight potential therapeutic targets (25).

To investigate the inflammatory response further, levels of 296 inflammatory plasma proteins were measured at five-months. Thirteen proteins including IL-6, were elevated in the ‘very severe’ and the ‘moderate with cognitive impairment’ clusters compared with the ‘mild cluster’ (**Figure 2**). These mediators of tissue damage and repair provide plausible

biological mechanisms behind the symptoms and health impairments associated with severe long COVID (19).

What are the main strengths and weaknesses?

The large number of clinical variables collected, coupled with the biological research sampling, makes PHOSP-COVID one of the largest deeply-phenotyped cohorts of hospitalised COVID-19 survivors in the world. Cross-sectional and longitudinal multi-omics markers are being measured in Tier 2 participants. These may uncover underlying mechanistic pathways implicated in long COVID pathology and inform interventional trials. We have linked participants in PHOSP-COVID to the ISARIC study data, where applicable (26). This provides additional information and linkage to samples taken during acute hospital admission. We are currently linking to other resources including vaccine data, viral strain data and electronic healthcare records e.g., OpenSAFELY.

The multi-dimensional results generated by the PHOSP-COVID cohort are helping to shape and prioritise provision of clinical care at times where the national health services both locally and globally are under significant pressure after the pandemic (27). Setting priority research questions and identifying risk groups will focus the efforts of both clinical and academic institutions at managing the large volume of patients with long COVID (13, 28).

The study was designed as a cohort with the study population being defined as COVID-19 hospitalised survivors with a range of outcomes captured enabling nested case-control analyses. As such, no external comparator groups (i.e., non-hospitalised COVID-19 survivors, individuals hospitalised with other viral infections) were recruited to the study. However, this has been partially mitigated by using external cohorts or healthy controls to examine certain hypotheses (29).

As participants were prospectively recruited following discharge from hospital, data pertaining to pre-COVID-19 health status were only available from healthcare records or by participant recall introducing the potential for recall bias. There is also unavoidable selection bias as some of the participants might have accepted the invitation to the study due to the severity of their ongoing symptoms. This is particularly relevant to Tier 2 participants who were younger, more ethnically diverse, less comorbid and required more respiratory support compared to the participants included in the ISARIC4C consortium outputs, which are likely more representative of the overall hospitalised population in the UK (30). However, the linkage to ISARIC and other public databases may help quantify and partially mitigate this bias.

As the PHOSP-COVID cohort included participants from 83 different sites and due to the pressure associated with providing clinical and academic services during the heights of the pandemic, there were considerable variations in the availability of collected data across these multiple sites. However, the large number of recruited participants still makes the PHOSP-COVID one of the largest multi-centre cohorts globally.

As recruitment began in August 2020, the cohort represents mainly patients who were admitted to hospital during the first year of the pandemic and so mostly preceded the

emergence of the delta and omicron SARS-CoV2 variants and the wide use of in-hospital acute therapies. In addition, as vaccination in the UK did not begin until late 2020, a large proportion of the cohort were vaccine naïve at initial hospital admission and at the five-month follow-up.

Can I get hold of the data? Where can I find out more?

The PHOSP-COVID study website (https://www.phosp.org) contains an overview of the study, resources, information about people involved, and publications. Research activity using the study is organised across a series of Working Groups (**Figure 3**). These were established at the outset of the study to coordinate research, minimise duplication of efforts, and facilitate communication across research and clinical specialties. Researchers interested in undertaking research using PHOSP-COVID are encouraged to contact the relevant Working Group leads (https://www.phosp.org/working-group/) in the first instance. The data are currently held in the Outbreak Data Analysis Platform (ODAP, https://odap.ac.uk/). Researchers seeking to access these data are directed to https://www.phosp.org/resource/ for information and forms. Correspondence to be directed to Dr Rachael A Evans, the Co-Principal Investigator of PHOSP-COVID study phosp@leicester.ac.uk.

Ethics approval

The study was approved by the Leeds West Research Ethics Committee (20/YH/0225) and is registered on the ISRCTN Registry (ISRCTN10980107).

Author contributions

The manuscript was initially drafted by OE, RAE, and LVW, and further developed by the writing committee. CEB, RAE, LVW, JDC, L-PH, AH, MM, KP, BR, OE, HJCM, OCL, MR, AShi, ASi, MS, RMS, NJG, VCH, LH-W and AShe made substantial contributions to the conception and design of the work. LGH, KEL, RA, PB, CEBo, JSB, GC, NDB, NE, CE, JF, NH, JRH, MGJ, DP, PP, NMR, SLR-J, AART, CJ AMS and DGW made substantial contributions to the acquisition of data. All authors contributed to data interpretation, critical review, and revision of the manuscript. OE, HJCM, OCL have accessed and verified the underlying data. OE, RAE, CEB, and LVW were responsible for the decision to submit the manuscript, and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Supplementary data

Supplementary data are available at IJE online.

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Conflict of interest

AShe has served on a number of UK and Scottish Government COVID-19 advisory bodies; all these roles were unremunerated. CEB declares that their institute was awarded a grant from UKRI/NIHR to complete this work; the author reports grants from GlaxoSmithKline, AstraZeneca, Sanofi, Regeneron, Boehringer Ingelheim, Chiesi, Novartis, Roche, Genentech, Mologic, and 4DPharma; and consultancy fees paid to their institution from GlaxoSmithKline, AstraZeneca, Sanofi, Boehringer Ingelheim, Chiesi, Novartis, Roche, Genentech, Mologic, 4DPharma, and Areteia. CEBo declares their institute was awarded a grant from the UK Research and Innovation UKRI/NIHR and institutional support from NIHR Nottingham BRC to complete this work; the author reports grants from Nottingham University Hospitals (NUH) Charity, University of Nottingham charitable donation and NUH Research and Innovation Department. JCP declares consultancy fees for Istesso and Tacit

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Table 1: Participants demographics, comorbidities, and admission characteristics of the PHOSP-COVID cohort.

	Complete PHOSP-COVID cohort (n=7935)		Tier 1 (n=5238)		Tier 2 (n=2697)	
	n	Value	n	Value	n	Value
Age at admission, years†	7926	59.3 (13.4)	5230	59.9 (13.8)	2696	58.0 (12.6)
Missing data, n (%)		9 (0.1%)		8 (0.2%)		1 (<0.1%)
Sex	7926		5230		2696	
Female		3206 (40.4%)		2168 (41.5%)		1038 (38.5%)
Male		4720 (59.6%)		3062 (58.5%)		1658 (61.5%)
Missing data, n (%)		9 (0.1%)		8 (0.2%)		1 (<0.1%)
Ethnicity	7697		5019		2678	
White		6298 (81.8%)		4291 (85.5%)		2007 (74.9%)
South Asian		629 (8.2%)		324 (6.5%)		305 (11.4%)
Black		375 (4.9%)		182 (3.6%)		193 (7.2%)
Mixed		120 (1.5%)		65 (1.3%)		55 (2.1%)
Other		275 (3.6%)		157 (3.1%)		118 (4.4%)
Missing data, n (%)		238 (3.0%)		219 (4.2%)		19 (0.7%)
Index of Multiple Deprivation (IMD) score	7869		5192		2677	
1 (most deprived)		1810 (23.0%)		1192 (23.0%)		618 (23.1%)
2		1717 (21.8%)		1095 (21.1%)		622 (23.2%)
3		1407 (17.9%)		944 (18.2%)		463 (17.3%)
4		1496 (19.0%)		1024 (19.7%)		472 (17.6%)
5 (least deprived)		1439 (18.3%)		937 (18.0%)		502 (18.8%)
Missing data, n (%)		66 (0.8%)		46 (0.9%)		20 (0.7%)
Body-mass index (BMI)	2693		417		2276	
Median††		31.2 [27.6-36.1]		31.8 [27.2-36.8]		31.2 [27.7-36.0]
<30 kg/m^2		1121 (41.6%)		169 (40.5%)		952 (41.8%)
≥30 kg/m^2		1572 (58.4%)		248 (59.5%)		1324 (58.2%)
Missing data, n (%)		5242 (66.1%)		4821 (92.0%)		421 (15.6%)
Healthcare worker	7175	879 (12.3%)	4620	503 (10.9%)	2555	376 (14.7%)
Missing data, n (%)		760 (9.6%)		618 (11.8%)		142 (5.2%)
Admission duration, days†	7935	13.5 (17.5)	5238	13.4 (17.2)	2697	14.1 (17.9)
WHO clinical progression scale	7927		5230		2697	
WHO class 3-4		1361 (17.2%)		914 (17.5%)		447 (16.6%)
WHO class 5		3530 (44.5%)		2395 (45.8%)		1,135 (42.0%)
WHO class 6		1938 (24.4%)		1305 (24.9%)		633 (23.5%)
WHO class 7-9		1098 (13.9%)		616 (11.8%)		482 (17.9%)
Missing data, n (%)		8 (0.1%)		8 (0.2%)		0
Comorbidities	7935		5238		2697	
Median number of comorbidities††		2 [1-3]		2 [1-3]		2 [1-3]
0		1792 (22.6%)		1,125 (21.5%)		667 (24.7%)
1		1721 (21.7%)		1150 (21.9%)		571 (21.2%)
≥2		4422 (55.7%)		2963 (56.6%)		1459 (54.1%)
Cardiovascular	7935	3763 (47.4%)	5238	2524 (48.2%)	2697	1239 (45.9%)
Respiratory	7935	2282 (28.8%)	5238	1558 (29.7%)	2697	724 (26.8%)
Neuro-psychiatric	7935	1689 (21.3%)	5238	1127 (21.5%)	2697	562 (20.8%)
Renal and endocrine	7935	959 (12.1%)	5238	672 (12.8%)	2697	287 (10.6%)
Type 2 diabetes	7913	1683 (21.3%)	5222	1146 (21.9%)	2691	537 (19.9%)
Missing data, n (%)		22 (0.3%)		16 (0.3%)		6 (0.2%)
Positive SARS-CoV-2 PCR	7309	6840 (93.6%)	4842	4557 (94.1%)	2467	2283 (92.5%)
Missing data, n (%)		626 (7.9%)		396 (7.6%)		230 (8.5%)
Systemic steroids	7529	4602 (61.1%)	4968	3154 (63.5%)	2561	1448 (65.5%)
Missing data, n (%)		406 (5.1%)		270 (5.2%)		136 (5.1%)
Antibiotic therapy	7719	6161 (79.8%)	5087	4086 (80.3%)	2632	2075 (78.8%)
Missing data, n (%)		216 (2.7%)		151 (2.9%)		65 (2.4%)
Anti-coagulants	7461	3616 (48.5%)	4896	2443 (49.9%)	2565	1173 (45.7%)
Missing data, n (%)		474 (5.9%)		342 (6.5%)		132 (4.9%)

Data are n (%) unless † mean (SD) or †† median [IQR]. Percentages are calculated by category after exclusion of missing data for that variable. WHO classes are as follows: 3–4=no continuous supplemental oxygen needed; 5=continuous supplemental oxygen only; 6=continuous or bi-level positive airway pressure ventilation or high-flow nasal oxygen; and 7–9=invasive mechanical ventilation or other organ support. IMD=Index of Multiple Deprivation. BMI=body-mass index. SARS-CoV-2 PCR=severe acute respiratory syndrome coronavirus 2 polymerase chain reaction. See Table S1 for further descriptions of variables.

Table 2: PHOSP-COVID outcome measures**.**

Module	Details	Tier 1	Tier 2	Tier 3
Time point: Hospital Discharge				
Baseline demographics	Age, sex at birth, ethnicity, education, household income	✓	✓	
	Occupation (including changes after hospitalisation)	✓	✓	
	Smoking & alcohol consumption	✓	✓	
	Index of multiple deprivation score	✓	✓	
	Clinical Comorbidities	✓	✓	
Hospitalisation Details	Length of stay	✓	✓	
	Presenting symptoms/signs and duration	✓	✓	
	Vital signs at admission	✓	✓	
	Level of respiratory and other organs support	✓	✓	
	Received treatment/intervention	✓	✓	
	Additional diagnoses e.g., Pulmonary Embolism, Myocarditis.	✓	✓	
	Medications pre-admission and on discharge	✓	✓	
	Enrolment into acute COVID-19 studies	✓	✓	
	Clinical blood results e.g., FBC, BNP/NT-proBNP, CRP.	✓	✓	
	SARS-CoV-2 Swab PCR status	✓	✓	
Time points: Research visits at five-month and one-year post discharge				
Clinical assessment at clinical follow up/research visits	ECG findings	¶	✓	
	Clinical investigation results: chest XR, echocardiogram, FeNO, CPET, 6MWT, etc.	¶	✓	
	Outcome of clinical review	¶	✓	
Clinical investigations	**Blood:** FBC, U&Es, LFTs, eGFR, CRP, Bone, Vitamin D, Troponin, BNP/NT-proBNP, D Dimer, INR, Fibrinogen, Ferritin, HbA1C, Lipid profile.	¶	✓	
	Fasting blood samples: Glucose, Insulin, fasting lipid profile		✓	
	Urine: urinalysis, albumin: creatinine ratio and protein: creatinine ratio		✓	
Biological samples for research	Blood (serum, plasma, DNA, RNA)		✓	
	Oral rinse		✓	
	Sputum (spontaneous)		✓	
	Urine		✓	
	Blood PBMCs		✓	✓
	Muscle biopsies			✓
	Saliva (DNA)	✓		

Health-related Quality of life and Disability	Euroqol EQ-5D-5L Washington Short Set of Functioning (WG-SS-Sco)	* *	✓ ✓	
Patient Reported Outcomes (PROMs)	PHOSP-COVID study specific tool - Patient Symptom Questionnaire (PSQ) MRC dyspnoea scale Dyspnoea12 Questionnaire Generalised Anxiety Disorder Questionnaire (GAD-7) Patient Health Questionnaire (PHQ-9) The Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue) Brief Pain Inventory Questionnaire (BPI) Nottingham activities of daily living (NEADL) Questionnaire Post-Traumatic Stress Disorder Checklist for DSM5 Questionnaire (PCL-5) Sleep questionnaires: - Pittsburgh Sleep Quality Index (PSQI) - Morningness-Eveningness Questionnaire (MEQ) Leicester Cough Questionnaire (LCQ)	* * * * * * * * *	✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓	 ✓ ✓ ✓
Cognitive assessment	Montreal Cognitive Assessment (MoCA) Cognitron online test	*	✓	 ✓
Physical Activity and performance	General Practice Physical Activity Questionnaire (GPPAQ) Daily physical activity by wearable monitor (Geneactive) Incremental Shuttle Walk Test (ISWT) Short Physical Performance Battery (SPPB) Handgrip Strength Quadriceps muscle strength		✓ ✓ ✓ ✓ ✓	 ✓
Frailty assessment	Rockwood Clinical Frailty Scale (CFS) Fried's frailty definition		✓ ✓	
Body composition	Body Mass Index (BMI) SARC-F Questionnaire Waist circumference measurement Bio-Electrical Impedance Analysis (BIA) Dual Energy X-ray Analysis (DXA)	✓	✓ ✓ ✓ ✓	 ✓
Pulmonary Function Tests	Spirometry (FEV1, FVC, FEV1/FVC) Transfer Factor (TLCO, KCO) Max inspiratory pressure (MIP) Max expiratory pressure (MEP)		✓ ✓	 ✓ ✓
Radiological images acquisition	Chest radiograph CT Thorax Multi-organs MRI scan	¶ ¶	¶ ¶	 ✓

¶ The results of these outcomes measures were only available for collection if performed for clinical indications by the local medical team. * A subset of Tier 1 participants remotely completed health related questionnaires using electronic app. FBC=full blood count. BNP=brain natriuretic peptide. NT-BNP=N-terminal BNP. CRP=C-reactive protein. SARS-CoV-2 swab PCR=severe acute respiratory syndrome coronavirus 2 swab polymerase chain reaction. ECG=electrocardiogram. FeNO=Fractional Exhaled Nitric Oxide. CPET=Cardiopulmonary Exercise Testing. 6MWT=6 Minute Walk Test. U&Es=urea, creatinine and electrolytes. LFTs=liver function tests. eGFR=estimated glomerular filtration rate. INR=International Normalised Ratio. HbA1C=glycated haemoglobin. DNA= Deoxyribonucleic acid. RNA= Ribonucleic acid. PBMCs=Peripheral blood mononuclear cell. MRC dyspnoea scale=Medical Research Council dyspnoea scale. FEV1=Forced expiratory volume

measured in 1 second. FVC=forced vital capacity. TLCO=transfer capacity of the lung for carbon monoxide. KCO=carbon monoxide transfer coefficient. CT scan= computed tomography scan. MRI= Magnetic resonance imaging.

Table 3: Patient-reported outcome measures, physiological and biochemical tests, among Tier 2 participants stratified by the research visits.

	Available data, n	5-month visit (n=2570)	Available data, n	1-year visit (n=2100)
Time from discharge, days†	2570	158.9 (47.4)	2100	380.9 (35.0)
Recovered from COVID-19?	2202		1787	
Yes		567 (25.7%)		541 (30.3%)
No		1215 (55.2%)		863 (48.3%)
Not sure		420 (19.1%)		383 (21.4%)
Missing data, n (%)		368 (14.3%)		313 (14.9%)
5-month recovery cluster assignment	2405		1881	
Mild		723 (30.1%)		567 (30.1%)
Moderate/cognitive		543 (22.6%)		426 (22.7%)
Severe		636 (26.4%)		502 (26.7%)
Very severe		503 (20.9%)		386 (20.5%)
Missing data, n (%)		165 (6.4%)		219 (10.4%)
PROMS				
Self-report symptom count††	2267	8 [3-13]	1814	9 [4-16]
Missing data, n (%)		303 (11.8%)		286 (13.6%)
GAD-7 total score†	2408	5.35 (5.72)	1950	5.06 (5.65)
Anxiety (GAD-7 >8)	2408	614 (25.5%)	1950	461 (23.6%)
Missing data, n (%)		162 (6.3%)		150 (7.1%)
PHQ-9 total score†	2406	7.04 (6.57)	1947	6.43 (6.39)
Depression (PHQ-9 ≥10)	2406	734 (30.5%)	1947	509 (26.1%)
Missing data, n (%)		164 (6.4%)		153 (7.3%)
PCL-5 total score†	2403	15.84 (17.24)	1937	14.28 (16.82)
PTSD (PCL-5 ≥38)	2403	321 (13.4%)	1937	221 (11.4%)
Missing data, n (%)		167 (6.5%)		163 (7.8%)
Dyspnoea-12†	2361	6.4 (8.2)	1892	5.7 (7.7)
Missing data, n (%)		209 (8.1%)		208 (9.9%)
FACIT fatigue subscale score†	2326	34.6 (13.1)	1802	35.8 (12.7)
Missing data, n (%)		244 (9.5%)		298 (14.2%)
BPI severity†	1847	13.2 (10.3)	1485	13.0 (10.0)
BPI interference†	1790	20.1 (19.5)	1435	19.5 (19.3)
Nottingham Extended ADL Scale†	2316	17.9 (5.0)	1780	18.4 (4.9)
Physical performance				
SPPB total score†	2342	9.8 (2.4)	1794	9.9 (2.2)
SPPB ≤10 (mobility disability)	2342	1196 (51.1%)	1794	860 (47.9%)
Missing data, n (%)		228 (8.9%)		306 (14.6%)
ISWT Distance (m)†	1975	423 (259)	1431	440 (253)
ISWT % predicted†	1399	57.1 (29.6)	1049	59.1 (27.9)
Frailty and cognition				
Rockwood CF score††	2285	3 [2-3]	1885	3 [2-3]
RCF ≥5	2285	135 (5.9%)		104 (5.5%)
Missing data, n (%)		285 (11.1%)		215 (10.2%)
SARC-F total score††	2326	1 [0-3]	1808	1 [0-3]
Missing data, n (%)		244 (9.5%)		292 (13.9%)
MoCA total score†	2100	25.6 (3.5)	1682	26.3 (3.4)
Corrected MoCA total score†	2100	25.9 (3.5)	1682	26.6 (3.3)
MoCA <23	2100	321 (12.1%)	1682	199 (11.8%)

Corrected MoCA <23	2100	279 (10.5%)	1682	178 (10.9%)
Missing data, n (%)		470 (18.3%)		418 (19.9%)
Lung Physiology				
FEV1 (L)†	1515	2.76 (0.80)	1081	2.81 (0.82)
Missing data, n (%)		1055 (41.1%)		1019 (48.5%)
FEV1 % predicted†	1438	90.1 (18.5)	1051	91.7 (18.5)
Missing data, n (%)		1132 (44.0%)		1049 (49.9%)
FEV1 % predicted <80%	1438	389 (27.1%)	1051	257 (24.5%)
Missing data, n (%)		1132 (44.0%)		1049 (49.9%)
FVC (L)†	1515	3.47 (1.02)	1081	3.56 (1.00)
Missing data, n (%)		1055 (41.1%)		1019 (48.5%)
FVC % predicted†	1440	89.2 (18.6)	1049	91.1 (18.1)
Missing data, n (%)		1130 (43.9%)		1051 (50.0%)
FVC % predicted <80%	1440	427 (29.7%)	1049	260 (24.8%)
Missing data, n (%)		1130 (43.9%)		1051 (50.0%)
FEV1/FVC†	1515	0.80 (0.15)	1079	0.79 (0.09)
Missing data, n (%)		1055 (41.1%)		1021 (48.6%)
FEV1/FVC <0.7	1515	163 (10.8%)	1079	118 (10.9%)
Missing data, n (%)		1055 (41.1%)		1021 (48.6%)
TLCO mmol/KPa/min†	511	7.42 (2.33)	339	7.62 (2.19)
Missing data, n (%)		2059 (80.1%)		1761 (83.9%)
TLCO % predicted†	499	91.6 (31.2)	336	94.7 (26.6)
Missing data, n (%)		2071 (80.6%)		1764 (84.0%)
TLCO % predicted <80%	499	175 (35.1%)	336	78 (23.2%)
Missing data, n (%)		2071 (80.6%)		1764 (84.0%)
KCO mmol/KPa/min†	519	1.45 (0.29)	353	1.44 (0.27)
Missing data, n (%)		2051 (79.8%)		1747 (83.2%)
KCO % predicted†	506	100.6 (18.6)	350	100.5 (17.5)
Missing data, n (%)		2064 (80.3%)		1,750 (83.3%)
KCO % predicted <80%	506	45 (8.9%)	350	33 (9.3%)
Missing data, n (%)		2064 (80.3%)		1750 (83.3%)
Biochemical Tests				
BNP Results (ng/L) †	152	98.9 (328.9)	59	82.5 (157.1)
Missing data, n (%)		2418 (94.1%)		2041 (97.2%)
Pro-NT-BNP (ng/L) †	1439	150.6 (674.5)	1004	187.9 (848.4)
Missing data, n (%)		1131 (44.0%)		1096 (52.2%)
BNP/Pro-NT-BNP above threshold	1591	107 (6.7%)	1063	93 (8.7%)
Missing data, n (%)		979 (38.1%)		1,037 (49.4%)
HbA1C % (DCCT/NGSP) †	1638	6.1 (1.2)	1289	6.2 (1.3)
Missing data, n (%)		932 (36.3%)		811 (38.6%)
HbA1C ≥6.0	1638	579 (35.3%)	1289	463 (35.9%)
Missing data, n (%)		932 (36.3%)		811 (38.6%)
eGFR (ml/min/1.73 m^2)†	2105	76.6 (15.6)	1600	74.6 (16.4)
Missing data, n (%)		465 (18.1%)		500 (23.8%)
eGFR <60 (ml/min/1.73 m^2)	2105	238 (11.3%)	1600	207 (12.9%)
Missing data, n (%)		465 (18.1%)		500 (23.8%)
Systemic inflammation				
CRP (mg/L) †	2075	5.5 (11.3)	1636	5.1 (6.9)
Missing data, n (%)		495 (19.3%)		464 (22.1%)
CRP >5 mg/L	2075	502 (24.2%)	1636	393 (24.0%)
Missing data, n (%)		495 (19.3%)		464 (22.1%)
CRP ≥10 mg/L	2075	231 (11.1%)	1636	174 (10.6%)
Missing data, n (%)		495 (19.3%)		464 (22.1%)
Ferritin (µg/L) †	1832	143.7 (170.6)	1399	140.1 (189.4)
Missing data, n (%)		738 (28.7%)		701 (33.4%)
Fibrinogen (g/L) †	1565	3.5 (0.9)	1310	3.5 (0.8)
Missing data, n (%)		1005 (39.1%)		790 (37.6%)

Missing not included in %. Number (%) unless † mean (SD), †† median [IQR]. GAD7=Generalized Anxiety Disorder 7-item scale. PHQ-9=Patient Health Questionnaire-9. PCL-5=Post Traumatic Stress Disorder Checklist. FACIT fatigue=Functional Assessment of Chronic Illness Therapy Fatigue Scale. BPI=Brief Pain Inventory Questionnaire. NEADL=Nottingham activities of daily living Questionnaire. SPPB=short physical performance battery. ISWT=incremental shuttle walk test. CFS=Clinical Frailty Scale. MoCA=Montreal Cognitive Assessment. FEV1=Forced expiratory volume measured in 1 second. FVC=forced vital capacity. TLCO=transfer capacity of the lung for carbon monoxide. KCO=carbon monoxide transfer coefficient. BNP=brain natriuretic peptide. NT-BNP=N-terminal BNP. HbA1C=glycated haemoglobin. DCCT/NGSP=Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program. eGFR=estimated glomerular filtration rate. CRP=C-reactive protein. Threshold of BNP ≥100 ng/L or NT-BNP ≥400 ng/L. Corrected MoCA adjusted for level of education. See Table SM1 for further descriptions of variables.

Table 4: Health-related quality of life and disability among Tier 2 participants stratified by the research visits.

	Available data, n	**Pre-COVID (n=2697)**	**Available data, n**	**5 months (n=2570)**	**Available data, n**	**1 year (n=2100)**
EQ-5D-5L utility index†	2170	0.82 (0.23)	2113	0.71 (0.25)	1740	0.71 (0.25)
Missing data, n (%)		527 (19.5%)		457 (17.8%)		360 (17.1%)
EQ-5D-5L utility index delta change†	-	-	1757	-0.11 (0.22)	1498	-0.11 (0.22)
Missing data, n (%)				813 (31.6%)		602 (28.7%)
EQ-5D-5L VAS†	2095	79.5 (17.5)	2106	70.1 (20.0)	1731	70.4 (20.6)
Missing data, n (%)		602 (22.3%)		464 (18.1%)		369 (17.6%)
EQ-5D-5L VAS delta change†	-	-	1697	- 9.9 (19.4)	1435	-9.8 (19.8)
Missing data, n (%)				873 (33.9%)		665 (31.7%)
WG-SS-SCo	-	-	2208	532 (24.1%)	1793	389 (21.7%)
Missing data, n (%)				362 (14.1%)		307 (14.6%)
WG-SS-SCo new disability	-	-	1659	317 (19.1%)	491	93 (18.9%)
Missing data, n (%)				911 (35.5%)		1609 (76.6%)
PSQ Breathlessness††	2162	0 [0-2]	2193	4 [1-6]	1770	2 [0-5]
Missing data, n (%)		535 (19.8%)		377 (14.7%)		330 (15.7%)
PSQ Cough††	2153	0 [0-1]	2184	1 [0-4]	1763	0 [0-2]
Missing data, n (%)		544 (20.2%)		386 (15.0%)		337 (16.0%)
PSQ Fatigue††	2152	0 [0-2]	2183	5 [2-7]	1765	3 [1-6]
Missing data, n (%)		545 (20.2%)		387 (15.1%)		335 (15.9%)
PSQ Poor Sleep††	2151	1 [0-4]	2177	4 [1-7]	1766	3 [0-6]
Missing data, n (%)		546 (20.2%)		393 (15.3%)		334 (15.9%)
PSQ Pain††	2138	0 [0-3]	2169	3 [0-6]	1763	2 [0-5]
Missing data, n (%)		559 (20.7%)		401 (15.6%)		337 (16.0%)

Missing not included in %. Number (%) unless † mean (SD), †† median [IQR]. EQ-5D-5L VAS = Euroqol five level visual analogue scale 0-100. WG-SS-SCo = Washington Group Short Set of Functioning Severity Continuum. PSQ = Patient Symptoms Questionnaires. See Table SM1 for further descriptions of variables.

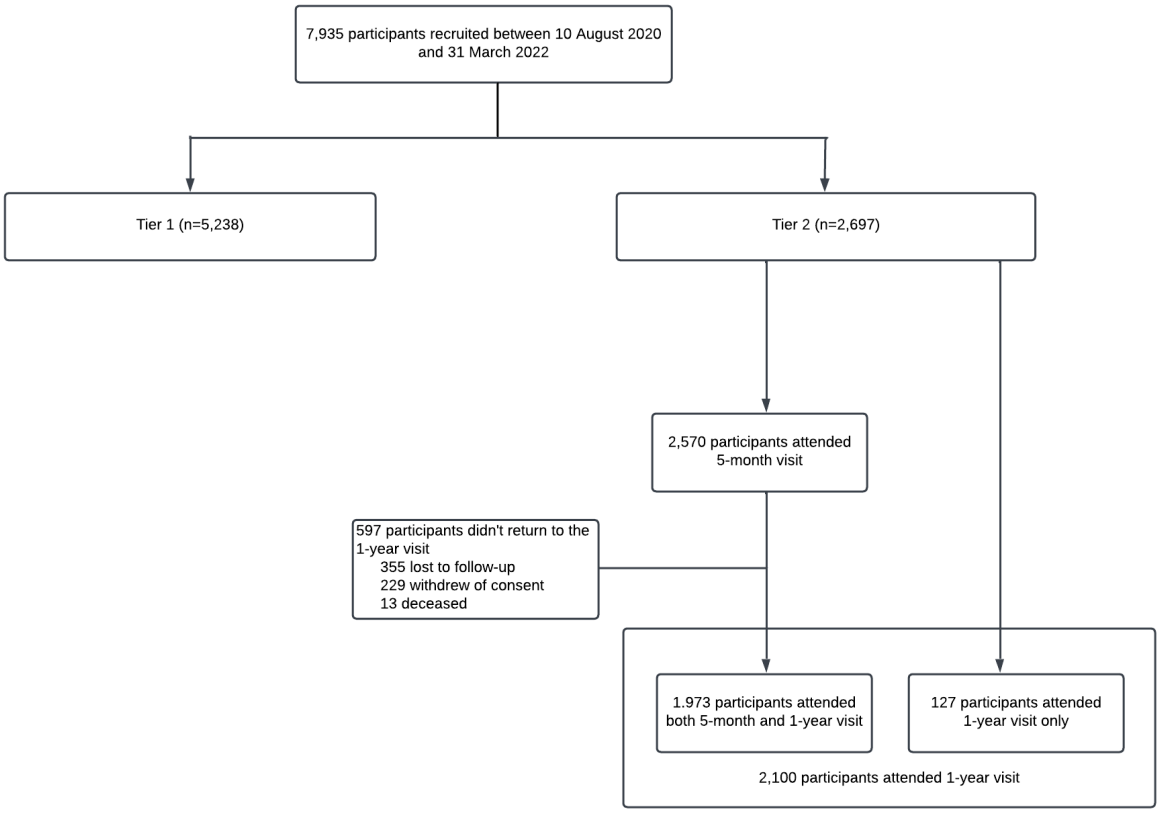

Figure 1: Consort diagram of the PHOSP-COVID study.

* The wide range window for the first research visit (2-7 months) was deliberately chosen to accommodate the variation of planned clinical follow up appointments across the different participating sites and to allow the research visit to coincide with the planned clinical follow-up appointments.

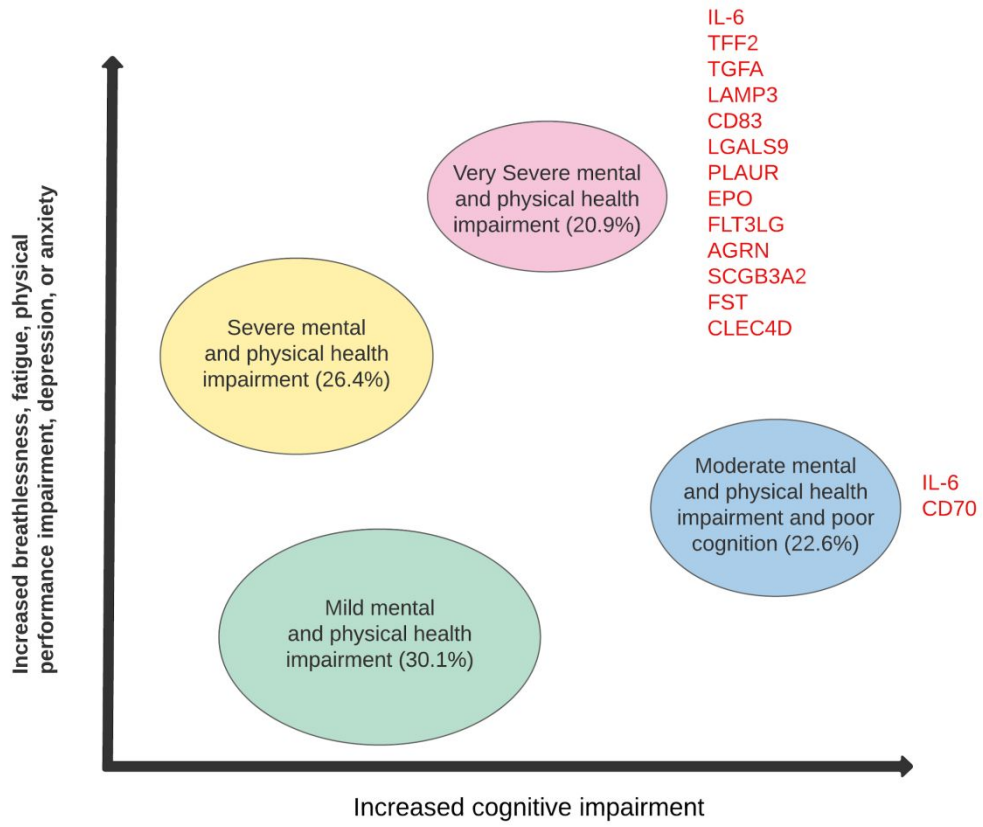

Figure 2: Illustration of the four cluster phenotypes mental, cognitive, and physical health impairments with associated inflammatory biomarkers.

The figure shows the distribution of the four recovery cluster phenotypes and the list of identified proteins that were significantly differentially expressed (compared with the reference mild cluster) after FDR adjustment. FDR=false detection rate. IL-6=interleukin-6. TFF2=trefoil factor 2. TGFA=transforming growth factor α. LAMP3=lysosomal associated membrane protein 3. CD83=CD83 molecule. LGALS9=galectin-9. PLAUR=urokinase plasminogen activator surface receptor. EPO=erythropoietin. FLT3LG=FMS-related receptor tyrosine kinase 3 ligand. AGRN=agrin. SCGB3A2=secretoglobin family 3A member 2. FST=follistatin. CLEC4D=C-type lectin domain family 4 member D. CD70=CD70 molecule.

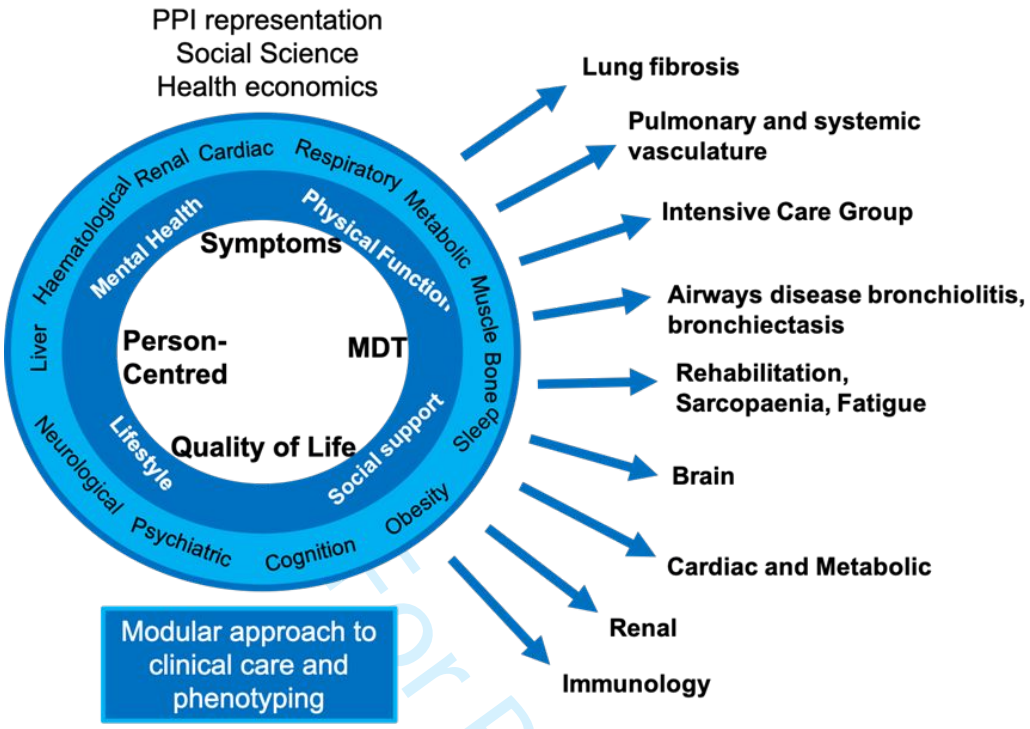

Figure 3: Modular approach to the clinical care and phenotyping with the PHOSP-COVID consortium different working groups.

MDT=Multidisciplinary team. PPI=Patient and public involvement.