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Supplementary appendix

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Supplementary Appendix

Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study

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Contents

Methods supplement

1. Description of the longitudinal cohort study of COVID-19

This is a longitudinal cohort study of COVID-19 survivors who had been discharged from Wuhan Jin Yin-tan hospital between Jan 7 and May 29, 2020 at three timepoints: 6 months, 12 months, and 2 years after symptom onset. Full details of study design, methods, follow-up procedures, and results of the 6-month and 12-month follow-up visits have been described previously.[1,2] For easy reading, the data collection of COVID-19 survivors at acute phase, the inclusion and exclusion criteria, and follow-up procedures at each follow-up visit are provided in the Appendix.

2. Data collection of COVID-19 survivors at acute phase

We defined the acute phase as the time between symptom onset and hospital discharge. Clinical data for acute phase were retrieved from electronic medical records, including demographic characteristics (age, sex, education, and cigarette smoking); clinical characteristics (self-reported comorbidities, symptom onset time, and chest images); laboratory test results; and treatment (corticosteroids, intravenous immunoglobulin, antibiotics, thymosin, and antivirals including lopinavir–ritonavir, arbidol, chloroquine phosphate, and hydroxychloroquine). The disease severity was characterised by the highest seven-category scale during the hospital stay (termed the severity scale),[3] which consisted of the following categories: 1, not admitted to hospital with resumption of normal activities; 2, not admitted to hospital, but unable to resume normal activities; 3, admitted to hospital but not requiring supplemental oxygen; 4, admitted to hospital but requiring supplemental oxygen; 5, admitted to hospital requiring high-flow nasal cannula (HFNC), non-invasive mechanical ventilation (NIV), or both; 6, admitted to hospital requiring extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation (IMV), or both; and 7, death.

3. Inclusion and exclusion criteria of COVID-19 survivors

Inclusion criteria:

- Laboratory confirmed COVID-19 patients who were discharged from Jin Yin-tan Hospital (Wuhan, China) between Jan 7, and May 29, 2020.

Exclusion criteria

- COVID-19 survivors died before the follow-up visits.
- COVID-19 survivors who were living in a nursing or welfare home.
- COVID-19 survivors who were difficult to complete the visit due to psychotic disorder or dementia.
- COVID-19 survivors who were unable to move freely due to concomitant osteoarthropathy or immobile.

4. Description of the data set of community-dwelling non-COVID-19 participants

To determine whether COVID-19 patients completely recovered at 12 months, we have recruited 3383 community-dwelling adults without SARS-CoV-2 infection (control) from two districts of Wuhan city between Dec 24, 2020, and Jan 16, 2021. Full details of the inclusion and exclusion criteria, recruitment strategy, health check items, and results have been described in our 1-year follow-up study.[2] For easy reading, these content are also included in the Appendix. The data set also serve as control to determine the recovery status of COVID-19 survivors at 2 years after acute infection.

4.1 Inclusion and exclusion criteria of community-dwelling non-COVID-19 participants

Inclusion criteria:

- At least 20 years of age or older

Exclusion criteria:

- History of laboratory confirmed SARS-CoV-2 infection
- Unable to complete the associated questionnaires, such as dementia and psychotic disease
- Inability to move autonomously

4.2 Recruitment of community-dwelling non-COVID-19 participants

A 4-stage stratified sampling method was used to select non-COVID study participants as controls from Wuhan. In the first stage, two districts were selected from 13 districts

of Wuhan stratified by geographical region and economic development level. One of the district (Jiangan District) is located at the center of Wuhan and the gross domestic product of which was high. The other district (Dongxihu District) is located relatively far away from the center of Wuhan and the gross domestic product of which was not that high. In the second stage, one sub-district each (Jinqiao sub-district and Jiangjunlu sub-district) was respectively selected from Jiangan District and Dongxihu District. In the third stage, 6 of 11 communities from Jinqiao sub-district and 6 of 11 communities from Jiangjunlu sub-district, the directors of which agreed the survey to be conducted in their communities, were selected. In the final stage, the grid administrators (each of whom is responsible for contacting some of the residents in the community and sending notification) from each community were contacted to recruit study population. The community members who were eligible and finished the survey were finally included. The selection of districts and sub-districts was not at random.

4.3 Health check items of community-dwelling non-COVID-19 participants

Community-dwelling non-COVID-19 adults were interviewed face to face at their community centre by trained medical staff from Jin Yin-tan Hospital. Standard questionnaires were administered to collect information about demographic characteristics, personal medical history, and lifestyle information. They were also asked to undergo physical examination and completed a series of questionnaires, including symptom questionnaire, the mMRC dyspnoea scale, the EQ-5D-5L questionnaire, and EQ-VAS. Venous blood samples were collected for laboratory tests, and full details are shown in the section of study procedure of the Appendix.

5. Study procedures

Time and Events schedule						
	COVID-19 patients				Community Non-COVD-19 participants	
	Data collection at acute phase (n=2469)	6-month visit (n=1733)	12-month visit (n=1307)	2-year visit (n=1666)	2020.12.24-2021.1.16 (n=3383)	2022.1.11-2022.1.24 (n=275)
Eligibility screening		X	X	X	X	X
Informed consent		X	X	X	X	X
Demographic data	X				X	
Medical history	X	X	X	X	X	X
Clinical and Laboratory data	X					
Treatment during hospitalization	X					
Physical examination		X	X	X	X	X
Questionnaire on symptom		X[a]	X[a]	X[a]	X[b]	X[b]
mMRC dyspnoea scale		X	X	X	X	X
EQ-5D-5L Questionnaire		X	X	X	X	X
EQ-VAS		X	X	X	X	X
Ischaemic stroke and cardiovascular event registration form		X	X	X		
GAD-7				X		X
PHQ-9				X		X
PCL-C				X		
SARS-CoV-2 vaccination survey				X		X

Blood specimen for complete blood count	X	X	X	X	X	X
Blood specimen for renal function*	X	X	X	X	X	X
Blood specimen for liver function†	X		X	X	X	X
Blood specimen for HbA1C	X	X	X	X	X	X
Blood specimen for lipid‡	X		X	X	X	X
Blood specimen for antibody testing	X	X[c]	X	X		
Blood specimen for cytokine testing	X[d]	X[d]	X[d]			
Routine urine	X		X	X	X	X
6-min walking test		X	X	X		X
Pulmonary function tests		X[e]	X[f]	X[h]		X
Lung HRCT		X[e]	X[g]	X[i]		
Ultrasonography		X[e]				

mMRC=modified British Medical Research Council. EQ-5D-5L=EuroQol five-dimension five-level questionnaire. EQ-VAS=EuroQol Visual Analogue Scale. HbA1C= glycated hemoglobin A1C. HRCT=high resolution computed tomography. GAD-7= Generalized Anxiety Disorder 7-item scale. PHQ-9=Patient Health Questionnaire-9. PCL-C= Post Traumatic Stress Disorder Checklist-Civilian version. High resolution computed tomography=HRCT.

a: Symptom was further divided into prevalent symptom and sequelae symptom

b: Only record the prevalent symptom during follow-up

c: Antibody test only for those who had previously been enrolled in LOTUS China trial and attended 6-month visit.

d: Cytokine test only for those who had plasma at each time period including at acute phase, discharge, 6- and 12-month visits.

e: At 6-month visit, a stratified disproportional random sampling procedure according to severity scale was used to select patients to undergo pulmonary function test and HRCT. Patients requiring HFNC, NIV, or IMV (severity scale$\geqslant$5) during hospitalization were all invited to receive the pulmonary function test and HRCT of chest. The ratio used to select patients not requiring supplemental oxygen (severity scale 3) and those requiring supplemental oxygen (severity scale 4) was 1:2. Finally, 349 patients completed the pulmonary function test and 353 completed chest HRCT at 6-month visit.

f: 349 patients who had completed the pulmonary function test at 6 months were all invited to administer the test at the 12-month visit.

g: Of 353 patients who had completed chest HRCT at 6 months, 186 presented with abnormal CT were invited to receive the test at the 12-month visit.

h: 349 patients who had completed the pulmonary function test at 6 months were all invited to administer the test at the 2-year visit.

i: Of 118 patients who had completed HRCT at 12 months, 65 presented with abnormal CT were invited to receive the test at the 2-year visit.

* Renal function includes creatine, estimate glomerular filtration rate (eGFR), and cystatin C.

† Liver function includes alanine aminotransferase (ALT), aspartate aminotransferase(AST), albumin, total protein, total bilrubin and direct bilrubin.

‡ Serum lipid includes total cholesterol, triglyceride, low density lipoprotein cholesterol and high density lipoprotein cholesterol.

6. Outcome measures and assessment tools

Outcomes measures in COVID-19 participants	
Outcome measures	**Assessment tools**
Prevalent and sequelae symptoms	Symptom questionnaire[1,2] Fatigue or muscle weakness, sleep difficulties, hair loss, smell disorder, palpitations, joint pain, decreased appetite, taste disorder, dizziness, nausea or vomiting, chest pain, sore throat or difficult to swallow, skin rash, myalgia, headache, and cough.
Dyspnea	mMRC dyspnea scale[4], 0, no breathlessness except on strenuous exercise; 1, shortness of breath when hurrying on the level or walking up a slight hill; 2, walks slower than people of the same age on the level because of breathlessness or has to stop to catch breath when walking at their own pace on the level; 3, stops for breath after walking approximately 100 m or after a few minutes on the level; 4, too breathless to leave the house, or breathless when dressing or undressing.
Health-related quality of life	Euroqol EQ-5D-5L[5] The EQ-5D-5L is a validated questionnaire to evaluate patients' quality of life by assessment of the following five factors: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Categorisation within each factor is divided into five levels that range from no problems to extreme problems. Utility index score: 1 indicates perfect health, 0 indicates death, and negative scores represent values as worse than death. EuroQol Visual Analogue Scale[6] The EQ-VAS is a patient's subjective assessment of generic health ranging from 0 to 100, with higher scores representing better subjective health experience.
Exercise capacity	6-min walking test The test was done according to the ATS practical guidelines.[7] Each participant walked on the flat ground as fast as possible without oxygen inhalation and completed the test independently.

	Predicted values were calculated according to the method of Enright and Sherrill.[8] The lower limit of the normal range was calculated by subtracting 153 m from the predicted value for men or by subtracting 139 m for women.
Anxiety symptom	The Generalised Anxiety Disorder (GAD-7) questionnaire[9] It is a patient reported outcome measure consists of 7 questions with total scores ranging from 0 to 21. Response options were "not at all," "several days," "more than half the days," and "nearly every day," scored as 0, 1, 2, and 3, respectively. The GAD-7 total score is divided into four severity levels: minimal (0-4), mild anxiety (5-9), moderate anxiety (10-14), and severe anxiety (15-21).[9]
Depression symptom	The Patient Health Questionnaire-9 (PHQ-9)[10,11] It is a patient reported outcome measure consisting of 9 questions with total scores ranging from 0 to 27. Response options were "not at all," "several days," "more than half the days," and "nearly every day," scored as 0, 1, 2, and 3, respectively. The PHQ-9 total score is divided into five severity levels: minimal or none (0-4), mild depression (5-9), moderate depression (10-14), moderately severe depression (15-19), and severe depression (20-27).[11]
Post-Traumatic stress symptom (PTSS)	The Post Traumatic Stress Disorder Checklist-Civilian version (PCL-C)[12] It is a 17-item self-report scale for examining post-traumatic stress symptoms (PTSS), with each item scoring from 1 (not at all) to 5 (extremely) in three domains: intrusion, avoidance and numbing, and hyperarousal. PCL-C total scores of ≥ 38 reflected "clinically relevant PTSS."[13,14]
New onset ischemic stroke and cardiovascular event after discharge	An ischaemic stroke and cardiovascular event registration form[15] Cardiovascular event includes stable angina pectoris, unstable angina pectoris, and myocardial infarction.
Health care utilization	A questionnaire was used to record the self-reported outpatient visit, emergency visit, and hospital admission.
Pulmonary function	The pulmonary function test was done in the Lung Function Laboratory of Jin Yin-tan Hospital using the Master Screen PFT (Vyaire Medical GmbH, Hoechberg, Germany) according to American Thoracic Society guidelines.[16] Lung function parameters include forced expiratory volume in one

	second (FEV1), forced vital capacity (FVC), total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV), and diffusion capacity for carbon monoxide (DLCO).
Lung image	Chest HRCT Chest HRCT was in the supine position during end-inspiration (SIEMENS SOMATOM PERSPECTIVE 64 CT scanner). Images were reconstructed at 1 mm slice thickness, with 1 mm increment, 512 mm × 512 mm. The CT features were evaluated by one experienced radiologist and one pulmonologist. To quantitative evaluation of lung lesions, a validated artificial intelligence was used to calculate the extent of anatomic involvement of each of the five lobes,[17] which was defined as the volume ratio of pneumonia lesions to each lung lobe, and then calculated a semi-quantitative CT score to assess the pulmonary involvement. Briefly, the score was calculated for each of the five lobes considering the extent of anatomic involvement, as follows: 0, no involvement; 1, less than 5% involvement; 2, 5–25% involvement; 3, 26–50% involvement; 4, 51–75% involvement; and 5, more than 75% involvement. The total CT score was the sum of the five lobe scores (0–25).
Cytokines	Cytokines levels were tested using the Bio-Plex Pro™ Human Cytokine Screening Panel 27-plex (Bio-rad, USA) in Bio-Plex 200 System (Bio-rad, USA) at Key Laboratory of Respiratory Disease Pathogenomics, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.
Complete blood count	Blood tests: leukocyte count, lymphocyte count, haemoglobin, and platelet count
Renal function	Blood tests: creatine, eGFR, and cystatin C Urine tests: protein
Liver function	Blood tests: ALT, AST, albumin, total protein, total bilrubin, and direct bilrubin
Lipid profile	Blood test: total cholesterol, triglyceride, low density lipoprotein cholesterol, and high density lipoprotein cholesterol
Blood glucose	Blood test: HbA1C
Outcomes measures in non-COVID-19 participants	

Prevalent symptoms	Symptom questionnaire[2] Fatigue or muscle weakness, sleep difficulties, hair loss, smell disorder, palpitations, joint pain, decreased appetite, taste disorder, dizziness, nausea or vomiting, chest pain, sore throat or difficult to swallow, skin rash, myalgia, headache, and cough.
Dyspnea	mMRC dyspnoea scale[4] 0, no breathlessness except on strenuous exercise; 1, shortness of breath when hurrying on the level or walking up a slight hill; 2, walks slower than people of the same age on the level because of breathlessness or has to stop to catch breath when walking at their own pace on the level; 3, stops for breath after walking approximately 100 m or after a few minutes on the level; 4, too breathless to leave the house, or breathless when dressing or undressing.
Health-related quality of life	Euroqol EQ-5D-5L[5] The EQ-5D-5L is a validated questionnaire to evaluate patient quality of life by assessment of the following five factors: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Categorisation within each factor is divided into five levels that range from no problems to extreme problems. EuroQol Visual Analogue Scale[6] The EQ-VAS is a patient's subjective assessment of generic health ranging from 0 to 100, with higher scores representing better subjective health experience.
Pulmonary function	The pulmonary function test was done in the Lung Function Laboratory of Jin Yin-tan Hospital using the Master Screen PFT (Vyaire Medical GmbH, Hoechberg, Germany) according to American Thoracic Society guidelines.[16] Lung function parameters include FEV1, FVC,TLC, FRC, RV, and DLCO.

7. Outcome definition used in the study

- **Sequelae symptoms:**

  For COVID-19 participants at each visit, sequelae symptoms are defined as those which are newly occurring and persistent, or worse than the status before COVID-19, and they cannot be explained by an alternative disease.

- COVID-19 participants with long COVID symptoms are defined as at least one sequelae symptom at follow-up.
- **Prevalent symptoms:**

  Prevalent symptoms are defined as the existing symptom at follow-up.

- **Dyspnea:**

  Dyspnea is defined as the mMRC score ≥1.

- **Lung diffusion impairment：**

  % predicted DLCO <80% indicates impaired lung diffusion.

- **Abnormal lung CT:**

  Abnormal lung CT is defined as the presence of at least one abnormal radiographic pattern on lung HRCT at follow-up.

- **Anxiety symptom:**

  A total score of GAD-7 greater than or equal to 5 indicates anxiety symptom.

- **Depression symptom:**

  A total score of PHQ-9 greater than or equal to 5 indicates depression symptom.

- **Post-traumatic stress symptom (PTSS) :**

  PCL-C total scores of ≥ 38 reflects “clinically relevant PTSS.”

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Table S1. Baseline characteristics of COVID survivors included and not included in final analysis

	COVID-19 survivors included in analysis (n=1192)	COVID-19 survivors not included in analysis (n=1014)	P value
Age at discharge, years	57.0 (48.0-65.0)	57.0 (47.0-67.0)	0.31
Sex			0.011
Men	641 (54%)	490/1013 (48%)	
Women	551 (46%)	523/1013 (52%)	
Cigarette smoking			0.037
Never-smoker	1076/1190 (90%)	924/993 (93%)	
Current smoker	82/1190 (7%)	43/993 (4%)	
Former smoker	32/1190 (3%)	26/993 (3%)	
Comorbidity			
Hypertension	343/1191 (29%)	294/991 (30%)	0.66
Diabetes	142/1190 (12%)	135/991 (14%)	0.24
Coronary heart diseases	82/1190 (7%)	80/991 (8%)	0.29
Cerebrovascular diseases	35/1191 (3%)	27/991 (3%)	0.76
Malignancy	31 (3%)	32/991 (3%)	0.38
Chronic obstructive pulmonary disease	18 (2%)	22/990 (2%)	0.22
Chronic kidney disease	16 (1%)	19/991 (2%)	0.29
Highest seven-category scale during hospital stay			0.0063
3: hospitalization, not requiring supplemental oxygen	295/1192 (25%)	289/992 (29%)	
4: hospitalization, requiring supplemental oxygen	806/1192 (68%)	650/992 (66%)	
5: hospitalization, requiring HFNC or non-IMV, or both	84/1192 (7%)	43/992 (4%)	
6: hospitalization, requiring ECMO or IMV, or both	7/1192 (1%)	10/992 (1%)	
Treatment received during hospital stay			
Corticosteroids	295 (25%)	170 (17%)	<0.0001
Antivirals	656 (55%)	525 (52%)	0.13
Lopinavir-ritonavir	166 (14%)	107 (11%)	0.016
Arbidol	576 (48%)	478 (47%)	0.58
Chloroquine phosphate	4 (0%)	2 (0%)	0.53
Hydroxychloroquine	1 (0%)	3 (0%)	0.24
Antibiotics	924 (78%)	738 (73%)	0.010
Thymosin	191 (16%)	170 (17%)	0.64
Intravenous immunoglobulin	235 (20%)	186 (18%)	0.41
Length of hospital stay, days	14.0 (10.0-20.0)	13.0 (9.0-18.0)	0.0004
ICU admission	51 (4%)	52/993 (5%)	0.29
Length of ICU stay, days	18.0 (6.0-30.0)	11.0 (7.5-17.0)	0.18

Data are n (%), n/N(%), or median (IQR). The differing denominators used indicate missing data. HFNC=high-flow nasal cannula for oxygen therapy. NIV=non-invasive ventilation. IMV=invasive mechanical ventilation. ECMO=extracorporeal membrane oxygenation. ICU=intensive care unit. Because only the information extracted from electronic medical record was available for nearly all of the study participant not included in analysis, data on smoking history and comorbidities was shown in this table according to the information collected at acute phase to make comparison. Thus, results of the two items shown in this table differs slightly from the validated data shown in Table 1.

Table S2. Health-related quality of life of 1192 COVID-19 survivors who completed three assessments

	Total (n=1192)			Scale 3:Not requiring supplemental oxygen (n=295)			Scale 4: Requiring supplemental oxygen (n=806)			Scale 5-6: Requiring HFNC, NIV or IMV (n=91)		
	6-mo	12-mo	2-y	6-mo	12-mo	2-y	6-mo	12-mo	2-y	6-mo	12-mo	2-y
Mobility (walking around)												
No problem	1041/1109 (94%)	1081/1187 (91%)	1149/1191 (96%)	274/289 (95%)	273/294 (93%)	285/295 (97%)	698/738 (95%)	724/802 (90%)	778/805 (97%)	69/82 (84%)	84/91 (92%)	86/91 (95%)
Slight	64/1109 (6%)	90/1187 (8%)	30/1191 (3%)	13/289 (4%)	19/294 (6%)	5/295 (2%)	39/738 (5%)	65/802 (8%)	21/805 (3%)	12/82 (15%)	6/91 (7%)	4/91 (4%)
Moderate	3/1109 (0%)	12/1187 (1%)	9/1191 (1%)	1/289 (0%)	1/294 (0%)	2/295 (1%)	1/738 (0%)	11/802 (1%)	6/805 (1%)	1/82 (1%)	0/91 (0%)	1/91 (1%)
Severe	1/1109 (0%)	3/1187 (0%)	2/1191 (0%)	1/289 (0%)	1/294 (0%)	2/295 (1%)	0/738 (0%)	1/802 (0%)	0/805 (0%)	0/82 (0%)	1/91 (1%)	0/91 (0%)
Unable to walk around	0/1109 (0%)	1/1187 (0%)	1/1191 (0%)	0/289 (0%)	0/294 (0%)	1/295 (0%)	0/738 (0%)	1/802 (0%)	0/805 (0%)	0/82 (0%)	0/91 (0%)	0/91 (0%)
Personal care (washing or dishing)												
No problem	1101/1109 (99%)	1170/1187 (99%)	1177/1191 (99%)	289/289 (100%)	291/294 (99%)	291/295 (99%)	731/738 (99%)	791/802 (99%)	797/805 (99%)	81/82 (99%)	88/91 (97%)	89/91 (98%)
Slight	7/1109 (1%)	5/1187 (0%)	9/1191 (1%)	0/289 (0%)	0/294 (0%)	3/295 (1%)	6/738 (1%)	4/802 (0%)	4/805 (0%)	1/82 (1%)	1/91 (1%)	2/91 (2%)
Moderate	1/1109 (0%)	5/1187 (0%)	2/1191 (0%)	0/289 (0%)	2/294 (1%)	0/295 (0%)	1/738 (0%)	3/802 (0%)	2/805 (0%)	0/82 (0%)	0/91 (0%)	0/91 (0%)
Severe	0/1109 (0%)	4/1187 (0%)	1/1191 (0%)	0/289 (0%)	1/294 (0%)	0/295 (0%)	0/738 (0%)	2/802 (0%)	1/805 (0%)	0/82 (0%)	1/91 (1%)	0/91 (0%)
Unable to wash or dish	0/1109 (0%)	3/1187 (0%)	2/1191 (0%)	0/289 (0%)	0/294 (0%)	1/295 (0%)	0/738 (0%)	2/802 (0%)	1/805 (0%)	0/82 (0%)	1/91 (1%)	0/91 (0%)
Usual activity (e.g. work, study, housework, family or leisure activities)												
No problem	1084/1100 (99%)	1173/1187 (99%)	1156/1191 (97%)	285/288 (99%)	292/294 (99%)	287/295 (97%)	721/731 (99%)	792/802 (99%)	785/805 (98%)	78/81 (96%)	89/91 (98%)	84/91 (92%)
Slight	12/1100 (1%)	6/1187 (1%)	24/1191 (2%)	3/288 (1%)	1/294 (0%)	4/295 (1%)	7/731 (1%)	4/802 (0%)	14/805 (2%)	2/81 (2%)	1/91 (1%)	6/91 (7%)
Moderate	3/1100 (0%)	5/1187 (0%)	5/1191 (0%)	0/288 (0%)	1/294 (0%)	2/295 (1%)	3/731 (0%)	3/802 (0%)	3/805 (0%)	0/81 (0%)	1/91 (1%)	0/91 (0%)
Severe	1/1100 (0%)	2/1187 (0%)	4/1191 (0%)	0/288 (0%)	0/294 (0%)	1/295 (0%)	0/731 (0%)	2/802 (0%)	2/805 (0%)	1/81 (1%)	0/91 (0%)	1/91 (1%)
Unable to usual activities	0/1109 (0%)	1/1187 (0%)	2/1191 (0%)	0/288 (0%)	0/294 (0%)	1/295 (0%)	0/731 (0%)	1/802 (0%)	1/805 (0%)	0/81 (0%)	0/91 (0%)	0/91 (0%)
Pain or discomfort												
No problem	804/1104 (73%)	839/1187 (71%)	907/1191 (76%)	208/286 (73%)	216/294 (73%)	222/295 (75%)	547/736 (74%)	562/802 (70%)	616/805 (77%)	49/82 (60%)	61/91 (67%)	69/91 (76%)
Slight	254/1104 (23%)	281/1187 (24%)	214/1191 (18%)	66/286 (23%)	67/294 (23%)	45/295 (15%)	156/736 (21%)	190/802 (24%)	149/805 (19%)	32/82 (39%)	24/91 (26%)	20/91 (22%)
Moderate	41/1104 (4%)	55/1187 (5%)	57/1191 (5%)	11/286 (4%)	9/294 (3%)	22/295 (7%)	29/736 (4%)	42/802 (5%)	33/805 (4%)	1/82 (1%)	4/91 (4%)	2/91 (2%)
Severe	5/1104 (0%)	10/1187 (1%)	12/1191 (1%)	1/286 (0%)	2/294 (1%)	6/295 (2%)	4/736 (1%)	7/802 (1%)	6/805 (1%)	0/82 (0%)	1/91 (1%)	0/91 (0%)

Extreme	0/1109 (0%)	2/1187 (0%)	1/1191 (0%)	0/286 (0%)	0/294 (0%)	0/295 (0%)	0/736 (0%)	1/802 (0%)	1/805 (0%)	0/82 (0%)	1/91 (1%)	0/91 (0%)
Anxiety or depression												
No problem	849/1105 (77%)	875/1187 (74%)	1048/1191 (88%)	218/288 (76%)	221/294 (75%)	261/295 (88%)	578/736 (79%)	589/802 (73%)	707/805 (88%)	53/81 (65%)	65/91 (71%)	80/91 (88%)
Slight	223/1105 (20%)	264/1187 (22%)	124/1191 (10%)	63/288 (22%)	59/294 (20%)	30/295 (10%)	135/736 (18%)	182/802 (23%)	83/805 (10%)	25/81 (31%)	23/91 (25%)	11/91 (12%)
Moderate	27/1105 (2%)	45/1187 (4%)	16/1191 (1%)	5/288 (2%)	13/294 (4%)	3/295 (1%)	19/736 (3%)	29/802 (4%)	13/805 (2%)	3/81 (4%)	3/91 (3%)	0/91 (0%)
Severe	6/1105 (1%)	3/1187 (0%)	3/1191 (0%)	2/288 (1%)	1/294 (0%)	1/295 (0%)	4/736 (1%)	2/802 (0%)	2/805 (0%)	0/81 (0%)	0/91 (0%)	0/91 (0%)
Extreme	0/1109 (0%)	0/1187 (0%)	0/1191 (0%)	0/288 (0%)	0/294 (0%)	0/295 (0%)	0/736 (0%)	0/802 (0%)	0/805 (0%)	0/81 (0%)	0/91 (0%)	0/91 (0%)

Data are n (%) or n/N(%).The differing denominators used indicate missing data. HFNC=high-flow nasal cannula for oxygen therapy. NIV=non-invasive ventilation. IMV=invasive mechanical ventilation.

Table S3. Mental health, healthcare use, and work status of COVID-19 survivors at 12 months and 2 years

	Total (n=1192)		Scale 3:Not requiring supplemental oxygen (n=295)		Scale 4: Requiring supplemental oxygen (n=806)		Scale 5-6: Requiring HFNC, NIV or IMV (n=91)	
	12-mo	**2-year**	**12-mo**	**2-year**	**12-mo**	**2-year**	**12-mo**	**2-year**
GAD-7								
Minimal (0–4)	NA	1089/1187(92%)	NA	268/294 (91%)	NA	736/802 (92%)	NA	85/91 (93%)
Mild (5–9)	NA	79/1187 (7%)	NA	24/294 (8%)	NA	51/802 (6%)	NA	4/91 (4%)
Moderate (10–14)	NA	14/1187 (1%)	NA	2/294 (1%)	NA	10/802 (1%)	NA	2/91 (2%)
Severe (≥15)	NA	5/1187 (0%)	NA	0/294 (0%)	NA	5/802 (1%)	NA	0/91 (0%)
PHQ-9								
Minimal (0–4)	NA	1115/1190(94%)	NA	270/295 (92%)	NA	759/804 (94%)	NA	86/91 (95%)
Mild (5–9)	NA	54/1190 (5%)	NA	23/295 (8%)	NA	27/804 (3%)	NA	4/91 (4%)
Moderate (10–14)	NA	13/1190 (1%)	NA	2/295 (1%)	NA	11/804 (1%)	NA	0/91 (0%)
Severe (≥15)	NA	8/1190 (1%)	NA	0/295 (0%)	NA	7/804 (1%)	NA	1/91 (1%)
PCL-C								
Minimal (<38)	NA	1162/1189(98%)	NA	283/295 (96%)	NA	789/803 (98%)	NA	90/91 (99%)
Clinical related PTSS (≥38)	NA	27/1189 (2%)	NA	12/295 (4%)	NA	14/803 (2%)	NA	1/91 (1%)
Healthcare use								
Outpatient clinic visit	215/1169(18%)	226/1187(19%)	54/290 (19%)	56/294 (19%)	149/790 (19%)	150/803 (19%)	12/89 (13%)	20/90 (22%)
Cardiology	39/1169 (3%)	56/1187 (5%)	10/290 (3%)	10/294 (3%)	26/790 (3%)	40/803 (5%)	3/89 (3%)	6/90 (7%)
Pulmonology	30/1169 (3%)	53/1187 (4%)	7/290 (2%)	17/294 (6%)	20/790 (3%)	30/803 (4%)	3/89 (3%)	6/90 (7%)
Infectious disease	3/1169 (0%)	1/1187 (0%)	0/290 (0%)	0/294 (0%)	2/790 (0%)	1/803 (0%)	1/89 (1%)	0/90 (0%)
Gastroenterology	21/1169 (2%)	31/1187 (3%)	5/290 (2%)	6/294 (2%)	16/790 (2%)	22/803 (3%)	0/89 (0%)	3/90 (3%)
Endocrinology	16/1169 (1%)	26/1187 (2%)	2/290 (1%)	11/294 (4%)	14/790 (2%)	12/803 (1%)	0/89 (0%)	3/90 (3%)
Rehabilitation	11/1169 (1%)	3/1187 (0%)	3/290 (1%)	1/294 (0%)	8/790 (1%)	2/803 (0%)	0/89 (0%)	0/90 (0%)
Nephrology	11/1169 (1%)	12/1187 (1%)	2/290 (1%)	0/294 (0%)	9/790 (1%)	10/803 (1%)	0/89 (0%)	2/90 (2%)
Neurology	8/1169 (1%)	8/1187 (1%)	2/290 (1%)	1/294 (0%)	6/790 (1%)	7/803 (1%)	0/89 (0%)	0/90 (0%)
Psychology	1/1169 (0%)	2/1187 (0%)	0/290 (0%)	0/294 (0%)	1/790 (0%)	2/803 (0%)	0/89 (0%)	0/90 (0%)
Others	98/1169 (8%)	93/1187 (8%)	31/290 (11%)	27/294 (9%)	62/790 (8%)	61/803 (8%)	5/89 (6%)	5/90 (6%)
Hospitalization	152/1169(13%)	159/1187(13%)	38/290 (13%)	45/294 (15%)	100/790 (13%)	95/803 (12%)	14/89 (16%)	19/90 (21%)

Respiratory disease	20/1169 (2%)	9/1187 (1%)	3/290 (1%)	1/294 (0%)	12/790 (2%)	6/803 (1%)	5/89 (6%)	2/90 (2%)
Cardiac disease	0/1169 (0%)	0/1187 (0%)	0/290 (0%)	0/294 (0%)	0/790 (0%)	0/803 (0%)	0/89 (0%)	0/90 (0%)
Hypertension	9/1169 (1%)	12/1187 (1%)	3/290 (1%)	3/294 (1%)	6/790 (1%)	8/803 (1%)	0/89 (0%)	1/90 (1%)
Diabetes mellitus	8/1169 (1%)	8/1187 (1%)	1/290 (0%)	1/294 (0%)	6/790 (1%)	4/803 (0%)	1/89 (1%)	3/90 (3%)
Neurological disorders	7/1169 (1%)	4/1187 (0%)	2/290 (1%)	1/294 (0%)	4/790 (1%)	2/803 (0%)	1/89 (1%)	1/90 (1%)
Physical examination	5/1169 (0%)	1/1187 (0%)	3/290 (1%)	1/294 (0%)	2/790 (0%)	0/803 (0%)	0/89 (0%)	0/90 (0%)
Kidney disease	4/1169 (0%)	8/1187 (1%)	1/290 (0%)	0/294 (0%)	3/790 (0%)	7/803 (1%)	0/89 (0%)	1/90 (1%)
Others	108/1169 (9%)	129/1187 (11%)	30/290 (10%)	39/294 (13%)	73/790 (9%)	76/803 (9%)	7/89 (8%)	14/90 (15%)
Emergency department visit	12/1169 (1%)	7/1187 (1%)	3/290 (1%)	2/294 (1%)	8/790 (1%)	5/803 (1%)	1/89 (1%)	0/90 (0%)
Professional rehabilitation program	5/1169 (0%)	1/1187 (0%)	1/290 (0%)	1/294 (0%)	2/790 (0%)	0/803 (0%)	2/89 (2%)	0/90 (0%)
ICU admission	0/1169 (0%)	0/1187 (0%)	0/290 (0%)	0/294 (0%)	0/790 (0%)	0/803 (0%)	0/89 (0%)	0/90 (0%)
Work status at follow-up								
Returned to original work*	401/455 (88%)	438/494 (89%)	99/115 (86%)	112/124 (90%)	268/300 (89%)	282/321 (88%)	34/40 (85%)	44/49 (90%)
Returned to pre-COVID level of work	306/401 (76%)	383/438 (87%)	84/99 (85%)	98/112 (88%)	202/268 (75%)	248/282 (88%)	20/34 (59%)	37/44 (84%)
Not returned to pre-COVID level of work	95/401 (24%)	55/438 (13%)	15/99 (15%)	14/112 (13%)	66/268 (25%)	34/282 (12%)	14/34 (41%)	7/44 (16%)
Not returned to original work	54/455 (12%)	56/494 (11%)	16/115 (14%)	12/124 (10%)	32/300 (11%)	39/321 (12%)	6/40 (15%)	5/49 (10%)
Due to decreased physical function	18/54 (33%)	21/56 (38%)	4/16 (25%)	5/12 (42%)	11/32 (34%)	14/39 (36%)	3/6 (50%)	2/5 (40%)
Unwilling to return to original work	10/54 (19%)	10/56 (18%)	3/16 (19%)	3/12 (25%)	6/32 (19%)	7/39 (18%)	1/6 (17%)	0/5 (0%)
Unemployment	12/54 (22%)	14/56 (25%)	4/16 (25%)	3/12 (25%)	8/32 (25%)	10/39 (26%)	0/6 (0%)	1/5 (20%)
Others	14/54 (26%)	11/56 (20%)	5/16 (31%)	1/12 (8%)	7/32 (22%)	8/39 (21%)	2/6 (33%)	2/5 (40%)

Data are n(%) or n/N (%). The differing denominators used indicate missing data. HFNC=high-flow nasal cannula for oxygen therapy. NIV=non-invasive ventilation. IMV=invasive mechanical ventilation. GAD-7= Generalized Anxiety Disorder-7. PHQ-9=Patient Health Questionnaire-9. PCL-C= Post Traumatic Stress Disorder Checklist-Civilian version. ICU=intensive care unit. *This category only includes those who had a full-time or part-time job before COVID-19.

Table S4. Health outcomes and healthcare use between COVID-19 participants with and without long COVID symptoms at 2 years

Characteristics	Participants with long COVID symptoms at 2 years (n=650)	Participants without long COVID symptoms at 2 years (n=540)	OR or β (95% CI)	P value
EQ-5D-5L questionnaire				
Pain or discomfort	228 (35%)	55 (10%)	4.42 (3.14-6.21)	<0.0001
Anxiety or depression	123 (19%)	19 (4%)	7.46 (4.12-13.52)	<0.0001
Mobility problem	33 (5%)	8 (1%)	3.81 (1.62-8.93)	0.0021
Usual activity problem	24 (4%)	10 (2%)	1.76 (0.79-3.94)	0.17
Personal care problem	8 (1%)	6 (1%)	1.11 (0.36-3.46)	0.86
EuroQol VAS score	80.0 (70.0-85.0)	85.0 (80.0-90.0)	-9.30 (-10.7- -7.91)	<0.0001
6MWD, m	510.0 (453.0-550.0)	525.0 (465.0-580.0)	-12.8 (-22.6- -3.03)	0.010
Percentage of predicted value†	93.5 (84.5-102.8)	94.7 (85.3-105.9)	-2.63 (-4.58- -0.68)	0.0083
Less than LLN‡	54/647 (8%)	34/533 (6%)	1.30 (0.81-2.11)	0.28
Mental health				
Anxiety symptom (GAD-7 ≥5)	83 (13%)	15/536 (3%)	4.63 (2.53- 8.50)	<0.0001
Depression symptom (PHQ-9 ≥5)	70/649 (11%)	5 (1%)	11.43 (4.55-28.72)	<0.0001
PTSD symptom (PCL-C ≥38)	27 (4%)	0/538 (0%)	NA	NA
Healthcare use after discharge				
Outpatient clinic visit	169/648 (26%)	57/538 (11%)	2.82 (1.99- 4.00)	<0.0001
Hospitalization	107/648 (17%)	52/538 (10%)	1.64 (1.12- 2.41)	0.011
Emergency department visit	7/648 (1%)	0/538 (0%)	NA	NA

Data are median (IQR), n(%) or n/N (%). The differing denominators used indicate missing data. EQ-5D-5L=EuroQol five-dimension five-level questionnaire. EQ-VAS=EuroQol Visual Analogue Scale. 6MWD= distance walked in 6 minutes. LLN=lower limit of normal range. GAD-7= Generalized Anxiety Disorder-7. PHQ-9=Patient Health Questionnaire-9. PCL-C= Post Traumatic Stress Disorder Checklist-Civilian version. NA= not applicable. The definition of long COVID-19 symptoms was shown in the appendix.

†Predicted values were calculated according to the method of Enright and Sherrill.

‡The lower limit of the normal range was calculated by subtracting 153 m from the predicted value for men or by subtracting 139 m for women

Table S5. Characteristics of 1127 matched COVID-19 survivors and their controls

Characteristics	Matched Non-COVID-19 participants (n=1127)	Matched COVID-19 survivors at 2-year visit (n=1127)*	*P* value
Age, years	59.0 (50.0-67.0)	59.0 (50.0-67.0)	0.72
Sex			1.00
Men	607 (54%)	607 (54%)	
Women	520 (46%)	520 (46%)	
Education			<0.0001
College or higher	204 (18%)	305/1120 (27%)	
High school or lower	923 (82%)	815/1120 (73%)	
Cigarette smoking			<0.0001
Never-smoker	745 (66%)	899 (80%)	
Current smoker	310 (28%)	115 (10%)	
Former smoker	72 (6%)	113 (10%)	
Comorbidity			
Hypertension	407 (36%)	407 (36%)	1.00
Diabetes	143 (13%)	143 (13%)	1.00
Cardiovascular diseases	65 (6%)	61 (5%)	0.71
Cerebrovascular diseases	27 (2%)	24 (2%)	0.67
Tumor	27 (2%)	16 (1%)	0.09
COPD	2 (0%)	5 (0%)	0.25
Chronic kidney disease	6 (1%)	6 (1%)	1.00

Data are n (%), n/N(%), or median (IQR). The differing denominators used indicate missing data. COPD=chronic obstructive pulmonary disease.

* The data of COVID-19 survivors in this table reflected their status at 2-year follow-up.

Table S6. Lung imaging among COVID-19 survivors who completed HRCT at 2-year follow-up

	Scale 3: not requiring supplemental oxygen (n=10)	Scale 4: requiring supplemental oxygen (n=20)	Scale 5-6: requiring HFNC, NIV, or IMV (n=27)
At least one abnormal CT pattern	9/10 (90%)	15/20 (75%)	23/27 (85%)
GGO	3/10 (30%)	10/19 (53%)	21/27 (78%)
Irregular lines	6/10 (60%)	10/20 (50%)	18/27 (67%)
Consolidation	0/10 (0%)	2/20 (10%)	0/27 (0%)
Interlobular septal thickening	0/10 (0%)	1/20 (5%)	3/27 (11%)
Subpleural line	1/10 (10%)	2/20 (10%)	4/27 (15%)
Reticular pattern	0/10 (0%)	0/20 (0%)	1/27 (4%)
Volume of lung lesions, cm^3	10.4 (3.3-26.1)	10.9 (5.8-23.3)	23.9 (9.1-61.3)
Volume of consolidation, cm^3	0.8 (0.4-4.8)	2.6 (0.9-8.1)	3.9 (0.9-5.8)
Volume of GGO, cm^3	5.7 (2.9-20.8)	8.5 (4.0-14.9)	21.9 (8.5-55.5)
Volume ratio of lung lesion to total lung, %	0.2 (0.1-0.5)	0.3 (0.1-0.5)	0.6 (0.2-1.8)
Volume ratio of consolidation to total lung, %	0.0 (0.0-0.1)	0.1 (0.0-0.2)	0.1 (0.0-0.3)
Volume ratio of GGO to total lung, %	0.1 (0.1-0.4)	0.2 (0.1-0.4)	0.5 (0.2-1.6)
CT-score	5.0 (4.0-5.0)	5.0 (4.0-5.0)	5.0 (5.0-5.0)

Data are absolute values, n (%), or n/N (%) when data are missing. HRCT=high resolution computed tomography. HFNC=high-flow nasal cannula for oxygen therapy. NIV=non-invasive ventilation. IMV=invasive mechanical ventilation. GGO = ground glass opacity. CT-score range from 0-25, with higher scores indicating more lung involvement.

Table S7. Characteristics of 223 matched COVID-19 survivors who completed PFTs at 2 years and their controls

Characteristics	Matched Non-COVID-19 participants (n=223)	Matched COVID-19 survivors (n=223)	*P* value
Age, years	58.0 (49.0-65.0)	58.0 (49.0-65.0)	0.94
Sex			1.00
Men	138 (62%)	138 (62%)	
Women	85 (38%)	85 (38%)	
BMI, kg/m^2	24.5 (22.6-26.0)	25.0 (22.6-27.1)	0.09
Cigarette smoking			<0.0001
Never-smoker	137 (61%)	170 (76%)	
Current smoker	69 (31%)	19 (9%)	
Former smoker	17 (8%)	34 (15%)	
Comorbidity			
Hypertension	64 (29%)	84 (38%)	0.044
Diabetes	27 (12%)	26 (12%)	0.88
Coronary heart diseases	16 (7%)	14 (6%)	0.71
Cerebrovascular diseases	6 (3%)	4 (2%)	0.52
Tumor	5 (2%)	0 (0%)	0.0082
COPD	1 (0%)	2 (1%)	0.56
Chronic kidney disease	3 (1%)	8 (4%)	0.13

Data are n (%), n/N(%), or median (IQR). The differing denominators used indicate missing data. BMI=body mass index. COPD=chronic obstructive pulmonary disease. PFTs=pulmonary function tests.

Figure S1. Venn diagram showing the COVID-19 survivors who completed at least one assessment

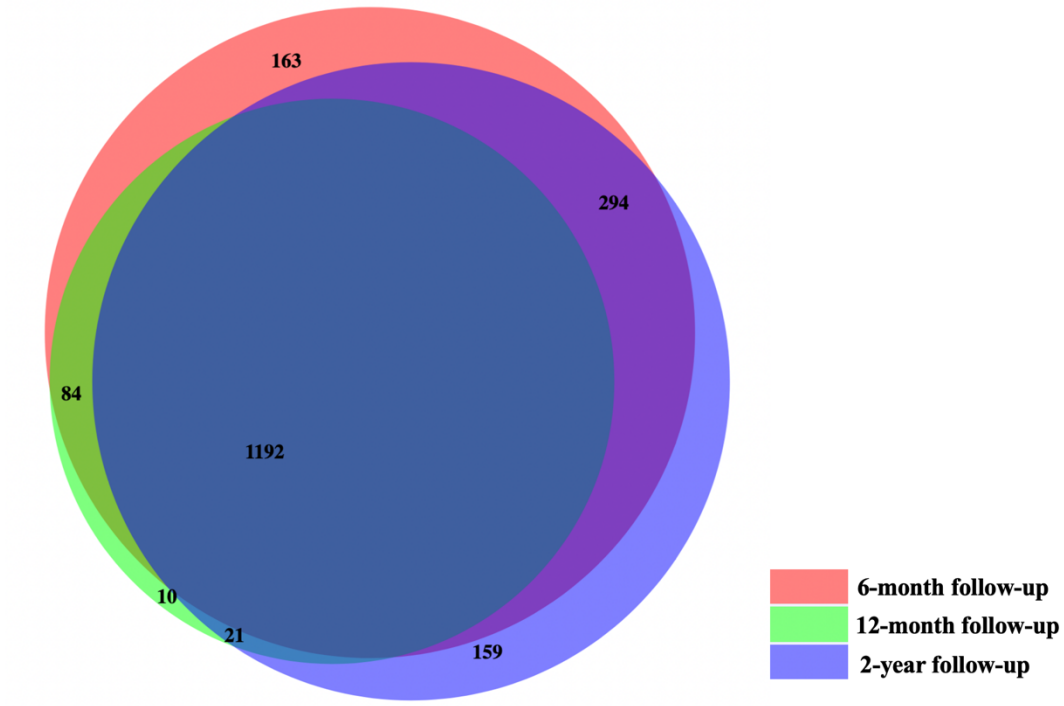


Figure S2. Flow chart of COVID-19 participants who completed pulmonary function tests

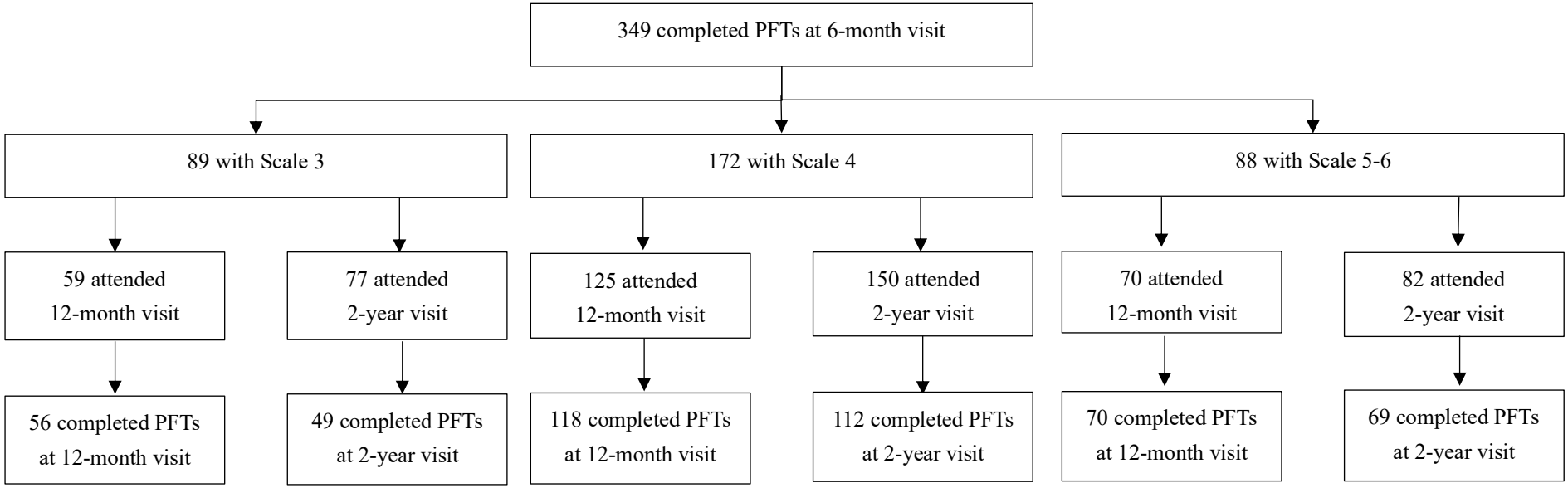


Figure S3. Flow chart of COVID-19 participants who completed chest HRCT

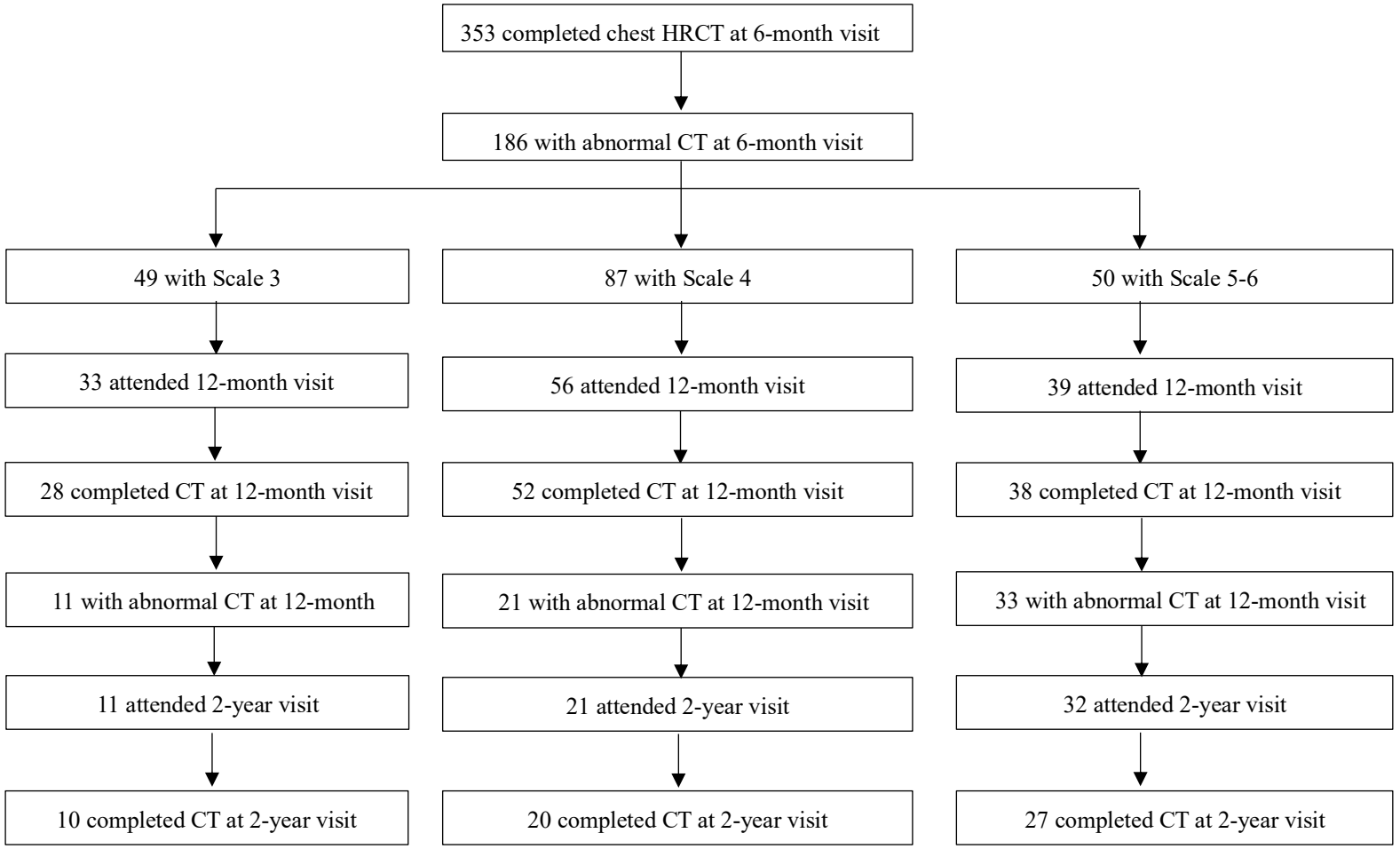
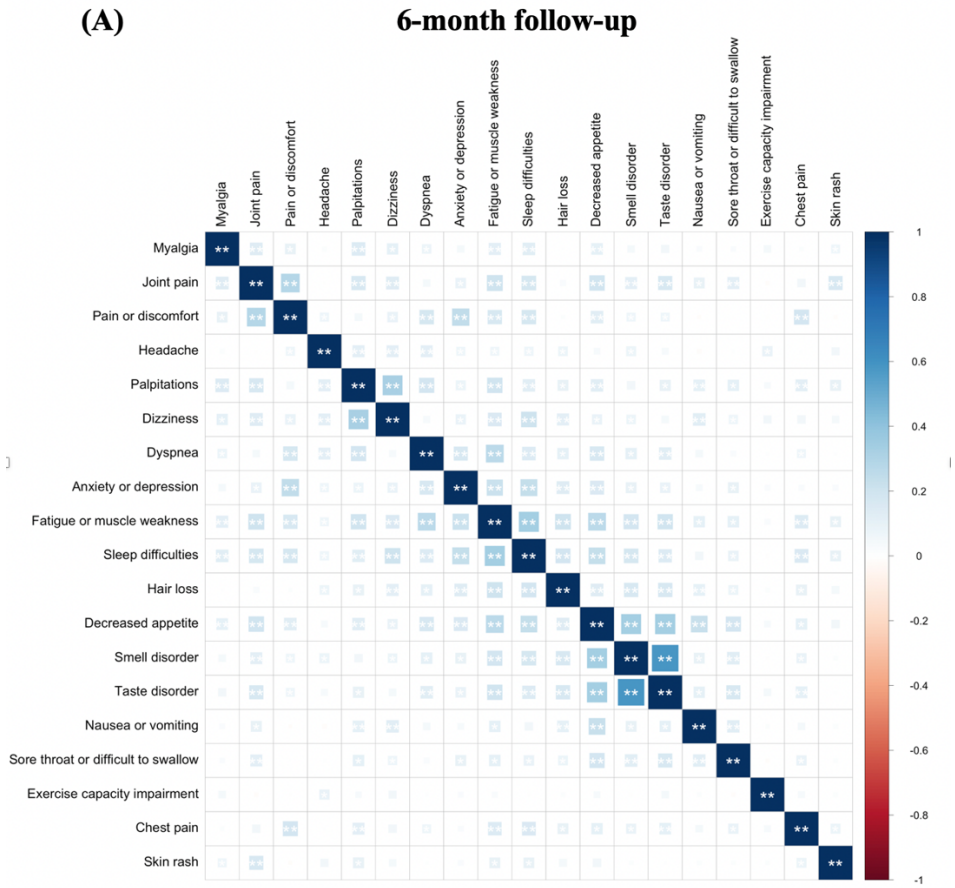
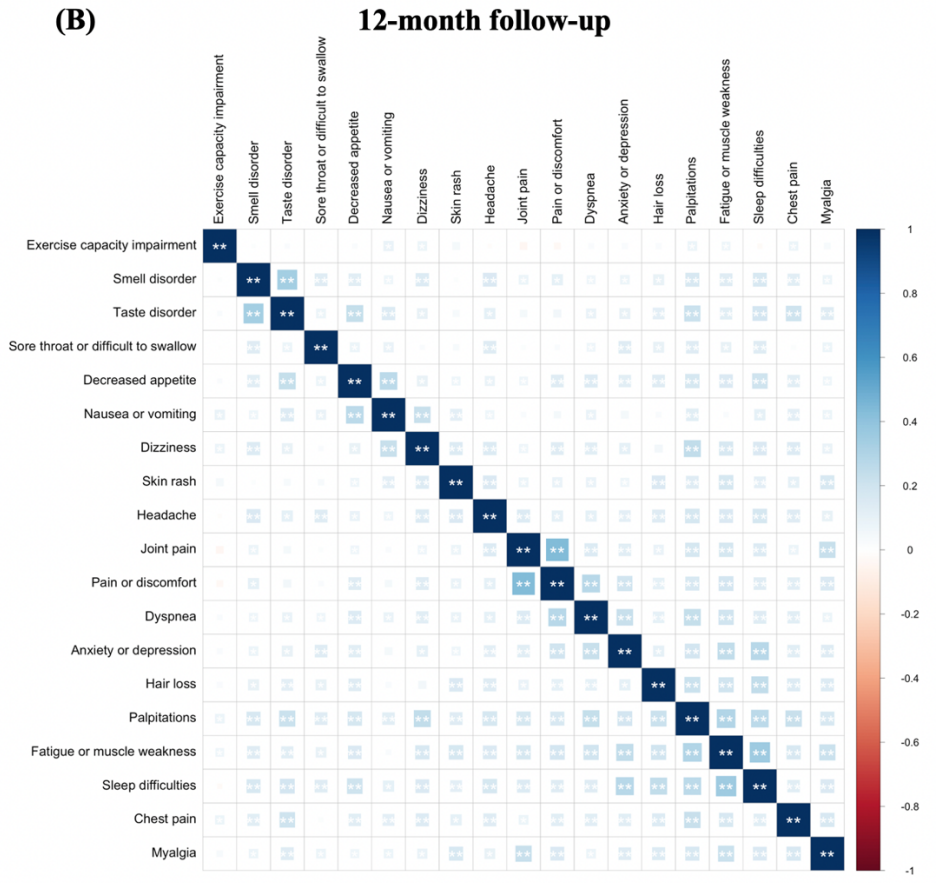
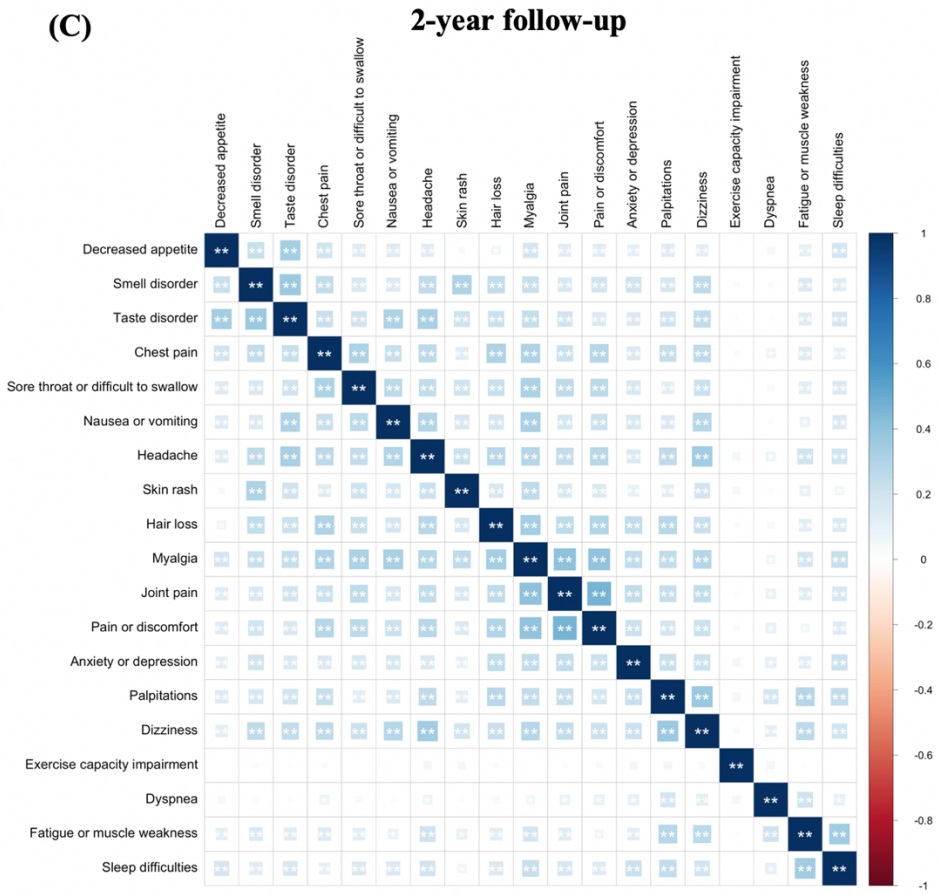


Figure S4. Pairwise co-occurrence heatmaps of sequelae symptoms at 6-month, 12-month, and 2-year follow-up







* $p<0.05$. ** $p<2.92\times10^{-4}$.