3-year outcomes of discharged survivors of COVID-19 following the SARS-CoV-2 omicron (B.1.1.529) wave in 2022 in China: a longitudinal cohort study

Hui Zhang, Chaolin Huang*, Xiaoying Gu*, Yeming Wang*, Xia Li, Min Liu, Qiongya Wang, Jiuyang Xu, Yimin Wang, Huaping Dai, Dingyu Zhang†, Bin Cao†*

Summary

Background There is a paucity of data on the natural trajectory of outcomes in survivors of COVID-19 beyond 2 years after symptom onset, and no evidence exists on the effect of re-infection in people with long COVID symptoms. We aimed to investigate the 3-year health outcomes of COVID-19 survivors and the effect of omicron re-infection.

Methods In this single-centre, longitudinal cohort study, we recruited participants with confirmed COVID-19 who were discharged from the Jin Yin-tan hospital in Wuhan, China, between Jan 7 and May 29, 2020. Participants completed three follow-up visits at 6 months (June 16 to Sept 13, 2020), 1 year (Dec 16, 2020, to Feb 7, 2021), and 2 years (Nov 16, 2021, to Jan 10, 2022) since symptom onset (reported previously). At 1-year follow-up, community controls without a history of SARS-CoV-2 infection were recruited from two communities in Wuhan and at 2 years were matched (1:1) with survivors of COVID-19 who underwent pulmonary function tests. We did a 3-year follow-up from Feb 23, 2023, to April 20, 2023, after the omicron (B.1.1.529) wave in winter, 2022. All eligible survivors of COVID-19 and community controls matched at 2-year follow-up were invited to the outpatient clinic at the hospital to complete several face-to-face questionnaires, a 6-min walking test (6MWT), and laboratory tests. A subgroup of survivors of COVID-19 identified by stratified sampling on the basis of disease severity scale score during hospitalisation and community controls underwent pulmonary function tests. Survivors of COVID-19 who received high-resolution CT and showed abnormal lung images at 2-year follow-up were invited for another assessment. We identified participants with and without long COVID at 2 years. The primary outcomes were sequelae symptoms, omicron infection, lung function, and chest imaging at the 3-year follow-up.

Findings Of 1359 COVID-19 survivors who completed 2-year and 3-year follow-up, 728 (54%) had at least one sequelae symptom at 3 years after symptom onset and before omicron infection, mainly mild to moderate severity. During the omicron wave, participants with long COVID at 2 years had a significantly higher proportion of re-infection (573 [76%] of 753 *vs* 409 [67%] of 606 without long COVID; p=0·0004), pneumonia (27 [5%] of 568 *vs* seven [2%] of 403; p=0·012). 3 months after omicron infection, 126 (62%) of 204 survivors with long COVID at 2 years had newly occurring or worse symptoms, which was significantly higher than the proportion in the non-long COVID group (85 [41%] of 205; p<0·0001) and community controls (81 [40%] of 205; p<0·0001), and not significantly different between COVID-19 survivors without long COVID and matched community controls (85 [41%] of 205 *vs* 81 [39%] of 206; p=0·66). Re-infection was a risk factor for dyspnoea (odds ratio 1·36 [95% CI 1·04 to 1·77]; p=0·023), anxiety or depression (OR 1·65 [1·24 to 2·20]; p=0·0007), EuroQol visual analogue scale score (β –4·51 [–6·08 to –2·95]; p<0·0001), but not for reduced daily activity (0·72 [0·38 to 1·37]; p=0·32) at 3 years. Lung function of survivors at 3 years was similar to that of matched community controls. We found irregular line, traction bronchiectasis, subpleural lines and ground glass opacity at 3 years, but the volume ratio of lung lesion to total lung was only 0·2–0·3%.

Interpretation Most long COVID symptoms at 3 years were mild to moderate, with lung function recovering to levels of matched controls. Survivors with long COVID had a higher proportion of participants with re-infection and newly occurring or worse symptoms 3 months after omicron infection than those without long COVID. Re-infection had increased symptom occurrence but not increased reduced daily activity. Although the organ function of survivors of COVID-19 recovered over time, those with severe long COVID symptoms, abnormal organ function, or limited mobility require urgent attention in future clinical practice and research.

Funding Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences, National Natural Science Foundation of China.

Lancet Respir Med 2024; 12: 55–66

Published Online November 21, 2023 https://doi.org/10.1016/S2213-2600(23)00387-9

See Comment page 7

*Contributed equally

†Contributed equally

Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship hospital, Capital Medical University, Beijing, China (H Zhang MD, Prof H Dai MD, Prof B Cao MD); **National Center for Respiratory Medicine, State Key Laboratory of Respiratory Health and Multimorbidity, National Clinical Research Center for Respiratory Diseases, Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing, China** (H Zhang, YeM Wang MD, J Xu MD, YiM Wang MD, Prof H Dai, Prof B Cao); **Wuhan Jinyintan Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei Province, China** (C Huang MD, Q Wang MD, D Zhang MD); **Wuhan Research Center for Communicable Disease Diagnosis and Treatment, Chinese Academy of Medical Sciences, Wuhan, Hubei Province, China** (C Huang, Q Wang, D Zhang); **National Center for Respiratory Medicine; State Key Laboratory of Respiratory Health and Multimorbidity; National Clinical Research Center for Respiratory Diseases; Institute of Respiratory Medicine, Chinese Academy of Medical Sciences; Department of Clinical Research and Data**

Management, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing, China (X Gu PhD); **Hubei Provincial Clinical Research Center for Infectious Diseases, Wuhan Research Center for Communicable Disease Diagnosis and Treatment, Chinese Academy of Medical Sciences, Wuhan, Hubei Province, China** (X Li MD); **Department of Radiology, China-Japan Friendship Hospital, Beijing, China** (M Liu MD); **Department of Pulmonary and Critical Care Medicine, Wuhan Jinyintan Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei Province, China** (YiM Wang); **Hubei Clinical Research Center for Infectious Diseases, Wuhan, Hubei Province, China** (D Zhang); **Tsinghua University-Peking University Joint Center for Life Sciences, Beijing, China** (Prof B Cao)

Correspondence to:
Prof Bin Cao, National Center for Respiratory Medicine; State Key Laboratory of Respiratory Health and Multimorbidity; National Clinical Research Center for Respiratory Diseases; Institute of Respiratory Medicine, Chinese Academy of Medical Sciences; Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing 100029, China
caobin_ben@163.com

For **worldwide COVID-19 data** see https://covid19.who.int

See **Online** for appendix

Research in context

Evidence before this study

We searched for articles in PubMed between March 16, 2022, and Aug 5, 2023, using the terms (COVID-19 OR SARS-CoV-2 OR Coronavirus disease 2019 OR 2019-nCoV) AND (follow up OR discharge* OR long term OR long covid OR post-acute COVID-19 syndrome OR lung function* OR pulmonary function*), without language restrictions. After screening, we found 16 studies on the health condition of survivors of COVID-19 up to 2 years after symptom onset. Most studies only focused on symptoms or one specific organ function. No study comprehensively assessed long-term health outcomes of survivors of COVID-19 3 years after hospital discharge, and the effect of re-infection in this group.

Added value of this study

To our knowledge, this study is the first to investigate the health outcomes of hospitalised COVID-19 survivors at 3 years. 728 (54%) of 1358 participants reported at least one sequelae symptom, mostly mild to moderate. Participants with long COVID at 2 years had higher proportions of re-infection and pneumonia compared with participants without long COVID. Newly occurring or worse symptoms 3 months after omicron infection were more prevalent in those with long COVID than in those without long COVID and community controls (survivors without long COVID had a similar prevalence of newly occurring or worse symptoms as community controls). Re-infection was associated with dyspnoea, EuroQol visual analogue scale (EQ-VAS) score, and anxiety or depression symptoms, but not with reduced daily activity at 3 years. Lung function of COVID-19 survivors returned to levels similar to those of matched community controls at 3 years, and changes in lung function were similar in survivors with and without long COVID and community controls. We found irregular lines, traction bronchiectasis, subpleural lines, and ground glass opacity at 3 years, but the volume ratio of lung lesion to total lung was only 0·2–0·3%.

Implications of all the available evidence

Although some COVID-19 survivors discharged from hospital had long COVID at 3 years, lung function recovered to similar levels to those of matched community controls. Survivors with long COVID had higher proportions of re-infection, pneumonia, and sequelae symptoms 3 months after omicron infection than those without long COVID. Re-infection was associated with dyspnoea, anxiety or depression symptoms, and reduced EQ-VAS score in COVID-19 survivors, but not with reduced daily activity. The findings of this study have important implications for the management of patients with long COVID, giving us more confidence to face this health challenge. These findings also need to be further verified in future studies on long COVID with larger sample sizes.

Introduction

Since the beginning of the COVID-19 pandemic, more than 771 million confirmed cases and nearly 7 million deaths have been reported worldwide. Growing evidence shows that many people infected have persistent somatic symptoms or organ dysfunction several weeks or months after infection, known as long COVID. The definition of long COVID varies, the main difference being the duration of post-acute sequelae symptom after COVID-19 infection, ranging from 4 to 12 weeks.[1–3] 36 million people across the European region might have developed long COVID during the first 3 years of the pandemic,[4] with the number estimated to be 65 million worldwide at 90 days after infection.[5] Compared with survivors of COVID-19 without long COVID, those with long COVID were at increased risk of varying adverse outcomes, such as diabetes, cardiovascular disease, neurological diseases, and kidney disease. These outcomes might reduce individuals' quality of life and limit daily activity, resulting in higher unemployment rates in those with long COVID than those without long COVID (12·3% *vs* 8·7%).[6–13]

Long COVID has become one of the foremost challenges currently confronting global health-care systems. Comprehensive assessments of physical health, psychological conditions, and organ function of COVID-19 survivors have only been done within a 2-year timeframe after the onset of symptoms. The longer-term consequences of infection in these individuals remain unknown. In the winter of 2022, China experienced a wave of omicron (B.1.1.529) infections,[14] and the dominant subvariants were BF.7 and BA.5.2 in Wuhan.[15,16] However, the effect of re-infection on pre-existing long COVID symptoms and health-related outcomes of COVID-19 survivors has not been studied. We aimed to investigate the 3-year health outcomes of COVID-19 survivors and the effect of re-infection in this patient population.

Methods

Study design and participants

We did a longitudinal cohort study including COVID-19 survivors aged 18 years or older who were discharged from Jin Yin-tan hospital in Wuhan, China, between Jan 7 and May 29, 2020. The inclusion and exclusion criteria of this cohort have been described previously (appendix pp 4–5).[17] We did three face-to-face follow-up interviews at 6 months (June 16 to Sept 13, 2020), 1 year (Dec 16, 2020, to Feb 7, 2021), and 2 years (Nov 16, 2021, to Jan 10, 2022) since symptom onset, and the details of these three follow-up timepoints have been reported previously.[13,17,18] At 1-year follow-up, community controls were recruited from two communities in Wuhan. These communities were located in districts representing higher and lower levels of economic development.[18] We included 3383 community members older than 20 years

and without a history of SARS-CoV-2 infection (ie, community controls). The detailed recruitment process is described in the appendix (pp 5–7). At 2-year follow-up, we matched community controls (1:1) by age, sex, and chronic pulmonary disease status with COVID-19 survivors who underwent pulmonary function tests at each visit. At the 3-year follow-up after the omicron (B.1.1.529) wave in winter, 2022, we invited COVID-19 survivors who met the inclusion and exclusion criteria of this cohort (appendix pp 4–5) and matched community controls to the hospital outpatient clinic for in-person interviews with trained researchers for physical examinations and routine blood tests. We did pulmonary function tests in the matched COVID-19 survivors and community controls and high-resolution CT in survivors with abnormal CT features at 2 years. The survey content for all participants in this follow-up is provided in the appendix (pp 8–9).

This study was approved by the research ethics committee of Jin Yin-tan Hospital (KY-2020-78.09). Written and oral informed consent was obtained from the control group and COVID-19 survivors who participated in face-to-face interviews, and from COVID-19 survivors who participated in telephone surveys, separately.

Questionnaires on symptoms and quality of life

COVID-19 cohort

Participants were invited to the hospital for a series of questionnaires at 3-year follow-up: an omicron-infection questionnaire, symptom questionnaire, health-care use and work-status questionnaire, modified British Medical Research Council (mMRC) dyspnoea scale, EQ-5D-5L, EuroQol visual analogue scale (EQ-VAS), Generalized Anxiety Disorder 7-item scale (GAD-7), Patient Health Questionnaire 9 (PHQ-9), and the Post-Traumatic Stress Disorder Checklist–civilian version (PCL-C; figure 1A). To confirm demographic information and self-reported comorbidity data collected at baseline, we designed a standard questionnaire administered to obtain information face-to-face by trained staff at 1-year and 2-year follow-up visits. The vaccination status was also recorded.

The omicron-infection questionnaire aimed to survey the symptoms and severity during the acute phase. We used the symptom questionnaire to assess the presence and severity of sequelae symptoms. We assessed the severity of sequelae symptoms using an ordinal 5-point Likert scale,[19] except for the visual analogue scale for joint

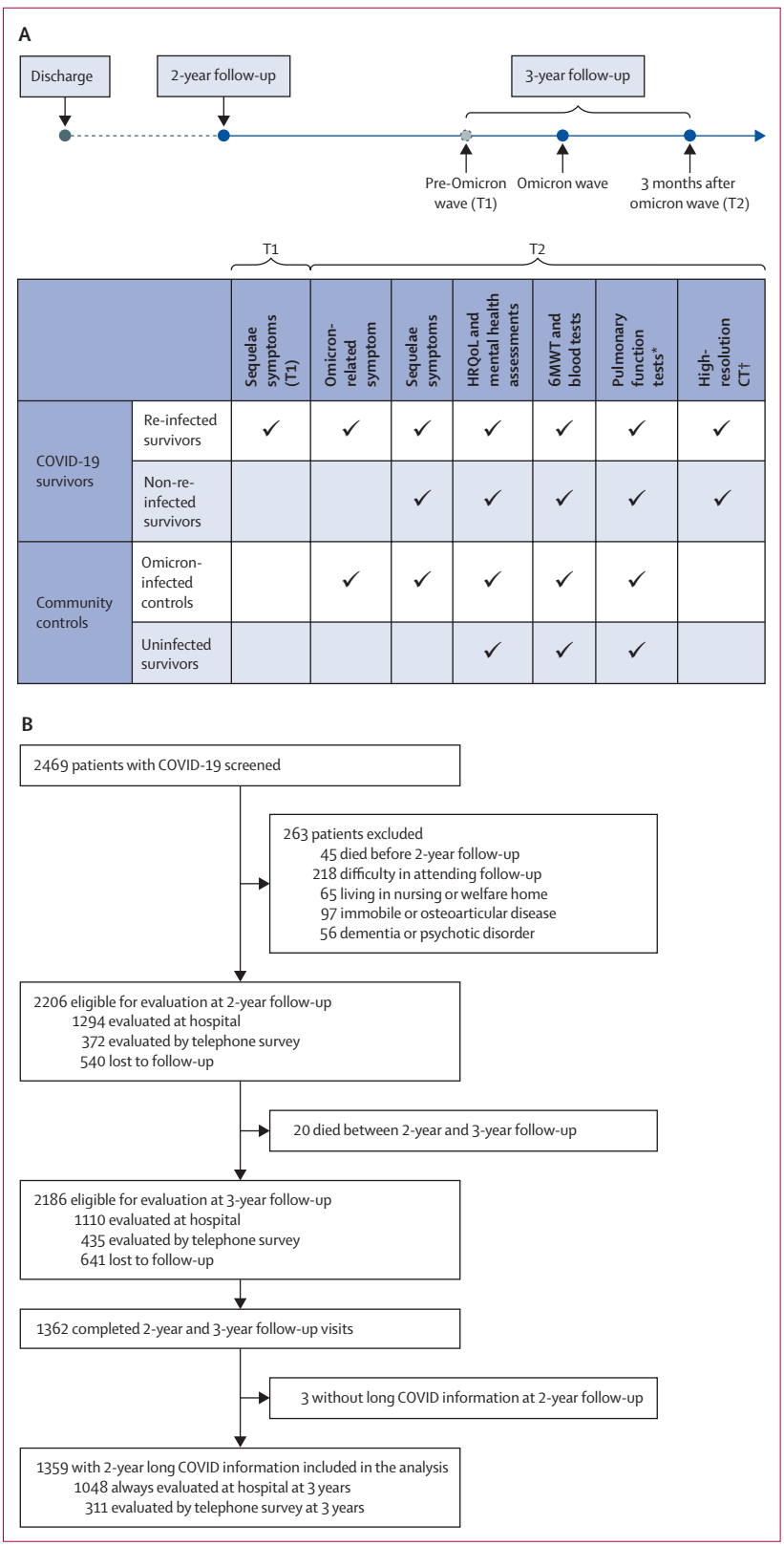

Figure 1: **Study design**

(A) Timepoints of questionnaire survey, 6MWT, pulmonary function tests, and high-resolution CT for COVID-19 survivors and community controls. (B) Trial profile. 6MWT=6 min walking test. Omicron=B.1.1.529. *A subgroup COVID-19 survivors at 6-month follow-up (described previously) and matched community controls were invited to undergo pulmonary function tests. †COVID-19 survivors with abnormal CT at 2-year follow-up who received high-resolution CT imaging at 3-year follow-up.

pain,[20] with a higher score representing greater severity (appendix p 10). The severity of joint pain was categorised as mild (1–3), moderate (4–6), or severe (7–10) according to a visual analogue scale. When assessing changes in symptom severity, every 2 points of the visual analogue scale of joint pain are converted into a level, with a total of five levels for consistency with other symptoms. After omicron infection, an increase in symptom severity by more than one level is defined as worse, a decrease by more than one level is defined as improved, and no change is defined as stable. The details for the classification of change in symptom severity before and after omicron infection are shown in the appendix (p 14). We used the health-care use and work-status questionnaire to assess the condition in the period before omicron infection. We used the EQ-5D-5L questionnaire and EQ-VAS to assess health-related quality of life (HRQoL) and the mMRC dyspnoea scale to assess dyspnoea. We used the other three psychiatric questionnaires to assess survivors' mental health, including the GAD-7 for anxiety symptom assessment, the PHQ-9 for depression symptom assessment, and the PCL-C for post-traumatic stress disoder symptom assessment. Details of these questionnaires and definitions of outcomes are given in the appendix (pp 10–14). COVID-19 survivors who could not attend an in-person interview were invited to complete all questionnaires by telephone interview.

Community controls

The community controls had no history of SARS-CoV-2 infection before the omicron wave in winter, 2022. Community controls who received pulmonary function tests at the 2-year follow-up were invited to the hospital for a face-to-face interview at 3-year follow-up (appendix pp 8–9). Additionally, community controls who reported omicron infection completed the omicron-infection questionnaire, symptom questionnaire, and health-care use and work-status questionnaire. Other questionnaires were consistent with those used for survivors of COVID-19, and definitions of outcomes were given in the appendix (pp 13–14).

Functional examination and high-resolution CT

All participants, including COVID-19 survivors and community controls, were invited to perform a 6-min walk test (6MWT). We used stratified disproportional random sampling according to the highest seven-category scale score during hospital stay (severity scale)—(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, non-invasive mechanical ventilation, or both; (6) admitted to hospital requiring extracorporeal membrane oxygenation, invasive mechanical ventilation, or both; and (7) death—to select patients who would undergo pulmonary function tests at the 6-month follow-up visit[18] and were invited for the same tests at the 3-year follow-up visit.

Participants with CT abnormalities at 2-year follow-up underwent high-resolution CT again at 3 years.[13] The original CT scans were assessed by experienced pulmonologists and radiologists for abnormal CT features, including ground glass opacity, irregular lines, subpleural lines, interlobular septal thickening, reticular pattern, consolidation, and traction bronchiectasis. A validated artificial intelligence software (chest CT image processing software [YT-CT-Lung, version 1.0], Yitu Network Technology, China) calculated the degree of anatomical involvement of the five lobes and summed a CT score on the basis of the volume ratio of lesions in the five lung lobes, with a higher score representing more lung involvement (appendix pp 10–11).

Outcomes

The primary outcomes were sequelae symptoms, omicron infection, lung function, and chest imaging at 3-year follow-up. Secondary outcomes were dyspnoea, HRQoL (evaluated by EQ-VAS score), exercise capacity, mental health assessments (anxiety, depression, and post-traumatic stress disorder symptoms), and health-care use and work status at 3 years. The definitions and assessment tools for primary and secondary outcomes are listed in the appendix (pp 10–14).

Statistical analysis

Demographic and clinical characteristics and long-term health consequences of COVID-19 survivors and matched community controls were presented as medians (IQRs) for continuous variables and as n (%) for categorical variables. We categorised COVID-19 survivors into either long COVID or non-long COVID groups according to the presence of at least one sequelae symptom at 2-year follow-up. For the comparison of demographic and clinical characteristics at baseline and clinical characteristics of omicron infection between long COVID and non-long COVID groups, we used the χ^2 test, Fisher's exact test, or Mann-Whitney *U* test as appropriate. We did similar tests for the comparison of newly occurring or worse symptoms after omicron infection and pulmonary function between COVID-19 survivors with long COVID at 2 years and matched controls, and also between non-long COVID survivors and matched controls. For the comparison of symptoms, HRQoL, exercise capacity, health-care use after discharge, and work status between the 2-year and 3-year follow-up visits, we used the Wilcoxon signed-rank test or McNemar test as appropriate.

We used multivariable adjusted logistic regression models in prespecified analyses to explore the association between independent variables such as age, sex, education, cigarette smoking, comorbidity, disease severity, corticosteroid use, re-infection with SARS-CoV-2, and vaccination status with dyspnoea, anxiety or depression

(assessed by GAD-7 and PHQ-9); reduced daily activity; diffusion impairment; and long COVID before omicron infection. We used generalised linear regression models to assess the association of these exposure variables with EQ-VAS score at 3-year follow-up. For the association of disease severity and vaccination status with dyspnoea, anxiety or depression, reduced daily activity, EQ-VAS score, diffusion impairment, and long COVID before omicron infection, we included age, sex, cigarette smoking (never-smoker *vs* current or former smoker), education (higher education or higher *vs* high school or lower), comorbidity, disease severity scale score during hospital stay (3 *vs* 4 *vs* 5–6), corticosteroid use, and vaccination status in the models. We analysed the effect of re-infection on these outcomes except for long COVID before omicron infection with the previously mentioned independent variables. For the association of sex and corticosteroid use with these outcomes, we included all the independent variables in the model. When exploring associations of education with these outcomes, we included the independent variables except for comorbidity; for the association of smoking with these outcomes, we included the independent variables except for comorbidity and disease severity (because of potential mediation). Only sex, smoking, education, and vaccination status were included for the association between age and these outcomes because of the potential mediation of other factors. For the association of comorbidity with these outcomes, we included the independent variables except for disease severity and re-infection status. All significance tests were two-sided, and a $p<0·05$ was considered significant, unless stated otherwise. Missing data were not imputed. All statistical analyses were done with SAS (version 9.4).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

After excluding 20 participants who died between the 2-year and 3-year follow-up period (five died from reinfection with SARS-CoV-2 in the winter of 2022, and another 15 died from other causes), 2186 COVID-19 survivors were eligible for 3-year follow-up. 641 (29%) participants were lost to follow-up and 1545 (71%) completed the 3-year follow-up from Feb 23, 2023, to April 20, 2023. We included 1359 survivors who completed both 2-year and 3-year follow-up and with long COVID information at 2 years in the final analysis, 1048 (77%) of whom were interviewed face-to-face at the hospital and 311 (23%) were interviewed by telephone (figure 1B).

Among 268 survivors of COVID-19 who had pulmonary function tests at 2 years, 238 (88·8%) had pulmonary function tests at 3 years; 243 community controls had pulmonary function tests at both 2 years and 3 years. Of

	Total (n=1359)	Long COVID at 2 years (n=753)	Non-long COVID at 2 years (n=606)	p value
Age at discharge, years	57·0 (48·0–65·0)	57·0 (48·0–65·0)	57·0 (46·0–65·0)	0·39
Sex	..	..	..	0·0004
Male	728 (54%)	371 (49%)	357 (59%)	..
Female	631 (46%)	382 (51%)	249 (41%)	..
BMI, kg/m²	23·9 (21·8–26·0)	23·9 (21·9–26·2)	24·0 (21·8–26·0)	0·90
Education level	..	..	..	0·49
College or higher	397/1251 (32%)	220/711 (31%)	177/540 (33%)	..
High school or lower	854/1251 (68%)	491/711 (69%)	363/540 (67%)	..
Cigarette smoking	..	..	..	0·75
Never-smoker	1123/1332 (84%)	624/740 (84%)	499/592 (84%)	..
Current smoker	96/1332 (7%)	56/740 (8%)	40/592 (7%)	..
Former smoker	113/1332 (9%)	60/740 (8%)	53/592 (9%)	..
Comorbidity				
Hypertension	454/1351 (34%)	245/749 (33%)	209/602 (35%)	0·44
Diabetes (type 1 or type 2)	183/1350 (14%)	99/749 (13%)	84/601 (14%)	0·69
Coronary heart diseases	117/1350 (9%)	73/749 (10%)	44/601 (7%)	0·12
Cerebrovascular diseases	64/1350 (5%)	41/750 (5%)	23/600 (4%)	0·16
Chronic kidney disease	48/1352 (4%)	29/750 (4%)	19/602 (3%)	0·48
Malignancy	38/1351 (3%)	22/750 (3%)	16/601 (3%)	0·76
Chronic obstructive pulmonary disease	21/1351 (2%)	14/750 (2%)	7/601 (1%)	0·30
Highest seven-category scale score during hospital stay	..	..	..	0·46
3: admitted to hospital and not requiring supplemental oxygen	347/1351 (26%)	189/750 (25%)	158/601 (26%)	..
4: admitted to hospital and requiring supplemental oxygen	903/1351 (67%)	506/750 (67%)	397/601 (66%)	..
5: admitted to hospital and requiring HFNC or non-IMV, or both	92/1351 (7%)	48/750 (6%)	44/601 (7%)	..
6: admitted to hospital and requiring ECMO or IMV, or both	9/1351 (1%)	7/750 (1%)	2/601 (0%)	..
Length of hospital stay, days	14·0 (10·0–20·0)	14·0 (10·0–21·0)	14·0 (10·0–19·0)	0·14
ICU admission	56/1351 (4%)	28/750 (4%)	28/601 (5%)	0·40
Length of ICU stay, days	18·0 (7·0–37·0)	18·5 (11·5–41·5)	10·5 (7·0–23·0)	0·11
Corticosteroid use	320/1336 (24%)	188/745 (25%)	132/591 (22%)	0·22
Vaccination status*	..	..	..	0·64
Unvaccinated	203 (15%)	121 (16%)	82 (14%)	..
One dose	205 (15%)	112 (15%)	93 (15%)	..
Two doses	268 (20%)	147 (20%)	121 (20%)	..
Three and more doses	683 (50%)	373 (50%)	310 (51%)	..
Time from symptom onset to 2-year follow-up, months	23·0 (22·5–23·4)	22·9 (22·5–23·3)	23·0 (22·6–23·6)	0·0001
Time from symptom onset to 3-year follow-up, months	38·5 (37·9–39·2)	38·5 (37·9–39·1)	38·6 (38·0–39·3)	0·057

Data are n (%), n/N (%), or median (IQR), unless otherwise indicated. The differing denominators used indicate missing data. Data on demographic characteristics, smoking history, and comorbidities were confirmed at the 12-month follow-up visit and self-reported by patients. All the included participants were Asian. ECMO=extracorporeal membrane oxygenation. HFNC=high-flow nasal cannula for oxygen therapy. ICU=intensive care unit. IMV=invasive mechanical ventilation. NIV=non-invasive ventilation. *Details of vaccination status were collected at the 3-year follow-up visit.

Table 1: **Baseline characteristics of COVID-19 survivors who completed 2-year and 3-year follow-up visits**

238 COVID-19 survivors and 243 controls who underwent pulmonary function tests at 3-year visits, we matched 186 pairs by age, sex, chronic pulmonary disease status, and omicron infection (appendix p 32). 40 survivors with CT abnormalities at 2 years had chest high-resolution CT at 3 years (appendix p 32).

The median duration from COVID-19 symptom onset to the 3-year follow-up visit was 38·5 months (IQR 37·9–39·2). Of 1359 study participants, the median age at discharge was 57·0 years (48·0–65·0), 631 (46%) were female, 728 (54%) were male, and hypertension (454 [34%] of 1351) and diabetes (183 [14%] of 1350) were the most common comorbidities (table 1). 1156 (85%) participants received at least one vaccination dose before the omicron wave, including inactivated vaccine (976 [72%] of 1359) and recombinant COVID-19 vaccine (12 [1%] of 1359), and only 203 (15%) were unvaccinated. 753 (55%) of 1359 survivors who reported at least one sequelae symptom at 2 years were classified into the long COVID group and 606 (45%) into the non-long COVID group. More female than male participants were in the long COVID group (382 [51%] of 753] *vs* 249 [41%] of 606), and vaccination status was similar between the two groups (table 1). Compared with participants included in the final analysis, excluded participants had a higher proportion of female participants (443 [54%] of 827 *vs* 631 [46%] of 1359) and lower proportion of those requiring oxygen therapy or ventilation (severity scale score 5–6 34 [4%] of 804 *vs* 101 [8%] of 1351; appendix p 16). We found no significant difference in comorbidities between those included and excluded from the final analysis, except for chronic kidney disease status (appendix p 16). The demographic characteristics of the community controls who attended the 3-year follow-up are shown in the appendix (p 17).

At 3 years after symptom onset and before omicron infection, 728 (54%) of 1358 survivors of COVID-19 had at least one sequelae symptom (appendix p 18). The proportions of most symptoms remained stable or decreased between the 2-year and 3-year visits (appendix p 18). We found a significant decrease in fatigue or muscle weakness (422 [31%] of 1359 *vs* 249 [18%] of 1358; p<0·0001) and increase in hair loss (152 [11%] *vs* 246 [18%]; p<0·0001) and joint pain (128 [9%] *vs* 226 [17%]; p<0·0001) at 3 years (appendix p 18). More than 80% of reports of each sequelae symptom were mild to moderate severity (Likert 1–3), except for joint pain (appendix p 33). Health-care use within 3 years increased significantly compared with that within 2 years of infection, including outpatient clinic visit (261 [19%] of 1356 *vs* 507 [37%] of 1353; p<0·0001), hospitalisation (168 [12%] *vs* 408 [30%]; p<0·0001), and emergency department visit (nine [1%] *vs* 56 [4%]; p<0·0001). 494 (87%) of 566 survivors of COVID-19 who worked before the primary infection returned to their original work, which was similar to the proportion at 2 years (appendix p 18). In survivors without self-reported omicron infection, 205 (54%) of 377 had at least

	COVID-19 survivors			Community controls (n=248)	p value, long COVID *vs* non-long COVID	p value, COVID-19 survivors *vs* community controls
	Long COVID at 2 years (n=753)	Non-long COVID at 2 years (n=606)	Total (n=1359)			
Omicron infection*	573 (76%)	409 (67%)	982 (72%)	206 (83%)	0·0004	0·0004
Positive SARS-CoV-2 rapid antigen test or RT-PCR	222/568 (39%)	163/403 (40%)	385/971 (40%)	86/206 (42%)	0·67	0·58
Clinical characteristics of Omicron infection						
Asymptomatic	5/568 (1%)	5/403 (1%)	10/971 (1%)	3/205 (1%)	0·59	0·60
Symptomatic	563/568 (99%)	398/403 (99%)	961/971 (99%)	203/205 (99%)	..	..
Number of symptoms†	3 (2–6)	3 (2–4)	3 (2–5)	3 (2–5)	<0·0001	0·27
Pneumonia	27/568 (5%)	7/403 (2%)	34/971 (4%)	6/206 (3%)	0·012	0·67
Treatment location	..	..	..	..	0·25	0·69
Outpatient clinic or emergency department visit	32/568 (6%)	14/403 (3%)	46/971 (5%)	10/206 (5%)	..	..
Admitted to hospital	11/568 (2%)	6/403 (1%)	17/971 (2%)	2/206 (1%)	..	..
Highest oxygen support therapy	..	..	..	..	0·89	0·45
Supplemental oxygen	10/573 (2%)	6/409 (1%)	16/982 (2%)	1/206 (<1%)	..	..
HFNC, NIV, or both	1/573 (<1%)	0	1/982 (<1%)	0	..	..

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. *Omicron infection was confirmed by a positive SARS-CoV-2 test result or symptoms of infection and contact with index patients. †COVID-related symptoms included fever, cough, sore or dry throat, fatigue, muscle or body aches (or soreness), congestion or runny nose, headache, chills or shaking, nausea, diarrhea, taste disorder, smell disorder, shortness of breath, and vomiting.

Table 2: **Clinical characteristics of omicron (B.1.1.529) infection in winter, 2022, among COVID-19 survivors and community controls**

one sequelae symptom, which was consistent with that of all COVID-19 survivors (appendix p 19). Comparisons of sequelae symptoms between 2 years and 3 years were similar to that among all included survivors of COVID-19, (primary outcome), which was the same for health-care use and work status (secondary outcomes).

Following the omicron wave in winter 2022, 982 (72%) of 1359 COVID-19 survivors were infected with omicron compared with 206 (83%) of 248 community controls (table 2). The median number of COVID-related symptoms in the acute phase was three (IQR 2–5) for both infected survivors and community controls (table 2). 34 (4%) of 971 omicron-infected participants progressed to pneumonia and 17 (2%) were admitted to hospital, 16 (2%) of 982 survivors requiring supplementary oxygen and one (<1%) requiring high-flow nasal cannula for oxygen therapy (table 2). The proportions of participants with pneumonia (six [3%] of 206 *vs* 34 [4%] of 971), admitted to hospital (two [1%] *vs* 17 [2%]), and who received oxygen therapy (one [<1%] *vs* 16 [2%]) were numerically lower in community controls than in survivors (table 2).

Notably, 573 (76%) of 753 survivors with long COVID at 2 years were reinfected, which was more than 409 (67%) of 606 in the non-long COVID group (table 2). Compared with non-long COVID survivors, those with long COVID had more symptoms (median 3 [2–6] *vs* 3 [2–4]) and a higher proportion had pneumonia (27 [5%] of 568 *vs* seven [2%] of 403, table 2). We found no significant difference between long COVID and non-long COVID survivors in proportions of symptomatic infection, hospitalisation, and oxygen therapy (table 2). Survivors with long COVID at 2 years had slightly higher proportions of re-infection and pneumonia than non-long COVID survivors in both male and female (appendix pp 20–21). Among all infected survivors of COVID-19 and community controls who had positive SARS-CoV-2 antigen or RT-PCR tests (appendix p 22), survivors with long COVID at 2 years had numerically higher proportions of pneumonia, hospitalisation, supplemental oxygen, and more symptoms than survivors without long COVID. These results were similar to those in table 2.

126 (62%) of 204 survivors with long COVID reported at least one newly occurring or worse symptom 3 months after omicron infection, which was significantly higher than the proportion in community controls matched by age and sex (81 [40%] of 205; p<0·0001; table 3). However, the proportion of newly occurring or worse symptoms was not significantly different between non-long COVID survivors and matched community controls (85 [41%] of 205 *vs* 81 [39%] of 206; p=0·66; table 3). Palpitations, dizziness, and chest pain were significantly more frequent in non-long COVID survivors than in matched controls, but other symptoms did not differ, except for sleep difficulties and joint pain. Fatigue or muscle weakness, sleep difficulties, smell disorder, palpitations, decreased appetite, sore throat or difficulty swallowing, myalgia, and headache after omicron infection were more prevalent in long COVID survivors than in non-long COVID participants (appendix p 23). Regarding symptom severity, most sequelae symptoms in survivors and community controls were mild and moderate (Likert scale score 1–3), although approximately 30% of survivors with long COVID had severe joint pain with a visual analogue scale score of 7–10 (appendix p 33). Regarding the change in severity of symptoms of reinfected survivors before and after omicron infection, symptoms in most participants remained stable (appendix p 34). For both male and female participants, survivors with long COVID had higher proportions of newly occurring or worse symptoms 3 months after omicron infection than survivors without long COVID and community controls (appendix pp 24–25). The proportions of newly occurring or worse symptoms between COVID-19 survivors and community controls matched by age, sex, smoking history, and comorbidities showed similar results (appendix p 26).

Among COVID-19 survivors and community controls who completed pulmonary function tests at 3 years, 186 COVID-19 survivors (113 [61%] with long COVID and 73 [39%] without) were matched (1:1) by age, sex, chronic pulmonary disease status, and omicron infection status with community controls. For survivors of COVID-19 with and without long COVID, the percentage of predicted

	Long COVID at 2-year (n=205)	Matched community controls (n=205)	p value	Non-long COVID at 2 years (n=206)	Matched community controls (n=206)	p value
Any symptom*	126/204 (62%)	81 (40%)	<0·0001	85/205 (41%)	81 (39%)	0·66
Fatigue or muscle weakness	72 (35%)	45 (22%)	0·0031	41 (20%)	45 (22%)	0·63
Sleep difficulties	30 (15%)	17 (8%)	0·044	7 (3%)	17 (8%)	0·035
Hair loss	14 (7%)	11 (5%)	0·54	11/205 (5%)	11 (5%)	0·99
Smell disorder	12 (6%)	5 (2%)	0·083	3 (1%)	5 (2%)	0·47
Joint pain	7/204 (3%)	18 (9%)	0·024	3 (1%)	18 (9%)	0·0008
Palpitations	38 (19%)	6 (3%)	<0·0001	22 (11%)	6 (3%)	0·0017
Decreased appetite	10 (5%)	3 (1%)	0·048	3 (1%)	3 (1%)	1·00
Taste disorder	9 (4%)	3 (1%)	0·079	4 (2%)	3 (1%)	0·70
Dizziness	31 (15%)	12 (6%)	0·0022	24 (12%)	12 (6%)	0·036
Chest pain	23 (11%)	5 (2%)	0·0004	17 (8%)	5 (2%)	0·0085
Sore throat or difficult to swallow	15 (7%)	2 (1%)	0·0013	5 (2%)	2 (1%)	0·25
Skin rash	8 (4%)	1 (0%)	0·012	5 (2%)	1 (0%)	0·086
Myalgia	35 (17%)	9 (4%)	<0·0001	15 (7%)	9 (4%)	0·21
Headache	28 (14%)	9 (4%)	0·0011	13 (6%)	9 (4%)	0·38
Nausea or vomiting	8 (4%)	3 (1%)	0·13	4 (2%)	3 (1%)	0·70

Data are n (%) or n/N (%), unless otherwise indicated. The differing denominators used indicate missing data. Community controls infected with omicron were matched with reinfected survivors with or without long COVID by age and sex. *Includes all symptoms listed in the table.

Table 3: **Newly occurring or worse symptoms 3 months after omicron (B.1.1.529) infection in COVID-19 survivors and matched community controls**

values of spirometry, lung volume, and diffusion capacity parameters were not statistically significantly different to those of matched community controls, except for the residual volume (89·5% for survivors with long COVID *vs* 92·6% for matched controls, p=0·0044, and 81·8% for survivors without long COVID *vs* 90·1% for matched controls, p=0·0009) and functional residual capacity between survivors without long COVID and matched controls (97·4% *vs* 106·6%; p=0·017; figure 2A, B). The proportion of abnormal lung function was not significantly different in long COVID or non-long COVID survivors versus matched community controls, except for the residual volume (32% for survivors with long COVID *vs* 16% for matched controls, p=0·0050, and 40% for survivors without long COVID *vs* 21% for matched controls, p=0·0098; figure 2C, D). With further matching for smoking history, the results were similar (appendix p 27). Changes in lung function between 2-year and 3-year follow-up visits did not differ between survivors and matched controls infected with omicron in the past year, except for total lung capacity between survivors with long COVID at 2 years and matched controls (50·0 mL [–160·0 to 310·0] *vs* –40·0 mL [–280·0 to 200·0]; p=0·043), regardless of whether the survivors had long COVID or not (appendix p 28).

Of 57 COVID-19 survivors who had high-resolution CT at 2 years, 48 (84%) had CT abnormalities. 40 (83%) of these 48 had chest high-resolution CT at 3-year follow-up, including 26 (65%) infected with omicron and 14 (35%) without infection (appendix p 29). 35 (87%) of 40 survivors who had CT abnormalities at 2 years persisted with abnormal CT features at 3 years

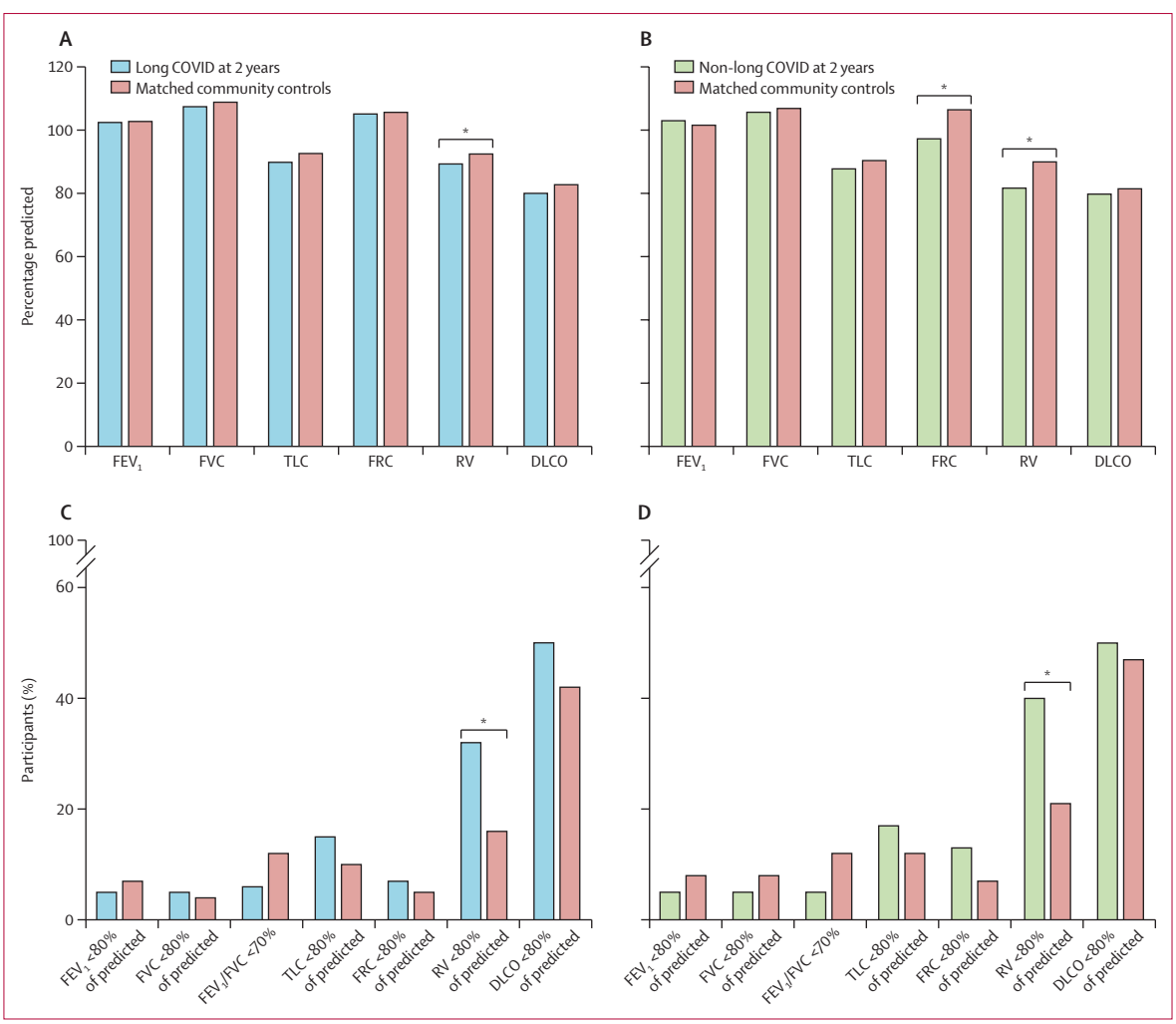

Figure 2: **Lung function of COVID-19 survivors and matched community controls at the 3-year visit**
Community controls were matched by age, sex, chronic pulmonary disease history, and re-infection history. The percentage of predicted values for pulmonary function test parameters in COVID-19 survivors with long COVID (A) and non-long COVID (B) and the matched community controls. Proportions of participants with abnormal pulmonary function test parameters in COVID-19 survivors with long COVID (C), non-long COVID (D) and the matched community controls. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. TLC=total lung capacity. FRC=functional residual capacity. RV=residual volume. DLCO=diffusion capacity for carbon monoxide. *p<0·05.

(appendix p 29). Irregular lines were the most common feature, followed by traction bronchiectasis and subpleural lines (appendix p 29). By using artificial intelligence software to calculate a CT score, the volume and ratio of ground glass opacity to total lung and the volume ratio of lung lesions decreased between the 2-year and 3-year visits (appendix p 29). The median ratio of lung lesion to total lung volume was 0·3% (IQR 0·2–1·1) in survivors infected with omicron and 0·2% (0·1–0·7) in survivors who were not infected with omicron (appendix p 29).

The appendix (p 35) shows the dynamic changes of CT imaging in four survivors who had high-resolution CT at 3 years as examples. Lung lesions continued to resolve or remained stable from 2 years to 3 years (appendix p 35). In a male survivor aged 64 years (severity scale score 3) who was infected with omicron in 2022, CT imaging showed irregular lines and traction bronchiectasis at 3 years, but these features were mild this survivor did not report dyspnoea symptoms (appendix p 35). Another male survivor aged 49 years (severity scale score 4) who was infected with omicron had nearly normal imaging and lung function and did not report dyspnoea at 3 years (appendix p 35). In a female survivor aged 60 years (severity scale score 5) infected with omicron who did not have dyspnoea at 3 years, we found that reticular pattern, ground glass opacity, subpleural lines, and irregular lines persisted at 2 years but continued to resolve at 3 years (appendix p 35). A male survivor aged 69 years (with severity scale 6) without omicron infection had obvious CT abnormalities at 3 years, with mainly irregular lines and traction bronchiectasis, reduced lung function, and dyspnoea (appendix p 35).

The numerical differences in the values of laboratory tests, including leukocyte counts, lymphocyte counts, serum creatinine, alanine aminotransferase, aspartate aminotransferase, and HbA_{1c} were not clinically significant between COVID-19 survivors and community controls (appendix p 30).

After the omicron wave, 581 (43%) of 1358 survivors had dyspnoea (mMRC score ≥1) at 3 years and the proportion of dyspnoea in long COVID survivors was higher than in non-long COVID survivors (401 [53%] of 752 *vs* 180 [30%] of 606; appendix p 31). Pain or discomfort was the most impaired dimension of HRQoL (543 [40%] of 1358), followed by anxiety or depression (398 [29%]), and a few survivors had problems with mobility (47 [3%]), personal care (11 [1%]) and usual activity (16 [1%]; appendix p 31). The median 6MWT result at 3 years was 488·0 m (IQR 445·0–533·0), which was slightly lower than that at 2 years (512·0 m [456·0–564·0]; appendix p 31). The percentage of predicted value less than the lower limit of normal at 3 years was higher than at 2 years (105 [10%] of 1022 *vs* 75 [8%] of 970; appendix p 31). The proportion of survivors with long COVID who had pain or discomfort, anxiety or depression, and worse mental health (GAD-7 score ≥5, PHQ-9 score ≥5, and PCL-C score ≥38) were all higher than that of survivors without long COVID at 3 years.

After multivariable adjustment, survivors of COVID-19 critical illness (severity scale score 5–6) during hospital stay were more likely to have dyspnoea at 3 years than were survivors with a severity scale score of 3 (odds ratio [OR] 1·75 [95% CI 1·05 to 2·90], p=0·031; reinfected *vs* non-reinfected 1·36 [1·04 to 1·77]; p=0·023; appendix p 36). Compared with non-reinfected survivors, reinfected survivors had a lower EQ-VAS score (β –4·51 [–6·08 to –2·95]; p<0·0001) and increased odds of anxiety or depressive symptoms (OR 1·65 [1·24 to 2·20]; p=0·0007), but re-infection had no effect on reduced daily activity (OR 0·72 [0·38 to 1·37; p=0·32; appendix p 36). For every 10 years increase in age, the odds of dyspnoea increased (OR 1·18 [1·06 to 1·30]; p=0·0017), as did the odds of reduced daily activity (OR 1·73 [1·29 to 2·31]; p=0·0002; appendix p 36). The odds of dyspnoea and anxiety or depression symptoms were higher, whereas the EQ-VAS score was lower, in female survivors compared with male survivors (appendix p 36). The disease severity scale score at primary infection no longer affected EQ-VAS score, daily activity, and anxiety or depression symptoms at 3 years (appendix p 36). Administrating three or more doses of COVID-19 vaccines was positively associated with EQ-VAS score (β 2·85 [0·72 to 4·98]; p=0·0089) and negatively associated with reduced daily activity at 3 years (OR 0·40 [0·18 to 0·89]; p=0·024; appendix p 36).

We used logistic regression models to explore the risk factors of sequelae symptoms and lung function at 3 years. Compared with male participants, female participants had increased odds for at least one sequelae symptom of long COVID (OR 2·05 [95% CI 1·58–2·65]; p<0·0001) and diffusion impairment (6·99 [3·41–14·37]; p<0·0001; appendix p 36). Age was positively associated with diffusion impairment, with higher odds for every 10 years increase in age (1·33 [1·01–1·75]; p=0·040). The disease severity of primary infection was not significantly associated with sequelae symptoms and diffusion impairment (appendix p 36).

Discussion

In this longitudinal cohort study, around half of COVID-19 survivors had at least one sequelae symptom at the 3-year follow-up, with the most prevalent being fatigue or muscle weakness, and hair loss. Compared with survivors without long COVID, survivors with long COVID had a higher proportion of re-infection and were prone to pneumonia after re-infection. Newly occurring or worse symptoms 3 months after omicron infection were more prevalent in survivors with long COVID than in those without long COVID and community controls, whereas omicron infection did not affect daily activity of COVID-19 survivors. Lung function of survivors recovered to levels similar to those of community controls.

Before this study, there were no data on the prevalence of long COVID at 3 years after primary infection. The proportion of survivors with long COVID varies in different studies, ranging from 20% to 55% of hospitalised COVID-19 survivors having long COVID at 2 years after acute infection.[13,21,22] Previous studies showed that long COVID symptoms gradually ease over time,[23,24] and fluctuations in long COVID symptoms have also been reported.[25,26] The diagnosis criteria of long COVID have not been standardised and relying only on symptoms without objective examination might not facilitate clinicians in making accurate diagnoses in clinical practice.[27] In our study, we found a marked increase in the proportion of participants with dyspnoea between 2-year and 3-year follow-up visits among COVID-19 survivors, but a similar lung function to that of matched community controls at 3 years. This inconsistency indicates the importance of more comprehensively assessing the health status of survivors of COVID-19, not only on subjective reports of symptoms.

Compared with the non-long COVID group, survivors with long COVID had a higher proportion of re-infection and more prevalent symptoms or pneumonia. Impairment of the immune response was indicated as a possible pathogenic mechanism for long COVID by previous published studies.[28–31] This immune dysfunction, which could persist for 8 months, was prevalent in survivors with long COVID,[32] including but not limited to increased exhaustion of CD4+ and CD8+ T cells and increased numbers of monocytes,[33,34] decreased naive T cells and B cells,[32] and reduced tendency to produce autoantibodies against chemokines.[35,36] Durable and functional immune responses are crucial for preventing re-infection.[37] The impaired immune function of survivors with long COVID might explain the increased proportion of re-infection; continuous immune evaluation might uncover the underlying mechanisms of susceptibility to reinfection. Our findings indicate that vaccination with three or more doses might be beneficial to improve HRQoL and daily activity after re-infection in patients with long COVID.

CT abnormalities discovered in several studies are unable to ascertain whether they indicate interstitial lung diseases or interstitial lung abnormalities following SARS-CoV-2 infection, or simply residual lung abnormalities after acute lung injury. In the interim analysis of the UKILD study,[38] an estimated 11·7% of hospitalised survivors of COVID-19 survivors who were discharged before March, 2021, had residual lung abnormalities within 240 days after infection. However, no data have been published on 3 year follow-up. In our cohort, although residual lung abnormality characteristics still existed—ie, irregular lines, traction bronchiectasis, and subpleural lines—the percentage of total lung lesions was lower (0·2–0·3%) than the threshold for the definition of interstitial lung abnormalities (≥5%),[39] indicating that a diagnosis of interstitial lung abnormalities cannot be made. Further, the residual abnormality on chest CT was too small to have an apparent effect on lung function. Previous studies also showed that the lung function of survivors with acute respiratory distress syndrome returned to a healthy range within 3 years after discharge.[40,41] However, because of the limited amount of imaging data in this study, this finding needs to be interpreted with caution and should be verified in other studies with larger sample sizes.

This study has several limitations. First, the information about omicron infection was self-reported by participants, and is not as accurate as a positive COVID-19 test. But, the interview was conducted shortly after the omicron wave, and trained researchers made judgments on the basis of an established unified definition of omicron infection when collecting this information. We defined omicron infection as either having positive SARS-CoV-2 antigen or RT-PCR tests, or in those without SARS-CoV-2 test results showing symptoms of COVID-19 and having known close contact with individuals positive for SARS-CoV-2. Second, this study only included survivors infected with wild-type SARS-CoV-2 who were hospitalised at a single centre. We included few participants with critically severe disease, who are at increased risk for long COVID.[42] Therefore, extrapolation of our findings might be limited to survivors without severe disease. Third, the trained investigators were not masked to the group of participants, although these investigators were not involved in the study design, statistical analysis, and interpretation of results. Therefore, the effect of interview bias is small. Finally, the cohort of COVID-19 survivors had high drop-out rates. However, the selection bias was low because most baseline characteristics were similar between participants who were included and not included in the final analysis. Additionally, our findings indicate an association but cannot prove causation because of the design of the cohort study, and the sample size of the control group in this study was small and the findings need to be further verified in future studies on long COVID.

In conclusion, most survivors of COVID-19 had mild to moderate long COVID symptoms at 3 years and lung function was similar to that of matched controls. The residual abnormalities on chest CT were too small to have an apparent effect on lung function. COVID-19 survivors with long COVID had higher proportions of omicron re-infection, pneumonia, and newly occurring or worse symptoms 3 months after omicron infection than those without long COVID. Omicron re-infection was associated with slightly increased symptom occurrence (dyspnoea, anxiety or depression symptoms, and HRQoL) in COVID-19 survivors but did not have an effect on reduced daily activity.

Contributors

BC, DZ, HZ, XG, and YeW conceived and designed the study. HZ, XG, YeW, JX, and BC drafted the paper. HZ and XG did the analysis. HZ, CH, XL, QW, YiW, JX, and HD collected and verified the data. BC, DZ, HZ, and XG accessed and verified the data in the study. ML assessed the lung imaging that acquires at 2-year and 3-year follow-up visits. All authors critically revised the manuscript for important intellectual content and agreed to submit the final version for publication. All authors agree to be 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. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

These data are not publicly available. Data can be made available upon reasonable request to the corresponding author and with the permission of the China-Japan Friendship Hospital and Wuhan Jinyintan Hospital.

Acknowledgments

This work was funded by the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (CIFMS 2021-I2M-1-048), the National Natural Science Foundation of China (82241056/82200114/82200009). This work was also supported by Changping Laboratory, the New Cornerstone Science Foundation, and Peking Union Medical College Education Foundation. We acknowledge all the individuals who participated in this study. We also thank all investigators who contributed to the longitudinal cohort of COVID-19 survivors.

References

1 US Centers for Disease Control and Prevention. Post-COVID Conditions. May 5, 2022. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html (accessed May 16, 2022).
2 Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis* 2022; **22:** e102–07.
3 Venkatesan P. NICE guideline on long COVID. *Lancet Respir Med* 2021; **9:** 129.
4 WHO. Statement—36 million people across the European region may have developed long COVID over the first 3 years of the pandemic. World Health Organization. https://www.who.int/europe/news/item/27-06-2023-statement---36-million-people-across-the-european-region-may-have-developed-long-covid-over-the-first-3-years-of-the-pandemic (accessed June 30, 2023).
5 Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol* 2023; **21:** 1–14.
6 US Centers for Disease Control and Prevention. Nearly one in five American adults who have had COVID-19 still have. 'long COVID'. June 22, 2022. https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/20220622.htm (accessed July 24, 2022).
7 Robertson MM, Qasmieh SA, Kulkarni SG, et al. The epidemiology of long COVID in US adults two years after the start of the US SARS-CoV-2 pandemic. medRxiv 2022; published online Sept 14. https://doi.org/10.1101/2022.09.12.22279862 (preprint).
8 Perlis RH, Lunz Trujillo K, Safarpour A, et al. Association of post-COVID-19 condition symptoms and employment status. *JAMA Netw Open* 2023; **6:** e2256152.
9 Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. *Lancet Diabetes Endocrinol* 2022; **10:** 311–21.
10 Bowe B, Xie Y, Xu E, Al-Aly Z. Kidney outcomes in long COVID. *J Am Soc Nephrol* 2021; **32:** 2851–62.
11 Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022; **28:** 583–90.
12 Xu E, Xie Y, Al-Aly Z. Long-term neurologic outcomes of COVID-19. *Nat Med* 2022; **28:** 2406–15.
13 Huang L, Li X, Gu X, et al. Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. *Lancet Respir Med* 2022; **10:** 863–76.
14 Carabelli AM, Peacock TP, Thorne LG, et al. SARS-CoV-2 variant biology: immune escape, transmission and fitness. *Nat Rev Microbiol* 2023; **21:** 162–77.
15 Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. *Nat Med* 2022; **28:** 2398–405.
16 Chinese Center for Disease Control and Prevention. National situation of novel coronavirus infection https://www.chinacdc.cn/jkzt/crb/zl/szkb_11803/jszl_13141/202301/t20230125_263519.html (accessed Jan 30, 2023).
17 Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2023; **401:** e21–33.
18 Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet* 2021; **398:** 747–58.
19 Ballering AV, van Zon SKR, Olde Hartman TC, Rosmalen JGM. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *Lancet* 2022; **400:** 452–61.
20 Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. *Ann Rheum Dis* 1978; **37:** 378-81
21 Li D, Liao X, Liu Z, et al. Healthy outcomes of patients with COVID-19 two years after the infection: a prospective cohort study. *Emerg Microbes Infect* 2022; **11:** 2680–88.
22 Yang X, Hou C, Shen Y, et al. Two-year health outcomes in hospitalized COVID-19 survivors in China. *JAMA Netw Open* 2022; **5:** e2231790.
23 Iwashyna TJ, Seelye S, Berkowitz TS, et al. Late mortality after COVID-19 infection among US veterans *vs* risk-matched comparators: a 2-year cohort analysis. *JAMA Intern Med* 2023; published online Aug 21. https://doi.org/10.1001/jamainternmed.2023.3587.
24 Bowe B, Xie Y, Al-Aly Z. Postacute sequelae of COVID-19 at 2 years. *Nat Med* 2023; **29:** 2347–57.
25 Ballering AV, van Zon SKR, Olde Hartman TC, Rosmalen JGM. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *Lancet* 2022; **400:** 452–61.
26 Ballouz T, Menges D, Anagnostopoulos A, et al. Recovery and symptom trajectories up to two years after SARS-CoV-2 infection: population based, longitudinal cohort study. *BMJ* 2023; **381:** e074425.
27 Munblit D, O'Hara ME, Akrami A, Perego E, Olliaro P, Needham DM. Long COVID: aiming for a consensus. *Lancet Respir Med* 2022; **10:** 632–34.
28 Moss P. The T cell immune response against SARS-CoV-2. *Nat Immunol* 2022; **23:** 186–93.
29 Altmann DM, Whettlock EM, Liu S, Arachchillage DJ, Boyton RJ. The immunology of long COVID. *Nat Rev Immunol* 2023; **23:** 1–17.
30 Merad M, Blish CA, Sallusto F, Iwasaki A. The immunology and immunopathology of COVID-19. *Science* 2022; **375:** 1122–27.
31 Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol* 2020; **20:** 355–62.
32 Phetsouphanh C, Darley DR, Wilson DB, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nat Immunol* **23:** 210–16.
33 Park J, Dean LS, Jiyarom B, et al. Elevated circulating monocytes and monocyte activation in COVID-19 convalescent individuals. *Front Immunol* 2023; **14:** 1151780.
34 Klein J, Wood J, Jaycox J, et al. Distinguishing features of long COVID identified through immune profiling. medRxiv 2022; published online Aug 10. https://doi.org/10.1101/2022.08.09.22278592 (preprint).
35 Muri J, Cecchinato V, Cavalli A, et al. Autoantibodies against chemokines post-SARS-CoV-2 infection correlate with disease course. *Nat Immunol* 2023; **24:** 604–11.
36 Bastard P, Rosen LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science 2020; **370:** 6615.
37 Antoun E, Peng Y, Dong T. Vaccine-induced CD8+ T cells are key to protection from SARS-CoV-2. *Nat Immunol* 2023; **24:** 1594–96.

38 Stewart I, Jacob J, George PM, et al. Residual lung abnormalities after COVID-19 hospitalization: interim analysis of the UKILD Post-COVID-19 study. *Am J Respir Crit Care Med* 2023; **207:** 693–703.

39 Hatabu H, Hunninghake GM, Richeldi L, et al. Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society. *Lancet Respir Med* 2020; **8:** 726–37.

40 Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011; **364:** 1293–304.

41 Herridge MS. Recovery and long-term outcome in acute respiratory distress syndrome. *Crit Care Clin* 2011; **27:** 685–704.

42 Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* 2021; **594:** 259–64.