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Prognosis and antibody profiles in survivors of critical illness from COVID-19: a prospective multicentre cohort study

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Abstract

Background: There is a need to assess the long-term outcomes of survivors of critical illness from COVID-19.
Methods: Ninety-two survivors of critical illness from COVID-19 from four hospitals in Hubei Province, China participated in this prospective cohort study. Multiple characteristics, including lung function (lung volumes, diffusing capacity for carbon monoxide, chest computed tomography scores, and walking capacity); immune status (SARS-CoV-2-neutralising antibody and all subtypes of immunoglobulin (Ig) G against SARS-CoV-2, immune cells in response to *ex vivo* antigen peptide stimuli, and lymphocyte count and its subtypes); liver, coagulation, and kidney functions; quality of life; cognitive function; and mental status, were assessed after 3, 6, and 12 months of follow-up.
Results: Amongst the 92 enrolled survivors, 72 (78%) patients required mechanical ventilation. At 12 months, the predicted percentage diffusing capacity of lung for carbon monoxide was 82% (inter-quartile range [IQR]: 76–97%) with a residual volume of 77 (64–88)%. Other lung function parameters and the 6-min walk test improved gradually over time and were almost back to normal by 12 months. The titres of IgG and neutralising antibody to COVID-19 remained high at 12 months compared with those of controls who were not infected with COVID-19, although IgG titres decreased significantly from 34.0 (IQR: 23.8–74.3) to 15.0 (5.8–24.3) AU ml^{-1} ($P<0.001$), whereas neutralising antibodies decreased from 29.99 (IQR: 19.43–53.93) AU ml^{-1} at 6 months to 19.75 (13.1–29.8) AU ml^{-1} ($P<0.001$) at 12 months. In general, liver, kidney, physical, and mental functions also improved over time.

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Conclusions: Survivors of critical illness from COVID-19 show some persistent long-term impairments in lung function. However, a majority of these tests were normal by 12 months. These patients still had detectable levels of neutralising antibodies against SARS-CoV-2 and all types of IgG at 12 months, but the levels had declined over this time period.
Clinical trial registration: None.

Keywords: antibody; COVID-19; critical illness; immunity; lung function

Editor's key points

- Lung function improved gradually over 1 yr amongst survivors of critical illness from COVID-19, and some parameters returned to near-normal levels.
- Acquired immunity against COVID-19 was still maintained with high titres of immunoglobulin G and neutralising antibodies 12 months later.

The long-term prognosis of survivors of critical illness from COVID-19 remains unknown.[1,2] Previous reports have shown there are persistent impairments in lung function, physical capacity, and psychological sequelae after severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome pneumonia; these can last from months to years.[3–7] Recent studies have reported that patients with mild COVID-19 infection often have complications, such as fatigue, dyspnoea, depression, and reduced lung function.[8–14] In addition, the titres of antibodies against SARS-CoV-2 in critically ill patients with COVID-19 remain unknown. A 6-month follow-up study of survivors of COVID-19 showed decreasing seropositivity of neutralising antibodies and immunoglobulin (Ig) G titres over time.[8] Another study reported an 11.7% decrease in antibody levels in more than half of the asymptomatic patients after 2 months of recovery.[15] In survivors, the memory B-cell response lasted no longer than 6 months, and the memory T-cell responses declined over time after SARS-CoV-2 infection.[8] Concerns about diminished immunity and reinfection of SARS-CoV-2 are emerging, as the level and timing of the immunity against reinfection remain unknown.[16] Survivors of critical illness are a cohort of patients with the most severe form of organ injuries; therefore, it is important to study their long-term outcomes in terms of physiological, haematological, biochemical, and humoral functions.

In this study, we aimed to evaluate the dynamic changes in (i) lung function (measured with lung volumes, diffusion capacity, chest CT scores, and walking capacity); (ii) immune status (measured with titres of neutralising antibody and all subtypes of IgG against SARS-CoV-2; immune response after *ex vivo* antigen peptide stimulus; and counts of lymphocytes, including subtype); (iii) organ (liver and kidney) functions and coagulation; and (iv) quality of life, cognitive function, and mental status in survivors of critical illness from COVID-19 at 3, 6, and 12 months after ICU discharge.

Methods

Study design

This prospective, observational, multicentre longitudinal follow-up study was conducted at Zhongnan Hospital of Wuhan University after ethical approval by the Ethics Committee of Wuhan University (references 2020089 and 2020099k). All enrolled patients gave their written consent to participate in the study.

Setting

The study enrolled critically ill patients with COVID-19 between January 7, 2020 and March 15, 2020 from Zhongnan Hospital, People's Hospital of Wuhan University, Leishenshan Hospital, and Xishui People's Hospital, Hubei, China. Survivors were followed at 3, 6, and 12 months after ICU discharge. At each visit, the patients were interviewed; underwent blood tests, lung function tests, high-resolution chest tomography, and 6 min walk test; and completed the Mini-Mental State Examination, the Hamilton Anxiety Scale, Zung's Self-Depression Scale, and Medical Study 36-Item Short-Form General Health Survey (SF-36).

Participants

All critically ill adult patients receiving invasive or noninvasive mechanical ventilation, high-flow nasal oxygen therapy, or vasopressors were included.[17] The exclusion criteria were (i) died before the first follow-up; (ii) had dementia, psychotic disorders, or other neurological dysfunctions leading to inability to communicate before the admission or after discharge; (iii) unable to mobilise freely because of severely impaired cardiopulmonary function (New York Heart Association functional class IV), disabilities (unable to walk), or sequalae at admission and after discharge; and (iv) prolonged hospitalisation or chronic lung disease before SARS-CoV-2 infection.

Primary and secondary outcomes

The primary outcome was the dynamic change in lung function. The secondary outcomes were walking capacity as assessed using the 6-min walk test, neutralising antibody, all subtypes of IgG against SARS-CoV-2, immune function, liver and kidney functions, coagulation function, quality of life, cognitive function, and mental status.

Data collection

We used electronic medical records to extract data, including patient characteristics, underlying comorbidities, laboratory measurements, treatment measures, and outcomes. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score within the first 24 h after admission, daily Sequential Organ Failure Assessment (SOFA) score, duration of mechanical ventilation, ICU stay, and hospital stay were also recorded.

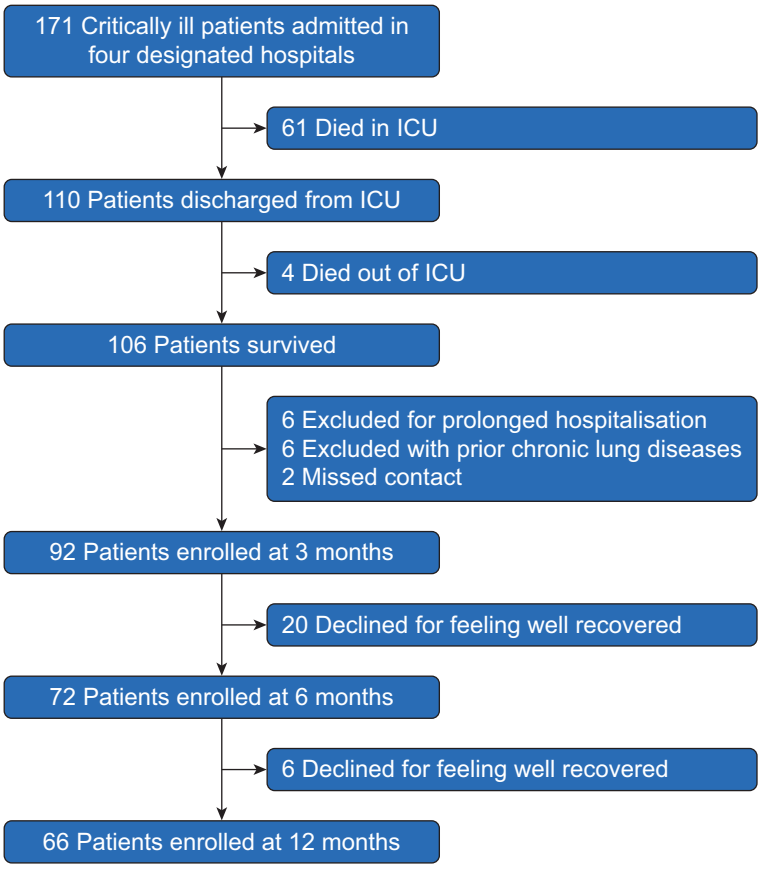


Fig 1. Enrolment of critically ill patients with COVID-19 and follow-up during 12 months after discharge from the ICU.

Lung function test and chest computed tomography

Lung function tests were performed according to guidelines published by the European Respiratory Society and the American Thoracic Society with a Vmax229 Pulmonary Function Instrument (SensorMedics, Yorba Linda, CA, USA). Lung volumes (total lung capacity [TLC], vital capacity [VC], residual volume [RV]), spirometry (forced vital capacity [FVC] and forced expiratory volume in 1 s [FEV1]), FEV1/FVC ratio, and surface area for gas exchange (diffusing capacity of lungs for carbon monoxide [DLCO]) were measured. TLC was determined using a body plethysmograph (6200 Autobox; SensorMedics). DLCO was determined by the single-breath method using an infrared analyser (Vmax229; SensorMedics). The value of DLCO was adjusted to the haemoglobin concentration.[18] Lung function data are presented as the percentage of the predicted value. High-resolution CT scans of the chest were evaluated by two chest radiologists using established methods.[19]

The 6 min walk test was performed by respiratory therapists in the pulmonary rehabilitation centre according to published guidelines.[20] Repeats were performed at the same time of the day to minimise intraday variability. The distances walked by the patients during the 6-min walk test are presented as a percentage of the predicted value.[21]

T cell, B cell, and natural killer cell lymphocyte counting and T-cell subset analysis

The numbers of CD4+ and CD8+ T cells, B cells, and natural killer (NK) cells were determined using Trucount™ tubes and BD Multitest 6-color TBNK reagent kit (BD Biosciences, San Jose, California, USA) according to the manufacturer's instructions. T-cell subset assay was performed as previously reported.[22] Different T-cell subsets were defined as follows: co-stimulatory molecule (CD28+CD4+ or CD28+CD8+ T cells), activated T cells (HLA-DR+CD3+ or HLA-DR+CD8+T cells), naive/memory CD4+ T cells (CD45RA+/CD45RO+CD4+ T cells), and regulatory T cells (CD25hiCD127lowCD4+T cells).

Cytokine release from *ex vivo* recombinant antigen peptide stimulus

To assess viral-specific cellular immunity, whole blood was stimulated with recombinant antigen peptides (nucleocapsid protein [NP], S1, S2, and receptor-binding domain [RBD]), and phytohaemagglutinin served as the control and followed by cytokine measurements. Six cytokines, including tumour necrosis factor-alpha, interferon-gamma, interleukin (IL)-6, IL-2, IL-4, and IL-10 were determined (Autobio Diagnostics Co., Zhengzhou, China). Briefly, 25 μl serum was mixed with equal

Table 1 Patient and clinical characteristics of 171 critically ill patients with COVID-19. *n*, Number of patients enrolled in testing; *N*, total number of patients. Chronic lung diseases were defined as asthma and chronic obstructive pulmonary disease. Cardiovascular diseases were defined as coronary heart disease, chronic heart failure, valvular heart disease, and arrhythmia. Immunocompromised conditions were defined as human immunodeficiency virus infection, malignancy, liver cirrhosis, or chronic renal failure, or if immunosuppressive therapy was being administered. $P<0.05$ was considered significant. Data were reported as no./total (%) or median (IQR). APACHE II, Acute Physiology and Chronic Health Evaluation II; CRRT, continuous renal replacement therapy; HFNO, high-flow nasal oxygen; IQR, inter-quartile range; SOFA, Sequential Organ Failure Assessment.

	All patients (*n*=171)	Survivors (*n*=106)	Non-survivors (*n*=65)	*P*-value
Age (yr), median (IQR)	63.00 [55.00–71.25]	60.00 [52.00–67.00]	70.00 [62.00–79.00]	<0.001
Male sex, *n*/*N* (%)	107/170 (62.9)	60/106 (56.6)	47/64 (73.4)	0.028
BMI (kg m^{-2}), median (IQR)	23.76 [21.97–26.73]	23.88 [22.20–27.54]	23.44 [21.17–25.46]	0.083
Comorbidities				
Hypertension, *n*/*N* (%)	66/171 (38.6)	38/106 (35.8)	28/65 (43.1)	0.346
Diabetes mellitus, *n*/*N* (%)	46/171 26.9)	26/106 (24.5)	20/65 (30.8)	0.372
Chronic lung disease, *n*/*N* (%)	21/171 (12.3)	10/106 (9.4)	11/65 (16.9)	0.148
Cardiovascular disease, *n*/*N* (%)	29/171 (17.0)	13/106 (12.3)	16/65 (24.6)	0.037
Immunocompromised conditions, *n*/*N* (%)	15/171 (8.8)	2/106 (1.9)	13/65 (20.0)	<0.001
Pa_{O_2}/FiO_2 (mm Hg), median (IQR)	113 [81–173]	133 [91–191]	94 [70–132]	0.001
Maximal lung injury score, median (IQR)	3.00 [2.00–3.50]	2.70 [2.00–3.50]	3.15 [2.00–3.70]	0.253
APACHE II score, median (IQR)	15.00 [10.50–19.00]	13.00 [9.25–16.00]	17.00 [14.50–22.50]	<0.001
SOFA score, median (IQR)				
Day 1	4.00 [3.00–6.00]	4.00 [3.00–5.00]	5.00 [4.00–7.00]	<0.001
Day 3	4.00 [3.00–6.00]	4.00 [3.00–5.00]	5.50 [4.25–8.00]	<0.001
Day 7	4.00 [3.00–7.00]	4.00 [3.00–4.00]	7.00 [5.25–10.00]	<0.001
Day 14	4.00 [2.00–6.00]	3.00 [1.25–4.75]	8.00 [5.00–10.00]	<0.001
Requirement of HFNO, *n*/*N* (%)	29/171 (17.0)	24/106 (22.6)	5/65 (7.7)	0.011
Requirement of ventilation, *n*/*N* (%)	142/171 (83.0)	82/106 (77.4)	60/65 (92.3)	0.011
Requirement of vasopressor, *n*/*N* (%)	87/170 (51.2)	30/106 (28.3)	57/64 (89.1)	<0.001
Requirement of CRRT, *n*/*N* (%)	31/170 (18.2)	6/106 (5.7)	25/64 (39.1)	<0.001
Tracheostomy, *n*/*N* (%)	24/170 (14.1)	12/106 (11.3)	12/64 (18.8)	0.178
Duration of ventilation (days), median (IQR)	10.00 [7.00–23.00]	9.50 [7.00–24.00]	12.00 [7.00–23.00]	0.561
Duration of ICU stay (days), median (IQR)	14.00 [8.00–21.75]	15.00 [9.00–22.00]	12.00 [7.00–21.75]	0.086
Duration of hospital stay (days), median (IQR)	25.00 [14.00–37.50]	28.00 [19.50–42.25]	16.00 [9.00–32.00]	<0.001

volumes of capture beads and incubated in the dark with 25 μl of phycoerythrin-conjugated antibodies for 2.5 h at room temperature. The beads were then centrifuged at 200 × *g* for 5 min; the supernatant was gently aspirated and resuspended in phosphate-buffered saline (100 μl) and analysed using a flow cytometer (BD Biosciences, San Jose, California, USA).

Measurements of SARS-CoV-2 antibody titres

SARS-CoV-2 antibody titres were measured at 6 and 12 months. The paramagnetic particle chemiluminescent immunoassay was used for the qualitative determination of 2019-nCoV neutralising antibody, IgG, IgM, and IgA in human serum and plasma using the automated iFlash Immunoassay Analyzer (Shenzhen Yhlo Biotech Co., Shenzhen, China). The IgM, IgA, and IgG antibodies included the different subtypes of antibodies against the nucleoprotein (N), spike protein (S), and RBD. The neutralising antibody assay used is a one-step competitive immunoassay using a direct chemiluminescence immunoassay, whereas the measurement for other antibodies used an indirect two-step immunoassay.

Health-related quality of life

The SF-36 was used to measure health-related quality of life, which includes eight multiple-item subscales and evaluates physical function, social functioning, and role limitations. Scores for each aspect range from 0 (worst) to 100 (best) with higher scores indicating better health-related quality of life. The Mini-Mental State Examination was used to assess cognition.[23] Zung's Self-Rating Anxiety Scale and Hamilton Rating Scale for Depression were used to assess anxiety and depressive symptoms.[24]

Statistical analysis

A prospective statistical analysis protocol was implemented in our study with all researchers who participated in the data collection and analyses were blinded to the patients' outcomes. Blood samples were analysed in duplicate. Data are presented as mean and standard deviation if normally distributed, or as median with inter-quartile range (IQR) if not. Categorical variables are presented as frequency and percentage. Comparisons between two continuous variables with a normal distribution were undertaken using a two-tailed Student's *t*-test; otherwise, Mann–Whitney, χ^2, or Fisher's exact test was used wherever appropriate. For repeated measures with a normal distribution, a two-way analysis of variance was used followed by Newman–Keuls test; otherwise, Kruskal–Wallis test was used. Multiple testing of *P*-values was corrected for with Bonferroni corrections, with a $P<0.05$ considered statistically significant. Statistical analysis was performed using statistical software (SPSS Inc., Chicago, IL, USA), and figures were constructed using Origin (version 9.6; OriginLab, Northampton, MA, USA) and GraphPad Prism (version 8.0; San Diego, CA, USA).

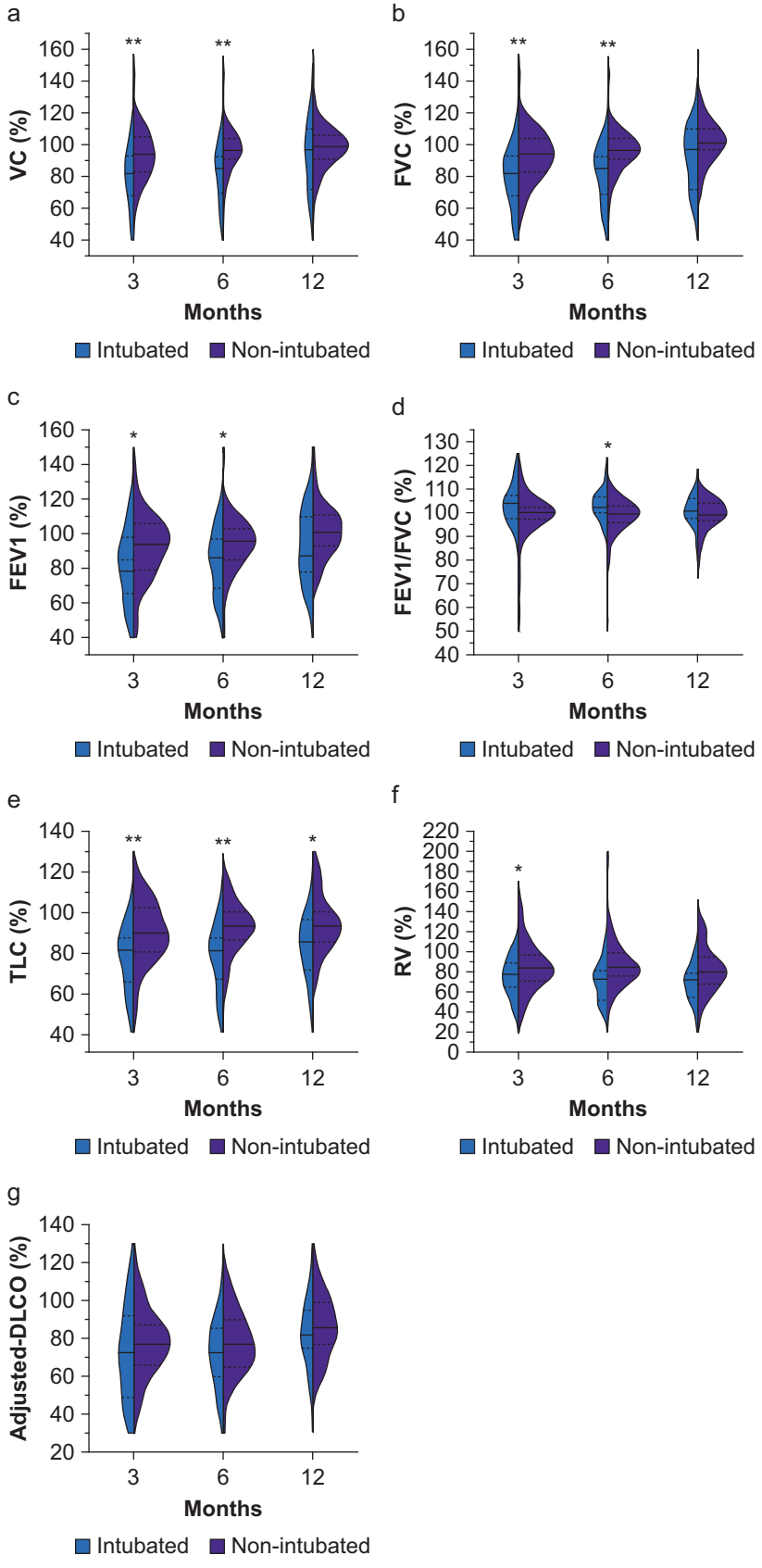


Fig 2. Comparisons of lung function tests over time between intubated and non-intubated survivors. Predicting values (%) of lung function based on age and gender are expressed as median with IQR; *P<0.05; **P<0.01, comparison between intubated and non-intubated survivors. adjusted-DLCO, diffusion capacity for carbon dioxide was adjusted for age, sex, and haemoglobin; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; VC, vital capacity.

Results

General characteristics

From January 7, 2020 to March 15, 2020, 171 critically ill patients were admitted to ICUs in the four hospitals (Fig. 1). Patient and clinical characteristics of the 171 patients are shown in Table 1. Amongst them, 110 patients were discharged from the ICUs and 106 patients survived up to the time of follow-up. Amongst the 106 survivors, six declined follow-ups because of the prolonged hospitalisation for rehabilitation, another six were excluded because of previous chronic lung diseases, and two patients were lost contacts. During follow-up, 20 patients declined further assessment at 6 months, as they felt good and were working, whereas another six patients declined follow-up at 12 months because they were working or living outside Hubei Province. Therefore, 92 survivors were included at 3 months, 72 survivors at 6 months, and 66 survivors at 12 months (Fig. 1).

The median age of the 92 enrolled survivors was 59 (range: 28–86) yr, and 63% of them were male. The median APACHE II score was 14 (IQR: 10–16). All were diagnosed with acute respiratory distress syndrome (ARDS) based on the Berlin criterion with median 135 (IQR: 95–192) mm Hg of Pa_{O_2}/FiO_2 at> ICU admission. In addition, 78.3% (72/92) received mechanical ventilation, whereas 21.7% (20/92) received high-flow nasal oxygen therapy. The survivors spent a median of 14 days in ICU and 29 days in hospital. No patients received additional vaccination against COVID-19 during the follow-up period.

Chest tomography, lung function test, and 6-min walk test

Overall, the greatest changes in lung function tests were observed in VC, FVC, FEV1, and DLCO. At 12 months, the median DLCO was still 82 (IQR: 76–97)% of predicted value, although this value had improved compared with those of 76 (65–88)% and 75 (64–88)% at 3 and 6 months, respectively (P=0.015). The RV at 12 months was 77 (IQR: 64–88)% of predicted compared with 80 (IQR: 67–95)% and 81 (IQR: 70–91)% at 3 and 6 months, respectively. The median predicted values of FVC were 91 (78–101)%, 94 (84–103)%, and 101 (89–111)% at 3, 6, and 12 months, respectively (P=0.001). There were no significant differences in FEV1/FEV, TLC, and chest CT scores over time (Supplementary Figs S1 and S2).

The median distances during the 6-min walk test were 486 (IQR: 428–548), 526 (463–584), and 533 (464–575) m at 3, 6, and 12 months, respectively (P=0.017). The median percentages of predicted values of the 6-min walk test were 89 (81–99)%, 97 (88–105)%, and 99 (91–106)% at 3, 6, and 12 months, respectively (P<0.001) (Supplementary Figs S1 and S2).

Lung function tests were also compared between intubated and non-intubated survivors (Fig. 2). Almost all the parameters at 3 months in the intubated survivors were worse than those in the non-intubated survivors (P<0.01). However, these differences were largely not evident at later time points. At 12 months, TLC and RV were still significantly lower in the intubated survivors than those of the non-intubated survivors.

Immune function assessments

All these survivors were SARS-CoV-2 nucleic acid amplification test negative. The neutralising antibody was detected (positive threshold >10 AU ml^{-1}) in 83.3% of the survivors at 12 months, although the titres had significantly decreased from 30.0 (IQR: 19.4–53.9) AU ml^{-1} at 6 months to 19.8 (13.1–29.8) AU ml^{-1} at 12 months (P<0.001) (Fig. 3). All the IgG antibodies were maintained at high titres at 12 months, although they were decreased significantly compared with the values at 6 months, with S-IgG 99.6 (IQR: 46.8–172.1) *vs* 213.1 (146.7–394.4) AU ml^{-1} (P<0.001) and RBD-IgG 66.4 (IQR: 27.4–123.7) *vs* 136.8 (90.4–238.0) AU ml^{-1} (P<0.001). The N-IgA and N-IgM were classed as negative (<10 AU ml^{-1}) from 6 months (Fig. 3). Recombinant antigen peptide (NP, S1, S2, and RBD) *ex vivo* stimulation test revealed higher levels of cytokine secretion in blood harvested at 12 months (P<0.05) relative to healthy non-infected controls (Table 2). In addition, there was no significant difference in cytokine release between survivors who were seropositive for the neutralising antibody *vs* survivors who were seronegative for the neutralising antibody. The absolute numbers of B cells, CD4+, and CD8+ cells in these survivors were within normal limits, and there was no change within 1 yr follow-up (Supplementary Table S1). T-lymphocyte function assay showed that the percentages of activated T cells (HLA-DR+CD3+/CD3+ T cells and HLA-DR+CD8+/CD8+ T cells) and naive/memory CD4+ T cells (CD45RA+CD4+ T cells and CD45RO+ CD4+ T cells) were far higher than the normal range, whereas the mean percentage of CD28+CD8+/CD8+T was relatively lower than the normal range (Supplementary Table S2).

Liver and kidney functions and blood coagulation

Liver functions were normal at 3 months. Serum cystatin C was used as a measure of kidney function instead of serum creatinine, which would underestimate kidney function because most patients lost weight during their admission. In addition, 20.5% (17/83) of the survivors presented with abnormally increased cystatin C at 3 months, but this improved over time with 17.5% at 6 months and 10.8% at 12 months. The overall cystatin C concentration decreased gradually from 1.07 (IQR: 0.91–1.18) mg L^{-1} at 3 months to 0.99 (0.84–1.11) and 0.98 (0.84–1.09) mg L^{-1} at 6 and 12 months, respectively (P=0.02). Prothrombin time, activated partial thromboplastin time, and D-dimer declined over time while still being within the normal range. Fasting glucose increased from 5.44 (IQR: 5.03–6.18) mM at 3 months to 5.50 (4.98–6.58) mM at 6 months to 5.92 (5.44–7.40) mM at 12 months (P=0.01), with abnormally increased glucose in 28.4%, 35.0%, and 43.1% of the survivors at 3, 6, and 12 months, respectively (Supplementary Table S3).

Patients reported feeling of shortness of breath after activities (54.4%) and palpitations (51.8%) at 3 months, but this was significantly reduced by 6 months (38.5% and 30.8%) and 12 months (31.3% and 30.9%). In addition, 12.8% patients had an element of cognitive impairment during the early phase of follow-up, but this had improved to 2.9% patients having it at 6 months, with full recovery by 12 months. Depression and anxiety occurred and peaked at 6 months with their presence in 32.8% and 17.6% of survivors, respectively, with this declining to 18.2% and 9.1% of patients at 12 months (Supplementary Table S4). At 3 months, less than 48.3% of survivors had returned to work with this increasing to 71% at 6 months and 74.2% at 12 months. There was also a general improvement in other assessments of physical and social functions, vitality, and general health from Month 3 to Month 12 (Table 3).

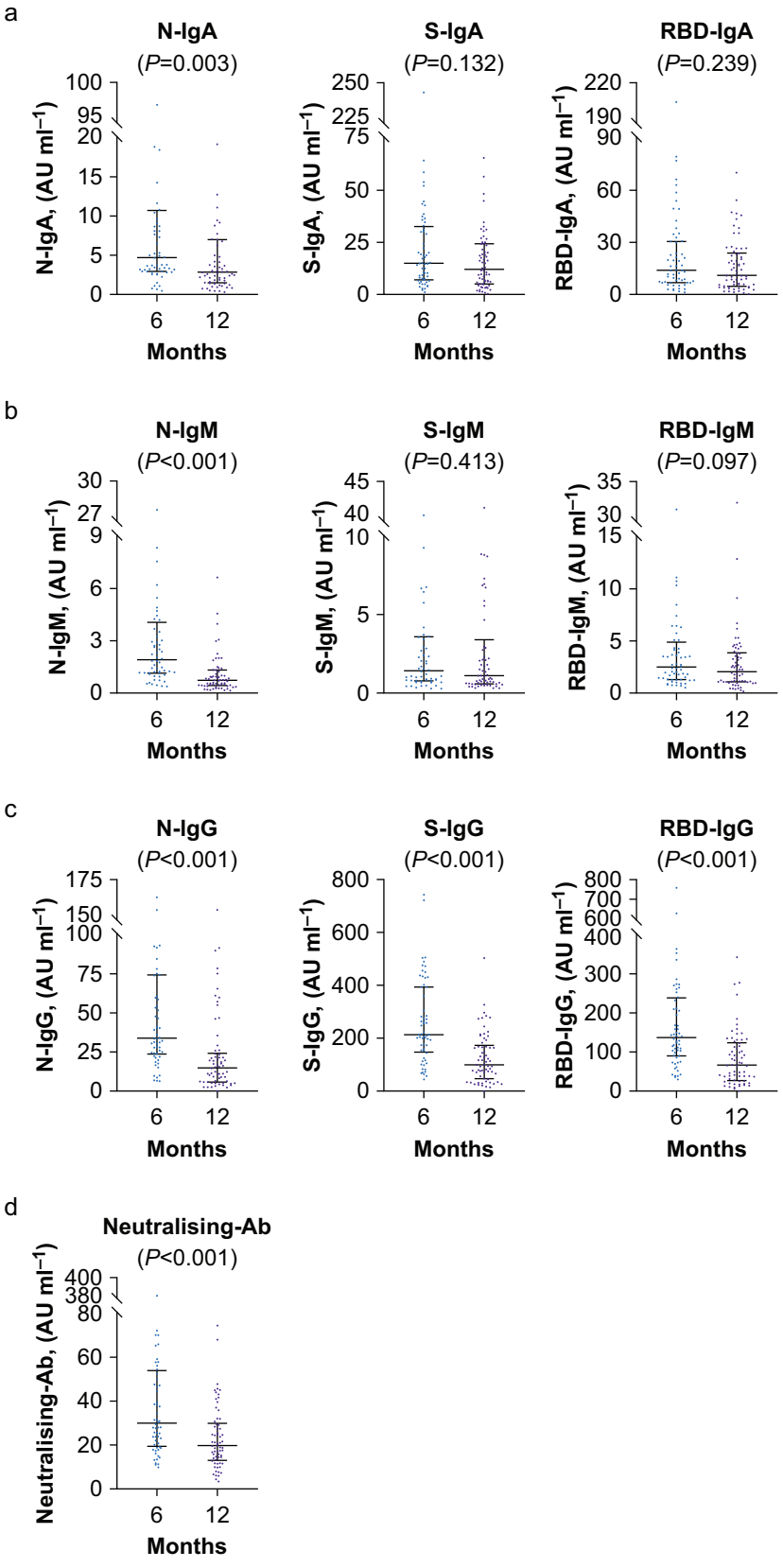


Fig 3. Changes of antibodies against SARS-CoV-2 in critically ill patients with COVID-19 during 12 months of follow-up. (a) Titres of N-IgA, S-IgA, and RBD-IgA; (b) titres of N-IgM, S-IgM, and RBD-IgM; (c) titres of N-IgG, S-IgG, and RBD-IgG; and (d) titres of neutralising antibody. Titres of each antibody indicated by the Y-axis. Data expressed as median with IQR. Ab, antibody; IQR, inter-quartile range; N, nucleoprotein; RBD, receptor-binding domain; S, spike protein.

Table 2 Cytokine release from whole blood with *ex vivo* recombinant antigen peptide stimulus at 12 months of follow-up. Negative control, negative stimulus; peptide group, stimulated by SARS-CoV-2 peptides (receptor-binding domain, S1, S2, and nucleocapsid). Data were reported as median (IQR). IFN-γ, interferon-gamma; IL, interleukin; IQR, inter-quartile range; TNF-α, tumour necrosis factor-alpha.

	Normal range (pg ml^{-1})	Negative control	Peptide stimulation group	*P*-value
IFN-γ, median (IQR)	0.1–18	0.82 [0.09–1.60]	45.67 [22.17–95.28]	<0.001
TNF-α, median (IQR)	0.1–23	3.17 [2.74–3.81]	266.23 [134.61–556.68]	<0.001
IL-2, median (IQR)	0.1–4.1	3.24 [2.64–3.83]	403.89 [202.65–801.31]	<0.001
IL-4, median (IQR)	0.1–3.2	2.45 [2.20–2.69]	2.78 [2.55–3.23]	<0.001
IL-6, median (IQR)	0.1–2.9	4.04 [2.96–9.87]	15 023.18 [9444.22–17 187.85]	<0.001
IL-10, median (IQR)	0.1–5	3.32 [2.83–4.42]	35.07 [16.82–67.24]	<0.001

Discussion

This was the first prospective study aimed at investigating the dynamic recovery of survivors of critical illness from COVID-19 during a 12-month follow-up period. It primarily focused on lung function, immune function, and other important markers (such as persistent changes in quality of life). We found lung function improved gradually and was almost back to the normal levels at 1 month post-ICU discharge except for DLCO and RV. There was also persistent immunity against SARS-CoV-2 as measured by high titres of antibodies to SARS-CoV-2 (although on a decreasing trend) and active virus-specific immune cell function. Other parameters, including liver, kidney, physical, and mental functions, also appeared to improve over time.

Previous SARS survivors had impaired DLCO ranging from 15.5% to 43.6%.[4,25–29] It has been reported that residual obstructions, restrictive defects, and impaired pulmonary gas exchange can last for up to 3 yr in survivors of severe ARDS.[30] A recent study demonstrated that lung function (except DLCO) after COVID-19 returned to normal within 1 yr, but all these results came from non-intubated patients.[31] In our study, two-thirds of the patients were mechanically ventilated for moderate-to-severe ARDS. Overall, significant impairments were present by Month 3, but these continued to improve over time. As expected, there was a trend that intubated survivors had worse lung function than non-intubated survivors. Overall, the most significant changes in lung function were gas diffusive capacity and RV with about 20–25% of impairments at 1 yr. Other measurements of lung function together with the 6 min walk test returned to near-normal levels by 12 months. Chest CT scores were not significantly improved over time, although the resolution of radiographic abnormalities began to be observed by the fourth week after admission.[26,32] This unchanged CT score might be explained either by an inherent limitation of the semi-quantitative CT score, but also possibly by fibrotic changes in the lung. The latter is supported by the lung function data. We propose that fibrosis and subsequently impaired diffusion capacity were the main changes of the lung function in the survivors of critical illness from COVID-19. Nevertheless, our patients recovered generally better than those patients previously reported.[8,10–12] This difference may be attributable to differing inclusion/exclusion criteria, where we excluded six patients because of prolonged hospital stay for neurological rehabilitation and another six patients with prior chronic lung diseases. Another reason may be that our patients were instructed to have respiratory exercises and rehabilitation at home immediately after discharge from hospital through social media (e.g. WeChat).

In the acute phase of COVID-19, peripheral lymphocyte subset alteration has been characterised by decreased numbers of CD4+ T cells, CD8+ T cells, B cells, and NK cells.[33] In our study, the absolute number of various T lymphocytes returned to the normal range at 12 months after ICU discharge. The increase in the activated T-cell population (HLA-DR+CD3+/CD3+ T cells, HLA-DR+CD8+/CD8+ T cells, and naive/memory CD4+ T cells [CD45RA+CD4+ T cells and CD45RO+ CD4+ T cells]) might indicate a restoration of cellular immunity. Interestingly, it was noted that all the subtypes of IgG and neutralising antibodies were maintained at high titres within 1 yr albeit with decreasing trend. These results were different from a previous report, in which these protective antibodies in most survivors disappeared by 6 months.[8] However, the survivors in that study were from all severity levels of the patients, including asymptomatic, mild, and severe cases. It is unknown whether the different severity of infection affected the subsequent immunity. To further evaluate the virus-specific immune cellular functions of these survivors, we used *ex vivo* blood stimulus test and found that the high levels of cytokines were released upon recombinant antigen peptide (NP, S1, S2, and RBD) challenge at 1 yr after ICU discharge. All these implied that the acquired immunity against SARS-CoV-2 was preserved within 1 yr in our critically ill patients with COVID-19.

Our study showed that the inflammatory biomarkers, such as ferritin, C-reactive protein, and erythrocyte sedimentation rate, were normal by 3 months of follow-up, and the coagulation and kidney functions were also gradually back to normal over time. However, some survivors presented an increased fasting glucose. It was postulated that SARS-CoV-2 induced the dysregulation of angiotensin-converting enzyme pathways in pancreatic endocrine tissues and led to the disorders of glucose metabolism.[34] Further studies on complications, including glucose metabolic disorders, and underlying mechanisms in patients with COVID-19 are needed.

This study is not without limitations. Firstly, there were no data to compare the disease severity and long-term outcomes of critically ill patients with COVID-19 with survivors of ARDS of other aetiologies. Secondly, there were no baseline data available on all variables examined within our cohort of patients because of the nature of the unprecedented pandemic. Although we have excluded patients with prior history of chronic lung disease and sought to use percentages of

Table 3 Return to work and health-related quality of life amongst survivors of critical illness from COVID-19 during 12 months after ICU discharge. IQR, inter-quartile range; SF-36, Short Form-36. Data were reported as no./total (%) or median (IQR).

	Normative data	3 months (*n*=92)	6 months (*n*=72)	12 months (*n*=66)	*P*-value
Return to work, *n*/*N* (%)	NA	43/89 (48.3)	49/69 (71.0)	49/66 (74.2)	0.001
SF-36 score					
Physical function, median (IQR)	90.6	85.00 [65.00–95.00] (*n*=90)	82.50 [70.00–92.63] (*n*=68)	90.00 [80.00–95.00] (*n*=66)	0.014
Role physical, median (IQR)	79.5	25.00 [0.00–100.00] (*n*=90)	60.00 [0.00–100.00] (*n*=68)	75.00 [25.00–100.00] (*n*=66)	0.019
Role emotional, median (IQR)	76.5	66.67 [33.33–100.00] (*n*=90)	86.67 [33.33–100.00] (*n*=68)	100.00 [33.33–100.00] (*n*=66)	0.316
Vitality, median (IQR)	70.3	75.00 [60.00–85.00] (*n*=90)	75.00 [60.00–85.00] (*n*=68)	82.50 [68.75–90.00] (*n*=66)	0.009
Mental health, median (IQR)	72.7	80.00 [64.00–92.00] (*n*=90)	75.10 [64.00–88.00] (*n*=68)	80.00 [67.00–92.00] (*n*=66)	0.172
Social function, median (IQR)	86.9	50.00 [25.00–75.00] (*n*=90)	62.50 [37.50–75.00] (*n*=68)	68.75 [50.00–100.00] (*n*=66)	0.002
Body pain, median (IQR)	85.6	77.50 [56.88–100.00] (*n*=90)	67.50 [55.63–90.00] (*n*=68)	80.00 [66.88–100.00] (*n*=66)	0.222
General health, median (IQR)	69.6	55.00 [40.00–70.00] (*n*=90)	55.00 [35.25–70.00] (*n*=68)	65.00 [50.00–80.00] (*n*=66)	0.029

predicted values based on age and gender, it is still unknown how our data represent critically ill patients with COVID-19 overall, particularly given our relatively small sample size. Thirdly, only limited immunological cell functions were measured; in particular, T-cell subset data were not available at 3 months, and therefore, a comprehensive 'picture' of immune status is not known. Lastly, the proportion of patients lost to follow-up is relatively high. The main reason for this loss to follow-up was that patients are now working/living outside Hubei. Nevertheless, we included their data at 3 months follow-up when they were interviewed via telephone and all were recovering well.

Conclusions

In survivors of critical illness as a result of COVID-19, markers of lung function improved gradually during 12 months of follow-up and were almost back to normal levels except for gas diffusive capacity and RV. The acquired immunity against COVID-19 was still maintained with high titres of both of IgG and neutralising antibody and active cellular immune function. COVID-19 is a systemic disease that affects multiple organ systems, and this also leads to persistent changes in quality of life.[35] Consequently, the long-term recovery of such patients needs to be closely monitored to allow the implementation of appropriate care and support.

Authors' contributions

Study design: ZP, DM.
Laboratory measurements: YP.
Data collection: XY, ZL, BW, CZ, CJ, XZ, YY, HX, YL, WL.
Data interpretation: All authors. Data analysis: CH, ZZ.
Drafting of paper: XY, MPV, RDS.
ZP and DM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors critically revised the paper for important intellectual content and gave final approval for the version to be published.

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Declarations of interest

DM and RDS are members of the *British Journal of Anaesthesia*. The other authors declare no conflicts of interest.

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Appendix A.Supplementary data

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References

1. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020; **180**: 934–43
2. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020; **323**: 2052–9
3. Hui DS, Joynt GM, Wong KT, et al. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. *Thorax* 2005; **60**: 401–9
4. Hui DS, Wong KT, Ko FW, et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function,

exercise capacity, and quality of life in a cohort of survivors. *Chest* 2005; **128**: 2247–61
5. Ngai JC, Ko FW, Ng SS, To KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. *Respirology* 2010; **15**: 543–50
6. Park WB, Jun KI, Kim G, et al. Correlation between pneumonia severity and pulmonary complications in Middle East respiratory syndrome. *J Korean Med Sci* 2018; **33**: e169
7. Lee AM, Wong JG, McAlonan GM, et al. Stress and psychological distress among SARS survivors 1 year after the outbreak. *Can J Psychiatry* 2007; **52**: 233–40
8. Huang C, Huang L, Wang Y, et al. 6-Month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021; **397**: 220–32
9. Qin W, Chen S, Zhang Y, et al. Diffusion capacity abnormalities for carbon monoxide in patients with COVID-19 at three-month follow-up. *Eur Respir J* 2021; **58**: 2003677
10. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep* 2021; **11**: 16144
11. Finney LJ, Doughty R, Lovage S, et al. Lung function deficits and symptom burden in survivors of COVID-19 requiring mechanical ventilation. *Ann Am Thorac Soc* 2021; **18**: 1740–3
12. Guler SA, Ebner L, Aubry-Beigelman C, et al. Pulmonary function and radiological features 4 months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study. *Eur Respir J* 2021; **57**: 2003690
13. Balbi M, Conti C, Imeri G, et al. Post-discharge chest CT findings and pulmonary function tests in severe COVID-19 patients. *Eur J Radiol* 2021; **138**: 109676
14. Santus P, Flor N, Saad M, et al. Trends over time of lung function and radiological abnormalities in COVID-19 pneumonia: a prospective, observational, cohort study. *J Clin Med* 2021; **10**: 1021
15. Long QX, Tang XJ, Shi QL, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med* 2020; **26**: 1200–4
16. Saadat S, Rikhtegaran Tehrani Z, Logue J, et al. Binding and neutralization antibody titers after a single vaccine dose in health care workers previously infected with SARS-CoV-2. *JAMA* 2021; **325**: 1467–9
17. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475–81
18. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005; **26**: 720–35
19. Burnham EL, Hyzy RC, Paine 3rd R, et al. Chest CT features are associated with poorer quality of life in acute lung injury survivors. *Crit Care Med* 2013; **41**: 445–56
20. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014; **44**: 1428–46
21. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998; **158**: 1384–7
22. Wang F, Hou H, Luo Y, et al. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. *JCI Insight* 2020; **5**, e137799
23. Li H, Jia J, Yang Z. Mini-Mental State Examination in elderly Chinese: a population-based normative study. *J Alzheimers Dis* 2016; **53**: 487–96
24. Dunstan DA, Scott N, Todd AK. Screening for anxiety and depression: reassessing the utility of the Zung scales. *BMC Psychiatry* 2017; **17**: 329
25. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020; **20**: 425–34
26. Han X, Cao Y, Jiang N, et al. Novel coronavirus disease 2019 (COVID-19) pneumonia progression course in 17 discharged patients: comparison of clinical and thin-section computed tomography features during recovery. *Clin Infect Dis* 2020; **71**: 723–31
27. Ong KC, Ng AW, Lee LS, et al. 1-Year pulmonary function and health status in survivors of severe acute respiratory syndrome. *Chest* 2005; **128**: 1393–400
28. Ong KC, Ng AW, Lee LS, et al. Pulmonary function and exercise capacity in survivors of severe acute respiratory syndrome. *Eur Respir J* 2004; **24**: 436–42
29. Su MC, Hsieh YT, Wang YH, Lin AS, Chung YH, Lin MC. Exercise capacity and pulmonary function in hospital workers recovered from severe acute respiratory syndrome. *Respiration* 2007; **74**: 511–6
30. Xie L, Liu Y, Fan B, et al. Dynamic changes of serum SARS-coronavirus IgG, pulmonary function and radiography in patients recovering from SARS after hospital discharge. *Respir Res* 2005; **6**: 5
31. Wu X, Liu X, Zhou Y, et al. 3-Month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. *Lancet Respir Med* 2021; **9**: 747–54
32. Mo X, Jian W, Su Z, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. *Eur Respir J* 2020; **55**: 2001217
33. Wang F, Nie J, Wang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. *J Infect Dis* 2020; **221**: 1762–9
34. Abramczyk U, Kuzan A. What every diabetologist should know about SARS-CoV-2: state of knowledge at the beginning of 2021. *J Clin Med* 2021; **10**: 1022
35. Iwasaki M, Saito J, Zhao H, et al. Inflammation triggered by SARS-CoV-2 and ACE2 augment drives multiple organ failure of severe COVID-19: molecular mechanisms and implications. *Inflammation* 2021; **44**: 13–34

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