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Respiratory recovery trajectories after severe-to-critical COVID-19: a 1-year prospective multicentre study

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Shareable abstract (@ERSpublications)
Among a cohort of 485 survivors of severe-to-critical COVID-19, including non-ICU patients, most recovered well but a high percentage had residual radiological and functional sequelae, and residual symptoms up to 1 year, justifying prolonged follow-up https://bit.ly/3Zlm1fD

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Abstract

Background Survivors of severe-to-critical coronavirus disease 2019 (COVID-19) may have functional impairment, radiological sequelae and persistent symptoms requiring prolonged follow-up. This pragmatic study aimed to describe their clinical follow-up and determine their respiratory recovery trajectories, and the factors that could influence them and their health-related quality of life.

Methods Adults hospitalised for severe-to-critical COVID-19 were evaluated at 3 months and up to 12 months post-hospital discharge in this prospective, multicentre, cohort study.

Results Among 485 enrolled participants, 293 (60%) were reassessed at 6 months and 163 (35%) at 12 months; 89 (51%) and 47 (27%) of the 173 participants initially managed with standard oxygen were reassessed at 6 and 12 months, respectively. At 3 months, 34%, 70% and 56% of the participants had a restrictive lung defect, impaired diffusing capacity of the lung for carbon monoxide (D_{LCO}) and significant radiological sequelae, respectively. During extended follow-up, both D_{LCO} and forced vital capacity percentage predicted increased by means of +4 points at 6 months and +6 points at 12 months. Sex, body mass index, chronic respiratory disease, immunosuppression, pneumonia extent or corticosteroid use during acute COVID-19 and prolonged invasive mechanical ventilation (IMV) were associated with D_{LCO} at 3 months, but not its trajectory thereafter. Among 475 (98%) patients with at least one chest computed tomography scan during follow-up, 196 (41%) had significant sequelae on their last images.

Conclusions Although pulmonary function and radiological abnormalities improved up to 1 year post-acute COVID-19, high percentages of severe-to-critical disease survivors, including a notable proportion of those managed with standard oxygen, had significant lung sequelae and residual symptoms justifying prolonged follow-up.

Introduction

Since its onset in January 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has been responsible for more than 600 million cases worldwide, with at least 6.6 million deaths attributed to coronavirus disease 2019 (COVID-19). During the pandemic's first wave, 10–20% of symptomatic patients developed moderate-to-severe forms, characterised by hypoxaemic pneumonia requiring hospitalisation for standard oxygen therapy, while 5–32% of hospitalised patients developed very severe COVID-19 forms that progressed to acute respiratory distress syndrome (ARDS) requiring additional ventilatory support and intensive care unit (ICU) admission [1].

In-hospital acute COVID-19 mortality, which initially exceeded 30% [1, 2] but was subsequently lower during the first wave [3], did not reflect the overall COVID-19 burden. As initially suspected based on follow-up studies of survivors of previous coronavirus outbreaks [4–7], influenza A(H1N1)-associated ARDS [8] or all-cause ARDS [9, 10], notable percentages of COVID-19 survivors have impaired lung function and persistent radiological lung abnormalities at short- and intermediate-term follow-up, especially those with the most severe disease [11–21]. In addition, many persistent symptoms and long-term complications, defined as "post-acute COVID-19 syndrome", also participate in survivors' impaired health-related quality of life (HR-QoL) [22]. Fortunately, 1-year mortality after hospital discharge for patients admitted to the ICU for COVID-19 seems to be limited [23].

To date, data on long-term respiratory outcomes after severe-to-critical COVID-19 remain sparse [24–26], with only a few published longitudinal studies up to 1 year after acute disease [27–32]. Overall, respiratory recovery trajectories after severe-to-critical COVID-19 and factors potentially influencing them remain insufficiently described, as does the percentage of these hospitalised patients requiring prolonged follow-up, which was only estimated in a monocentric cohort of ICU survivors [32].

Given the presumed high frequency of intermediate- to long-term respiratory sequelae after severe-to-critical COVID-19 and the huge number of hospital-discharged patients eligible for follow-up, we designed a pragmatic multicentre study to describe those survivors' respiratory recovery early after the pandemic onset. The primary objective was to assess survivors' short-term (month 3 (M3)), intermediate-term (month 6 (M6)) and long-term (month 12 (M12)) trajectories of lung function recovery after severe-to-critical COVID-19, and their determinants. Secondary objectives were to determine the frequencies and outcomes of residual radiological abnormalities on chest computed tomography (CT) scans, exercise capacity impairment, persistent symptoms and HR-QoL.

Methods

Study design and participants

RE_2COVERI (REspiratory REcovery after COVid-19 sevERe Infection), a prospective, multicentre, cohort study, was conducted in 13 French university and university-affiliated hospitals. It included, at the first follow-up visit post-hospital discharge, adults (⩾18 years) previously hospitalised for severe COVID-19

(hospital length of stay (LOS) ⩾7 days and oxygen flow ⩾3 L·min^{-1}, including those managed with non-invasive ventilatory support (NIVS; *i.e.* continuous positive airway pressure, bi-level positive airway pressure or high-flow oxygen) without further invasive mechanical ventilation (IMV) required) or critical COVID-19 (IMV ⩾48 h). Patients opposed to data collection, not affiliated with national health insurance, pregnant or breastfeeding women, or receiving long-term oxygen prior to acute COVID-19 were not included. The Henri Mondor University Hospital Institutional Review Board approved the study protocol (00011558, 2020-063) that was supported by the Fondation du Souffle.

Follow-up visits and procedures

A follow-up visit was scheduled at ⩽4.5 months (henceforth M3) post-hospital discharge. Additional follow-up visits at 4.5–9 months (M6) and 9–15 months (M12) were planned for patients with persistent dyspnoea, impaired lung function (*e.g.* forced vital capacity (FVC) <80% predicted and/or diffusing capacity of the lung for carbon monoxide (D_{LCO}) <70% predicted) and/or significant radiological sequelae at the previous assessment. A senior pulmonologist collected clinical data at each visit. Additional procedures were, whenever possible: pulmonary function tests (PFTs), including D_{LCO} measurement, 6-min walk test (6MWT), 1-min sit-to-stand test (1MSST) and chest CT scan, if justified. Dyspnoea was assessed using the modified Medical Research Council (mMRC) scale, and HR-QoL and specific symptoms were assessed with questionnaires (36-item Short-Form Health Survey (SF-36), Fatigue Severity Scale, Hospital Anxiety and Depression Scale (HADS), and Post-traumatic stress disorder Check-List Scale (PCL-S)).

Statistical analyses

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were applied (www.strobe-statement.org). Data are expressed as n (%) or median (interquartile range (IQR)), as appropriate. Baseline characteristics were compared according to the World Health Organization (WHO) Clinical Progression Scale (WHO 5 *versus* WHO 6 *versus* WHO 7–9; for class definitions, see Results) using Pearson's Chi-squared test, ANOVA or the Kruskal–Wallis test, as appropriate. At M3, M6 and M12, median (IQR) pulmonary function (D_{LCO} and FVC) and HR-QoL (SF-36 dimensions Physical Component Summary (PCS) and Mental Component Summary (MCS) scores) values were plotted *versus* month and according to follow-up duration (patients followed until M3 *versus* until M6 and until M12) to visualise respiratory and HR-QoL recovery trajectories. For patients followed until M12, chained-equation multiple imputation of missing M6 data used 30 imputation sets. Evolution and factors associated with evolution of respiratory function (D_{LCO} and FVC) and HR-QoL (PCS and MCS) outcomes were assessed using a mixed linear model with random intercept adjusted for follow-up visits, known prognostic factors and management. Interactions between follow-up visits and prognostic factors or management were systematically assessed. Linear regression models adjusted for follow-up visits, known prognostic factors and management evaluated factors associated with best follow-up D_{LCO} (D_{LCOmax}) or FVC (FVC_{max}) values. All tests were two-tailed, with $p<0.05$ defining significance. Analyses were computed with Stata SE version 15.0 (StataCorp, College Station, TX, USA).

Results

Study population and acute COVID-19 characteristics

Between 10 March 2020 and 25 November 2020, 485 hospital-discharged participants were enrolled. Their clinical and main acute COVID-19 characteristics are summarised in table 1: median (IQR) patient age 60.7 (53.4–67.6) years; 354 (73%) males; most frequent comorbidities: cardiovascular disease (50.3%), obesity (36.5%), diabetes (22.1%) and chronic respiratory disease (CRD) (13%); and 53 (10.7%) were immunocompromised. Reverse transcriptase PCR confirmed SARS-CoV-2 infection in 454 (93.8%) patients.

Three patient groups were constituted according to maximum disease severity during hospitalisation applying the WHO Clinical Progression Scale [33]: WHO 5 patients (173 (35.7%)) received only standard oxygen by mask or nasal prongs, WHO 6 patients (96 (19.8%)) received NIVS without further IMV required and all WHO 7–9 patients (216 (44.5%)) required IMV ⩾48 h. Most WHO 7–9 patients (112 (51.9%)) received NIVS(s) pre-intubation. Age, sex, smoking status and comorbidities did not differ among groups; only obesity was over-represented among intubated patients. Median (IQR) IMV lasted 15 (9–26) days, with 20 (9.3%) patients also requiring extracorporeal membrane oxygenation assistance.

Acute COVID-19 pneumonia extent, assessed on chest CT scans, differed significantly among groups ($p<0.001$) (table 1), as did several blood disease severity markers obtained during hospitalisation (supplementary table S1). Patients received anticoagulant therapy (468/474 (98.7%)), antibiotics (438/483

TABLE 1 Characteristics of COVID-19 survivors, their respiratory management during acute COVID-19 and outcomes, according to initial disease severity

	All	WHO 5	WHO 6	WHO 7–9	p-value
Participants	485	173	96	216	
Age (at admission) (years)	60.7 (53.4–67.6)	60.6 (54.4–67.4)	58.6 (49.3–65.1)	61.9 (54.2–69.3)	0.084
Male	354 (73.0)	119 (68.8)	76 (79.2)	159 (73.6)	0.178
Body mass index (kg·m^{-2})	28.4 (25.5–32.3)	27.6 (24.7–32.1)	27.7 (25.2–29.6)	29.2 (26.1–33.0)	**0.002**
⩾30 kg·m^{-2}	177 (36.5)	59 (34.1)	23 (24.0)	95 (44.0)	**0.002**
Smoking status (n=474/172/91/211)					0.667
Never-smoker	297 (62.7)	103 (59.9)	56 (61.5)	138 (65.4)	
Ex-smoker (⩾5 pack-years)	159 (33.5)	62 (36.0)	30 (33.0)	67 (31.8)	
Current smoker	18 (3.8)	7 (4.1)	5 (5.5)	6 (2.8)	
Comorbidities					
Number	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	0.110
0	155 (32)	58 (33.5)	35 (36.5)	62 (28.7)	0.223
1	140 (28.9)	55 (31.8)	28 (29.2)	57 (26.4)	
⩾2	190 (39.2)	60 (34.7)	33 (34.4)	97 (44.9)	
Cardiovascular disease	244 (50.3)	78 (45.1)	46 (47.9)	120 (55.6)	0.106
Chronic respiratory disease (OSA excluded)	63 (13.0)	26 (15.0)	10 (10.4)	27 (12.5)	0.537
COPD	12 (2.5)	6 (3.5)	2 (2.1)	4 (1.9)	0.599
Emphysema	17 (3.5)	9 (5.2)	4 (4.2)	4 (1.9)	0.160
Asthma	32 (6.6)	10 (5.8)	7 (7.3)	15 (6.9)	0.859
Interstitial lung disease	8 (1.6)	5 (2.9)	0 (0)	3 (1.4)	0.202
Non-cystic fibrosis bronchiectasis	5 (1.0)	2 (1.2)	1 (1.0)	2 (0.9)	>0.999
Obstructive sleep apnoea	46 (9.5)	12 (6.9)	12 (12.5)	22 (10.2)	0.294
Diabetes	107 (22.1)	35 (20.2)	19 (19.8)	53 (24.5)	0.498
Immune deficiency (all causes)	52 (10.7)	20 (11.6)	8 (8.3)	24 (11.1)	0.693
Symptom onset to admission interval (days) (n=471/170/93/208)	8 (5–10)	8 (5–11)	8 (5–10)	7 (5–10)	0.531
SARS-CoV-2 genome detection (n=484/173/95/216)	454 (93.8)	153 (88.4)	90 (94.7)	211 (97.7)	**0.001**
Chest CT findings typical of COVID-19 pneumonia (n=479/171/96/212)	428 (89.4)	156 (91.2)	90 (93.8)	182 (85.8)	0.070
Maximum COVID-19 pneumonia extent on chest CT (n=424/161/88/175)					**<0.001**
<25%	68 (16.0)	42 (26.1)	11 (12.5)	15 (8.6)	
25–49%	158 (37.3)	71 (44.1)	34 (38.6)	53 (30.3)	
50–75%	143 (33.7)	44 (27.3)	31 (35.2)	68 (38.9)	
>75%	55 (13.0)	4 (2.5)	12 (13.6)	39 (22.3)	
ICU admission	345 (71.1)	41 (23.7)	88 (91.7)	216 (100)	**<0.001**
Oxygen and ventilatory support					
Maximum oxygen flow (L·min^{-1}) (n=412/172/84/156)	15 (6–15)	6 (4–9)	30 (15–50)	15 (15–15)	**<0.001**
Non-invasive ventilatory support	208 (42.9)		96 (100)	112 (51.9)	
High-flow oxygen	156 (32.2)		68 (70.8)	88 (40.7)	
Continuous positive airway pressure	73 (15.1)		39 (40.6)	34 (15.7)	
Bi-level non-invasive ventilation	45 (9.3)		7 (7.3)	38 (17.6)	
Invasive mechanical ventilation	216 (44.5)			216 (100)	
Extracorporeal membrane oxygenation	20 (4.1)			20 (9.3)	
Prone positioning	167 (34.4)	0 (0)	16 (16.7)	151 (69.9)	**<0.001**
Hospital length of stay (days)[#] (n=475/170/94/211)	18 (11–31)	11 (8–14)	15 (11–20)	31 (22–49)	**<0.001**
Discharged to home (n=477/172/95/210)	254 (53.2)	125 (72.7)	65 (68.4)	64 (30.5)	**<0.001**
Discharged to a rehabilitation unit (n=477/172/95/210)	223 (46.8)	47 (27.3)	30 (31.6)	146 (69.5)	**<0.001**

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated. Percentages were calculated by category after exclusion of patients with missing values for that variable. WHO: World Health Organization; OSA: obstructive sleep apnoea; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; CT: computed tomography; ICU: intensive care unit. WHO Clinical Progression Scale: WHO 5: standard oxygen only; WHO 6: non-invasive ventilation (continuous or bi-level positive airway pressure ventilation) or high-flow oxygen; WHO 7–9: invasive mechanical ventilation with/without other organ support. [#]: rehabilitation unit excluded. Chi-squared or Kruskal–Wallis tests were used, as appropriate. Bold indicates statistically significant (p<0.05).

(90.7%)) or corticosteroids (dexamethasone or methylprednisolone; 100/485 (20.6%)). After hospital discharge, some patients continued corticosteroids (42/484 (8.7%)) and/or oxygen therapy (90/484 (18.6%)). For other treatments and complications during hospitalisation, see supplementary table S1.

Median (IQR) hospital LOS was 18 (11–31) days and 223/477 (46.8%) patients were discharged to a rehabilitation unit (table 1).

Sequential follow-up assessments

All 485 participants were assessed at M3 (median (IQR) 2.8 (2.3–3.3) months) post-discharge (figure 1). As per protocol directives, 293 (60.4%) patients were reassessed at M6 and 170 (35.1%) at M12. Comparisons of the patients' characteristics according to follow-up duration (M3 only *versus* until M6 or M12) are given in supplementary table S2: although the distribution of patients among WHO groups significantly differed (p=0.004), more than a half of WHO 5 patients were reassessed at M6 and more than a quarter at M12 (figure 1). Overall, 36 (7.4%) patients were lost to follow-up, and five (1.0%) deaths during the study period were attributed to four underlying malignancies and one *Pneumocystis* pneumonia. One patient refused to pursue follow-up after the M3 visit and two others after M6.

Main persistent symptoms, and physical examination, dyspnoea, fatigue, anxiety/depression and PCL-S findings, are described in table 2. Dyspnoea on exertion was the most frequent symptom, reported by almost two-thirds of the patients at M3, with no significant difference among initial disease severity groups. Dyspnoea evaluation revealed that higher percentages of intubated patients had significant (mMRC >0) or severe (mMRC ⩾2) dyspnoea (p<0.001). Fatigue was also a common complaint (52.3%), with frequencies differing significantly among groups, without Fatigue Severity Scale score differences. When considering the 21 symptoms available in our database, 377/390 (96.7%) patients reported ⩾1 symptoms at M3, 223/276 (80.8%) at M6 and 117/156 (75.0%) at M12. HADS-assessed anxiety and depression frequencies were comparable among groups. However, the percentage of patients with PCL-S-suspected post-traumatic stress disorder was about twice as high for WHO 7–9 patients. Among patients with prolonged follow-up, more than half still complained of dyspnoea and more than one-third reported persistent fatigue; globally, other physical symptoms were relatively uncommon. Notably, the percentages of reassessed patients with psychological disorders remained stable over time.

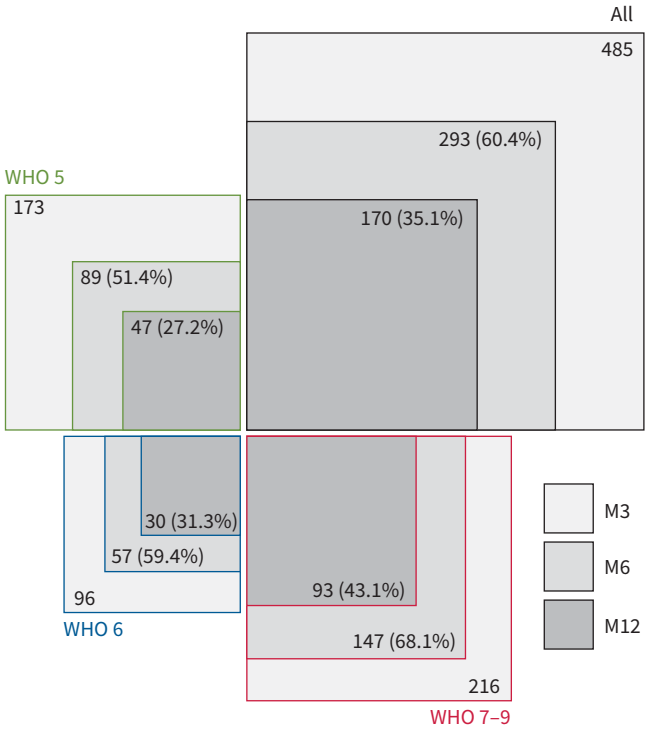

FIGURE 1 Follow-up of the 485 participants included in the RE_2COVERI cohort. Representation of follow-up visits completed by 485 study participants (All), further divided into three groups according to the World Health Organization (WHO) Clinical Progression Scale during their hospitalisation for acute COVID-19 (WHO 5: standard oxygen only; WHO 6: non-invasive ventilation (continuous or bi-level positive airway pressure ventilation) or high-flow oxygen; WHO 7–9: invasive mechanical ventilation with/without other organ support). Participants were assessed at month 3 (M3), month 6 (M6) and month 12 (M12) after hospital discharge for acute COVID-19.

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TABLE 2 COVID-19 survivors' persistent symptoms, essential clinical signs, and evaluation of dyspnoea, fatigue, anxiety/depression and post-traumatic stress disorder during 1-year follow-up

	Month 3						Month 6		Month 12	
	Available	All	WHO 5	WHO 6	WHO 7–9	p-value	Available	All	Available	All
Dyspnoea on exertion	475 (97.9)	290 (61.1)	101 (59.1)	50 (54.3)	139 (65.6)	0.15	282 (96.2)	160 (56.7)	166 (97.6)	89 (53.6)
Fatigue	474 (97.7)	248 (52.3)	89 (51.7)	36 (38.7)	123 (58.9)	**0.005**	279 (95.2)	96 (34.4)	163 (95.9)	54 (33.1)
OSA-suggestive symptoms	423 (87.2)	117 (27.7)	49 (32.7)	18 (21.4)	50 (26.5)	0.16	244 (83.3)	48 (19.7)	159 (93.5)	28 (17.6)
Myalgias/muscle stiffness	472 (97.3)	109 (23.1)	32 (18.8)	19 (20.4)	58 (27.8)	0.097	274 (93.5)	27 (9.9)	165 (97.1)	13 (7.9)
Cough	473 (97.5)	93 (19.7)	36 (20.9)	12 (13.0)	45 (21.5)	0.20	282 (96.2)	37 (13.1)	165 (97.1)	25 (15.2)
Neuropsychiatric disorders	465 (95.9)	84 (18.1)	32 (19.0)	10 (10.9)	42 (20.5)	0.13	273 (93.2)	34 (12.5)	165 (97.1)	26 (15.8)
Chest pain	473 (97.5)	51 (10.8)	17 (9.9)	10 (10.9)	24 (11.5)	0.88	277 (94.5)	27 (9.7)	165 (97.1)	11 (6.7)
ENT neurosensorial disorders	470 (96.9)	47 (10)	20 (11.7)	5 (5.5)	22 (10.6)	0.26	274 (93.5)	12 (4.4)	163 (95.9)	10 (6.1)
Palpitations	471 (97.1)	34 (7.2)	17 (9.9)	2 (2.2)	15 (7.2)	0.068	277 (94.5)	6 (2.2)	165 (97.1)	4 (2.4)
Headache	471 (97.1)	15 (3.2)	4 (2.4)	0 (0)	11 (5.2)	**0.037**	278 (94.9)	7 (2.5)	164 (96.5)	0 (0)
Heart rate (beats·min^{-1})	451 (93.0)	78 (69–87)	79 (69–87)	74.5 (66–85)	78 (70–88)	0.20	232 (79.2)	78 (70–90)	141 (82.9)	77 (66–86)
S_{pO_2} on room air (%)	472 (97.3)	98 (97–99)	98 (97–99)	98 (97–99)	98 (96–98)	**0.002**	261 (89.1)	97 (96–98)	151 (88.8)	97 (96–98)
No pulmonary rales	470 (96.9)	424 (90.2)	159 (93.5)	87 (92.6)	178 (86.4)	**0.048**	271 (92.5)	237 (87.5)	162 (95.3)	136 (84)
Dyspnoea (mMRC)	468 (96.5)					**<0.001**	269 (91.8)		160 (94.1)	
0		199 (42.5)	83 (48.8)	49 (52.8)	67 (32.4)			136 (50.6)		87 (54.4)
1		173 (37.0)	56 (32.9)	35 (38.5)	82 (39.6)			90 (33.5)		48 (30)
⩾2		96 (20.5)	31 (18.2)	7 (7.7)	58 (28.0)			43 (16)		25 (15.6)
Fatigue Severity Scale (points)	272 (56.1)	2.67 (1.44–4.67)	2.28 (1.44–4.67)	2.78 (1.28–4.73)	2.95 (1.56–4.56)	0.80	86 (29.4)	2.73 (1.44–3.89)	63 (37.1)	3.11 (1.33–4.78)
Anxiety/depression (HADS)	302 (62.3)						87 (29.7)		65 (38.2)	
Anxiety score (points)		5 (3–8)	5 (3–8)	5 (3–7)	5 (3–8)	0.84		4 (2–8)		5 (3–8)
Score >7		86 (28.5)	36 (30.3)	14 (23.0)	36 (29.5)	0.56		22 (25.3)		18 (27.7)
Depression score (points)		4 (2–8)	3 (1–8)	4 (2–7)	4 (2–8)	0.62		3 (1–8)		4 (2–8)
Score >7		79 (26.2)	30 (25.2)	15 (24.6)	34 (27.9)	0.85		24 (27.6)		17 (26.2)
Post-traumatic stress disorder (PCL-S)										
Score >43	217 (44.7)	30 (13.8)	10 (11.2)	4 (8.5)	16 (19.8)	0.14	49 (16.7)	9 (18.4)	48 (28.2)	9 (18.8)

Data are presented as n (%) or median (interquartile range), unless otherwise stated. Percentages are calculated by category after exclusion of patients with missing values for that variable. WHO: World Health Organization; OSA: obstructive sleep apnoea; ENT: ear, nose and throat; S_{pO_2}: peripheral oxygen saturation; mMRC: modified Medical Research Council dyspnoea scale (0–4); HADS: Hospital Anxiety and Depression Scale; PCL-S: Post-traumatic stress disorder Check-List Scale. WHO Clinical Progression Scale: WHO 5: standard oxygen only; WHO 6: non-invasive ventilation (continuous or bi-level positive airway pressure ventilation) or high-flow oxygen; WHO 7–9: invasive mechanical ventilation with/without other organ support. Chi-squared or Kruskal–Wallis tests were used, as appropriate. Bold indicates statistically significant ($p<0.05$).

PFT and exercise capacity assessment results are summarised in table 3. At M3, median lung volumes were within normal ranges; total lung capacity (TLC), residual volume and D_{LCO} values differed significantly among initial disease severity groups. A third of participants had a restrictive lung defect (TLC <80% predicted) and 70.2% had impaired diffusion capacity (D_{LCO} <80% predicted). The percentages of patients with markedly impaired gas diffusion (D_{LCO} <70% predicted) differed significantly among initial disease severity groups (p=0.005), but only tended towards significance for the most severe cases (D_{LCO} <50% predicted; p=0.07). PFT results frequently remained abnormal at M6 and M12, with restriction and markedly impaired D_{LCO} persisting in ∼40% and almost half of patients with prolonged follow-up, respectively. While the decreased 6MWT distance reflected initial disease severity, no significant difference among groups was observed for the number of repetitions during the 1MSST or the peripheral oxygen saturation change during both exercise capacity tests. For patients with repeated assessments, their median (IQR) 6MWT distances increased by 25 (−7– +68) m between M3 and M6 (n=154) and by 34.5 (+5.5– +90) m between M3 and M12 (n=80). Median numbers of repetitions during the 1MSST increased by 2 (−1– +5) between M3 and M6 (n=103), and by 2 (+0– +6) between M3 and M12 (n=54).

Analyses of sequential CT scans are reported in supplementary table S3. Among 422 (87.0%) patients with M3 scans, the global assessment of residual COVID-19-attributable radiological lesions differed significantly among initial disease severity groups: 82 (19.4%) normalised completely, 104 (24.6%) had minimum residual COVID-19 pneumonia signs, while 236 (55.9%) scans showed significant residual lung abnormalities; ground-glass opacities (216 (91.5%)) and reticulations (192 (81.4%)) were the most frequent abnormalities, predominantly located subpleurally (144 (61.0%)). Radiological findings suggestive of fibrotic changes were common: curvilinear lines (183/232 (78.9%)), traction bronchiectasis (125/236 (53%)) and/or scissural distortion (49/234 (20.9%)). Only traction bronchiectasis frequency differed significantly among the three groups. While most M6 scan images with significant residual lung abnormalities (96/139 (69.1%)) showed attenuated lung sequelae, only 33/87 (37.9%)) were still affected at M12. Overall, 475/485 (97.9%)) patients had at least one CT scan during follow-up. When considering each patient's last available scan, 196/475 (41.3%) showed significant COVID-19-attributable residual lung abnormalities: 51/207 (24.6%) at M3, 53/132 (40.2%) at M6 and 87/123 (70.7%) at M12. Again, the global assessment of residual COVID-19-attributable lung abnormalities reflected initial disease severity (supplementary table S4).

Respiratory function trajectories and HR-QoL

D_{LCO} (% pred), FVC (% pred), and SF-36-assessed PCS and MCS score evolutions, according to follow-up duration (until M3, M6 or M12) are illustrated in figure 2a–d.

The mean D_{LCO} and FVC gains (% pred), respectively, were +4.1 and +4.3 points at M6 and +6.5 and +5.9 points at M12 (for each, p<0.001) (table 4). D_{LCOmax} (% pred) and FVC_{max} (% pred) values obtained for patients followed until M6 or M12 were not significantly lower than those of patients who ended their follow-up at M3 (supplementary table S5). Furthermore, WHO 6 patients' respiratory trajectories merged with those of WHO 5 patients, while WHO 7–9 patients' mean D_{LCO} (but not FVC) values remained lower throughout follow-up until M12 (supplementary figure S1). Finally, we looked at the percentages of patients with D_{LCO} (% pred) changes <5 points between each assessment visit: only 65/232 (28.0%) patients assessed at M3 and M6 and 43/113 (38.1%) patients assessed at M6 and M12 could be considered stabilised.

Multivariate analysis retained underlying CRD, immunodeficiency, COVID-19-attributable lung abnormality extent (⩾50%) on CT scans obtained during acute illness, prolonged IMV duration (⩾14 days) or corticosteroid use during acute COVID-19 as being significantly and independently associated with impaired D_{LCO}, whereas male sex and obesity (body mass index ⩾30 $kg \cdot m^{-2}$) were associated with better functional recovery (table 4). Notably, initial acute clinical, radiological and management factors, except prolonged IMV for FVC, did not interact with D_{LCO} or FVC trajectories, meaning the identified risk factors of poorer recovery had no impact on respiratory trajectories beyond M3. A sensitivity analysis, with missing follow-up data imputation (until M12) to obtain a complete dataset (supplementary table S6), yielded similar results (except positive interactions between ⩾50% pneumonia extent or prolonged IMV and month for FVC). Strong correlation between variables (Cramér's V, not shown) eliminated the significant association between prolonged IMV duration and D_{LCO} recovery when the variable "ventilator-associated pneumonia" (together with "documented bacterial infection") was added to the initial model (supplementary table S7) or a model focused on critical (WHO 7–9) patients (supplementary table S8). The latter included other variables pertinent to this subgroup's analysis; immunosuppression, CT pneumonia extent and prolonged IMV duration were no longer significantly associated with impaired D_{LCO}. A positive interaction was also found between prolonged IMV duration (⩾14 days) and times for both D_{LCO} and FVC.

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TABLE 3 Lung function and exercise capacity assessment results of COVID-19 survivors during 1-year follow-up

	Month 3						Month 6		Month 12	
	Available	All (n=485)	WHO 5 (n=173)	WHO 6 (n=96)	WHO 7–9 (n=216)	p-value	Available	All (n=293)	Available	All (n=170)
TLC (% pred)	447 (92.2)	86 (75–97)	89 (79–100)	85 (75–95)	84 (73–93)	**0.002**	228 (77.8)	83 (74.5–92.5)	130 (76.5)	82 (75–96)
FVC (% pred)	464 (95.7)	89 (76–102)	89.5 (78.5–106)	88 (76–98)	90 (75–100)	0.25	252 (86.0)	90 (75.5–102.5)	143 (84.1)	87 (76–102)
FEV_1 (% pred)	465 (95.9)	90 (78–103)	92 (78–106)	89 (80.5–99)	91 (77–103)	0.79	251 (85.7)	91 (78–105)	143 (84.1)	90 (77–105)
FEV_1/FVC (ratio)	466 (96.1)	0.82 (0.78–0.86)	0.81 (0.76–0.85)	0.83 (0.79–0.87)	0.83 (0.78–0.86)	**0.007**	252 (86.0)	0.82 (0.78–0.86)	143 (84.1)	0.82 (0.77–0.85)
RV (% pred)	445 (91.8)	85 (72–100)	88 (75–105)	83 (68–99)	83 (71–96)	**0.032**	228 (77.8)	76.5 (65.5–90)	129 (75.9)	81 (68–97)
D_{LCO} (% pred)	436 (89.9)	70 (58–82)	73 (62–86)	71 (62–83)	65.5 (53–79)	**0.001**	235 (80.2)	70 (60–80)	132 (77.6)	70 (61–80.5)
K_{CO} (% pred)	387 (79.8)	93 (81–105)	94 (83–106)	93.5 (84–102)	92 (79–105)	0.51	210 (71.7)	95 (80–108)	125 (73.5)	94 (79–107)
TLC <80% pred	447 (92.2)	152 (34.0)	43 (26.1)	32 (37.6)	77 (39.1)	**0.025**	228 (77.8)	90 (39.5)	130 (76.5)	53 (40.8)
FVC <80% pred	464 (95.7)	139 (30.0)	45 (26.8)	29 (31.5)	65 (31.9)	0.53	252 (86.0)	80 (31.7)	143 (84.1)	48 (33.6)
FEV_1/FVC <0.7	466 (96.1)	36 (7.7)	22 (13.1)	5 (5.4)	9 (4.4)	**0.005**	252 (86.0)	16 (6.3)	143 (84.1)	8 (5.6)
D_{LCO} <80% pred	436 (89.9)	306 (70.2)	103 (63.6)	57 (69.5)	146 (76.0)	**0.038**	235 (80.2)	172 (73.2)	132 (77.6)	98 (74.2)
D_{LCO} <70% pred	436 (89.9)	209 (47.9)	67 (41.4)	34 (41.5)	108 (56.3)	**0.009**	235 (80.2)	113 (48.1)	132 (77.6)	63 (47.7)
D_{LCO} <50% pred	436 (89.9)	51 (11.7)	15 (9.3)	6 (7.3)	30 (15.6)	0.070	235 (80.2)	20 (8.5)	132 (77.6)	11 (8.3)
K_{CO} <80% pred	387 (79.8)	87 (22.5)	33 (21.3)	13 (18.1)	41 (25.6)	0.40	210 (71.7)	49 (23.3)	125 (73.5)	33 (26.4)
6MWT distance (m)	409 (84.3)	480 (420–544)	510 (428–554)	498 (442–579)	463.5 (390–520)	**<0.001**	174 (59.4)	480 (420–560)	90 (52.9)	478.5 (394–555)
ΔS_{pO_2} (%)	392 (80.8)	2 (0–4)	1 (0–3)	1 (0–3)	2 (0–4)	0.076	169 (57.7)	2 (0–4)	89 (52.4)	3 (1–7)
$\Delta S_{pO_2} \geqslant 4\%$	392 (80.8)	103 (26.3)	33 (23.9)	15 (18.1)	55 (32.2)	**0.042**	169 (57.7)	48 (28.4)	89 (52.4)	44 (49.4)
S_{pO_2} (final) $\leqslant 88\%$	393 (81.0)	30 (7.6)	14 (10.1)	5 (6.0)	11 (6.4)	0.40	169 (57.7)	23 (13.6)	89 (52.4)	14 (15.7)
1MSST repeats	282 (58.1)	24 (19–31)	24 (19–32)	26 (20–35)	23 (19–28)	0.14	137 (46.8)	25 (21–30)	70 (41.2)	26 (22–28)
ΔS_{pO_2} (%)	280 (57.7)	1 (0–3)	1 (0–2)	1 (0–2.5)	1 (0–3)	0.40	136 (46.4)	2 (0–3)	68 (40.0)	1 (0.5–3)
$\Delta S_{pO_2} \geqslant 4\%$	280 (57.7)	47 (16.8)	19 (17.4)	7 (13.5)	21 (17.7)	0.78	136 (46.4)	26 (19.1)	68 (40.0)	10 (14.7)
S_{pO_2} (min) $\leqslant 88\%$	280 (57.7)	9 (3.2)	2 (1.8)	2 (3.9)	5 (4.2)	0.60	136 (46.4)	7 (5.1)	68 (40.0)	2 (2.9)

Data are presented as n (%) or median (interquartile range), unless otherwise stated. Percentages are calculated by category after exclusion of patients with missing values for that variable. WHO: World Health Organization; TLC: total lung capacity; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; RV: residual volume; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: carbon monoxide transfer coefficient; 6MWT: 6-min walk test; S_{pO_2}: peripheral oxygen saturation; 1MSST: 1-min sit-to-stand test. WHO Clinical Progression Scale: WHO 5: standard oxygen only; WHO 6: non-invasive ventilation (continuous or bi-level positive airway pressure ventilation) or high-flow oxygen; WHO 7–9: invasive mechanical ventilation with/without other organ support. Chi-squared or Kruskal–Wallis tests were used, as appropriate. Bold indicates statistically significant ($p<0.05$).

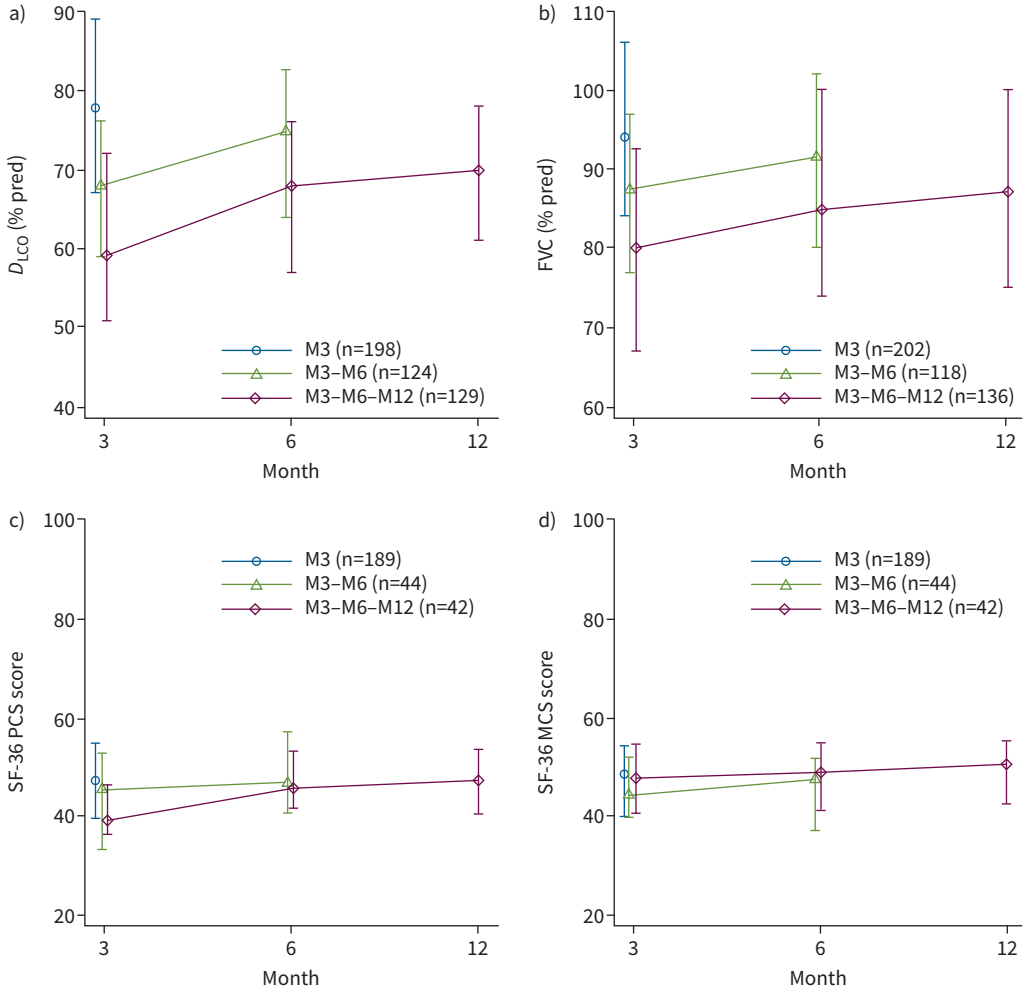

FIGURE 2 a, b) Respiratory (diffusing capacity of the lung for carbon monoxide (D_{LCO}) and forced vital capacity (FVC)) and c, d) health-related quality of life (36-item Short-Form Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS)) recovery trajectories up to month 12 (M12) after acute COVID-19 presented according to length of follow-up post-hospital discharge: up to month 3 (M3), month 6 (M6) (M3–M6) or M12 (M3–M6–M12). Data are presented as median (interquartile range). For patients followed until M12, chained-equation multiple imputation of missing M6 data used 30 imputation sets: n=19 for D_{LCO}, n=19 for FVC, and n=22 for SF-36 PCS and MCS.

SF-36 PCS and MCS scores evaluated HR-QoL (figure 2c and d) and their determinants (table 4); only the PCS scores increased significantly between M3 and M6, whereas both scores rose between M3 and M12. Worse PCS scores were associated with M3 D_{LCO}, female sex, and IMV and its duration. Female sex and acute pneumonia extent negatively influenced the MCS score, with a positive interaction between female sex and M12 outcome. Supplementary table S9 (physical domains) and supplementary table S10 (mental domains) report the evolutions and multivariate analysis results of factors associated with SF-36 domains. M3 D_{LCO} was associated with all SF-36 physical domains except Bodily Pain, prolonged IMV with all but General Health, and female sex with Physical Health and Role Physical Vitality. Female sex was associated with all SF-36 mental domains except Role Emotional, while M3 D_{LCO}, acute pneumonia extent, age or IMV, respectively, was only associated with Vitality, Mental Health, Social Functioning or Role Emotional.

Discussion

This longitudinal study describes short- to long-term respiratory recovery in a large multicentric cohort of survivors of severe-to-critical COVID-19 using a pragmatic approach, with conditional prolonged monitoring based on sequential clinical, radiological and functional assessments. Participants selected for

TABLE 4 Multivariate analysis: factors associated with respiratory function and quality of life evolution between follow-up M3 and M12

	D_{LCO} (716 measures/389 patients)		FVC (734 measures/398 patients)		SF-36 PCS (370 measures/255 patients)		SF-36 MCS (370 measures/255 patients)	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
M3 outcome	Reference		Reference		Reference		Reference	
M6 outcome[#]	4.1 (2.4–5.7)	**<0.001**	4.3 (2.8–5.8)	**<0.001**	3.0 (0.4–5.6)	**0.023**	0.2 (−4.9–5.3)	0.942
M12 outcome[¶]	6.5 (4.5–8.5)	**<0.001**	5.9 (4.0–7.9)	**<0.001**	2.9 (0.4–5.4)	**0.025**	7.2 (2.0–12.3)	**0.006**
M3 D_{LCO}					0.1 (0.1–0.2)	**0.001**	0.1 (−0.02–0.1)	0.182
Immunosuppression	−8.2 (−13.7– −2.7)	**0.003**	−10.7 (−16.6– −4.8)	**<0.001**	0.2 (−3.6–4.1)	0.903	−2.3 (−6.3–1.6)	0.241
Cardiovascular disease	−3.4 (−6.9–0.02)	0.052	−6.3 (−10.1– −2.4)	**0.001**	−1.1 (−3.6–1.5)	0.408	−0.1 (−2.7–2.4)	0.909
Chronic respiratory disease[+]	−8.8 (−13.5– −4.1)	**<0.001**	−2.7 (−7.9–2.4)	0.301	−1.1 (−4.5–2.3)	0.532	−0.7 (−4.1–2.8)	0.705
Acute COVID-19 pneumonia extent on chest CT								
<25%	Reference		Reference		Reference		Reference	
25–49%	−3.2 (−8.1–1.7)	0.203	−1.5 (−6.9–3.8)	0.573	1.7 (−1.8–5.1)	0.354	−0.8 (−4.3–2.7)	0.654
50–75%	−7.2 (−12.2– −2.2)	**0.005**	−3.5 (−9.0–2.0)	0.208	2.7 (−1.0–6.4)	0.150	−3.8 (−7.6– −0.1)	**0.045**
>75%	−8.5 (−14.9– −2.1)	**0.009**	−9.5 (−16.5– −2.5)	**0.007**	2.6 (−1.9–7.0)	0.260	−1.7 (−6.3–2.9)	0.463
Male sex	9.0 (5.1–12.8)	**<0.001**	−5.6 (−9.8– −1.4)	**0.009**	3.9 (1.0–6.8)	**0.010**	3.2 (−0.03–6.3)	**0.048**
Age (by quartiles)								
<54.1	Reference		Reference		Reference		Reference	
[54.1–61.1[	−0.2 (−4.9–4.4)	0.917	4.1 (−0.9–9.2)	0.111	−1.2 (−4.2–1.9)	0.444	1.5 (−1.6–4.6)	0.342
[61.1–68.1[	−1.3 (−6.0–3.4)	0.582	4.6 (−0.6–9.8)	0.082	−2.2 (−5.7–1.2)	0.196	2.7 (−0.7–6.2)	0.120
⩾68.1	−1.1 (−6.1–3.8)	0.648	12.4 (7.0–17.8)	**<0.001**	−1.7 (−5.2–1.8)	0.347	0.9 (−2.7–4.4)	0.630
Body mass index								
<24.9 kg·m^{-2}	Reference		Reference		Reference		Reference	
25–29.9 kg·m^{-2}	2.6 (−1.7–6.8)	0.232	4.7 (0.1–9.3)	**0.047**	0.8 (−2–3.7)	0.562	−1.0 (−3.9–1.8)	0.481
⩾30 kg·m^{-2}	8.7 (4.2–13.3)	**<0.001**	2.2 (−2.8–7.2)	0.385	−0.1 (−3.5–3.2)	0.931	0.1 (−3.3–3.5)	0.943
IMV								
No	Reference		Reference		Reference		Reference	
<14 days	−1.7 (−6.1–2.8)	0.456	2.9 (−2.1–7.8)	0.255	−4.6 (−7.7– −1.5)	**0.004**	−1.0 (−4.2–2.1)	0.516
⩾14 days	−6.6 (−10.9– −2.4)	**0.002**	−3.1 (−7.8–1.6)	0.201	−6.8 (−9.9– −3.8)	**<0.001**	0.6 (−2.5–3.7)	0.716
Corticosteroids[§]	−4.5 (−8.5– −0.5)	**0.027**	−2.8 (−7.2–1.5)	0.205	0.4 (−2.3–3.1)	0.761	−0.5 (−3.3–2.2)	0.703
Interaction: month×IMV				**0.001**				
M3 outcome×no IMV			Reference					
M6 outcome× <14 days			−2.0 (−5.2–1.1)	0.201				
M6 outcome× ⩾14 days			4.2 (1.7–6.8)	**0.001**				
M12 outcome× <14 days			−3.0 (−6.9–0.9)	0.131				
M12 outcome× ⩾14 days			3.4 (0.3–6.4)	**0.030**				
Interaction: month×sex								**0.013**
M3 outcome×female sex							Reference	
M6 outcome×male sex							0.6 (−4.8–6.1)	0.815
M12 outcome×male sex							−8.8 (−14.5– −3.1)	**0.002**

Mixed linear model with random intercept adjusted for all variables in the table. M3: month 3; M6: month 6; M12: month 12; D_{LCO}: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; SF-36: 36-item Short-Form Health Survey; PCS: Physical Component Summary; MCS: Mental Component Summary; CT: computed tomography; IMV: invasive mechanical ventilation. D_{LCO} and FVC expressed as percentage predicted value. PCS and MCS score range 0–100. [#]: outcome value difference for patients followed at M6 *versus* M3; [¶]: outcome value difference for patients followed at M12 *versus* M3; [+]: obstructive sleep apnoea was excluded from this category; [§]: during hospitalisation for acute COVID-19 (hydrocortisone hemisuccinate excluded). Bold indicates statistically significant (p<0.05).

longer follow-up were indeed those with the most consequential respiratory sequelae at the time of their first post-hospital discharge assessment. Most patients with prolonged follow-up had progressive lung function, exercise capacity and radiological improvements, with greater progress made during the first 6 months post-hospital discharge than thereafter. Our results are consistent with the smaller pragmatic monocentric study of González *et al.* [32] showing that among 100 critical COVID-19 survivors, around half of them were followed until 1 year and almost a third were considered to need an extended follow-up due to functional or radiological sequelae, or persistent symptoms. Pertinently, we further showed that not only critically ill patients, including a notable proportion of patients managed with standard oxygen, were followed until M12, suggesting that early post-discharge assessment is relevant to identify, among the whole spectrum of severe-to-critical COVID-19 survivors, those requiring longer surveillance. Based on the risk factors retained (acute COVID-19 pneumonia extent, prolonged IMV, underlying CRD, immunocompromised status and female sex) for persistent impaired lung function, this pragmatic approach seems particularly pertinent. Inversely, obesity was predictive of better respiratory recovery, despite its known detrimental impact on acute COVID-19 prognosis. Notably, only IMV and acute COVID-19 pneumonia extent positively affected the respiratory function recovery trajectory beyond M3 post-hospital discharge.

Thus, our results confirmed the negative impact of female sex previously highlighted in Chinese studies that had excluded intubated patients [27] or only included small numbers of them [28]. That negativity is probably not explained only by the less-than-perfect D_{LCO} references for women [34] and requires further investigation, as their poorer prognoses are probably multifactorial. Our results might also support the debated hypothesis of the obesity paradox, but the specific mechanisms leading to severe hypoxaemia in obese patients could possibly explain this specific outcome. Indeed, we confirmed the results of Eberst *et al.*'s [35] monocentre ICU survivor cohort and the trend observed in Faverio *et al.*'s [29] Italian cohort. Any formal conclusion concerning our findings on underlying CRDs would be merely supposition. Previously, only Faverio *et al.* [29] had reported asthma being associated with impaired D_{LCO} [29]. The negative impact of immunocompromised status could be explained by delayed healing of acute COVID-19 lesions. Finally, the effect of corticosteroids prescribed during acute COVID-19 should also be interpreted with caution, as it might be related to more severe lung injury (*e.g.* fibrotic changes) motivating their use as salvage therapy, when it was not yet considered the standard of care. Such an effect was not found in previous studies assessing it [17, 18, 28, 29, 35], except one showing corticosteroids were associated with severe impairment in D_{LCO} (<60% predicted) at 6 months [36], nor in our multivariate analysis focusing on critical WHO 7–9 patients.

Given the limited knowledge on post-acute COVID-19 and the multifactorial stresses on our healthcare system, identification of patients hospitalised for COVID-19 requiring follow-up was particularly challenging during the first pandemic wave. Overall, our results confirmed that our selection criteria (hospital LOS $\geqslant$7 days and maximum oxygen flow $\geqslant 3\ L \cdot min^{-1}$) for early follow-up assessment indeed selected non-critical COVID-19 survivors at risk of respiratory sequelae. Pertinently, the percentages of patients with notable M3 radiological sequelae, markedly impaired gas diffusion (D_{LCO} <70% predicted) and restrictive lung defect (TLC <80% predicted) were higher than those of previously published global patient populations hospitalised for COVID-19 [11–14, 16, 18, 24], even when only patients managed with standard oxygen were considered. Thus, we think that our pragmatic study results could help refine the selection criteria for patients requiring closer multidisciplinary, clinical monitoring, as also proposed by others [22].

Concerning the fear of progressive interstitial lung diseases (ILDs) after acute COVID-19 [37], except for the fatal *Pneumocystis* pneumonia in an immunocompromised patient who had prematurely stopped prophylaxis, fortunately, no notable residual lung lesion worsening was observed beyond M3 assessment in our cohort. However, a sizeable percentage of participants had significant radiological sequelae suggestive of post-COVID-19 pulmonary fibrotic changes, most with little radiological improvement beyond M6. Longer follow-up of those patients seems mandatory to exclude the possibility of late progressive ILD.

High percentages of patients still complained of dyspnoea, fatigue and other symptoms during their prolonged follow-up. Each of their monitoring visits should be an opportunity to devise a patient-centred approach with specific interventions (*e.g.* rehabilitation, physiotherapy or psychotherapy), referral to other specialists and/or additional procedures (*e.g.* echocardiography, cardiopulmonary exercise tests, sleep study, *etc.*), especially when patient-identified symptoms and routine respiratory assessment findings differ. Indeed, specific management of dysfunctional breathing [38], sleep apnoea [39, 40], deconditioning and

muscle wasting [41, 42], cardiovascular dysfunction or psychological disorders may accelerate global recovery [22].

Our study has several strengths. Its multicentre and nation-wide design included university hospitals and university-affiliated general hospitals, unlike Chinese [15, 24, 25] or European [26, 27, 30] longitudinal studies up to M12, except the large UK PHOSP-COVID study that did not focus on respiratory recovery [31]. Many severe-to-critical COVID-19 patients were enrolled, providing good representation of initial disease severity subgroups. The follow-up visits, comprising symptom collection, imaging, PFTs, exercise capacity tests and HR-QoL assessments, were conducted by pulmonologists trained in global assessment and management of patients with ILDs or other disabling respiratory conditions. Thus, it is likely that most patients requiring specific interventions were offered them, and that difficult cases benefited from multidisciplinary management and discussion, as widely recommended [43–46]. Finally, our study has the specificity of providing a realistic picture of clinical follow-up of patients recovering from severe-to-critical COVID-19 that may be applicable in most outpatient facilities.

However, this study also has some limitations. Unfortunately, only one recruiting centre applied the spirometry Global Lung Initiative references and we were unable to correct this afterwards because French law does not allow patient ethnicity to be recorded for clinical research purposes. However, we think that non-application does not change the essential messages of our work because we focused primarily on lung function changes over time. Due to the pragmatic study design, we do not know whether any of the participants who suspended follow-up at M3 or M6 subsequently deteriorated, although this seems unlikely. Additionally, more than a quarter of the participants fulfilling at least one extended follow-up criterion were not reassessed. We postulate that clinicians considered further evaluation to be unwarranted based on their overall assessment of the patient's recovery status, which could explain their non-adherence to protocol directives. Furthermore, selection bias might have influenced the results of our multivariate model, even though a sensitivity analysis on a full dataset after missing follow-up data imputation gave similar results. Finally, we only included patients from the first pandemic wave in France, when therapeutic management was less consensual, and later therapeutic advances or other SARS-CoV-2 variants could possibly have modified these patients' outcomes. Further studies are needed to elucidate those last possibilities.

In conclusion, the results of this pragmatic, longitudinal study bring additional insights on the short- to long-term respiratory recovery of severe-to-critical COVID-19 patients. Although most of the participants globally recovered, high percentages had radiological and functional sequelae and residual symptoms throughout follow-up, all of which might have affected their HR-QoL. Our findings also highlight the burdens of post-hospital monitoring for such patients and their clinicians, and provide additional clues for how to organise that follow-up after severe-to-critical disease.

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