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Early View

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

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Summary "take home" message

Among a cohort of 485 survivors of severe-to-critical COVID-19, including non-ICU patients, most recovered well but high percentages had residual radiological and functional sequelae, and residual symptoms up to 1 year, justifying prolonged follow-up.

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Abstract (250 words)

Background: Survivors of severe-to-critical 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 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 ones 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 DL_{CO} and significant radiological sequelae, respectively. During extended follow-up, DL_{CO} and FVC (% of predicted value) 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 DL_{CO} at month 3, 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.

Conclusion: 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 >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- (month (M) 3), intermediate- (M6) and long-term (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 (hospital length of stay (LOS) ≥7 days and oxygen flow ≥3 L/min, including those managed with non-invasive ventilatory support (NIVS; i.e., CPAP, BiPAP or HFO) without further invasive mechanical ventilation (IMV) required) or critical (IMV ≥48 h) COVID-19. 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 (IRB#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 M6 (4.5–9) and M12 (9–15) were planned for patients with persistent dyspnoea, impaired lung function (e.g., forced vital capacity (FVC) <80% of predicted value (pred.) and/or diffusing capacity for carbon monoxide (DL_{CO}) <70% pred.) 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 DL_{CO} measurement, 6-minute walk test (6MWT), 1-minute sit-to-stand test (1MSST) and chest CT scan, if justified. Dyspnoea was assessed using the modified Medical Research Council (mMRC) scale, HR-QoL and specific symptoms 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 guidelines were applied. Data are expressed as n (%) or median [1^{st};3^{rd} quartiles; (IQR)], as appropriate. Baseline characteristics were compared according to WHO clinical progression scale (WHO 5 versus WHO 6 versus WHO 7–9; for class definitions see Results) using Pearson's chi-square test, analysis of variance (ANOVA) or Kruskal–Wallis test, as appropriate. At M3, M6 and M12, median [IQR] pulmonary function (DL_{CO} 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 (DL_{CO}, 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 DL_{CO} (DL_{COmax}) or FVC (FVC_{max}) values. All tests were two-tailed, with $p<0.05$ defining significance. Analyses were computed with Stata SE v15.0 (College Station, TX, USA).

Results

Study population and acute COVID-19 characteristics

Between 10/03/2020 and 25/11/2020, 485 hospital-discharged participants were enrolled. Their clinical and main acute COVID-19 characteristics are summarized in **table 1**: median patient age, 60.7 [53.4;67.6] years; 354 (73%) men; most frequent co-morbidities: cardiovascular disease (50.3%), obesity (36.5%), diabetes (22.1%) and chronic respiratory disease (CRD) (13%); and 53 (10.7%) were immunocompromised. Reverse transcriptase–polymerase chain reaction 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 (n=173, 35.7%) received only supplemental oxygen by mask or nasal prongs, WHO 6 patients (n=96, 19.8%) received NIVS without further IMV required and all WHO 7–9 patients (n=216, 44.5%) required IMV ≥48 h. Most WHO 7–9 patients (n=112, 51.9%) received NIVS(s) pre-intubation. Age, sex, smoking status and co-morbidities did not differ among groups; only obesity was overrepresented among intubated patients. Median 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 (**table S1**). Patients received anticoagulant therapy (468/474, 98.7%), antibiotics (438/483, 90.7%) or corticosteroids (dexamethasone or methylprednisolone; n=100, 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 **table S1**. Median 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 **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 *Pneumocystis* pneumonia for one. 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 percentages 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.

PFT and exercise-capacity–assessment results are summarized in **table 3**. At M3, median lung volumes were within normal ranges, total lung capacity (TLC), residual volume and DL_{CO} values differed significantly among initial disease-severity groups. One-third of the participants had a restrictive lung defect (TLC<80% pred.) and 70.2% had impaired diffusion capacity (DL_{CO}<80% pred.). The percentages of patients with markedly impaired gas diffusion (DL_{CO}<70% pred.) differed significantly among initial disease-severity groups (p=0.005) but only tended towards significance for the most severe cases (DL_{CO}<50% pred., p=0.07). PFT results frequently remained abnormal at M6 and M12, with restriction and markedly impaired DL_{CO} 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 1MSST or the peripheral oxygen saturation (SpO_2) change during both exercise-capacity tests. For patients with repeated assessments, their median [IQR] 6MWT distances increased by 25 [–7;+68] meters between M3 and M6 (n=154), and by 34.5 [+5.5;+90] meters 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 **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%) normalized completely, 104 (24.6%) had minimum residual COVID-19-pneumonia signs; while 236 (55.9%) scans showed significant residual lung abnormalities: ground-glass opacities (n=216; 91.5%,) and reticulations (n=192; 81.4%) were the most frequent, predominantly located subpleurally (n=144, 61.0%). Radiological findings suggestive of fibrotic changes were common: curvilinear lines (n=183/232; 78.9%), traction bronchiectasis (n=125/236; 53%) and/or scissural distortion (n=49/234; 20.9%). Only traction-bronchiectasis frequency differed significantly among the three groups. While most M6 scan images with significant residual lung abnormalities (n=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-attributed 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 with initial disease severity (**table S4**).

Respiratory function trajectories and HR-QoL

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

The mean DL_{CO} 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**). DL_{COmax} (% 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 (**table S5**). Furthermore, WHO-6 patients' respiratory trajectories merged with those of WHO-5 patients,

while WHO-7–9 patients' mean DL_{CO} (but not FVC) values remained lower throughout follow-up until M12 (**figure S1**). Finally, we looked at the percentages of patients with DL_{CO} (% 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 stabilized.

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 DL_{CO}, whereas male sex and obesity (BMI≥30) 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 DL_{CO} 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 DL_{CO} recovery when the variable "ventilator associated pneumonia" (together with "documented bacterial infection") was added to the initial model (**table S7**) or a model focused on critical (WHO-7–9) patients (**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 DL_{CO}. A positive interaction was also found between prolonged IMV duration (> 14 days) and times for both DLCO and FVC.

SF-36 PCS- and MCS-scores evaluated HR-QoL (**figure 2**) 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-DL_{CO}, 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. **Table S9** (physical domains) and **table S10** (mental domains) report the evolutions and multivariate analysis results of factors associated with SF-36 domains. M3-DL_{CO} 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-DL_{CO}, acute pneumonia extent, age or IMV, respectively, was only associated with Vitality, Mental Health, Social Functioning and Role Emotional.

Discussion

This longitudinal study described 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 longer follow-up were indeed those with 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 a hundred critical COVID-19 survivors, around half of them was followed until one year and almost a third was 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 DL_{CO} 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 monocentre ICU-survivor cohort [35] and the trend observed in Faverio *et al*.'s Italian cohort [29]. Any formal conclusion concerning our findings on underlying CRDs would be merely suppositions. Previously, only Faverio *et al*. had reported asthma being associated with impaired DL_{CO} [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 effect was not found in previous studies assessing it [17,18,28,29,35], except one showing corticosteroids were

associated with severe impairment in DL_{CO} (<60% pred.) 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 ≥7 days and maximum oxygen flow ≥3 L/min) 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 (DL_{CO}<70% pred.) and restrictive lung defect (TLC<80% pred.) 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 sizable 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-centered 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 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 ILD 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 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 data set 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 into 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 highlighted the burdens of post-hospital monitoring for such patients and their clinicians, and provided additional clues for how to organise that follow-up after severe-to-critical disease.

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Figure legends

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 WHO clinical progression scale during their hospitalisations for acute COVID-19 (WHO 5: standard oxygen only; WHO 6: high-flow oxygen and/or non-invasive mechanical ventilation; WHO 7–9: invasive mechanical ventilation during ≥48 h). Participants were assessed at month 3 (M3), M6 and M12 after hospital discharge for acute COVID-19.

FIGURE 2. Respiratory (DL_{CO}, FVC) and health-related quality-of-life recovery trajectories up to month (M) 12 after acute COVID-19 are presented according to length of follow-up post-hospital discharge: up to M3, M6 (M3–M6) or M12 (M3–M6–M12). Data are median [1^{st};3^{rd} quartiles: T bars]. For patients followed until M12, chained-equation multiple imputation of missing M6 data used 30 imputation sets: n=19 for DL_{CO}, n=19 for FVC, n=22 for SF-36 PCS and MCS. SF-36: Short-Form Health Survey.

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

Characteristic	All	WHO 5	WHO 6	WHO 7–9	p-value
Participants, n	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
Males	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	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)	
Former 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)	
Co-morbidities					
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
Chronic obstructive pulmonary disease	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)	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, liter/min (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 n (%) for categorical variables and median [1st;3rd quartile] for continuous variables. Percentages were calculated by category after exclusion of patients with missing values for that variable. Chi-square or Kruskal–Wallis tests were used, as appropriate. WHO clinical progression scale: WHO 5: continuous supplemental oxygen only; WHO 6: non-invasive ventilation (continuous or bi-level positive airway pressure ventilation) or high-flow oxygen; and WHO 7–9: invasive mechanical ventilation with/without other organ support; ICU: intensive care unit; OSA: obstructive sleep apnoea. * Rehabilitation unit excluded.

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)
Neuropsychic 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 (/min)	451 (93)	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]
SpO_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)	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	2.28	2.78	2.95	0.80	86 (29.4)	2.73	63 (37.1)	3.11
		[1.44;4.67]	[1.44;4.67]	[1.28;4.73]	[1.56;4.56]			[1.44;3.89]		[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 n (%) for categorical variables and median [1st;3rd quartile] for continuous variables. Percentages are calculated by category after exclusion of patients with missing values for that variable. Chi-square or Kruskal–Wallis tests were used, as appropriate. WHO clinical progression scale: WHO 5: continuous supplemental oxygen only; WHO 6: non-invasive ventilation (continuous or bi-level positive airway pressure ventilation) or high-flow oxygen; and WHO 7–9: invasive mechanical ventilation +/– other organ support; ENT: ear, nose and throat; HADS: Hospital Anxiety and Depression Scale; mMRC: modified Medical Research Council dyspnea scale (0–4); OSA: obstructive sleep apnoea syndrome; PCL-S: post-traumatic stress disorder Check-List Scale.

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

Parameter	Month 3						Month 6		Month 12	
		All	WHO 5	WHO 6	WHO 7–9	p value		All		All
	Available	485	173	96	216		Available	293	Available	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]
DL_{CO} (% 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)
DL_{CO} <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)
DL_{CO} <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)
DL_{CO} <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]
Delta SpO_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 SpO_2 ≥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)

SpO_2 (final) ≤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 no. of 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]
Delta SpO_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)	1 [0.5;3]
Delta SpO_2 ≥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)	10 (14.7)
SpO_2 (min) ≤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)	2 (2.9)

Data are n (%) for categorical variables and median [1st;3rd quartile] for continuous variables. Percentages are calculated by category after exclusion of patients with missing values for that variable. Chi-square or Kruskal–Wallis tests were used as appropriate. WHO clinical progression scale: WHO 5: continuous supplemental oxygen only; WHO 6: non-invasive ventilation (continuous or bi-level positive airway pressure ventilation) or high-flow oxygen; and WHO 7–9: invasive mechanical ventilation +/– other organ support; DL_{CO}: diffusing capacity for carbon monoxide; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; K_{CO}: carbon monoxide transfer coefficient; pred.: predicted value; RV: residual volume; TLC: total lung capacity; 6MWT: 6-minute walk test; SpO_2: peripheral oxygen saturation; 1MSST: 1-minute sit-and-stand test.

TABLE 4 Multivariate analysis: factors associated with respiratory function and quality-of-life evolution between follow-up months 3 and 12

Variable	DL_{CO} (716 measures/n=389 patients)		FVC (734 measures/n=398 patients)		SF-36 PCS (370 measures/n=255 patients)		SF-36 MCS (370 measures/n=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 DL_{CO}	–		–		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 (kg/m^2)								
<24.9	Reference		Reference		Reference		Reference	
25–29.9	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	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
Invasive mechanical ventilation								
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. DL_{CO} and FVC expressed in % of the predicted value. PCS- and MCS-score range (0–100).

IMV, invasive mechanical ventilation.

* 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). DL_{CO}: diffusing capacity for carbon monoxide; FVC: forced vital capacity; PCS: Physical Component Summary of the 36-item Short Form Health Survey (SF-36); MCS: Mental Component Summary of SF-36.

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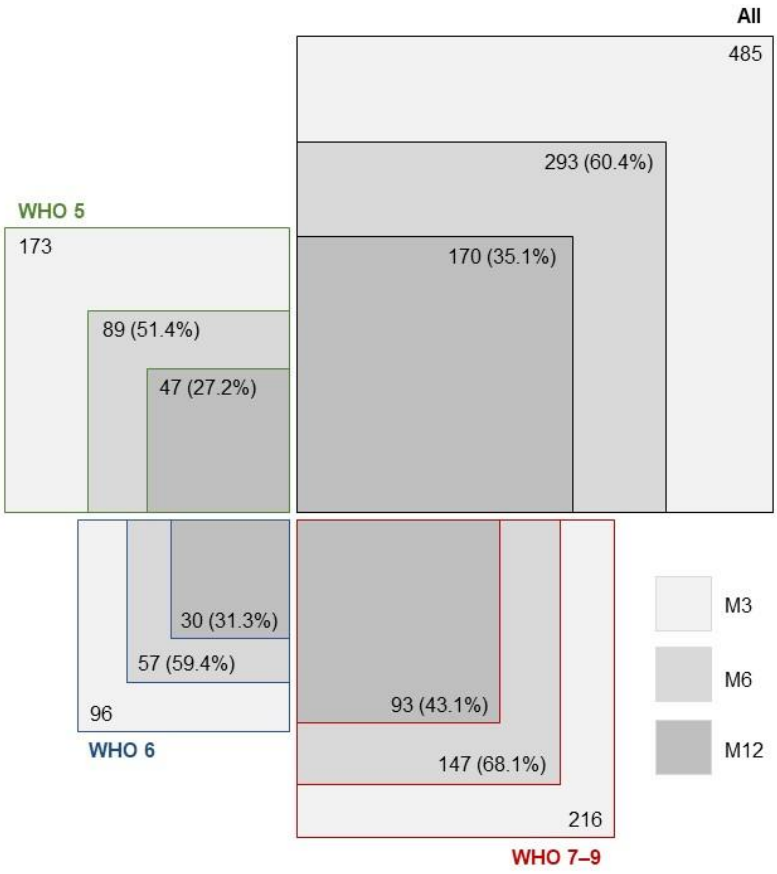
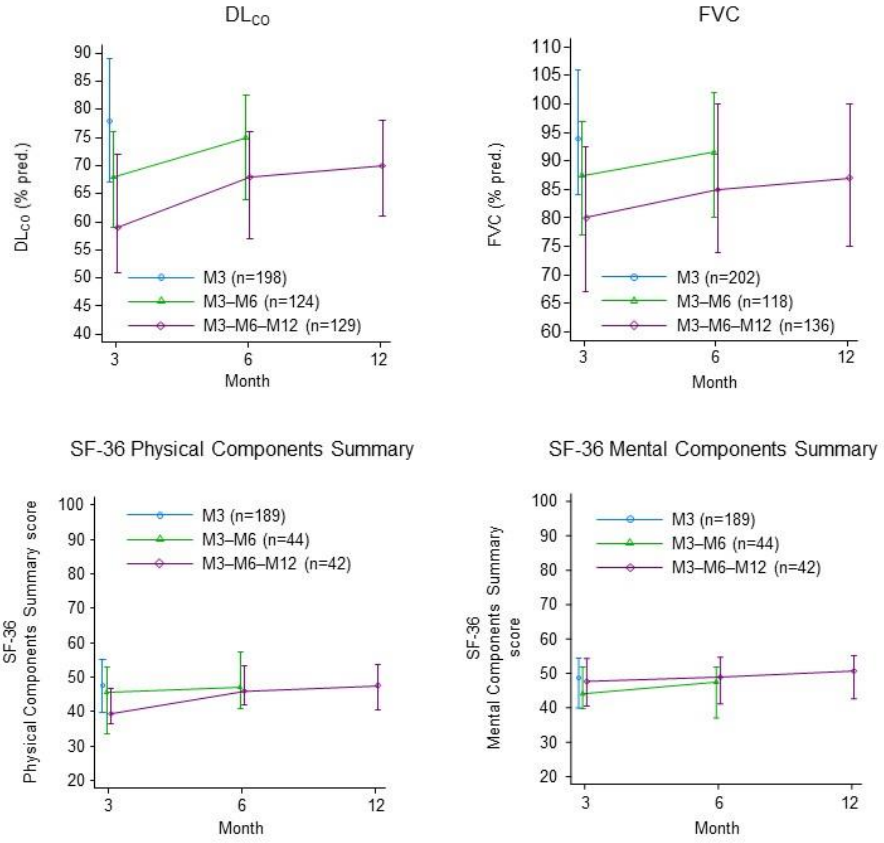

All
485
293 (60.4%)
170 (35.1%)
WHO 5
173
89 (51.4%)
47 (27.2%)
30 (31.3%)
57 (59.4%)
96
WHO 6
93 (43.1%)
147 (68.1%)
216
WHO 7–9
M3
M6
M12


DLCO
DLCO (% pred.)
90
85
80
75
70
65
60
55
50
45
40
3
6
12
Month
M3 (n=198)
M3–M6 (n=124)
M3–M6–M12 (n=129)
FVC
FVC (% pred.)
110
105
100
95
90
85
80
75
70
65
60
3
6
12
Month
M3 (n=202)
M3–M6 (n=118)
M3–M6–M12 (n=136)
SF-36 Physical Components Summary
SF-36 Physical Components Summary score
100
90
80
70
60
50
40
30
20
3
6
12
Month
M3 (n=189)
M3–M6 (n=44)
M3–M6–M12 (n=42)
SF-36 Mental Components Summary
SF-36 Mental Components Summary score
100
90
80
70
60
50
40
30
20
3
6
12
Month
M3 (n=189)
M3–M6 (n=44)
M3–M6–M12 (n=42)

Online data supplement

Methods

Acute COVID-19 diagnosis

Acute COVID-19 was diagnosed based on a positive reverse transcriptase–polymerase chain reaction or typical chest CT-scan images and clinical features.

In-hospital acute-disease information

Patients' medical history and clinical information regarding acute COVID-19, including smoking status and respiratory co-morbidities (COPD, emphysema, asthma, interstitial lung diseases (ILDs), bronchiectasis, obstructive sleep apnoea), were collected retrospectively from medical charts onto a standardised electronic e-Case Report Form (REDCap, version 12.016, Vanderbilt University).

Pulmonary function tests (PFTs)

PFTs were conducted at each centre according to the ATS/ERS consensus guidelines (45). DL_{CO} and carbon monoxide-transfer coefficient (K_{CO}) were corrected for haemoglobin. Results are expressed as the percentage of predicted normal values using reference values taken from Global Lung Initiative 2012 spirometry prediction equations [46] or ATS/ERS consensus guidelines [47], according to each centre's usual practices.

Chest CT-scan analysis

An expert panel comprised of two radiologists (PYB, IS) and three pulmonologists (FS, BM, YU), all experienced in chest-imaging analysis of ILDs and participating in weekly multidisciplinary ILD discussions, reached consensus around items listed on a dedicated form

to analyse follow-up chest CT scans. Given the pragmatic nature of the study, follow-up CT scans were classified into three groups: 1) completely normalised; 2) minor residual signs of COVID-19 pneumonia not warranting systematic monitoring (mild residual ground-glass opacities and/or reticulations without other lung abnormalities attributable to COVID-19); and 3) significant sequelae, this category required more detailed descriptions of residual radiological findings and comparison with the patient's previous CT scan(s) (**table S2**). Two pulmonologists from each of the five centres outside APHP were responsible for the analyses of chest CT scans obtained in their centre, with the help of a local radiologist, if necessary, while one pulmonologist (FS) and one radiologist (IS) analysed the chest CT scans from the eight APHP hospitals. No difficulties in reaching a consensus were reported. If multiple CT scans were available during hospitalisation for acute COVID-19, the worst one was retained to assess COVID-19-attributed lung-lesion extent.

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 manuscript.

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Supplemental Figure Legend

FIGURE S1 Respiratory (DL_{CO}, FVC) recovery trajectories up to month (M) 12 after acute COVID-19, according to initial disease severity.

Participants were divided into three groups according to their initial WHO clinical progression-scale of disease severity during hospitalisation for acute COVID-19 (WHO 5: standard oxygen only; WHO 6: high-flow oxygen and/or non-invasive mechanical ventilation; WHO 7–9: invasive mechanical ventilation during ≥48 h). Data are median [1^{st};3^{rd} quartiles: T bars]. For patients not followed until M12, their missing M6 and/or M12 data were imputed from their last available values.

TABLE S1 Laboratory findings, pharmacological management and complications during acute COVID-19, according to disease severity

Parameter	All	WHO 5	WHO 6	WHO 7–9	p value
Participants, n	485	173	96	216	–
Laboratory findings during hospitalisation					
C-reactive protein (mg/L, maximum value) (n=434)	186 [106;258]	154 [85;232]	191 [109;267]	204 [134;274]	**0.001**
Procalcitonin (ng/mL, maximum value) (n=366)	0.37 [0.15;1.2]	0.20 [0.1;0.48]	0.40 [0.19;0.79]	0.64 [0.25;1.9]	**<0.001**
Fibrinogen (g/L, maximum value) (n=377)	7.6 [6.5;9.0]	7.18 [6;8.44]	7.15 [6.3;8.25]	8.19 [6.92;9.3]	**<0.001**
D-dimers (ng/mL, maximum value) (n=347)	2340 [1107;4950]	1410 [760;2691]	1940 [1040;3881]	3551 [1617;7407]	**<0.001**
Lactate dehydrogenase (IU/L, maximum value) (n=363)	515 [403;683]	482.5 [352;626]	516 [403;681]	528.5 [429;733]	**0.025**
Albumin (g/L, minimum value) (n=334)	25 [22;30]	28.9 [24.2;32]	26 [24;30]	23.6 [18.7;27.0]	**<0.001**
Pharmacological management					
Antibiotics (n=483)	438 (90.7)	148 (86.1)	84 (87.5)	206 (95.8)	**0.002**
Hydroxychloroquine (n=480)	124 (25.9)	41 (24.0)	34 (35.4)	49 (23.1)	0.057
Antivirals (n=482)	132 (27.4)	36 (20.8)	19 (19.8)	77 (36.2)	**0.001**
Anti-cytokine (n=482)	48 (10.0)	18 (10.4)	15 (15.8)	15 (7.0)	0.057
Tocilizumab	31 (64.6)	10 (55.6)	9 (60.0)	12 (80.0)	0.311
Anakinra	10 (20.8)	6 (33.3)	3 (20.0)	1 (6.7)	0.176
Corticosteroids*	100 (20.6)	31 (17.9)	23 (24.0)	46 (21.3)	0.476
Anticoagulants (n=474)	468 (98.7)	162 (97.0)	94 (100)	212 (99.5)	0.076
Preventive	204 (43.0)	104 (62.3)	40 (42.6)	60 (28.2)	**<0.001**
Intermediate	98 (20.7)	25 (15.0)	22 (23.4)	51 (23.9)	0.077
Curative	165 (34.8)	33 (19.8)	32 (34.0)	100 (46.9)	**<0.001**
Inclusion in a clinical trial (n=480)	93 (19.4)	29 (16.9)	24 (25.3)	40 (18.8)	0.240
Complications during hospitalization					
Documented bacterial infection (VAP excluded)	65 (13.4)	9 (5.2)	5 (5.2)	51 (23.6)	**<0.001**
Ventilator-associated pneumonia (n=214)	–	–	–	130 (60.7)	–

Acute cardiac failure	43 (8.9)	5 (2.9)	4 (4.2)	34 (15.7)	**<0.001**
Acute renal failure	118 (24.3)	20 (11.6)	9 (9.4)	89 (41.2)	**<0.001**
Acute renal failure requiring haemodialysis	24 (4.9)	2 (1.2)	2 (2.1)	20 (9.3)	**<0.001**
ICU-related neuromyopathy (n=333)	–	–	2 (2.3)	127 (62.3)	–
Venous thromboembolism (n=482)	70 (14.5)	14 (8.1)	11 (11.6)	45 (21.0)	**0.001**
Pulmonary embolism	46 (65.7)	12 (85.7)	10 (90.9)	24 (53.3)	**0.015**
Deep venous thrombosis	12 (17.1)	2 (14.3)	1 (9.1)	9 (20.0)	0.813
Catheter-associated DVT	12 (17.1)	0 (0)	0 (0)	12 (26.7)	**0.017**
Treatment at hospital discharge					
Oxygen therapy (n=484)	90 (18.6)	36 (20.8)	21 (21.9)	33 (15.3)	0.243
Corticosteroids (n=484)	42 (8.7)	19 (11)	10 (10.4)	13 (6.0)	0.182

Data are n (%) for categorical variables and median [1st;3rd quartile] for continuous variables. Percentages are calculated by category after exclusion of patients with missing values for that variable. WHO clinical progression scale: WHO 5: continuous supplemental oxygen only; WHO 6: non-invasive ventilation (continuous or bi-level positive airway pressure ventilation) or high-flow oxygen; and WHO 7–9: invasive mechanical ventilation +/– other organ support; DVT=deep venous thrombosis; ICU: intensive care unit; VAP: ventilator-associated pneumonia. *Hydrocortisone hemisuccinate excluded.

TABLE S2 Characteristics of COVID-19 survivors, their respiratory management during acute COVID-19 and outcomes, according to length of follow-up

Characteristic	All	Month-3 only	Until month 6 or 12	p value
Participants	485 (100)	176 (36.3)	309 (63.7)	–
Age (at admission), years	60.7 [53.4;67.6]	59.7 [51.6;66.1]	61.7 [54.4;68.6]	0.068
Males	354 (73.0)	129 (73.3)	225 (72.8)	0.909
Body mass index (kg/m^2)	28.4 [25.5;32.3]	28.7 [25.4;32.8]	28.4 [25.7;31.8]	0.574
≥30	177 (36.5)	67 (38.1)	110 (35.6)	0.587
Initial disease severity				**0.004**
WHO 5	173 (35.7)	78 (44.3)	95 (30.7)	
WHO 6	96 (19.8)	36 (20.5)	60 (19.4)	
WHO 7–9	216 (44.5)	62 (35.2)	154 (49.8)	
Co-morbidities				
Number	1 [0;2]	1 [0;2]	1 [0;2]	**0.024**
0	155 (32.0)	63 (35.8)	92 (29.8)	0.103
1	140 (28.9)	55 (31.2)	85 (27.5)	
≥2	190 (39.2)	58 (33.0)	132 (42.7)	
Cardiovascular disease	244 (50.3)	82 (46.6)	162 (52.4)	0.216
Chronic respiratory disease (OSA excluded)	63 (13.0)	15 (8.6)	48 (15.6)	**0.029**
Obstructive sleep apnoea	46 (9.5)	17 (9.7)	29 (9.4)	0.921
Diabetes	107 (22.1)	32 (18.2)	75 (24.3)	0.120
Immune deficiency (all causes)	52 (10.7)	21 (11.9)	31 (10.0)	0.516
Maximum COVID-19 pneumonia extent on chest CT (n=424/160/264)				**<0.001**
<25%	68 (16.0)	32 (20.0)	36 (13.6)	
25–49%	158 (37.3)	71 (44.4)	87 (33.0)	
50–75%	143 (33.7)	49 (30.6)	94 (35.6)	
>75%	55 (13.0)	8 (5.0)	47 (17.8)	

Oxygen and ventilatory support				
Maximum oxygen flow, liter/min (n=412/153/259)	15 [6;15]	10 [6;15]	15 [6;15]	**0.013**
Non-invasive ventilatory support	208 (42.9)	66 (37.5)	142 (46.0)	0.070
High-flow oxygen	156 (32.2)	52 (30.0)	104 (33.7)	0.351
Continuous positive airway pressure	73 (15.1)	24 (13.6)	49 (15.9)	0.511
Bi-level non-invasive ventilation	45 (9.3)	16 (9.1)	29 (9.4)	0.914
Invasive mechanical ventilation	216 (44.5)	62 (35.2)	154 (49.8)	**0.002**
Extracorporeal membrane oxygenation	20 (4.1)	3 (1.7)	17 (5.5)	**0.043**
Prone-positioning	167 (34.4)	42 (23.9)	125 (40.5)	**<0.001**
Hospital length-of-stay, days* (n=475/169/306)	18 [11;31]	14 [10;22]	21.5 [13;37]	**<0.001**
Discharged to a rehabilitation unit (n=477/172/305)	223 (46.7)	65 (37.8)	158 (51.8)	**0.003**
Dyspnoea (mMRC) at M3 (n=468/172/296)				**<0.001**
0	199 (42.5)	102 (59.3)	97 (32.8)	
1	173 (37.0)	47 (27.3)	126 (42.6)	
≥2	96 (20.5)	23 (13.4)	73 (24.7)	
FVC <80% pred. at M3 (n=464/169/295)	139 (30.0)	27 (16.0)	112 (38.0)	**<0.001**
DL_{CO} <70% pred. at M3 (n=436/154/282)	209 (47.9)	39 (25.3)	170 (60.3)	**<0.001**
Global assessment of residual COVID-19–attributed abnormalities at M3 (n=422/155/267)				**<0.001**
Complete resolution	82 (19.4)	58 (37.4)	24 (9.0)	
Minor residual abnormalities†	104 (24.6)	57 (36.8)	47 (17.6)	
Significant sequelae	236 (56.0)	40 (25.8)	196 (73.4)	
Composite criterion for extended follow-up (mMRC>0 or FVC<80% or DLco <70% or significant radiological sequelae) at M3 (n=465/165/300)	406 (87.3)	114 (69.1)	292 (97.3)	**<0.001**

Data are n (%) for categorical variables and median [1st;3rd quartile] for continuous variables. Percentages were calculated by category after exclusion of patients with missing values for that variable. WHO clinical progression scale: WHO 5: continuous supplemental oxygen only; WHO 6: non-invasive ventilation (continuous or bi-level positive airway pressure ventilation) or high-flow

oxygen; and WHO 7–9: invasive mechanical ventilation with/without other organ support; OSA; obstructive sleep apnoea. * Rehabilitation unit excluded. † Mild residual ground-glass opacities and/or reticulations without other lung COVID-19-attributable abnormalities.

TABLE S3 Chest CT assessment at 3 months according to acute COVID-19 severity, and at follow-up months 6 and 12

Parameter	Month 3					Month 6	Month 12
	All	WHO 5	WHO 6	WHO 7–9	p value	All	All
Number of cases (% available)	422 (87.0)	152 (87.9)	87 (90.6)	183 (84.7)		225 (76.8)	123 (72.4)
Hospital-discharge-to-chest CT interval, months	2.9 [2.5;3.4]	2.9 [2.5;3.3]	2.9 [2.6;3.4]	2.9 [2.2;3.4]	0.120	6.1 [5.6;6.5]	11.8 [11.2;12.5]
Global assessment of residual COVID-19–attributed abnormalities					**<0.001**		
Complete resolution	82 (19.4)	48 (31.6)	18 (20.7)	16 (8.7)		29 (12.9)	9 (7.3)
Minor residual abnormalities*	104 (24.6)	40 (26.3)	22 (25.3)	42 (23.0)		57 (25.3)	27 (22.0)
Significant sequelae	236 (56.0)	64 (42.1)	47 (54.0)	125 (68.3)		139 (61.8)	87 (70.7)
Ground-glass opacities	216 (91.5)	57 (89.1)	45 (95.7)	114 (91.2)	0.497	122 (87.8)	73 (83.9)
Mild (n=215/121/73)	90 (41.9)	24 (42.1)	17 (37.8)	49 (43.4)	0.801	79 (65.3)	53 (72.6)
Moderate	111 (51.6)	31 (54.4)	24 (53.3)	56 (49.6)		39 (32.2)	18 (24.7)
Diffuse	14 (6.5)	2 (3.5)	4 (8.9)	8 (7.1)		3 (2.5)	2 (2.7)
Reticulations	192 (81.4)	50 (78.1)	40 (85.1)	102 (81.6)	0.644	111 (79.9)	74 (85.1)
Consolidations (n=234/138/85)	17 (7.3)	4 (6.4)	2 (4.3)	11 (8.9)	0.669	9 (6.5)	1 (1.2)
Curvilinear lines (n=232/139/87)	183 (78.9)	49 (76.6)	37 (80.4)	97 (79.5)	0.860	104 (74.8)	68 (78.2)
Traction bronchiectasis/bronchiolectasis	125 (53.0)	26 (40.6)	18 (38.3)	81 (64.8)	**0.001**	92 (66.2)	71 (81.6)
Diffuse (≥3 lobes)	57 (45.6)	9 (34.6)	8 (44.4)	40 (49.4)	0.264	43 (46.7)	32 (45.1)
Honeycombing (n=236/138/86)	14 (5.9)	2 (3.1)	1 (2.1)	11 (8.8)	0.205	11 (8.0)	13 (15.1)
Cysts (n=235/139/87)	19 (8.1)	6 (9.4)	5 (10.6)	8 (6.5)	0.563	12 (8.6)	6 (6.9)
Scissural distortion (n=234/139/87)	49 (20.9)	11 (17.2)	8 (17.4)	30 (24.2)	0.430	35 (25.2)	22 (25.3)
Subpleural predominance of lung lesions (n=236/139/86)	144 (61.0)	37 (57.8)	31 (66.0)	76 (60.8)	0.684	90 (64.8)	66 (76.7)
Pneumothorax	1 (0.4)	0 (0)	0 (0)	1 (0.9)	>0.999	0 (0)	0 (0)
Pneumomediastinum	1 (0.4)	1 (1.6)	0 (0)	0 (0)	0.470	0 (0)	0 (0)
Evolution since previous CT evaluation (n=221/136/86)					0.375		

Improvement	210 (95.0)	60 (98.4)	44 (97.8)	106 (92.2)		96 (70.6)	33 (38.4)
Stability	5 (2.3)	1 (1.6)	0 (0)	4 (3.5)		39 (28.7)	53 (61.6)
Aggravation	6 (2.7)	0 (0)	1 (2.2)	5 (4.4)		1 (0.7)	0 (0)
Emphysema (n=422/225/123)	65 (15.4)	30 (19.7)	13 (14.9)	22 (12.0)	0.149	40 (17.8)	21 (17.1)
Nodule or mass, suspected neoplasia (n=421/224/121)	12 (2.9)	2 (1.3)	2 (2.3)	8 (4.4)	0.237	9 (4.0)	6 (5.0)
Coronary calcifications (n=421/225/122)	139 (33.0)	52 (34.2)	28 (32.2)	59 (32.4)	0.926	84 (37.3)	46 (37.7)

Data are n (%) for categorical variables and median [1st;3rd quartile] for continuous variables. Percentages are calculated by category after exclusion of patients with missing values for that variable. Chi-square or Kruskal–Wallis tests were used as appropriate. WHO clinical progression scale: WHO 5: continuous supplemental oxygen only; WHO 6: non-invasive ventilation (continuous or bi-level positive airway pressure ventilation) or high-flow oxygen; and WHO 7–9: invasive mechanical ventilation +/– other organ support. * Mild residual ground-glass opacities and/or reticulations without other lung COVID-19-attributable abnormalities.

TABLE S4 Global assessment of residual COVID-19-attributed abnormalities on the last available chest CT obtained during follow-up, according to initial disease severity

	All	WHO 5	WHO 6	WHO 7–9	p value
Available	476 (98.1)	167 (96.5)	95 (99.0)	213 (98.6)	
Complete resolution	117 (24.6)	67 (40.1)	24 (25.3)	26 (12.2)	<0.001†
Minor residual abnormalities*	162 (34.0)	53 (31.7)	39 (41.0)	70 (32.9)	trend‡ <0.001
Significant sequelae	196 (41.2)	47 (28.1)	32 (33.7)	117 (54.9)	

Data are n (%). WHO clinical progression scale: WHO 5: continuous supplemental oxygen only; WHO 6: non-invasive ventilation (continuous or bi-level positive airway pressure ventilation) or high-flow oxygen; and WHO 7–9: invasive mechanical ventilation +/– other organ support. * Mild residual ground-glass opacities and/or reticulations without other lung COVID-19-attributable abnormalities. † Chi-square test. ‡ Jonckheere trend test.

TABLE S5 Multivariate analysis: factors associated with the best DL_{CO} or FVC values obtained during 1-year follow-up

Variable	DL_{COmax} (n=370 patients)	p value	FVC_{max} (n=379 patients)	p value
	Coefficient [95% CI]		Coefficient [95% CI]	
M3 outcome	Reference		Reference	
M6 outcome*	–4.7 [–9.8;0.4]	0.069	0.2 [–4.4;4.8]	0.927
M12 outcome†	–5.9 [–11.8;0.03]	0.051	–3.4 [–8.2;1.4]	0.164
Immunosuppression	–9.3 [–15.0;–3.6]	**0.002**	–11.6 [–17.9;–5.4]	**<0.001**
Cardiovascular disease	–2.2 [–5.9;1.4]	0.226	–4.7 [–8.7;–0.6]	**0.023**
Chronic respiratory disease‡	–6.5 [–11.6;–1.5]	**0.012**	–1.5 [–7.1;4.0]	0.585
Extension of pneumonia during acute COVID-19				
<25%	Reference		Reference	
25–49	–2.6 [–7.6;2.4]	0.312	–1.4 [–6.9;4.2]	0.631
50–75	–6.1 [–11.2;–0.9]	**0.022**	–2.0 [–7.7;3.7]	0.485
>75	–4.6 [–11.5;2.4]	0.197	–5.4 [–12.8;2]	0.154
Male sex	9.0 [4.8;13.0]	**<0.001**	–6.2 [–10.7;–1.7]	**0.007**
Age (by quartiles)				
<54.1	Reference		Reference	
[54.1–61.1[	–0.6 [–5.4;4.2]	0.810	3.5 [–1.8;8.7]	0.197
[61.1–68.1[	–0.9 [–5.9;4.0]	0.709	4.9 [–0.5;10.4]	0.075
≥68.1	0.9 [–4.3;6.0]	0.740	13.4 [7.8;19.0]	**<0.001**
Body mass index				
<24.9	Reference		Reference	
25–29.9	2.3 [–2.1;6.7]	0.306	3.7 [–1.1;8.6]	0.134
≥30	7.7 [2.9;12.5]	**0.002**	0.02 [–5.3;5.3]	0.995
Invasive mechanical ventilation				
No	Reference		Reference	
<14 days	–9.0 [–15.2;-2.7]	**0.005**	1.0 [–4.1;6.1]	0.706
≥14 days	–3.6 [–11.3;4.1]	0.355	2.4 [–2.6;7.3]	0.351
Corticosteroids§	–3.4 [–7.6;0.8]	0.111	–2.0 [–6.7;2.7]	0.405
Interaction: month x IMV		**0.020**		
M3 outcome × No IMV	Reference			
M6 outcome × <14 days	14.4 [2.8;26.1]	**0.015**		
M6 outcome × ≥14 days	–7.3 [–18.7;4.2]	0.252		
M12 outcome × <14 days	11.4 [0.1;22.7]	**0.048**		
M12 outcome × ≥14 days	2.9 [–7.7;13.4]	0.594		

Mixed linear model with random intercept adjusted for all variables in the table. Diffusing capacity for carbon monoxide (DL_{COmax}) and forced vital capacity (FVC_{max}) expressed as % of the predicted value.

IMV, invasive mechanical ventilation.

* Outcome-value difference for patients followed at M6 *versus* M3. † Outcome-value difference for patients followed at M12 versus M3. ‡ Obstructive sleep apnea was excluded from this category. § During hospitalization for acute COVID-19

(hydrocortisone hemisuccinate excluded).

TABLE S6. Multivariate analysis: factors associated with respiratory trajectories between follow-up months 3 and 12, after imputation of missing follow-up data until M12

Variable	DL_{CO} (1167 measures/n=389 patients)		FVC (1194 measures/n=398 patients)	
	Coefficient [95% CI]	p value	Coefficient [95% CI]	p value
M3 outcome	Reference		Reference	
M6 outcome*	2.9 [1.9;3.9]	**<0.001**	2.1 [0.4;3.8]	**0.018**
M12 outcome†	3.9 [3.0;4.9]	**<0.001**	1.6 [0.03;3.2]	**0.046**
M3 DL_{CO}	–		–	
Immunosuppression	–8.8 [–14.2;–3.3]	**0.002**	–11.1 [–17.0;–5.3]	**<0.001**
Cardiovascular disease	–3.0 [–6.5;0.4]	0.083	–6.1 [–9.9;–2.2]	**0.002**
Chronic respiratory disease‡	–8.5 [–13.2;–3.8]	**<0.001**	–2.2 [–7.4;2.9]	0.393
Acute COVID-19 pneumonia extent on chest CT				
<25%	Reference		Reference	
25–49	–3.4 [–8.3;1.4]	0.164	–2.0 [–7.4;3.3]	0.457
50–75	–7.2 [–12.1;–2.3]	**0.004**	–4.3 [–9.8;1.2]	0.129
>75	–8.4 [–14.8;–2]	**0.010**	–11.2 [–18.2;–4.1]	**0.002**
Male sex	8.8 [5.0;12.6]	**<0.001**	–5.4 [–9.5;–1.2]	**0.012**
Age (by quartiles)				
<54.1	Reference		Reference	
[54.1–61.1[	–0.5 [–5.2;4.1]	0.818	4.3 [–0.8;9.3]	0.097
[61.1–68.1[	–0.9 [–5.6;3.8]	0.712	4.7 [–0.4;9.9]	0.073
≥68.1	–1.1 [–6.0;3.8]	0.655	12.4 [7.0;17.8]	**<0.001**
Body mass index (kg/m^2)				
<24.9	Reference		Reference	
25–29.9	2.5 [–1.7;6.7]	0.250	4.9 [0.3;9.5]	**0.039**
≥30	8.3 [3.7;12.8]	**<0.001**	2.0 [–3.0;7.0]	0.429
Invasive mechanical ventilation				
No	Reference		Reference	
<14 days	–1.7 [–6.2;2.7]	0.441	3.2 [–1.8;8.1]	0.209
≥14 days	–6.0 [–10.3;–1.8]	**0.006**	–2.8 [–7.5;1.9]	0.239
Corticosteroids§	–4.3 [–8.3;–0.4]	**0.032**	–2.2 [–6.5;2.1]	0.318
Interaction: month × acute pneumonia extent				**0.002**
M3 outcome × extent<25%			Reference	
M6 outcome × 25–49			0.3 [–1.8;2.3]	0.782
M6 outcome × 50–75			1.0 [–1.1;3.1]	0.363
M6 outcome × >75			2.9 [0.1;5.6]	**0.039**
M12 outcome × 25–49			1.2 [–0.7;3.1]	0.223
M12 outcome × 50–75			2.2 [0.3;4.1]	**0.024**
M12 outcome × >75			4.8 [2.3;7.3]	**<0.001**

Interaction: month × IMV		**<0.001**
M3 outcome × no IMV	Reference	
M6 outcome × <14 days	–1.5 [–3.4;0.3]	0.108
M6 outcome × ≥14 days	3.2 [1.5;4.9]	**<0.001**
M12 outcome × <14 days	–1.9 [–3.7;–0.2]	**0.032**
M12 outcome × ≥14 days	3.1 [1.5;4.8]	**<0.001**

Mixed linear model with random intercept adjusted for all variables in the table. DL_{CO} and FVC expressed in % of the predicted value. PCS- and MCS-score range (0–100).

IMV, invasive mechanical ventilation.

* Outcome-value difference for patients followed at M6 *versus* M3. † Outcome-value difference for patients followed at M12 versus M3. ‡ Obstructive sleep apnea was excluded from this category. § During hospitalization for acute COVID-19 (hydrocortisone hemisuccinate excluded). DL_{CO}: diffusing capacity for carbon monoxide; FVC: forced vital capacity.

TABLE S7 Multivariate analysis: factors associated with respiratory trajectories (DLCO) between follow-up months 3 and 12, after inclusion of the variables "VAP" and "Documented bacterial infection" during acute COVID-19, with the variable "invasive mechanical ventilation" or without

Variable	DL_{CO} [version 1] (712 measures/n=387 patients)		DL_{CO} [version 2] (717 measures/n=390 patients)	
	Coefficient [95% CI]	p value	Coefficient [95% CI]	p value
M3 outcome	Reference		Reference	
M6 outcome*	4.1 [2.5;5.7]	**<0.001**	4.1 [2.5;5.7]	**<0.001**
M12 outcome†	6.7 [4.7;8.7]	**<0.001**	6.6 [4.7;8.6]	**<0.001**
M3 DL_{CO}	–		–	
Immunosuppression	–8.2 [–13.7;–2.8]	**0.003**	–8.2 [–13.6;–2.7]	**0.003**
Cardiovascular disease	–3.4 [–6.8;0.1]	0.057	–3.1 [–6.6;0.3]	0.074
Chronic respiratory disease‡	–8.8 [–13.5;–4.2]	**<0.001**	–8.7 [–13.3;–4.0]	**<0.001**
Acute COVID-19 pneumonia extent on chest CT				
<25%	Reference		Reference	
25–49	–3.3 [–8.2;1.6]	0.183	–3.3 [–8.2;1.6]	0.183
50–75	–7.3 [–12.3;–2.3]	**0.004**	–7.3 [–12.2;–2.3]	**0.004**
>75	–8.4 [–14.7;–2.0]	**0.010**	–9.0 [–15.2;–2.8]	**0.005**
Male sex	9.4 [5.5;13.2]	**<0.001**	9.2 [5.4;13.0]	**<0.001**
Age (by quartiles)				
<54.1	Reference		Reference	
[54.1–61.1[	–0.3 [–4.9;4.4]	0.912	–0.6 [–5.2;4.0]	0.786
[61.1–68.1[	–1.0 [–5.7;3.7]	0.674	–1.3 [–6.0;3.4]	0.592
≥68.1	–1.7 [–6.6;3.2]	0.503	–1.6 [–6.5;3.2]	0.510
Body mass index (kg/m^2)				
<24.9	Reference		Reference	
25–29.9	2.8 [–1.5;7.0]	0.202	2.7 [–1.5;6.9]	0.203
≥30	8.5 [3.9;13]	**<0.001**	8.1 [3.7;12.6]	**<0.001**
Invasive mechanical ventilation				
No	Reference			

<14 days	–0.6 [–5.6;4.4]	0.819		
≥14 days	–4.0 [–10.9;2.9]	0.251		
Corticosteroids§	–4.5 [–8.5;–0.6]	**0.025**	–4.6 [–8.5;–0.6]	**0.023**
Ventilator-associated pneumonia	–4.4 [–10.4;1.7]	0.155	–7.0 [–10.9;–3.1]	**<0.001**
Documented bacterial infection (VAP excluded)	3.6 [–1.6;8.8]	0.180	2.6 [–2.4;7.5]	0.307

Mixed linear model with random intercept adjusted for all variables in the table. DL_{CO} and FVC expressed in % of the predicted value. * Outcome-value difference for patients followed at M6 *versus* M3. † Outcome-value difference for patients followed at M12 versus M3. ‡ Obstructive sleep apnea was excluded from this category. § During hospitalization for acute COVID-19 (hydrocortisone hemisuccinate excluded). DL_{CO}: diffusing capacity for carbon monoxide; FVC: forced vital capacity; VAP: Ventilator-associated pneumonia.

TABLE S8 Multivariate analysis: factors associated with respiratory trajectories (DL_{CO}, FVC) between follow-up months 3 and 12, only for critical WHO 7–9 patients

Variable	DL_{CO} (303 measures/n=150 patients)		FVC (307 measures/n=153 patients)	
	Coefficient [95% CI]	p value	Coefficient [95% CI]	p value
M3 outcome	Reference		Reference	
M6 outcome*	3.9 [0.04;7.7]	**0.047**	1.9 [-1.1;4.9]	0.220
M12 outcome†	3.1 [-1.3;7.5]	0.167	2.5 [-1.2;6.2]	0.192
M3 DL_{CO}	–		–	
Immunosuppression	–1.6 [–9.3;6.0]	0.680	–7.2 [–16.0;1.5]	0.105
Cardiovascular disease	–0.9 [–5.9;4.1]	0.726	–9.2 [–15.3;–3.1]	**0.003**
Chronic respiratory disease‡	–9.4 [–16.7;–2.0]	**0.012**	–1.2 [–9.8;7.3]	0.782
Acute COVID-19 pneumonia extent on chest CT				
<25%	Reference		Reference	
25–49	3.8 [–5.1;12.7]	0.402	1.2 [–9.0;11.4]	0.822
50–75	–4.9 [–13.5;3.6]	0.261	0.8 [–9.0;10.7]	0.867
>75	–7.6 [–16.6;1.4]	0.097	–3.4 [–13.9;7.1]	0.522
Male sex	7.8 [2.5;13.1]	**0.004**	–7.1 [–13.6;–0.6]	**0.033**
Age (by quartiles)				
<54.1	Reference		Reference	
[54.1–61.1[	–3.0 [–9.9;3.8]	0.383	8.6 [0.5;16.7]	**0.037**
[61.1–68.1[	–1.9 [–8.8;5.0]	0.590	4.9 [–3.3;13.0]	0.240
≥68.1	–2.1 [–9.5;5.2]	0.573	16.3 [7.7;25.0]	**<0.001**
Body mass index (kg/m^2)				
<24.9	Reference		Reference	
25–29.9	2.0 [–4.9;8.9]	0.572	7.3 [–1.0;15.5]	0.083
≥30	7.9 [0.3;15.5]	**0.041**	8.2 [–0.8;17.2]	0.074
Invasive mechanical ventilation				
No	–		–	
<14 days	Reference		Reference	
≥14 days	–2.6 [–8.4;3.2]	0.382	–6.6 [–13.4;0.1]	0.055
Corticosteroids§	–3.9 [–9.4;1.5]	0.156	–6.7 [–13.3;-0.1]	**0.048**
Acute renal failure	–3.2 [–8.2;1.8]	0.206	–4.6 [–10.5;1.3]	0.129
Venous thromboembolism	–0.7 [–7.0;5.5]	0.814	–1.9 [–9.3;5.5]	0.616
Curative anticoagulant	1.1 [–4.2;6.3]	0.689	–0.3 [–6.5;5.9]	0.923
Documented bacterial infection (VAP excluded)	4.6 [–0.9;10.2]	0.101	4.1 [–2.5;10.8]	0.221
VAP	–4.2 [–9.4;1.1]	0.120	1.6 [–4.7;7.8]	0.620
Interaction: month × IMV		**0.040**		**<0.001**
M3 outcome × <14 days	Reference		Reference	
M6 outcome × ≥14 days	–1.1 [–5.8;3.8]	0.679	6.8 [3.0;10.6]	**<0.001**

M12 outcome × ≥14 days	5.8 [0.3;11.2]	**0.038**	6.9 [2.4;11.4]	**0.003**

Mixed linear model with random intercept adjusted for all variables in the table. DL_{CO} and FVC expressed in % of the predicted value.

IMV, invasive mechanical ventilation.

* Outcome-value difference for patients followed at M6 *versus* M3. † Outcome-value difference for patients followed at M12 versus M3. ‡ Obstructive sleep apnea was excluded from this category. § During hospitalization for acute COVID-19 (hydrocortisone hemisuccinate excluded). DL_{CO}: diffusing capacity for carbon monoxide; FVC: forced vital capacity; VAP: Ventilator-associated pneumonia.

TABLE S9 Multivariate analysis: factors associated with SF-36 dimensions (physical domains) between follow-up months 3 and 12

Variable	General Health (408 measures /n=275 patients)		Physical Functioning (415 measures /n=280 patients)		Role Physical (386 measures /n=264 patients)		Bodily Pain (407 measures /n=275 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 [–0.3;8.5]	0.065	5.2 [–0.2;10.5]	0.057	7.9 [–4.2;19.9]	0.200	5.9 [–0.2;12]	0.058
M12 outcome†	2.5 [–1.9;6.8]	0.265	6.2 [0.7;11.6]	**0.028**	9.2 [–1.1;19.6]	0.080	3.9 [–2.3;10.2]	0.215
M3 DL_{CO}	0.2 [0.05;0.3]	**0.010**	0.3 [0.1;0.4]	**<0.001**	0.4 [0.1;0.7]	**0.004**	0.2 [–0.004;0.3]	0.056
Immunosuppression	–9.1 [–16.9;–1.3]	**0.023**	–2.4 [–9.9;5.2]	0.540	2.5 [–12.4;17.4]	0.745	1.4 [–7.9;10.7]	0.769
Cardiovascular disease	–3.1 [–8.1;2.0]	0.233	–5.8 [–10.8;–0.8]	0.022	0.9 [–9.1;10.8]	0.866	–0.1 [–5.9;5.7]	0.967
Chronic respiratory disease‡	–0.7 [–7.4;5.9]	0.832	–2.2 [–8.6;4.3]	0.505	–0.7 [–13.7;12.3]	0.915	–5.1 [–12.7;2.5]	0.191
Acute COVID–19 pneumonia extent on chest CT								
<25%	Reference		Reference		Reference		Reference	
25–49	–0.8 [–7.8;6.2]	0.833	1.8 [–5.2;8.8]	0.610	10.1 [–3.4;23.7]	0.144	–1.4 [–9.5;6.7]	0.727
50–75	–5.5 [–12.9;1.9]	0.144	3.9 [–3.5;11.2]	0.304	7.8 [–6.5;22.1]	0.283	–0.2 [–8.7;8.3]	0.963
>75	–0.2 [–9.4;9.0]	0.961	1.5 [–7.4;10.3]	0.747	8.9 [–8.5;26.4]	0.316	3.9 [–6.7;14.5]	0.470
Male sex	3.1 [–2.9;9.0]	0.310	11.0 [5.1;16.9]	**<0.001**	15.7 [4.3;27.0]	**0.007**	4.2 [–2.8;11.1]	0.238
Age (by quartiles)								
<54.1	Reference		Reference		Reference		Reference	
[54.1–61.1[	2.5 [–3.9;8.9]	0.450	–2.1 [–8.5;4.3]	0.518	–6.1 [–18.3;6.1]	0.324	–0.9 [–8.3;6.4]	0.803
[61.1–68.1[	2.3 [–4.6;9.2]	0.519	–8.0 [–14.7;–1.2]	**0.021**	–3.6 [–16.7;9.6]	0.596	–1.4 [–9.3;6.5]	0.729
≥68.1	–0.1 [–7.3;7.0]	0.971	–6.2 [–13.3;0.9]	0.085	–4.8 [–18.6;9.0]	0.495	–0.3 [–8.5;7.9]	0.938
Body mass index (kg/m^2)								
<24.9	Reference		Reference		Reference		Reference	

25–29.9	–0.2 [–6.1;5.7]	0.938	–1.5 [–7.4;4.4]	0.618	3.6 [–7.6;14.8]	0.525	0.4 [–6.4;7.1]	0.913
≥30	–2.1 [–8.8;4.6]	0.544	–4.0 [–10.7;2.7]	0.244	6.4 [–6.4;19.2]	0.326	–4.7 [–12.4;3.1]	0.237
Invasive mechanical ventilation								
No	Reference		Reference		Reference		Reference	
<14 days	0.4 [–5.9;6.7]	0.896	–2.0 [–8.2;4.2]	0.534	–23.3 [–35.2;–11.3]	**<0.001**	–10.4 [–17.7;–3.1]	**0.005**
≥14 days	–2.2 [–8.5;4.2]	0.507	–10.2 [–16.3;–4.0]	**0.001**	–22.4 [–34.3;–10.6]	**<0.001**	–12.8 [–20.1;–5.5]	**0.001**
Corticosteroids§	0.5 [–5.0;6.0]	0.856	2.7 [–2.7;8.1]	0.333	1.4 [–9.2;12.0]	0.801	–3.3 [–9.6;3.1]	0.311

Mixed linear model with random intercept adjusted for all variables in the table. Each SF36-domain 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 hospitalization for acute COVID-19 (hydrocortisone hemisuccinate excluded). SF-36: 36-item Short Form Health Survey; DL_{CO}: diffusing capacity for carbon monoxide.

TABLE S10. Multivariate analysis: factors associated with the SF-36 dimensions (mental domains) between follow-up months 3 and 12

Variable	Mental Health (410 measures /n=277 patients)		Vitality (410 measures /n=277 patients)		Social Functioning (413 measures /n=278 patients)		Role Emotional (378 measures /n=261 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*	-1.0 [–7.9;6.0]	0.782	7.1 [2.9;11.3]	**0.001**	8.6 [–2.0;19.2]	0.110	10.6 [–12.6;33.9]	0.368
M12 outcome†	3.4 [–3.9;10.8]	0.360	3.8 [–0.3;7.9]	0.072	20.5 [9.3;31.6]	**<0.001**	36.8 [14.7;59.0]	**0.001**
M3 DL_{CO}	0.1 [–0.02;0.2]	0.116	0.2 [0.1;0.3]	**0.003**	0.1 [–0.1;0.3]	0.256	0.2 [–0.1;0.5]	0.175
Immunosuppression	–2.2 [–8.5;4.2]	0.504	–1.7 [–8.8;5.3]	0.629	0.03 [–9.3;9.3]	0.994	–12.8 [–27.5;1.9]	0.088
Cardiovascular disease	–0.4 [–4.5;3.7]	0.849	0.1 [–4.4;4.7]	0.956	–3.7 [–9.7;2.3]	0.228	7.2 [–3.0;17.4]	0.167
Chronic respiratory disease‡	–1.1 [–6.6;4.3]	0.691	–2.7 [–8.7;3.3]	0.382	–5.1 [–12.9;2.8]	0.209	–6.4 [–19.4;6.6]	0.333
Acute COVID-19 pneumonia extent on chest CT								
<25%	Reference		Reference		Reference		Reference	
25–49	–2.5 [–8.1;3.2]	0.389	–2.7 [–9.0;3.6]	0.396	0.4 [–7.9;8.7]	0.921	8.3 [–5.0;21.7]	0.222
50–75	–6.5 [–12.5;–0.5]	**0.034**	–1.4 [–8.0;5.3]	0.685	–4.0 [–12.8;4.7]	0.364	–3.3 [–17.5;10.9]	0.648
>75	–6.8 [–14.2;0.8]	0.078	1.9 [–6.4;10.2]	0.659	–1.2 [–12.1;9.7]	0.832	4.2 [–13.1;21.5]	0.637
Male sex	5.5 [0.6;10.3]	**0.027**	8.7 [3.4;14.1]	**0.001**	9.4 [2.4;16.4]	**0.009**	12.0 [–0.1;24.2]	0.052
Age (by quartiles)								
<54.1	Reference		Reference		Reference		Reference	
[54.1–61.1[	–1.1 [–6.6;4.4]	0.705	–0.5 [–6.3;5.3]	0.858	8.5 [–0.4;16.7]	**0.040**	–1.6 [–13.6;10.3]	0.788
[61.1–68.1[	0.8 [–5.2;6.7]	0.801	0.7 [–5.5;7.0]	0.824	7.6 [–1.2;16.4]	0.090	1.2 [–12.0;14.5]	0.857
≥68.1	–3.2 [–9.3;2.9]	0.305	–2.1 [–8.5;4.4]	0.530	7.4 [–1.6;16.4]	0.108	–7.5 [–21.0;6.1]	0.280
Body mass index (kg/m^2)								
<24.9	Reference		Reference		Reference		Reference	
25–29.9	–2.1 [–6.9;2.7]	0.386	0.3 [–5.1;5.6]	0.925	–2.3 [–9.8;4.2]	0.428	-1.9 [–12.9;9.1]	0.735
≥30	–1.5 [–6.9;3.9]	0.584	–1.1 [–7.2;4.9]	0.714	–0.2 [–8.2;7.7]	0.951	1.3 [–11.5;14.1]	0.847

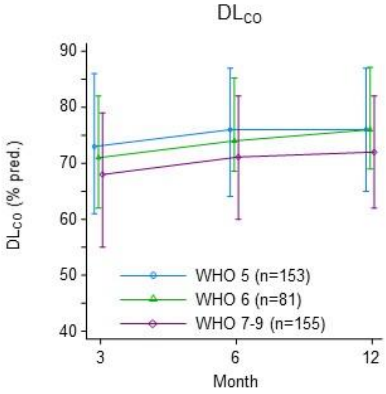
Invasive mechanical ventilation								
No	Reference		Reference		Reference		Reference	
<14 days	–0.3 [–5.6;5.1]	0.921	0.9 [–4.8;6.6]	0.763	–1.9 [–9.3;5.6]	0.626	–23.3 [–35.2;–11.3]	**<0.001**
≥14 days	2.1 [–3.5;7.8]	0.463	–1.2 [–7.0;4.5]	0.676	–3.5 [–11.1;4.1]	0.362	–19.6 [–31.6;–7.6]	**0.001**
Corticosteroids§	-0.1 [–4.6;4.3]	0.950	–0.7 [–5.6;4.3]	0.788	–0.7 [–7.2;5.8]	0.828	–1.7 [–12.1;8.8]	0.861
Interaction: month × age		**0.013**				**0.011**		
M3 outcome × age<54.1 years	Reference				Reference			
M6 outcome × [54.1–61.1[	4.6 [–3.9;13.0]	0.288			–7.9 [–21.6;5.8]	0.257		
M6 outcome × [61.1–68.1[	1.0 [–8.0;10.0]	0.824			–12.2 [–26.2;1.7]	0.086		
M6 outcome × ≥68.1	13.7 [4.4;23.1]	**0.004**			–1.5 [–16.5;13.6]	0.849		
M12 outcome × [54.1–61.1[	–4.2 [–14.1;-5.8]	0.412			–21.3 [–37.3;-5.3]	**0.009**		
M12 outcome × [61.1–68.1[	–4.0 [–13.6;5.6]	0.417			–21.0 [–36.4;-5.7]	**0.007**		
M12 outcome × ≥68.1	–5.0 [–15.0;5.0]	0.329			–28.5 [–44.2;-12.9]	**<0.001**		
Interaction: month × CVD								**0.026**
M3 outcome or no CVD							Reference	
M6 outcome × CVD							–22.7 [–41.2;-4.3]	**0.016**
M12 outcome × CVD							–18.1 [–37.2;0.9]	0.062
Interaction: month × sex								**0.008**
M3 outcome or female sex							Reference	
M6 outcome × male sex							3.1 [–21.4;-27.7]	0.802
M12 outcome × male sex							–40.3 [–63.7;-16.9]	**0.001**
Interaction: month × IMV		**0.017**						
M3 outcome × no IMV	Reference							
M6 outcome × <14 days	–0.7 [–10.2;8.8]	0.886						
M6 outcome × ≥14 days	–9.0 [–16.4;-1.7]	**0.016**						
M12 outcome × <14 days	–1.4 [–12.9;10.1]	0.808						

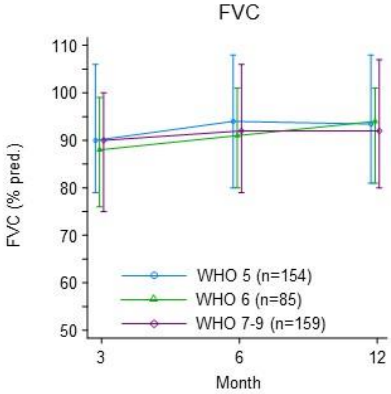
M12 outcome × ≥14 days	4.6 [–3.1;-12.2]	0.242

Mixed linear model with random intercept adjusted for all variables in the table. Each SF36-domain score range (0–100).

CVD, cardiovascular disease; IMV, invasive mechanical ventilation.

* 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 hospitalization for acute COVID-19 (hydrocortisone hemisuccinate excluded). SF-36: 36-item Short Form Health Survey; DL_{CO}: diffusing capacity for carbon monoxide


DLCO
DLCO (% pred.)
90
80
70
60
50
40
3
6
12
Month
WHO 5 (n=153)
WHO 6 (n=81)
WHO 7-9 (n=155)


FVC
FVC (% pred.)
110
100
90
80
70
60
50
3
6
12
Month
WHO 5 (n=154)
WHO 6 (n=85)
WHO 7-9 (n=159)