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Original research article

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Functional respiratory complaints among COVID-19 survivors: a prospective cohort study

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ABSTRACT

***Background*:** Dyspnoea is a common persistent symptom after COVID-19. Whether it is associated with functional respiratory disorders remains unclear.

***Methods*:** We assessed the proportion and characteristics of patients with "functional respiratory complaints" (FRCs) (as defined by Nijmegen Questionnaire > 22) among 177 post-COVID-19 individuals who benefited from outclinic evaluation in the COMEBAC study (i.e., symptomatic and/or ICU survivors at 4 months). In a distinct explanatory cohort of 21 consecutive individuals with unexplained post-COVID-19 dyspnoea after routine tests, we also analysed the physiological responses to incremental cardio-pulmonary exercise testing (CPET).

***Findings*:** In the COMEBAC cohort, 37 had significant FRCs (20.9%, IC95: 14.9-26.9). The prevalence of FRCs ranged from 7.2% (ICU patients) to 37.5% (non-ICU patients). The presence of FRCs was significantly associated with more severe dyspnoea, lower 6-minute walk distance, more frequent psychological and neurological symptoms (cognitive complaint, anxiety, depression, insomnia and post-traumatic stress disorders) and poorer quality of life (all $p<0.01$). In the explanatory cohort, 7/21 patients had significant FRCs. Based on CPET, dysfunctional breathing was identified in 12/21 patients, 5/21 had normal CPET, 3/21 had deconditioning and 1/21 had evidence of uncontrolled cardiovascular disease.

***Interpretation*:** FRCs are common during post-COVID-19 follow-up, especially among patients with unexplained dyspnoea. Diagnosis of dysfunctional breathing should be considered in those cases.

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Key words: COVID-19; dysfunctional breathing; hyperventilation syndrome; post-acute COVID-19 syndrome.

RESEARCH IN CONTEXT

Evidence before this study: Persistent dyspnoea is a frequent long-term complication of COVID-19. However, it poorly correlates with radiological findings. Limited data suggest that post-COVID-19 functional respiratory disorders might be prevalent.

Added value of this study: This study demonstrates that functional respiratory complaints (FRCs) are common in the context of post-COVID-19 follow-up. In the COMEBAC cohort characterised by a recruitment close from a real-life setting (i.e., symptomatic and/or ICU patients), 21% of patients had significant FRC. Those had more severe dyspnoea, poorer quality of life, more frequent psychological and neurological symptoms. In a distinct cohort which specifically enrolled patients with post-COVID-19 unexplained dyspnoea at 6 months, we found that 33% of patients had FRCs. Using cardiopulmonary exercise testing (CPET), we identified dysfunctional breathing as a major cause of exercise intolerance among those patients.

Implications of all the available evidence: Dysfunctional breathing should not be overlooked when investigating post-COVID--19 dyspnoea. CPET is useful to corroborate this diagnosis.

INTRODUCTION

As the world faces the pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there is increasing evidence of the long-term consequences of coronavirus disease 2019 (COVID-19) [1]. The various symptoms and organ-related injuries have been referred to as "post-acute COVID-19 syndrome" [2]. Carfì et al. reported that 87.4% of COVID-19 patients discharged from hospital still had at least one symptom after a mean of 60 days, the most frequent being fatigue (53.1%) and dyspnoea (43.4%) [3]. Likewise, Garrigues et al. reported that most patients requiring hospitalisation for COVID-19 still had persistent symptoms 110 days after being discharged, particularly fatigue (55%) and dyspnoea (42%). In the prospective COMEBAC (COnsultation Multi-Expertise de Bicêtre Après COVID-19) cohort (NCT04704388) evaluating COVID-19 survivors four months after hospitalisation in a university hospital in the Paris region (France), 51% of the patients declared at least one symptom that did not exist before COVID-19 [4]. The underlying mechanisms of post-covid dyspnoea remain unclear. In the present study we investigated post-covid "functional respiratory complaints" (FRCs) using the Nijmegen Questionnaire. As mentioned by van Dixhoorn and Folgering who described this concept, the word "respiratory" refers to ventilation, dyspnoea and breathing movement; the word "functional" refers to the relationship with stress and anxiety [5]. The presence of FRCs is associated with the diagnosis of dysfunctional breathing (DB), of which hyperventilation syndrome (HVS) is a well-known form [5 6]. On one hand, dyspnoea is a subjective symptom that poorly correlates with radiological findings among COVID-19 survivors [7] and HVS have been suggested as a cause of exercise intolerance among COVID-19 survivors [8]. On the other hand, there are evidence of long-term organic injuries that result in interstitial lung disease and impaired gas diffusion several months after the infection [9]. The objectives of this study were: 1) to investigate the proportion and characteristics of patients with FRCs after hospital discharge in the context of

post-COVID-19 follow-up (COMEBAC study); and 2) to analyse the physiological responses to incremental cardiopulmonary exercise testing (CPET) in patients presenting with post-COVID-19 unexplained dyspnoea.

MATERIAL AND METHODS

Patients and study design

The main cohort consisted of 177 patients from the COMEBAC study[4] who had been hospitalised in Bicêtre university hospital (Université Paris-Saclay, AP-HP, France) during the first epidemic wave in France. They were evaluated at the outpatient facility 4 months after hospital discharge in the context of persistent symptoms and/or as a systematic follow-up after ICU management (see **supplementary Figure 1**). Psychological, cognitive and respiratory characteristics of patients with or without FRCs were compared. Details and thresholds of questionnaires and tests used for psychological, cognitive and respiratory assessment are presented in **supplementary Table 1**.

The explanatory cohort consisted of 21 distinct, consecutive patients who had new or worsened dyspnoea 6 months after discharge from Bicêtre university hospital (Université Paris-Saclay, AP-HP, France) for COVID-19 management during the second epidemic wave in France. They were offered cardiopulmonary exercise testing (CPET) in the context of unexplained dyspnoea after completing routine tests at rest (i.e., detection for hypoxaemia and anaemia, CT-scan of the chest and pulmonary function tests, see details below).

All patients provided written informed consent to participate. This study was approved by The Ethics Committee of the French Intensive Care Society (CE20-56).

Respiratory assessment

We used the Nijmegen Questionnaire (NQ, **Table 1**) as a measure of FRCs, as it has been suggested by the authors who initially elaborated this questionnaire [5]. A threshold > 22/64 defined patients with significant FRCs [10]. The functional impact of dyspnoea was evaluated using the modified Medical Research Council (mMRC) scale (**supplementary Table 2**). A 6-minute walk test was performed according to current recommendations [11].

Patients completed standard pulmonary function tests (PFTs) with spirometry, whole-body plethysmography and single-breath diffusing lung capacity for carbon monoxide (DLCO) according to the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines [12]. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), total lung capacity (TLC) and DLCO were expressed as percentages of predicted values using the Global Lung Function Initiative (GLI) 2012 [13] and (European Community for Coal and Steel) ECCS 1993 equations [14,15]. A high-resolution lung CT-scan was performed for all patients and blindly reviewed by two radiologists, who reached a consensus regarding any disagreements.

Hyperventilation provocation test (HVPT)

In the COMEBAC study, all patients with positive NQ were offered a HVPT. End-tidal carbon dioxide partial pressure ($P_{ET}CO_2$) was monitored with a single-use nasal cannula connected to a gas analyser through a sampling system (Perma Pure®), and tidal volume and respiratory rate (RR) were assessed breath-by-breath using a turbine flowmeter adapted with a silicon facemask (Cosmed Quark CPET). A 3-min baseline recording period of quiet breathing was followed by a 3-min voluntary hyperventilation period designed to reach both an RR > 30/min and a $P_{ET}CO_2 \leq 20$ mmHg. If the patient could not maintain these criteria because of clinical intolerance, the manoeuvre was interrupted before the end of the 3 min period. After the hyperventilation period, patients were instructed to breathe normally for 6 min. Patients were then asked to list the symptoms experienced during the test. The HVPT was considered positive if at least 2 daily symptoms were reproduced and/or in case of abnormal $P_{ET}CO_2$ kinetic ($P_{ET}CO2<67\%$ at 3 min and/or < 91% at 5 min), as described elsewhere [16].

Cardiopulmonary exercise testing (CPET)

All patients from the explanatory underwent a maximal symptom-limited incremental exercise on a cycle ergometer (Quark CPET, Cosmed, Italy). The following data were recorded: 1 min of rest period, followed by 3 min of warmup with minimal workload and incrementally increased load until the patient reached maximum exhaustion, or until the physician stopped the test due to safety concerns. The work rate increment was estimated to attain maximal exertion after 8–12 min of loaded exercise (range from 10 to 30 W/min). Spiroergometric variables were measured using breath-by-breath analysis and included oxygen consumption ($\dot{V}O_2$), output of carbon dioxide ($\dot{V}CO_2$), $P_{ET}CO_2$, tidal volume (V_T), breathing frequency (BF) and minute ventilation ($\dot{V}_E$) from which was derived the $\dot{V}_E/\dot{V}CO_2$ ratio. As previously suggested by other authors [17], the CPET pattern was suggestive of dysfunctional breathing in the absence of cardiac, ventilatory, gas exchange or metabolic abnormality associated with one or more of the following features: high $\dot{V}_E/\dot{V}CO_2$ (>35 at 40 W), low $P_{ET}CO_2$ (<30 mmHg) both at rest and during work; erratic V_T and/or RR response to workload. Deconditioning was defined as reduced oxygen uptake at peak exercise ($_{peak}\dot{V}O_2$< 80%), without cardiocirculatory impairment or ventilatory limitation.

Psychiatric, cognitive and general assessment

Global cognitive assessment was performed through the Montreal Cognitive Assessment (MoCA) adapted to age and education level, and attention was assessed through the d2-R test. Memory complaints were assessed through the McNair self-questionnaire and personal interview with a neuropsychologist. A cognitive complaint was defined by a low McNair score, reports of cognitive symptoms, or both. Cognitive impairment was defined by an impairment of either the MoCA or the d2-R score.

Anxiety symptoms were evaluated through the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A); depression symptoms, through the 13-item Beck Depressive Inventory (BDI-13) score; and post-traumatic symptoms, through the Post-traumatic Stress Disorder (PTSD) Checklist for DSM-5 (PCL-5). Insomnia was evaluated through the Insomnia Severity Index (ISI). Psychiatric symptoms were defined as HADS-A >7 or BDI-13 >7 or PCL-5 >30 [4]. Quality of life was assessed through the 36-item short-form health survey (SF-36).

Statistical analysis

Study data were collected and managed with Research Electronic Data Capture tools hosted at Assistance Publique - Hôpitaux de Paris. Raw data were extracted with Omnia software (Cosmed, Italy). For the respiratory rate and $P_{ET}CO_2$, the mean values obtained every 10 seconds were plotted against time. For tidal volumes, instantaneous values were used to detect deep sighing. Out-of-ranges values were all displayed and analysed, and automatic curve smoothing was applied. No assumption was made for missing values. Quantitative data are expressed as the mean (standard deviation) or median (interquartile range (IQR): first quartile to third quartile), according to the normality of the distribution. Qualitative data are expressed as the number of occurrences, i.e., n (%). To compare continuous variables between two

groups, the t-test or Mann–Whitney U-test (if the variables were not normally distributed) was used. Pearson's chi-squared test or Fisher's exact test, as appropriate, was used to compare discrete variables between two groups. The most relevant variables associated with DB with a p value < 0.20 in the bivariate analysis were entered in a multivariable logistic regression model. The adjusted odds ratio (OR) of DB and the 95% confidence interval (95% CI) were calculated for all independent factors associated with DB. Statistical analyses were performed with R (version 4.01, http://cran.rproject.org). All p values were two-sided, and values <0.05 were deemed statistically significant.

RESULTS

Main cohort (COMEBAC)

General characteristics

Among the 177 patients (97 ICU patients and 80 non-ICU patients) evaluated in the outpatient clinic, 37 (20.9%, IC95: 14.9-26.9) had significant FRCs (7.2% in ICU patients and 37.5% in non-ICU patients). Compared with the rest of the population evaluated in the outpatient clinic (n=140), these patients were more often female (59.5% vs 32.9%, p<0.01) but had a similar age, body mass index (BMI) and degree of tobacco exposure. COVID-19-related comorbidities did not differ significantly between the two groups (**Table 1**).

Respiratory assessment

As shown in **Table 2**, patients with FRCs reported a more significant functional impact of their dyspnoea, with 13.5%, 67.6% and 18.9% having a mMRC score of 0, 1-2 and 3-4, respectively, compared to 58.6%, 36.4%, and 5% among the other patients (p<0.001). The distance covered during the 6-minute walk test was shorter among patients with FRCs (404 vs 474 m, p<0.01). Cough was significantly more frequently observed in patients with FRCs (30.6% vs 8.8%, p<0.01). At revaluation, patients with FRCs were more likely to have normal CT-scans of the chest (58.3% vs 31.1%, p<0.01**).** Persistent ground glass opacities and fibrotic lesions were observed in 37.1% and 5.7% of patients with FRCs, respectively, versus 45.9% (p<0.01) and 23.0% (p<0.01) of patients without FRCs. The results of the PFTs did not significantly differ between the 2 groups **(Table 2)**. Details regarding the distribution of each item of the Nijmegen questionnaire in the 37 patients with FRCs are given in **Table 3**. “Shortness of breath” was the most reported item, with 81% of patients describing this

sensation as occurring “often” or “very often”; “anxiety” was the second most frequent finding, followed by “unable to breathe deeply” and “palpitations”. Abnormal responses to HVPT were found in 21/25 (84%) patients, thus representing 12% of the patients evaluated at the outpatient clinic. Typical examples of abnormal breathing patterns are shown in **Figure 1**.

Quality of life, psychiatric and cognitive assessment.

Patients with FRCs reported a poorer quality of life throughout the 8 dimensions of the SF-36 score (physical functioning, role physical, mental health, vitality, role emotional, social functioning, bodily pain, general health) (all $p<0.01$). Having FRCs was associated with more cognitive complaints (61.8% vs 23.9%, $p<0.001$), but no difference was observed in cognitive impairment (39.4% and 38.1%, respectively). Symptoms of anxiety (HADS-A), depression (BDI-13), post-traumatic symptoms (PCL-5) and insomnia (ISI) were significantly increased in patients with FRCs (**Table 2**). **Figure 2** shows a visualisation of symptoms in the 37 patients with FRCs at the outpatient clinic 4 months after COVID-19 hospitalisation.

Multivariate analysis

In patients evaluated in the outpatient clinic, the following variables were considered clinically relevant and included in the multivariate analysis: gender, ICU admission, cognitive complaint, psychiatric symptoms and pathological CT-scan of the chest at revaluation. The following factors were independently associated with higher risk of FRCs: having cognitive complaints (OR=3.41, IC95=1.32-9.58, p=0.014) and psychiatric symptoms (OR=3.19, IC95=1.23-8.68, p=0.019). ICU admission was not associated with higher risk of FRCs (OR=0.15, IC95=0.05-0.45, p=0.001) (**Table 4**).

Explanatory cohort

General characteristics

The 21 consecutive patients who reported new or worsened dyspnoea at 6 months had a mean age of 55 (± 10) years; 12/21 were women. Eleven reported at least grade 2 on mMRC scale. The mean NQ in the overall population was 22 (±11). Sixteen had no evidence of organ damage on routine tests; the 5 other patients had disproportionate dyspnoea with regards to their tests (3 had mild ground glass lesions on CT-scan, 1 had a chronic and stable anaemia due to beta-thalassemia and 1 had isolated mild hypoxaemia at rest). Overall, 7 patients (33%) had a NQ > 22 indicating significant FRCs.

Results of CPET

Among the 21 patients with unexplained dyspnoea, none had evidence of effort hypoxaemia; 12 had anomalies consistent with dysfunctional breathing, 5 had normal CPET and 3 had evidence of deconditioning (associating low value of $_{peak}\dot{V}O_2$, decreased oxygen pulse and early anaerobic threshold). One patient had symptomatic systemic hypertension leading to premature interruption of exercise. Among patients with dysfunctional breathing, 10/12 had $P_{ET}CO_2$<30 mmHg at rest and during exercise; 10/12 had increased $\dot{V}_E/\dot{V}CO_2$ (>35 at 40 W) and 11/12 had evidence of erratic breathing pattern, including 2 patients (17%) with deep sighs. Representative examples are presented in **Figure 3**.

DISCUSSION

In the context of the COMEBAC study, patients underwent extensive work-up in an outpatient clinic, including multi-dimensional dyspnoea assessments, PFTs, chest CT-scans, HVPT, and psychiatric symptoms and cognitive evaluation. Implementing the Nijmegen questionnaire, we found that 20.9% of post-COVID-19 patients had significant FRCs 4 months after hospital discharge. Twelve of 21 patients with post-COVID-19 unexplained dyspnoea at 6 months showed evidence of dysfunctional breathing on CPET. Taken together, these results support the idea that functional respiratory disorders should not be overlooked during COVID-19 follow-up.

The prevalence of FRCs is higher than the prevalence of 9.5% previously reported in a general primary care population [18] but lower than in other conditions such as difficult-to-treat asthma (47%) [19]. Consistent with the previously reported sex-ratio imbalance [18], 59.5% of patients with FRCs were female. Despite the lower number of pathological CT-scans and similar DLCO values, individuals with FRCs were more likely to report severe breathlessness. Using HVPT and breath-by-breath analysis, we were able to identify abnormal breathing patterns in most cases. Notably, some patients displayed a pattern of isolated “deep sighing”, which is thought to be related to anxiety state [20]. The major strength of this study is to provide a detailed assessment of psychological and neurological symptoms, and quality of life and their relationships with FRCs. Our study demonstrates that FRCs are strongly associated with symptoms of anxiety and depression, post-traumatic stress disorders and cognitive complaints. However, whether FRCs are causative or secondary effects of psychiatric symptoms remains uncertain. Some authors have suggested that it could be the consequence of severe psychological trauma [21], while others have emphasised the role of underlying organic respiratory diseases such as asthma [22]. Our results do not support a major role of altered COVID-19-related lung properties in the pathophysiology of FRCs, since patients with

DB had less severe disease at the acute phase and infrequent fibrotic sequelae. To note, mental disorders are risk factors of COVID-19 [23], and psychiatric symptoms are broadly reported in COVID-19 survivors [24 25]. The overlap between FRCs and anxiety symptoms [26] could also explain, at least in part, the high rate of FRCs in COVID-19 survivors.

Since SARS-CoV-2 has neuro-invasive potential [27], other hypotheses can be proposed to explain post-COVID-19 FRCs. First, SARS-CoV-2-mediated neuronal inflammation might interfere with the respiratory drive since the viral receptor angiotensin-converting enzyme 2 (ACE2) is found in the brainstem nuclei involved in the regulation of ventilation [28]. Second, COVID-19 can trigger several neuropsychiatric manifestations, including anxiety [27], which was strongly correlated with FRCs in our study. We found indeed that psychiatric symptoms were independently associated with FRCs. Direct viral infiltration of the central nervous system and immune-based reactions are two potential underlying mechanisms [29]. Studies investigating the relationship between biomarkers and post-acute COVID-19 syndrome are required. We can also speculate that COVID-19 might worsen a pre-existing or latent functional respiratory disorder, favoured by the negative socio-economics effects of the pandemic on mental health [30]. However, in our cohort, the majority of patients did not report any symptoms before their hospitalisation.

Finally, since FRCs are subjective symptoms, we can also hypothesise that FRCs are part of a larger post-COVID-19 somatoform disorder that includes other manifestations of unclear aetiology, such as headache, fatigue and cognitive complaints. Of note, we observed more cognitive complaints (either self-reported or after evaluation by a neuropsychologist) in patients with FRCs but similar cognitive impairment after objective evaluation (MOCA or D2R scores). This difference between subjective and objective symptoms might be related to fatigue, anxiety or depression [4]. As previously described with HVS [31], we highlight that FRCs

severely impacts the quality of life of post-COVID-19 patients, which may induce a significant burden for health-care services.

Limitations.

In an effort to improve the management of the most fragile individuals, we invited all ICU patients to join the COMEBAC cohort (whether or not they complained of persistent symptoms). This recruitment is close from a real-life setting (i.e., symptomatic and/or ICU patients), however it may have contributed to reduce the proportion of patients with FRCs among ICU patients. Nevertheless, the presence of FRCs in patients with mild or moderate COVID-19 suggests that post-COVID-19 functional respiratory disorders should not be sought only in patients with severe pneumonia. In the explanatory cohort of patients with post-COVID-19 unexplained dyspnoea, we established the diagnosis of DB based on criteria available in the current literature [17]. Since there is no current consensus-determined gold standard for the diagnosis of DB, misdiagnoses cannot be excluded. However, we found evidence of abnormal breathing pattern during CPET in 12/21 patients, including 2 patients with typical deep sighing, a feature that we also observed in other patients who underwent HVPT. Our results are consistent with those of Frésard et al. [32] who also described using CPET in post-COVID-19 patients, an erratic type of breathing mainly without hyperventilation corresponding to deep sighs. Other approaches might have been be relevant to assess the ventilatory response of patients. It has been suggested that higher regional inhomogeneity (as assessed by Electrical Impedance Tomography) may contributed to dyspnoea in post-COVID-19 patients. Using CPET, other authors evaluated a method to classify the breathing pattern in terms of inter-rater agreement: among 20 patients, 7 had an abnormal breathing patterns associated with lower exercise capacity, which could possibly explain exercise related symptoms in some patients with post-acute COVID-19 syndrome [33].

The role of dysfunctional breathing and deconditioning has been highlighted in larger cohorts [34] [35]. Deconditioning was uncommon in our explanatory cohort, which was characterized by long-term dyspnoeic patients with normal routine tests and mostly evidence of DB on CPET. When indicated, patients were invited to perform breathing exercises with a physiotherapist. A systematic Cochrane review was unable to inform clinical practice based on the inclusion of only small and poorly reported randomised controlled trials [36]. In our experience, this strategy is effective when the patient is compliant and has access to a well-trained physiotherapist. Unfortunately, these conditions are difficult to meet in a pandemic situation. Promising new therapeutic approaches have emerged, such as the English programme "ENO Breathe", which is based on singing techniques [37].

In conclusion, this study provides new data regarding the occurrence and mechanisms of COVID-19-related functional respiratory complaints and their relationships with psychological and neurological symptoms, and quality of life. Physicians should be aware of these symptoms and incorporate it into their decision-making algorithm when treating patients with post-acute COVID-19 syndrome.

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TABLES

Table 1. Baseline and hospitalisation characteristics according to Nijmegen score.

	Nijmegen score ≤22 (n=140)	Nijmegen score >22 (n=37)	p-value
Age, years	57.3 (13.7)	55.2 (11.1)	0.39
Female	46 (32.9%)	22 (59.5%)	<0.01
Body mass index, kg/m²	28.9 (5.1)	30.5 (6.4)	0.28
Obesity (BMI > 30 kg/m²)	53 (37.9%)	14 (41.2%)	0.99
Hypertension	63 (45.0%)	12 (32.4%)	0.17
Diabetes	43 (30.7%)	9 (24.3%)	0.45
Chronic kidney disease	17 (3.9%)	0	-
COPD	4 (2.9%)	1 (2.7%)	0.61
Asthma	13 (9.3%)	7 (18.9%)	0.17
Smoking (n=169)			
Active	13 (9.6%)	2 (5.9%)	0.64
Former (>5 PY)	21 (15.6%)	4 (11.8%)	
No (<5 PY)	101 (74.8%)	28 (82.4%)	
Management of COVID-19			
Duration of hospitalization, days	13 [6-23]	7.5 [3-15]	<0.01
Pulmonary embolism	25 (17.9%)	4 (10.8%)	0.30
Corticosteroids	7 (5.0%)	0	-
COVID-19-related ICU	90 (64.3%)	7 (18.9%)	<0.001
admission	48 (34.3%)	3 (8.1%)	<0.01
Intubation	7	1	0.88
HFNC	7	1	0.88
ECMO			

COPD: chronic obstructive pulmonary disease; ECMO: extracorporeal membrane oxygenation; HFNC: high flow nasal cannula; ICU: intensive care unit; PY: pack-years.

Table 2. Results of the in-person outpatient clinic visit according to Nijmegen score.

	Nijmegen score ≤22 (n=140)	**Nijmegen score >22 (n=37)**	**p-value**
mMRC (0-4) (n=177)			
0	82 (58.6%)	5 (13.5%)	<0.001
1-2	51 (36.4%)	25 (67.6%)	
3-4	7 (5%)	7 (18.9%)	
Cough (n=172)	12 (8.8%)	11 (30.6%)	<0.01
Lung CT-scan (n=171)			
Normal lung CT-scan	42 (31.1%)	21 (58.3%)	<0.01
Persistent ground glass opacities	62 (45.9%)	13 (37.1%)	
Lung fibrotic lesions	31 (23%)	2 (5.7%)	
Pulmonary function tests (n=157)			
FEV1, %pred	91.4 (18.6)	88.7 (14.8)	0.37
FVC, %pred	89.7 (16.4)	87.0 (16.5)	0.40
FEV1/FVC	82.1 (7.7)	82.2 (6.5)	0.96
TLC, %pred	82.4 (15.7)	84.2 (13.5)	0.51
DLCO, %pred	86.7 (22.7)	88 (20.5)	0.70
Obstructive pattern	5 (4.1%)	1 (2.9%)	0.84
Restrictive pattern	55 (47.4%)	12 (36.4%)	0.26
DLCO < 70%pred	27 (22.7%)	6 (18.2%)	0.93
6MWT distance, m	474 [395-516]	404 [338-472]	<0.01
Psychological and neurological assessment			
Cognitive complaint (n=159)	55 (43.7%)	24 (72.7%)	<0.01
Cognitive impairment (n=159)	48 (38.1%)	13 (39.4%)	1.00

Symptoms of anxiety (HADS-A) (n=169)	32 (23.9%)	21 (61.8%)	<0.001
Symptoms of depression (BDI-13) (n=170)	20 (14.7%)	14 (43.8%)	<0.01
Insomnia (ISI) (n=168)	64 (47.8%)	26 (76.5%)	<0.01
Symptoms of PTSD (PCL-5) (n=169)	12 (8.9%)	12 (35.3%)	<0.01
36-item Short-form Health Survey (n=130)			
Physical functioning	80 [55-90]	50 [35-65]	<0.001
Role physical	50 [25-100]	25 [0-25]	<0.01
Mental health	66.7 [33.3-100]	33.3 [0-66.7]	<0.01
Vitality	56.2 [37.5-75]	31.2 [25-37.5]	<0.001
Role emotional	80 [65-90]	55 [40-55]	<0.001
Social functioning	75 [50-100]	50 [37.5-62.5]	<0.001
Bodily pain	83 [66.5-100]	29 [16.5-58]	<0.001
General health	60 [45-80]	35 [25-60]	<0.001

6MWT 6-minute walk test; BDI-13: Beck Depression Inventory-13 items; DLCO: diffusing capacity for carbon monoxide; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; HADS-A: *Hospital Anxiety and Depression Scale; ISI: Insomnia Severity Index; mMRC: modified Medical Research Council; PCL-5*: *Post-traumatic Stress Disorder Checklist; PTSD: Post-traumatic Stress Disorder; TLC: total lung capacity.*

Cognitive complaint was defined as an impaired McNair score, reported cognitive symptoms, or both. Cognitive impairment was defined as an impairment of either the MoCA or d2-R score. Symptoms of anxiety are defined as a HADS-A score >7. Symptoms of depression were defined as a BDI-13 test score >7. Insomnia was defined as an ISI > 7, and PTSD was defined as a PCL-5 score > 30 ***(supplementary Table 1)****.*

The European Community for Coal and Steel (ECCS) reference values were used for lung volume and TLC was expressed without adjustment for ethnicity.

Table 3. Detailed results of the Nijmegen questionnaire item in the 37 patients with a score >22

Item	Mean (SD)	Median (IQR)	Sum
Shortness of breath	3.13 (0.85)	3 (3-4)	75
Anxiety	2.42 (1.53)	3 (1-4)	58
Unable to breathe deeply	2.29 (1.20)	2 (2-3)	55
Palpitations	2.29 (1.20)	2 (1.75-3)	55
Bloated abdominal sensation	2.21 (1.22)	2 (2-3)	53
Constricted chest	2.08 (1.10)	2 (2-3)	50
Chest pain	2.08 (1.02)	2 (1.75-3)	50
Accelerated or deepened breathing	2.04 (0.91)	2 (2-3)	49
Dizzy spells	1.88 (0.90)	2 (1-3)	45
Cold hands or feet	1.79 (1.14)	2 (1-3)	43
Feeling tense	1.75 (1.11)	2 (1-3)	42
Tingling fingers	1.71 (1.16)	2 (1-2.25)	41
Blurred vision	1.58 (1.02)	2 (1-2)	38
Stiffness of fingers or arm	1.58 (1.32)	1.5 (0.75-2)	38
To be confused, losing touch with environment	1.21 (1.02)	1 (0-2)	29
Tightness around the mouth	1.17 (1.09)	1 (0-3)	28
Total score	31.21 (5.05)	29.5 (27-35)	749

Each item was quantified as 0: never, 1: rarely, 2: sometimes, 3: often, 4: very often

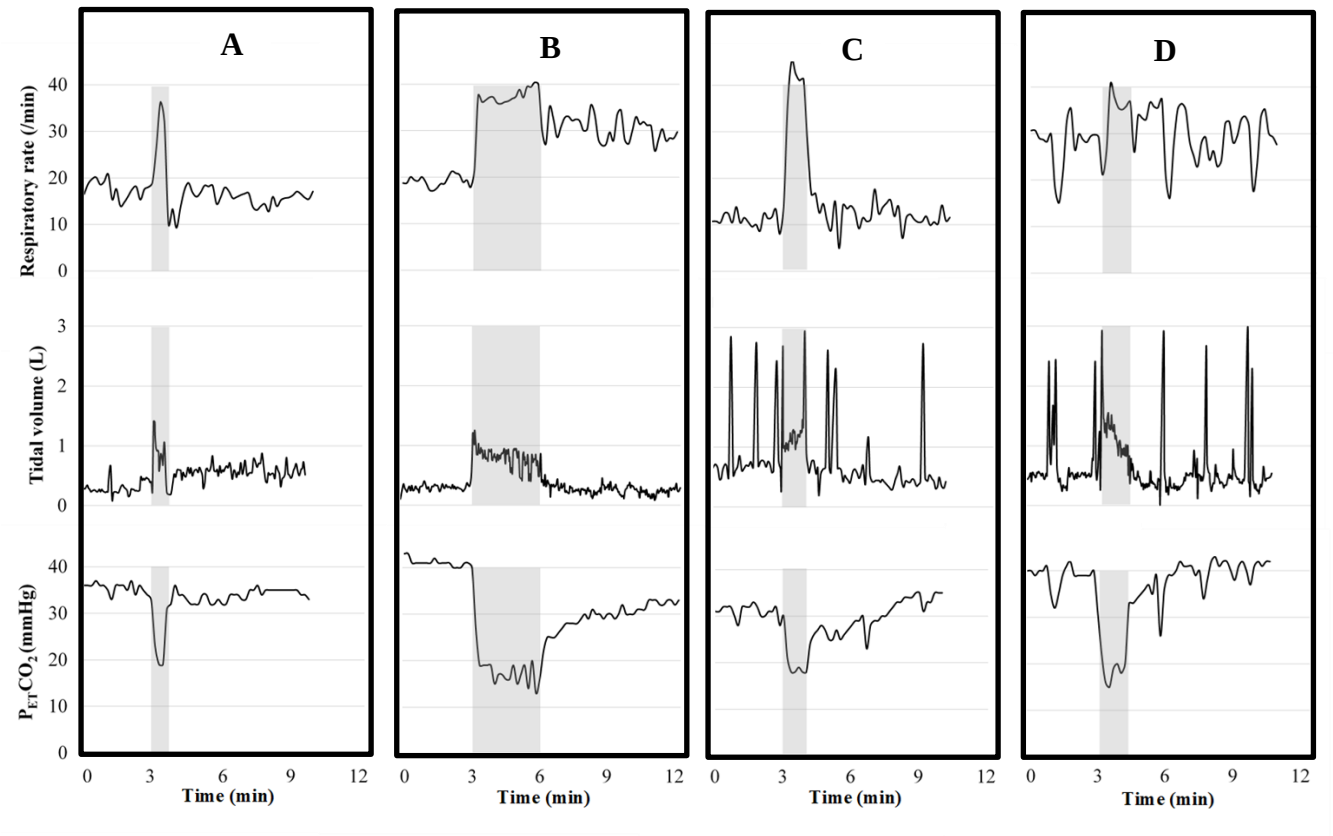
Table 4. Multivariate analysis

Variable	Odds-ratio	95% CI	p-value
Gender (male)	0.85	0.33-2.27	0.006
ICU admission	0.15	0.05-0.45	0.001
Cognitive complaints	3.41	1.32-9.58	0.014
Psychiatric symptoms*	3.19	1.23-8.68	0.019
Pathological CT-scan of the chest	0.78	0.29-2.16	0.625

CI: confidence interval; ICU: intensive care unit

* Psychiatric symptoms were defined as HADS-A >7 or BDI-13 >7 or PCL-5 >30.

Figure 1. Representative examples of positive HVPT from 4 patients with normal PFTs and lung CT-scans at evaluation in the outpatient clinic.



The hyperventilation manoeuvre (grey area) began at the 3rd min and was interrupted at the 6th min or when clinical intolerance was reached. The first 3 min and the last 6 min characterise the breathing pattern at rest.

A. Premature interruption of the hyperventilation manoeuvre. The HVPT provoked a rapid reproduction of daily symptoms with major discomfort that led to premature interruption of the hyperventilation (HV) manoeuvre. The patient's breathing pattern was considered normal, as the mean respiratory rate at rest was <20/min (upper panel) and the tidal volume remained stable without hyperpnoea or deep sighing (middle panel), allowing quick recovery of the baseline $P_{ET}CO_2$ after HV (lower panel).

B. Hyperventilation. After completion of the HV manoeuvre, an abnormal breathing pattern appeared with persistent tachypnoea that reached 30/min even after 6 min of resting breathing (upper panel). Tidal volumes were normal (middle panel). The recovery of $P_{ET}CO_2$ was delayed and it remained below its baseline value at the end of the test (lower panel).

C and D. Deep sighing. The HVPT provoked a rapid reproduction of daily symptoms with major discomfort that led to premature interruption of the HV manoeuvre. The patient's breathing pattern consisted of either normal (C) or increased (D) respiratory rate at rest (upper panel) with frequent deep sighs that resulted in several spikes on the volume-time curve (middle panel) which are mirrored by transient drops in the $P_{ET}CO_2$ (lower panel).

Figure 2. Visualisation of symptoms in 37 patients with functional respiratory complaints (i.e., Nijmegen score >22) at the outpatient clinic 4 months after COVID-19 hospitalisation.

Numbers represent patients with the symptoms or association of symptoms; 67 patients did not report these symptoms.. Psychiatric symptoms were defined as HADS-A >7 or BDI-13 >7 or PCL-5 >30.

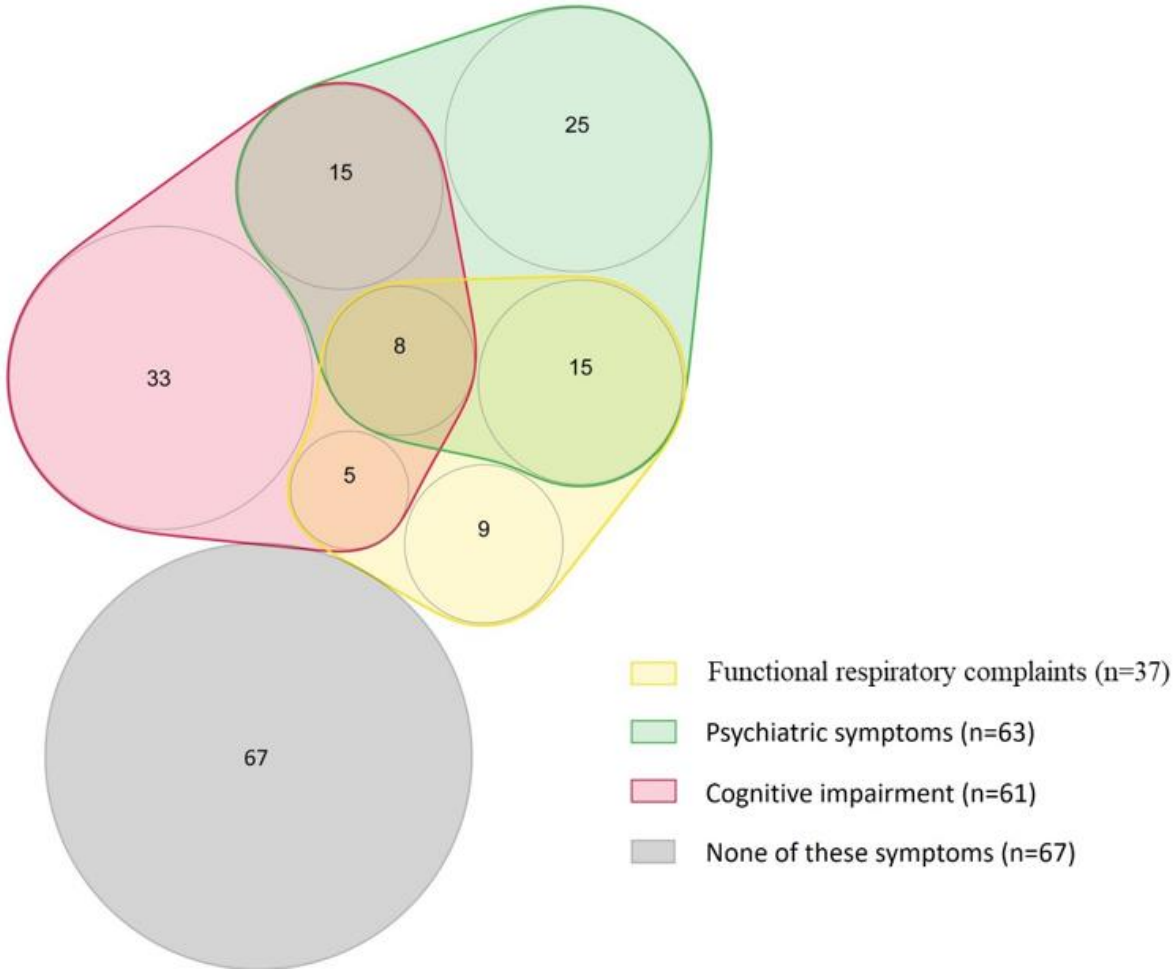
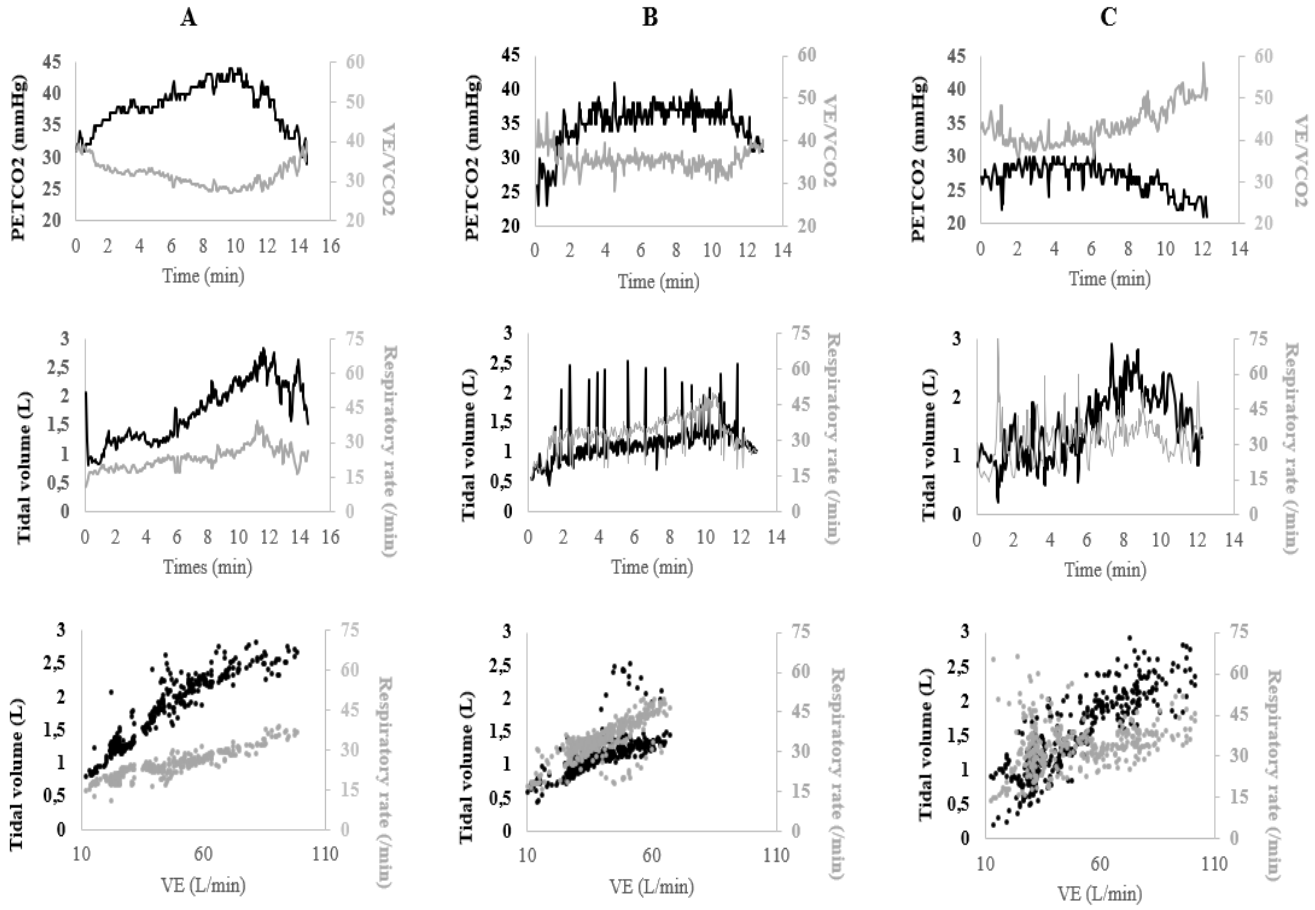


Figure 3. Representative examples of breathing patterns during CPET in 3 patients with post-COVID-19 unexplained dyspnoea.



A. Normal CPET. $P_{ET}CO_2$ > 30 mmHg both at rest and during exercise; $\dot{V}_E/\dot{V}CO_2$<35 at 40 W (upper panel); predictable pattern of breathing frequency and tidal volume increases (middle and low panels).

B. Dysfunctional breathing with deep sighs. $P_{ET}CO_2$ is broadly normal and $\dot{V}_E/\dot{V}CO_2$ is just above the limit of 35 at 40 W (upper panel); breathing pattern response is abnormal with typical deep sighing as reflected by spikes on the volume-time curve (middle and low panels).

C. Dysfunctional breathing with hyperventilation. $P_{ET}CO_2$ < 30 mmHg both at rest and during exercise; $\dot{V}_E/\dot{V}CO_2$ > 35 regardless of power (upper panel); erratic breathing pattern (middle and low panel).

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SUPPLEMENT ONLINE

Post-COVID-19 dysfunctional breathing: a prospective cohort study

Supplemental methods

Telephone Assessment

Three to 4 months after hospital or ICU discharge, patients were contacted by telephone by a medical officer and administered a questionnaire that included general condition and respiratory, cognitive, and neurologic symptoms (with the Q3PC cognitive screening questionnaire). Patients were asked whether symptoms existed before they developed COVID-19. All symptoms were listed, without any interpretation. No psychological evaluation was performed.

In addition, patients with no history of chronic kidney disease and with high plasma creatinine levels (>1.47 mg/dL [130 μmol/L]) or estimated glomerular filtration rate less than 60 mL/min/1.73 m2 at hospital discharge were requested to have their serum creatinine levels reassessed. Patients were asked whether a lung CT scan had been performed after hospitalization, and if so, the lung CT scan was reviewed.

All ICU patients and those who were symptomatic were invited for further evaluation in the ambulatory setting. Symptomatic patients were defined as those reporting symptoms at the telephone interview (except for anosmia), all patients who had persistent creatinine-level elevation, and all those who had persistent abnormalities on a lung CT scan conducted after hospitalization (including any residual ground-glass opacities, bronchial or bronchioloalveolar abnormalities, lung condensations, or interstitial thickening).

Supplementary Table 1. Tests used for psychological, cognitive and respiratory assessment.

Test	Self-evaluation (Yes/No)	Symptom assessed	Best score	Worst score	Cut-off value
SF36 [1]	Yes	General health	0	100	None
BDI-13 [2]	Yes	Depression	0	39	>7
HADS-A [3]	Yes	Anxiety	0	21	>7
PCL-5 [4]	Yes	Post-traumatic stress	0	80	>30
ISI [5]	Yes	Insomnia	0	28	>7
MoCA [6]	No	Global cognitive functioning	30	0	<21 to <25
Mac NAIR [7]	Yes	Memory complaint	0	156	>54 to >66
d2-R [8]	No	Attention	135	65	<76
Nijmegen [9]	No	Dysfunctional breathing	0	64	>22

*BDI-13: Beck Depressive Inventory 13-item; HADS-1: Anxiety subscale of the Hospital Anxiety and Depression Scale; ISI: Insomnia Severity Index (ISI); MoCA: Montreal Cognitive Assessment; PCL-5: Post-traumatic Stress Disorder (PTSD) Checklist; SF-36: 36-item short-form health survey; * depends on age and educational level; ** depends on age; *** mean score is 100 with standard deviation of 15*

Supplementary Table 2. Modified Medical Research Council (mMRC) dyspnoea scale

Grade	Description of breathlessness
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace
3	I stop for breath after walking about 100 yards or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing

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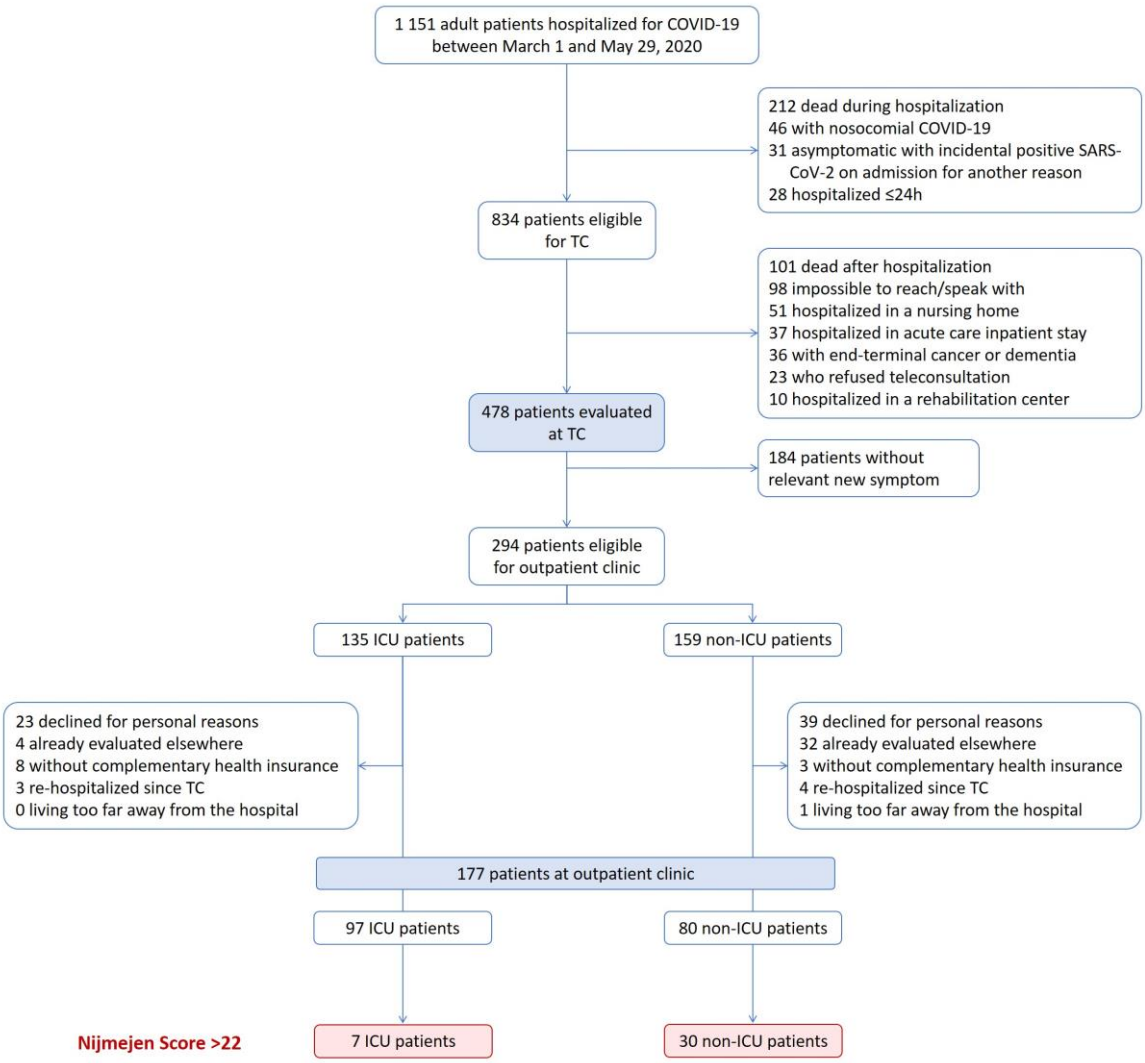

Supplementary Figure 1