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

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Shareable abstract (@ERSpublications)

Functional respiratory complaints are common during post-COVID-19 follow-up, especially among patients with unexplained dyspnoea. Diagnosis of dysfunctional breathing should be considered in those cases. <https://bit.ly/3HXWwCq>

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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 intensive care unit (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 cardiopulmonary exercise testing (CPET).

Findings In the COMEBAC cohort, 37 patients 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-min 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, seven out of

21 patients had significant FRCs. Based on CPET, dysfunctional breathing was identified in 12 out of 21 patients, five out of 21 had normal CPET, three out of 21 had deconditioning and one out of 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.

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.* [3] 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%). Likewise, GARRIGUES *et al.* [4] 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 (COntultation Multi-Expertise de Bicêtre Après COVID-19) cohort (NCT04704388) evaluating COVID-19 survivors 4 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 [5]. The underlying mechanisms of post-COVID-19 dyspnoea remain unclear. In the present study we investigated post-COVID-19 “functional respiratory complaints” (FRCs) using the Nijmegen Questionnaire. As mentioned by van DIXHOORN and FOLGERING [6] 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. The presence of FRCs is associated with the diagnosis of dysfunctional breathing (DB), of which hyperventilation syndrome (HVS) is a well-known form [6, 7]. On the one hand, dyspnoea is a subjective symptom that poorly correlates with radiological findings among COVID-19 survivors [8], and HVS has been suggested as a cause of exercise intolerance among COVID-19 survivors [9]. On the other hand, there is evidence of long-term organic injuries that result in interstitial lung disease and impaired gas diffusion several months after the infection [10]. 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 [5] 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 (supplementary figure S1). 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 for COVID-19 management during the second epidemic wave in France. They were offered CPET in the context of unexplained dyspnoea after completing routine tests at rest (*i.e.*, detection for hypoxaemia and anaemia, computed tomography (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 as a measure of FRCs, as has been suggested by the authors who initially elaborated this questionnaire [6]. A threshold >22 out of 64 defined patients with significant FRCs [11]. The functional impact of dyspnoea was evaluated using the modified Medical Research Council (mMRC) scale (supplementary table 2). A 6-min walk test was performed according to current recommendations [12].

Patients completed standard pulmonary function tests (PFTs) with spirometry, whole-body plethysmography and single-breath diffusing capacity of the lung for carbon monoxide (D_{LCO}) according to the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines [13]. Forced vital

TABLE 1 Baseline and hospitalisation characteristics according to Nijmegen score

	Nijmegen score ≤ 22	Nijmegen score > 22	p-value
Patients n	140	37	
Age years	57.3 \pm 13.7	55.2 \pm 11.1	0.39
Female	46 (32.9)	22 (59.5)	<0.01
Body mass index kg·m⁻²	28.9 \pm 5.1	30.5 \pm 6.4	0.28
Obesity (>30 kg·m⁻²)	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)			0.64
Active	13 (9.6)	2 (5.9)	
Former (>5 pack-years)	21 (15.6)	4 (11.8)	
No (<5 pack-years)	101 (74.8)	28 (82.4)	
Management of COVID-19			
Duration of hospitalisation 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 admission	90 (64.3)	7 (18.9)	<0.001
Intubation	48 (34.3)	3 (8.1)	<0.01
HFNC	7	1	0.88
ECMO	7	1	0.88

Data are presented as n (%), mean \pm SD or median (IQR) unless otherwise stated. ICU: intensive care unit; HFNC: high-flow nasal cannula; ECMO: extracorporeal membrane oxygenation.

capacity, forced expiratory volume in 1 s, total lung capacity and D_{LCO} were expressed as percentages of predicted values using the Global Lung Function Initiative (GLI) 2012 [14] and European Community for Coal and Steel (ECCS) 1993 equations [15, 16]. 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

In the COMEBAC study, all patients with positive Nijmegen Questionnaire were offered a hyperventilation provocation test (HVPT). End-tidal carbon dioxide tension (P_{ETCO_2}) was monitored with a single-use nasal cannula connected to a gas analyser through a sampling system (Perma Pure®; Perma Pure, Lakewood, NJ, USA), and tidal volume and respiratory rate (RR) were assessed breath-by-breath using a turbine flowmeter adapted with a silicon face mask (Cosmed Quark CPET; Cosmed, Rome, Italy). 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 ·breaths·min⁻¹ and a $P_{ETCO_2} \leq 20$ 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 two daily symptoms were reproduced and/or in case of abnormal P_{ETCO_2} kinetic ($P_{ETCO_2} < 67\%$ at 3 min and/or $<91\%$ at 5 min from baseline), as described elsewhere [17].

Cardiopulmonary exercise testing

All patients from the explanatory cohort 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⁻¹). Spiroergometric variables were measured using breath-by-breath analysis and included oxygen consumption (V_{O_2}), output of carbon dioxide (V_{CO_2}), P_{ETCO_2} , tidal volume (V_T), breathing frequency and minute ventilation (V_E) from which was derived the V_E/V_{CO_2} ratio. As previously suggested by other authors [18], the CPET pattern was suggestive of DB in the absence of cardiac, ventilatory, gas exchange or metabolic abnormality associated with one or more of the following features: high V_E/V_{CO_2} (>35 at 40 W), low P_{ETCO_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 [5]. 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 RR and P_{ETCO_2} , the mean values obtained every 10 s 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 \pm SD 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% *versus* 32.9%, $p < 0.01$) but had a similar age, body mass index 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 an 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-min walk test was shorter among patients with FRCs (404 *versus* 474 m, $p < 0.01$). Cough was significantly more frequently observed in patients with FRCs (30.6% *versus* 8.8%, $p < 0.01$). At reevaluation, patients with FRCs were more likely to have normal CT scans of the chest (58.3% *versus* 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 two 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 out of 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.

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

	Nijmegen score ≤ 22	Nijmegen score > 22	p-value
Patients n	140	37	
mMRC (0–4) (n=177)			<0.001
0	82 (58.6)	5 (13.5)	
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)			<0.01
Normal lung CT scan	42 (31.1)	21 (58.3)	
Persistent ground-glass opacities	62 (45.9)	13 (37.1)	
Lung fibrotic lesions	31 (23)	2 (5.7)	
Pulmonary function tests (n=157)			
FEV ₁ % pred	91.4±18.6	88.7±14.8	0.37
FVC % pred	89.7±16.4	87.0±16.5	0.40
FEV ₁ /FVC	82.1±7.7	82.2±6.5	0.96
TLC % pred	82.4±15.7	84.2±13.5	0.51
D _{LCO} % 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
D _{LCO} <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

Data are presented as n (%), mean±SD or median (IQR) unless otherwise stated. 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. mMRC: modified Medical Research Council; CT: computed tomography; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; 6MWT: 6-min walk test; HADS-A: Hospital Anxiety and Depression Scale; BDI-13: Beck Depression Inventory-13 items; ISI: Insomnia Severity Index; PTSD: post-traumatic stress disorder; PCL-5: Post-traumatic Stress Disorder Checklist for DSM-5.

Quality of life, psychiatric and cognitive assessment

Patients with FRCs reported a poorer quality of life throughout the eight 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% versus 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.

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.

Multivariate analysis

In patients evaluated in the outpatient clinic, the following variables were considered clinically relevant and included in the multivariate analysis: sex, ICU admission, cognitive complaint, psychiatric symptoms and pathological CT scan of the chest at reevaluation. 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 out of 21 were women. 11 reported at least grade 2 on the mMRC scale. The mean±SD Nijmegen Questionnaire in the overall population was 22±11. 16 had no evidence of organ damage on routine tests; the five other patients had disproportionate dyspnoea with regard to their tests (three had mild ground-glass lesions on CT scan, one had chronic and stable anaemia due to β -thalassaemia and one had isolated mild hypoxaemia at rest). Overall, seven patients (33%) had a Nijmegen Questionnaire >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 DB, five had normal CPET and three had evidence of deconditioning (associating low value of peak 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 DB, 10 out of 12 had $P_{ETCO_2} < 30$ mmHg at rest and during exercise; 10 out of 12 had increased V'_E/V'_{CO_2} (>35 at 40 W) and 11 out of 12 had evidence of erratic breathing pattern, including two patients (17%) with deep sighs. Representative examples are presented in figure 3.

Discussion

In the context of the COMEBAC study, patients underwent extensive workup in an outpatient clinic, including multidimensional 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. 12 of 21 patients with post-COVID-19 unexplained dyspnoea at 6 months showed evidence of DB on CPET. Taken together, these results support the idea that functional respiratory disorders should not be overlooked during COVID-19 follow-up.

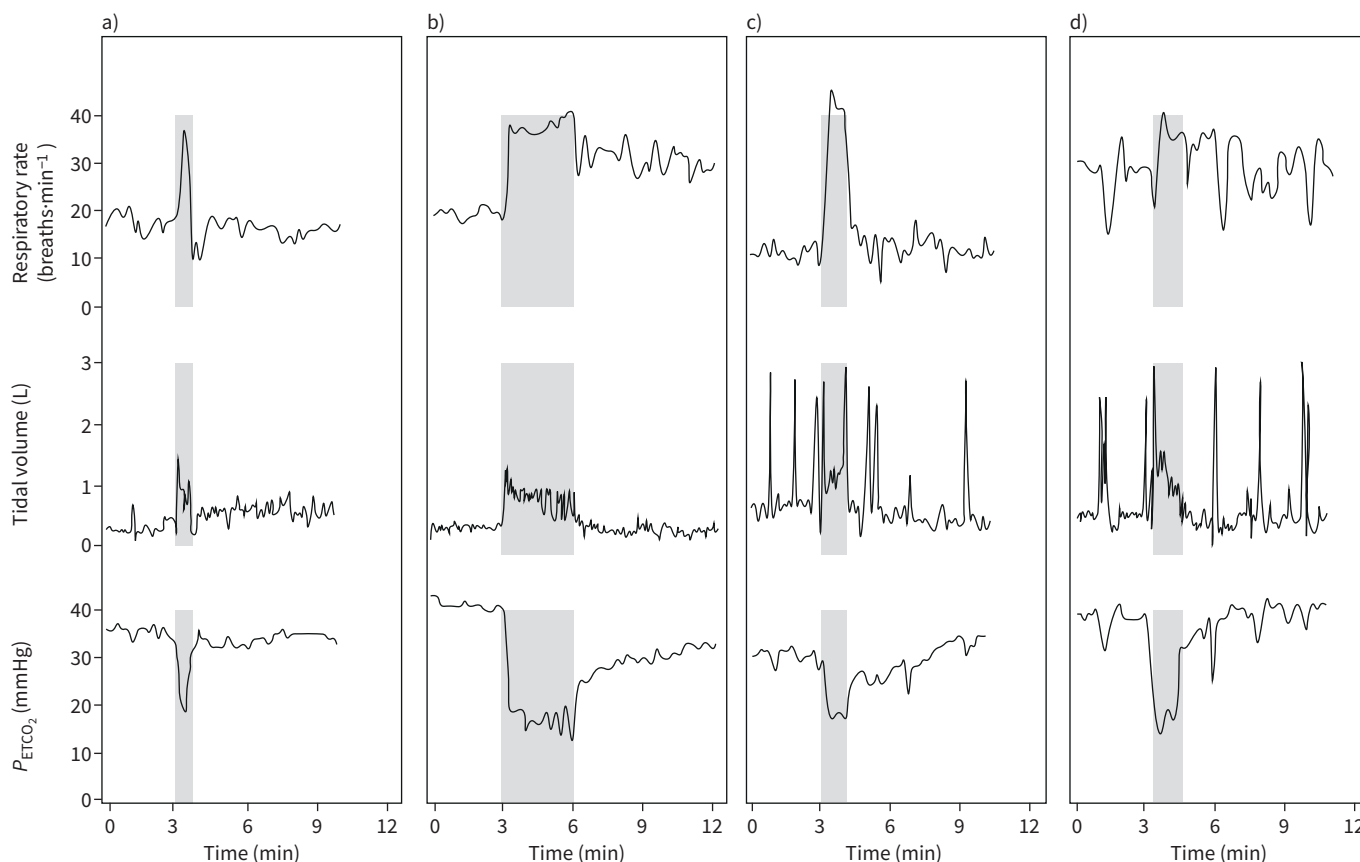


FIGURE 1 Representative examples of positive hyperventilation provocation test (HVPT) from four patients with normal pulmonary function tests and lung computed tomography scans at evaluation in the outpatient clinic. The hyperventilation manoeuvre (grey area) began at the 3rd min and was interrupted 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 (HV) 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 breaths·min⁻¹ (upper panel) and the tidal volume remained stable without hyperpnoea or deep sighing (middle panel), allowing quick recovery of the baseline end-tidal carbon dioxide tension (P_{ETCO_2}) after HV (lower panel). **b)** Hyperventilation. After completion of the HV manoeuvre, an abnormal breathing pattern appeared with persistent tachypnoea that reached 30 breaths·min⁻¹ even after 6 min of resting breathing (upper panel). Tidal volumes were normal (middle panel). The recovery of P_{ETCO_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_{ETCO_2} (lower panel).

The prevalence of FRCs is higher than the prevalence of 9.5% previously reported in a general primary care population [19] but lower than in other conditions such as difficult-to-treat asthma (47%) [20]. Consistent with the previously reported sex ratio imbalance [19], 59.5% of patients with FRCs were female. Despite the lower number of pathological CT scans and similar D_{LCO} 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 [21]. 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 [22], while others have emphasised the role of underlying organic respiratory diseases such as asthma [23]. Our results do not support a major role of altered COVID-19-related lung properties in the pathophysiology of FRCs, since

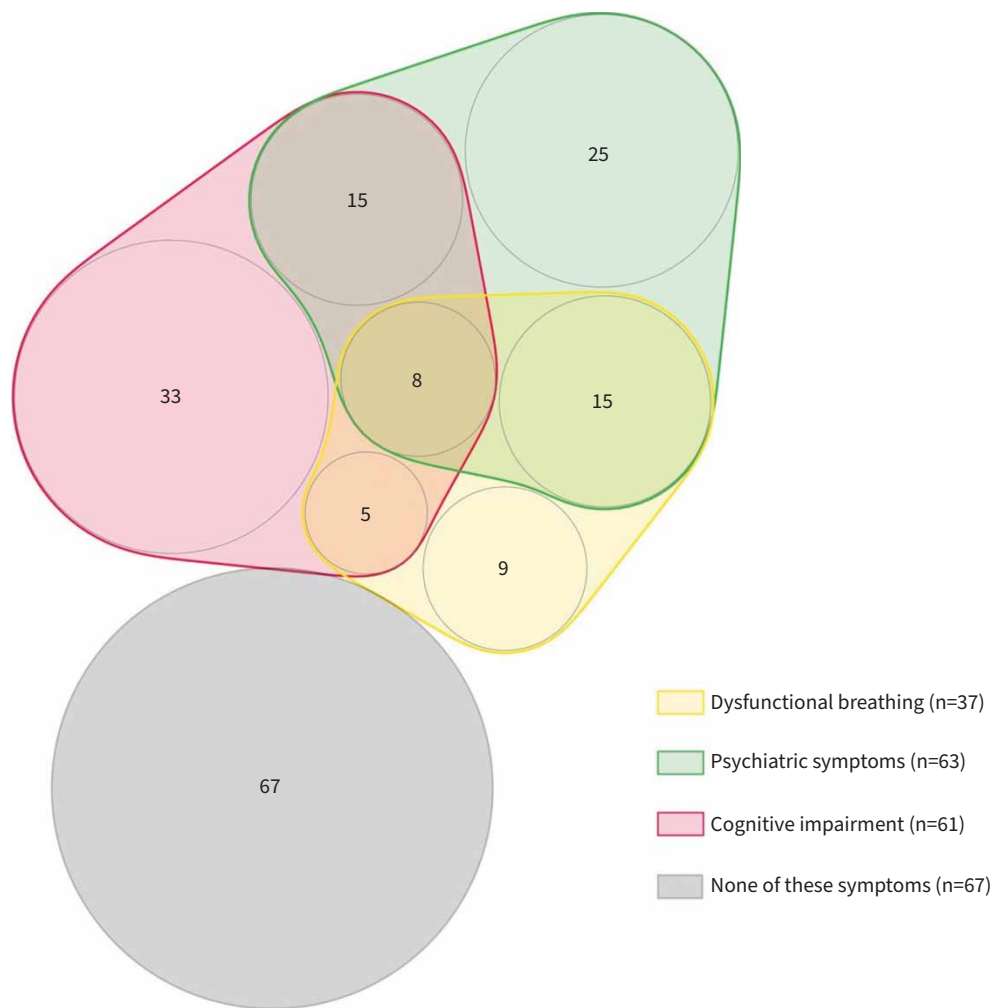


FIGURE 2 Visualisation of symptoms in 37 patients with functional respiratory complaints (*i.e.* Nijmegen score >22) at the outpatient clinic 4 months after COVID-19 hospitalisation. Numbers represent patients with the symptoms or association of symptoms; 67 patients did not report these symptoms. Psychiatric symptoms were defined as Hospital Anxiety and Depression Scale >7, 13-item Beck Depressive Inventory >7 or Post-Traumatic Stress Disorder Checklist for DSM-V >30.

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 [24], and psychiatric symptoms are broadly reported in COVID-19 survivors [25, 26]. The overlap between FRCs and anxiety symptoms [27] could also explain, at least in part, the high rate of FRCs in COVID-19 survivors.

TABLE 4 Multivariate analysis		
Variable	Odds ratio (95% CI)	p-value
Sex (male)	0.85 (0.33–2.27)	0.748
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

ICU: intensive care unit; CT: computed tomography; [#]: psychiatric symptoms were defined as Hospital Anxiety and Depression Scale >7 or 13-item Beck Depression Inventory >7 or Post-Traumatic Stress Disorder Checklist for DSM-V >30.

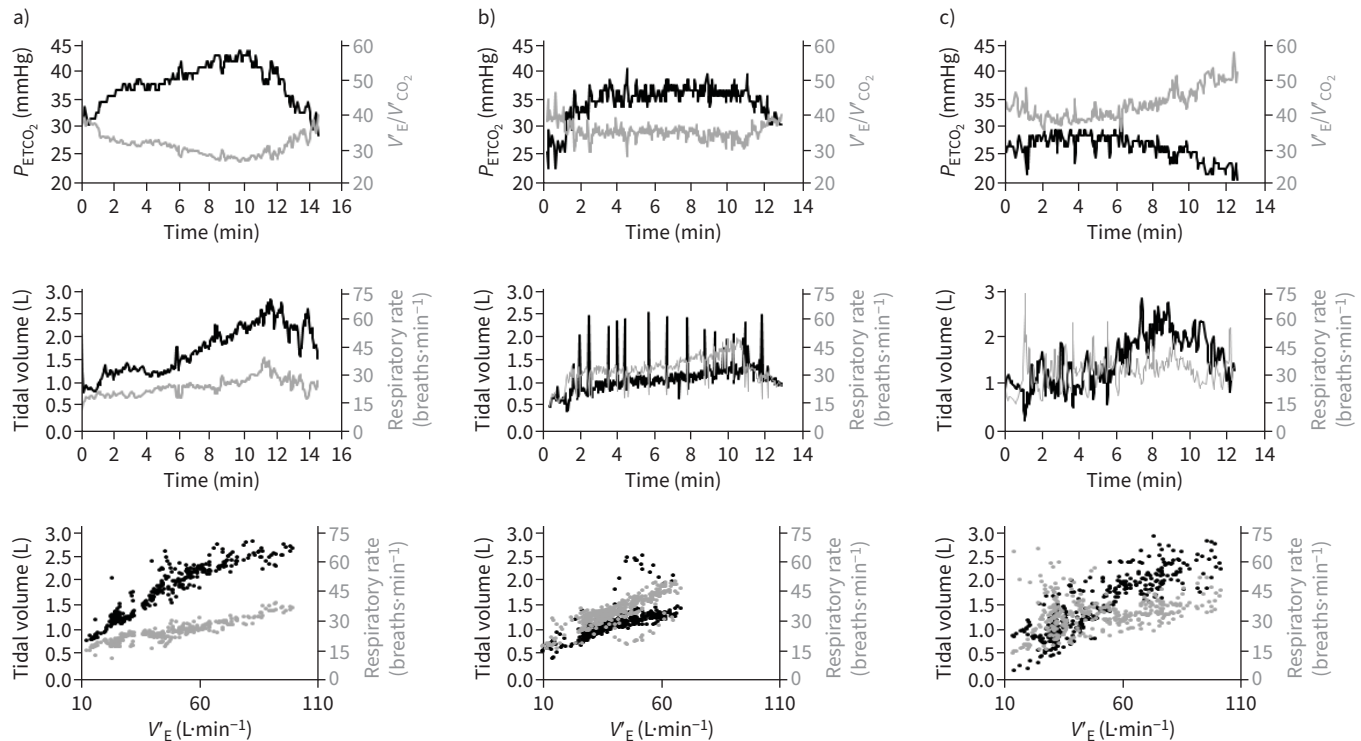


FIGURE 3 Representative examples of breathing patterns during cardiopulmonary exercise testing (CPET) in three patients with post-COVID-19 unexplained dyspnoea. **a**) Normal CPET. End-tidal carbon dioxide tension (P_{ETCO_2}) >30 mmHg both at rest and during exercise; minute ventilation (V_E)/carbon dioxide production (V_{CO_2}) <35 at 40 W (upper panel); predictable pattern of breathing frequency and tidal volume increases (middle and lower panels). **b**) Dysfunctional breathing with deep sighs. P_{ETCO_2} is broadly normal and V_E/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 lower panels). **c**) Dysfunctional breathing with hyperventilation. P_{ETCO_2} <30 mmHg both at rest and during exercise; V_E/V_{CO_2} >35 regardless of power (upper panel); erratic breathing pattern (middle and lower panel).

Since SARS-CoV-2 has neuro-invasive potential [28], 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 is found in the brainstem nuclei involved in the regulation of ventilation [29]. Second, COVID-19 can trigger several neuropsychiatric manifestations, including anxiety [28], 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 [30]. 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 socioeconomic effects of the pandemic on mental health [31]. 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 [5]. As previously described with HVS [32], we highlight that FRCs severely impact the quality of life of post-COVID-19 patients, which may induce a significant burden for healthcare 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 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 [18]. 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 out of 21 patients, including two 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.* [33] 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 relevant to assess the ventilatory response of patients. It has been suggested that higher regional inhomogeneity (as assessed by Electrical Impedance Tomography) may have contributed to dyspnoea in post-COVID-19 patients [34]. Using CPET, other authors evaluated a method to classify the breathing pattern in terms of inter-rater agreement: among 20 patients, seven had an abnormal breathing pattern associated with lower exercise capacity, which could possibly explain exercise-related symptoms in some patients with post-acute COVID-19 syndrome [35]. The role of DB and deconditioning has been highlighted in larger cohorts [36, 37]. Deconditioning was uncommon in our explanatory cohort, which was characterised 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 [38]. 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 [39].

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

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