

Article

Presence, Severity and Evolution of Long COVID Dyspnea Correlate with Functional Capacity Measured with the Six-Minutes Walking Test (6MWT): Data from a Multicenter Cohort from Italy

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Abstract

The present national observational cohort study investigated in patients followed for long COVID—mostly hospitalized during acute infection—the presence, severity and evolution of dyspnea and its functional correlates. Dyspnea was assessed with the modified Medical Research Council (mMRC) dyspnea scale and its functional correlates via six-minutes walking distance (6MWD). A total of 217 individuals were evaluated. The mean difference in 6MWD between patients with and without dyspnea (mMRC score ≥ 1) was 87 m (95%CI 56–117, $p < 0.001$). Significant declines were observed between four and eight months from COVID-19 in prevalence of dyspnea (from 56.7% to 36.4%, $p < 0.001$), mean mMRC score (from 0.95 to 0.63, $p < 0.001$), and proportion of patients with 6MWD $< 65\%$ of predicted value (from 15.5% to 9.4%, $p = 0.035$). Each additional point in mMRC score corresponded to -56.3 m walked at first assessment and to -47.7 m walked at second assessment. In the longitudinal analysis, each unitary mMRC score increase between the two assessments corresponded to a concurrent 6MWD reduction of 22.5 m (95%CI -40.1 to -4.8 m, $p = 0.013$). Although the prevalence of dyspnea reduced significantly over time, roughly one-third of patients remained affected eight months after COVID-19. The 6MWD was a sensitive measure in capturing the functional correlates of presence, severity and evolution of dyspnea.

Keywords: long COVID; symptoms; dyspnea; mMRC dyspnea scale; six-minutes walking test; cohort study; exercise capacity

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1. Introduction

Dyspnea is widely recognized as a highly prevalent symptom and a relevant cause of disability in patients with long COVID, but its evolution and its functional correlates remain incompletely defined. In terms of persistence, most of the studies in patients with long COVID have reported a spontaneous reduction in dyspnea during follow up [1–5], but some showed an unchanged persistence of the symptom [6] or its possible new insurgence in previously unaffected patients [7,8]. Similarly, not all the studies that evaluated its functional and imaging correlates have provided consistent results, highlighting possible discrepancies between subjectively reported dyspnea and presence of abnormalities in spirometry, diffusing capacity of the lungs for carbon monoxide (DLCO) testing, or chest imaging [2,4,6,7,9,10]. Such inconsistencies may, in part, be explained by the difficulty in substantiating subjective complaints and by the inadequacy of spirometry, DLCO testing and chest imaging in capturing non-pulmonary causes of dyspnea [2,9,11,12]. A combined clinical–instrumental assessment based on less subjective measures and on more comprehensive functional tests could be of help. In this context, the modified Medical Research Council (mMRC) dyspnea scale describes five levels of dyspnea (score range: 0–4) related to physical activity and based on patients' experiences, providing a more "objective" measurement of patient disability [13]. With respect to the assessment of functional performance, the six-minutes walking test (6MWT) represents a general test that measures the exercise capacity, evaluating the integrated response of the pulmonary, cardiovascular, and muscular systems [14].

Based on these premises, we used data from a national cohort of patients followed for long COVID to define the rates of persistence and resolution of dyspnea using the mMRC dyspnea scale and to assess the agreement between 6MWT results and mMRC dyspnea scores in both cross-sectional and longitudinal analyses.

2. Materials and Methods

2.1. Study Overview

The present clinical study was structured as an observational cohort, reported as per STROBE guidelines. Participation was offered to all consecutive patients attending the study clinics during the study (from January 2023 to March 2024), with data extracted on 2 April 2024. Not all patients were followed prospectively since acute SARS-CoV-2 infection: the study population included patients who returned for a programmed follow-up visit after acute infection, independent of presence of symptoms, patients already followed before the study start for occurrence/persistence of potential long COVID symptoms, and new patients that attended for the first time the long COVID clinics after the study start. All patients provided written informed consent. Symptom collection was retrospective, based on clinical records and patient interviews, for patients already followed, and prospective for patients newly accessing the centers. Data on demographics, acute infection and comorbidities were taken from clinical records. Study data were entered by medical staff at the participating centers using an online dedicated platform [15].

2.2. Data Collection

For data collection, a shortened version of the Post COVID-19 Case Report Form (CRF) from the WHO Global Clinical Platform for COVID-19 was used [16], which included patient demographics, comorbidities, severity and timing of acute COVID, plus 30 different symptoms [16]. The analysis used all available data according to the following inclusion criteria: age at least 18, a recorded date of acute SARS-CoV-2 infection (defined by date of first positive swab), a clinical assessment performed at least 4 weeks after acute

SARS-CoV-2 infection, and available information for the mMRC dyspnea scale in at least two subsequent timepoints separated by at least four weeks.

2.3. Definitions

Severity of acute SARS-CoV-2 disease was defined as mild (grade 1), moderate (grade 2), severe (grade 3) or critical (grade 4) according to the WHO grading [16]. Respiratory assistance was categorized as no assistance, low- or high-flow oxygen, continuous positive airway pressure (CPAP), mechanical ventilation (MV), and extracorporeal membrane oxygenation (ECMO). Phase of the pandemic was categorized as pre-Omicron or Omicron according to occurrence date of acute infection before or after 23 December 2021 [17].

2.4. Procedures

Dyspnea was evaluated by the mMRC dyspnea scale, which contains five statements describing dyspnea in relation to physical activity. The scale has a 0–4 score range, where higher scores indicate higher degrees of dyspnea experienced by the patient. The cutoff for dyspnea was set at mMRC ≥ 1 , corresponding to breathlessness when hurrying on the level or walking up a slight hill [13]. The 6 min walking test was conducted according to the ATS/ERS standard protocol [14]. Briefly, each patient walked on flat ground as fast as possible without oxygen inhalation and performed the test independently. The distance completed (6MWD) was expressed in meters [18]. Predicted values for 6MWD according to sex, age, height and weight were calculated using the equations from Delbressine et al., and the individual ratio between observed and predicted value was reported as percentage of the predicted [19].

2.5. Data Analysis

Data were summarized as proportions for categorical variables and as means with standard deviations (SD) for quantitative variables. Differences between non-paired groups for quantitative variables were analyzed using the *t* test for independent samples. Longitudinal changes in mean values between the two assessments were evaluated using Student's *t* test for paired samples and reported as mean differences with 95% confidence intervals. For categorical variables, proportions were analyzed using the chi-square test when comparing independent samples and with the McNemar test when comparing paired samples. The correlations between 6MWD and the mMRC score were assessed using multivariable linear regression models that used as dependent variables the six-minute walking distances (at first assessment, at second assessment and as difference between the two assessments), and as independent variables the mMRC dyspnea score, age, severity of acute SARS-CoV-2 disease, admission to intensive care unit, ischemic heart disease, respiratory failure/chronic obstructive pulmonary disease (COPD), asthma and obesity, calculating the changes in 6MWD per additional unit of mMRC score with 95% confidence intervals. No input was used to substitute missing data. Primary comparisons were prespecified. *p* values below 0.05 were considered significant, with no correction for multiplicity. All analyses were performed using the SPSS software, version 29.0 (IBM Corp, 2022, Armonk, NY, USA).

3. Results

3.1. Study Sample

At study closure, after exclusion of 70 patients with no sequential assessment of dyspnea with the mMRC dyspnea scale, 217 individuals, mostly followed in internal medicine (n: 111) or pneumology units (n: 104), had available information for the mMRC dyspnea scale in two subsequent assessments. The 70 patients with no sequential

assessments did not differ significantly from the 217 patients with sequential assessments in terms of sex ($p = 0.204$), age > 65 ($p = 0.115$), presence of ischemic heart disease ($p = 0.625$), respiratory failure/COPD ($p = 0.504$), admission to intensive care unit ($p = 0.276$), presence of severe or critical acute SARS-CoV-2 disease ($p = 0.892$) and more intensive respiratory support (CPAP, mechanical ventilation or ECMO) ($p = 0.645$). The first assessment was conducted after a mean interval from acute SARS-CoV-2 infection of 130 days (SD 48), and the second at a mean interval from acute COVID-19 of 261 days (SD 84). The general characteristics of the study sample are reported in Table 1. Overall, the study sample was characterized by a slight prevalence of male sex (57.1%), a relatively advanced age (mean: 63.6 years), common presence of comorbidities (77.0%), relatively high body mass index (mean: 28.9 kg/m²), and frequent occurrence of hospitalization during acute COVID-19 (91.7%). More than half of the patients (56.3%) had presented severe or critical acute SARS-CoV-2 infection, and 45.6% had received CPAP (27.2%), mechanical ventilation (17.5%) or ECMO (0.9%) as respiratory support for acute disease. The treatments administered in this phase included systemic steroids (86.1%), and less frequently, antivirals (28.1%, mostly remdesivir), IL-6 inhibitors (18.9%) and neutralizing antibodies (1.8%).

Table 1. Population characteristics.

Clinical and Demographic		Acute Phase Treatments	
Female sex (n, %)	93 (42.9)	Systemic steroids (n, %)	186 (86.1)
Age (years, mean, SD)	63.6 (11.7)	Antivirals (n, %)	61 (28.1)
Body mass index (kg/m ² , mean, SD)	28.9 (5.4)	IL-6 inhibitors (n, %)	41 (18.9)
Current smoking (n, %) (n: 215)	14 (8.5)	Monoclonal antibodies (n, %)	4 (1.8)
Comorbidities: mean number, SD	1.7 (1.5)		
Any (n, %)	167 (77.0)	Persisting symptoms	
Hypertension (n, %)	110 (50.7)	Dyspnea (n, %)	124 (57.1)
Obesity (n, %)	70 (32.3)	Fatigue (n, %)	113 (52.1)
Diabetes (n, %)	36 (16.6)	Joint pain or swelling (n, %)	34 (15.7)
Ischemic heart disease (n, %)	23 (10.6)	Muscle pain (n, %)	31 (14.3)
Neoplastic disease (n, %)	21 (9.7)	Cough (n, %)	29 (13.4)
Autoimmune diseases (n, %)	17 (7.8)	Sleep disturbances (n, %)	27 (12.4)
Respiratory failure or COPD (n, %)	14 (6.5)	Skin disorders, alopecia (n, %)	27 (12.4)
Asthma (n, %)	13 (6.0)	Memory loss (n, %)	22 (10.1)
Anxiety (n, %)	13 (6.0)	Thoracic pain (n, %)	21 (9.7)
Atrial fibrillation (n, %)	11 (5.1)	Difficult concentration (n, %)	19 (8.8)
Depression (n, %)	8 (3.7)	Taste reduction (n, %)	17 (7.8)
Renal failure (n, %)	8 (3.7)	Anxiety (n, %)	16 (7.4)
Stroke (n, %)	7 (3.2)	Depressed mood (n, %)	16 (7.4)
OSAS (n, %)	3 (1.4)	Smell reduction (n, %)	15 (6.9)
Chronic liver disease (n, %)	2 (0.9)	Equilibrium or gait disorders (n, %)	8 (3.7)
Heart failure (n, %)	2 (0.9)	Palpitations, tachycardia (n, %)	8 (3.7)
Other major conditions (n, %)	17 (7.8)	Headache (n, %)	8 (3.7)
		Paresthesia (n, %)	7 (3.2)
SARS-CoV-2 disease		Brain fog (n, %)	6 (2.8)
Vaccinated * (n: 151):	Before infection (n, %)	Weight loss (n, %)	5 (2.3)
	After infection (n, %)	Diarrhea (n, %)	5 (2.3)
	Not vaccinated (n, %)	Loss of appetite (n, %)	4 (1.8)
Acute infection pandemic phase:	Pre-omicron (n, %)	Pharyngodynia (n, %)	4 (1.8)
	Omicron (n, %)	Visual disturbances (n, %)	2 (0.9)
Hospitalization in acute phase:	In any unit (n, %):	Nausea or vomiting (n, %)	2 (0.9)
	In intensive care unit (n, %)	Fever (n, %)	1 (0.5)
WHO COVID severity:	Mild (n, %)	Delirium, hallucinations (n, %)	1 (0.5)

	Moderate (n, %)	74 (34.1)	Hearing disturbances (n, %)	0 (0)
	Severe (n, %)	88 (40.6)	Menstrual disorders (n, %)	0 (0)
	Critical (n, %)	34 (15.7)	Chilblains (n, %)	0 (0)
Respiratory assistance:	None (n, %)	26 (12.0)		
	Low-flow O ₂ (n, %)	74 (34.1)	6 minutes walking distance (n: 165)	
	High-flow O ₂ (n, %)	18 (8.3)	Mean (SD), meters	447 (113)
	CPAP (n, %)	59 (27.2)	% of predicted (mean, SD)	81.0 (19.2)
	Mechanical ventilation (n, %)	38 (17.5)	<65% of predicted (n, %)	26 (16.3)
	ECMO (n, %)	2 (0.9)	<50% of predicted (n, %)	16 (10.0)

Data are presented as means with standard deviations (SD) for continuous variables and as numbers and proportions (n, %) for categorical variables. COPD: Chronic Obstructive Pulmonary Disease; OSAS: Obstructive Sleep Apnea Syndrome; O₂: oxygen; CPAP: Continuous Positive Airway Pressure; ECMO: Extracorporeal Membrane Oxygenation. * Any dose. Bold refers to main categories.

3.2. Symptoms

At first assessment, 185 patients (85.3%) presented one or more persisting symptoms, with a clear predominance of dyspnea (57.1%) and fatigue (52.1%). All the other symptoms affected less than twenty percent of individuals, with the more common (>10%) represented by joint pain or swelling (15.7%), muscle pain (14.3%), cough (13.4%), sleep disturbances (12.4%), skin disorders/alopecia (12.4%) and memory loss (10.1%). The full spectrum of the reported persisting symptoms is shown in Table 1.

3.3. mMRC Dyspnea Score

The mean mMRC score at first assessment was 0.95 (SD 1.01). The case distribution by mMRC score at the two study assessments is shown in Table 2. At first assessment, 94 patients (43.3%) reported no dyspnea (mMRC score = 0) and 123 (56.7%) reported some grade of dyspnea (mMRC score ≥ 1); in this group, 60 (27.6%) had an mMRC score of 1, 42 (19.4%) a score of 2 and 21 (9.7%) a score of 3; none had a score of 4.

Table 2. Distribution of mMRC dyspnea score at first and second assessment.

	Distribution by Timing of Assessment (n, %)			Distribution by Score Change from First to Second Assessment (n, %)		
	First Assessment	Second Assessment	<i>p</i> Value	Unchanged	Decreased	Increased
No dyspnea (mMRC score = 0) (n, %)	94 (43.3)	138 (63.6)	<0.001	86 (91.5)	-	8 (8.5) (n: +1 = 5; +2 = 1; +3 = 2)
Dyspnea (mMRC score ≥ 1) (n, %)	123 (56.7)	79 (36.4)		41 (33.3)	75 (61.0) (n: -1 = 60; -2 = 15)	7 (5.7) (n: +1 = 7)
mMRC score = 0	94 (43.3)	138 (63.6)	<0.001			
mMRC score = 1	60 (27.6)	39 (18.0)				
mMRC score = 2	42 (19.4)	22 (10.1)				
mMRC score = 3	21 (9.7)	18 (8.3)				

At second assessment, the mean mMRC score in the entire population significantly decreased by 0.32 points (95%CI: 0.22–0.43), from 0.95 to 0.63 points ($p < 0.001$). Similarly, the proportion of patients reporting any grade of dyspnea (mMRC score ≥ 1) declined significantly from 56.7% to 36.4% ($p < 0.001$), with reduced proportions also in all the individual classes of scores ≥ 1 at first assessment ($p < 0.001$, Table 2). As for first

assessment, no patient had a score of 4. Among the 123 patients with dyspnea at first assessment, 75 (61.0%) showed a reduction of at least one grade in mMRC score and 52 (42.3%) showed regression of dyspnea to score 0. The proportions of patients with an increase in mMRC score between the two assessments were low in both groups (6.9% cumulatively; 5.7% and 8.5% in patients with and without dyspnea at first assessment, $p = 0.417$). In most of the patients (5/8) without initial dyspnea, the score increase ranged from 0 to 1 (Table 2).

3.4. Six-Minute Walking Distance in Relation to mMRC Dyspnea Score

A total of 165 patients (76.0%) had a recorded 6MWD at first assessment, and 120 had two sequential 6MWD assessments. Compared to patients without 6MWD assessments, patients with available 6MWD information showed no significant differences in sex ($p = 0.233$), age > 65 ($p = 0.327$), presence of severe or critical acute SARS-CoV-2 disease ($p = 0.094$), more intensive respiratory support (CPAP, mechanical ventilation or ECMO) ($p = 0.234$), ischemic heart disease ($p = 0.194$) and respiratory failure or COPD ($p = 0.287$), but were more likely to have been admitted to intensive care during acute SARS-CoV-2 disease ($p = 0.013$). At first assessment, patients with dyspnea (mMRC score ≥ 1 , $n = 93$) had a significantly lower 6MWD compared to patients without dyspnea (mMRC score = 0, $n = 72$), with distances of 409 and 496 m, respectively (mean difference: 87 m, 95%CI 56–117 m, $p < 0.001$). The distance walked showed a progressive reduction with the increasing of the mMRC score (460, 404 and 290 m in patients with mMRC scores of 1, 2 and 3, respectively, $p < 0.001$).

For the 120 patients with two 6MWD assessments, the longitudinal changes in 6MWD in relation to the mMRC dyspnea scores at first assessment are reported in Table 3. The absolute 6MWD increased from first to second assessment in all the score classes, but such increases were not statistically significant and, in some cases, had a minimal amplitude.

In the entire population, the proportion of patients who had a 6MWD below 65% of the predicted value by age, sex, height and weight declined significantly from 15.5% at first assessment to 9.4% at second assessment ($p = 0.035$), with a similar trend for the proportions in the two subgroups of patients with mMRC scores ≥ 1 and ≥ 2 , respectively ($p = 0.059$ for both comparisons).

The mean changes in 6MWD between the two assessments were significantly different between patients with and without increases and with and without reductions in mMRC scores over time. Patients with a worsened mMRC score over time had a reduction of 34.0 m in 6MWD compared to an increase of 16.2 m in patients without such worsening, with a mean difference of 50.2 m between the two groups ($p = 0.041$). Similarly, among patients with dyspnea at first assessment (mMRC score ≥ 1), those with a reduced score over time had a concurrent 6MWD increase of 39.9 m from first assessment, compared to a 9.4 m reduction in those who showed no reduction in the mMRC score between the two assessments ($p = 0.035$). Similar findings were observed in the subgroup of patients with more severe dyspnea at first assessment (mMRC score ≥ 2), with a difference of 60.0 m between the groups with and without mMRC score reduction ($p = 0.050$) (Table 3).

Finally, we explored in multivariable linear regression models the relationship between unitary differences in mMRC scores and 6MWD in both cross-sectional and longitudinal analyses adjusted for age, severity of acute SARS-CoV-2 disease, admission to intensive care unit, ischemic heart disease, respiratory failure/COPD, asthma and obesity. In the cross-sectional analyses, each additional point in mMRC score corresponded to −56.3 m walked (95%CI −69.8 to −42.9 m, $p < 0.001$) at first assessment and to −47.7 m walked (95%CI −62.5 to −32.8 m, $p < 0.001$) at second assessment. In the

longitudinal analysis, each unitary mMRC score increase between the two assessments corresponded to a concurrent reduction of 22.5 m in 6MWD (95%CI −40.1 to −4.8, $p = 0.013$) (Table 3).

Table 3. Six-minutes walking distance (6MWD) according to mMRC dyspnea scores at the two assessments.

6MWD absolute values (meters, mean, SD) at the two study assessments								
mMRC Initial Score Group	First		Second		Difference (95%CI)		p	
All (n: 120)	455 (110)		467 (109)		+11.6 (−2.4, +25.7)		0.105	
mMRC score ≥ 1 (n: 67)	413 (124)		432 (127)		+18.5 (−4.6, +41.8)		0.116	
mMRC score ≥ 2 (n: 40)	371 (132)		401 (148)		+30.1 (−5.9, +66.2)		0.099	
mMRC score = 0 (n: 53)	508 (58)		511 (60)		+2.9 (−10.2, +15.9)		0.659	
mMRC score = 1 (n: 27)	477 (75)		478 (64)		+1.3 (−21.8, +24.4)		0.907	
mMRC score = 2 (n: 22)	436 (70)		470 (91)		+32.7 (−17.2, +82.7)		0.187	
mMRC score = 3 (n: 18)	290 (147)		316 (183)		+26.9 (−30.8, +84.7)		0.339	
Proportion of patients with 6MWD below 65% of predicted (n, %) at the two study assessments								
	First		Second		p			
All (n: 116)	18 (15.5)		11 (9.4)		0.035			
mMRC score ≥ 1 (n: 67)	15 (23.8)		10 (15.8)		0.059			
mMRC score ≥ 2 (n: 37)	14 (37.8)		9 (24.3)		0.059			
6MWD mean changes (meters) between the two assessments, by concurrent mMRC score modifications								
	Score increased (n: 11)	Score not increased (n: 109)	Difference (95%CI) between groups	p	Score decreased (n: 38)	Score not decreased (n: 29)	Difference (95%CI) between groups	p
All (n: 120)	−34.0	+16.2	50.2 (2.1–98.3)	0.041				
mMRC score ≥ 1 (n: 67)					+39.9	−9.4	49.3 (3.7–95.0)	0.035
mMRC score ≥ 2 (n: 40)					+60.0	−10.2	70.2 (0–140.0)	0.050
Estimated impact of each additional mMRC point on 6MWD (meters, 95%CI)								
	Estimate	95%CI	p					
For score at 1st assessment (n: 165)	−56.3	−69.8 –42.9	<0.001					
For score at 2nd assessment (n: 139)	−47.7	−62.5 –32.8	<0.001					
For unitary score increase over time (n: 120)	−22.5	−40.1 –4.8	0.013					

4. Discussion

The current study, assessing patients followed at mean intervals of roughly four and eight months from acute SARS-CoV-2 infection, confirmed the major role of dyspnea among persistent post-COVID symptoms, with more than half of the patients affected after four months from acute infection. The data at eight months showed a reassuring trend: more than forty percent of the patients that suffered from persistent dyspnea at four months showed a complete symptom regression, and an additional twenty percent showed a reduction in severity grade. However, not all the patients improved, and despite the general reduction observed in the prevalence of the symptom, slightly more than one third of the individuals followed had some degree of dyspnea at eight months from COVID-19, including a small proportion of cases who showed worsening or new occurrence of this symptom. The above findings are concerning, and underline the necessity of longer-term studies intended to define to which extent the symptom and the associated functional impairment will persist, improve or completely regress.

The concurrent evaluation of the exercise capacity through the six-minutes walking test helped in defining the functional correlates of dyspnea and of its changes over time.

The results showed that the mMRC dyspnea score and the 6MWD were strictly correlated. Reductions and increases in the dyspnea score were associated with significant differences in the distances walked at the two assessments, suggesting that the test can be effectively coupled to the administration of the mMRC dyspnea scale in both cross-sectional and longitudinal studies in the context of long COVID.

The differences in the distances walked were not only statistically but also clinically significant. We quantified in roughly 50–60 m the impact of each additional mMRC grade on the cumulative distance walked at each assessment, at roughly 50 m the differences in the distances walked between patients with and without longitudinal mMRC score reductions and with and without longitudinal mMRC score increases, and at 22.5 m the reduction in 6MWD associated with each unitary mMRC score increase over time. Such distances have clinical relevance, considering the minimum clinically important difference of 26 m defined for adults with long-term conditions in the systematic review and meta-analysis by Daynes et al. [20].

In interpreting the study data, it should be noted that they were collected in a population with relatively advanced age, common presence of comorbidities, and frequent occurrence of hospitalization and intensive respiratory support during acute COVID-19. The prevalence of dyspnea and the observed 6MWD may therefore not apply to more healthy populations or to cases with previous mild or asymptomatic acute SARS-CoV-2 infection. Not all the patients evaluated for dyspnea had a concurrent 6MWT available. Although severity of acute disease, respiratory support, ischemic heart disease and chronic pulmonary disease were not significantly different between patients with and without 6MWT information, the occurrence of admission to intensive care units during acute disease was more frequent among patients of the first group, possibly indicating some sample selection based on preferential use of 6MWT after ICU admission. Data on pulmonary tests and chest imaging were not collected, limiting the possibility of better defining structural lung damage (e.g., pulmonary fibrosis). Other limitations include potential regression to the mean in sequential assessments, and an additional possible selection bias from the two-assessment inclusion requirement. We also lacked a control group of COVID-negative individuals, but the diffusion of COVID-19 infection and SARS-CoV-2 vaccination currently makes it almost impossible to recruit COVID-negative individuals in clinical cohorts.

The strengths of the present study include, in addition to the use of validated instruments for the assessment of dyspnea and exercise capacity, the multicentric data collection, a relatively long follow up after acute infection, and a longitudinal design based on two subsequent evaluations, which allowed for the definition of post-COVID trajectories for both dyspnea and exercise capacity, conferring robustness and consistency to the associations found. Standardized equations were also used to report the distances as percentages of the expected values by age, sex, height and weight.

From a pathogenetic point of view, the significant correlations between subjective symptoms and functional capacity in both cross-sectional and longitudinal analyses reinforce the hypothesis that long COVID dyspnea, in many cases, and possibly in the majority, relies on organic causes, although the 6MWT results may also be affected by non-organic causes. The direction of functional changes in longitudinal data suggests that the still ill-defined organ damage or dysfunction producing dyspnea may be reversible in a significant proportion of individuals. Different and possibly overlapping pulmonary, cardiovascular, muscular and psychological factors may be involved, and extensive evaluations that were beyond the aim of this study may be necessary to define the causes of dyspnea and of its persistence in individual patients [2,4,9,21]. The 6MWT is a general functional test that evaluates the integrated response of the pulmonary, cardiovascular, and muscular systems. It could be usefully included in a multidisciplinary diagnostic

approach to post-COVID dyspnea as a first-level test, to be accompanied or complemented by additional investigations, also according to the results observed. For example, given the possible role of psychological factors in many cases of dyspnea [2], normal 6MWT results may orientate toward non-organic causes, limiting other functional evaluations.

5. Conclusions

Dyspnea was confirmed as the most frequent symptom in patients followed for long COVID. Longitudinal data showed a substantial regression over time in most patients, but not in all, with roughly one third of patients complaining about symptom persistence at eight months, and a small proportion experiencing new occurrence or worsening. The six-minutes walking test proved to be sensitive to the presence, degree and evolution of dyspnea, indicating that it could effectively be used in conjunction with the mMRC dyspnea scale in the evaluation and monitoring of the patients affected. The present study was observational in nature, and the observed mMRC–6MWD association should be further explored in specifically designed instrumental studies.

Author Contributions: M.F. was responsible for data acquisition, directly accessed and verified the underlying data reported in the manuscript, performed the analyses and drafted the manuscript. L.E.W. was responsible for data acquisition. M.F. and G.O. were responsible for study design and conceptualization. L.E.W., P.R.Q., M.B.C., D.L., T.C., E.B., T.A., G.V., S.G. and M.T. contributed to the data acquisition. All authors contributed to the interpretation of results and review of the manuscript for intellectual content. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The Italian National Ethics Committee approved the project on 19 April 2022 (AOO-ISS–19/04/2022–0015066 Class: PRE BIO CE 01.00). Written informed consent was required for patient inclusion, using a patient information and consent form also approved by the Italian National Ethics Committee.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The study data can be made available upon reasonable request. Ethics Committee consultation may be necessary in order to obtain permission to share. Requests to access the datasets should be directed to marco.floridia@iss.it.

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Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be considered as a potential conflict of interest.

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