Ann Ig. 2024 Mar 1. doi: 10.7416/ai.2024.2617. Online ahead of print

Low-intensity rehabilitation in persistent post COVID-19 dyspnoea: the value of Spa health resort as appropriate setting

Emanuela Resta[1], Carla Maria Irene Quarato[2], Giulia Scioscia[2,3], Eustachio Cuscianna[4], Pasquale Tondo[3], Giuseppe Mansueto[3], Ernesto Lulay[5], Simone Sorangelo[3], Onofrio Resta[5], Maria Pia Foschino Barbaro[2,3], Silvio Tafuri[4], Donato Lacedonia[2,3]

Received: 2023 October 23
Accepted after revision: 2024 February 21
Published online ahead of print: 2024 March 1

Keywords: Post COVID-19 syndrome; dyspnoea; fatigue; exercise intolerance; low-intensivity rehabilitation setting; Spa rehabilitation setting
Parole chiave: Sindrome post COVID-19; dispnea; affaticamento; intolleranza all'esercizio; contesto riabilitativo a bassa intensità; riabilitazione termale

Abstract

Background. *Post COVID-19 syndrome is a frequent disabling outcome, leading to a delay in social reintegration and return to working life.*
Study design. *This was a prospective observational cohort study. The main objective was to explore the effectiveness of a Spa rehabilitation treatment on the improvement of post COVID-19 dyspnoea and fatigue, also analyzing the relationship between such symptoms. Additionally, it was assessed if different clinical characteristics could predispose patients in experiencing post COVID-19 symptoms or could influence the effectiveness of a Spa intervention.*
Methods. *From July to November 2021, 187 post COVID-19 patients were enrolled in the study. All the patients complained persisting dyspnoea, whose impact on daily activities was assessed using the modified Medical Research Council dyspnoea scale. 144 patients (77.0%) reported also fatigue. The Spa treatment was started at least 3 months after COVID-19 acute phase. At the end of the treatment, patients were asked to rate the improvement in the dyspnoea and fatigue sensation. 118 patients also underwent*

[1] *Translational Medicine and Health System Management, Department of Economy, University of Foggia, Foggia, Italy*
[2] *Institute of Respiratory Diseases, Policlinico Universitario "Riuniti" di Foggia, Foggia, Italy*
[3] *Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy*
[4] *Interdisciplinary Department of Medicine, Aldo Moro University of Bari, Bari, Italy*
[5] *Department of Basic Medical Sciences, Neuroscience and Sense Organs, Section of Respiratory Disease, University "Aldo Moro" of Bari, Bari, Italy*

co-first authors: Emanuela Resta, PhD and Carla Maria Irene Quarato, MD
co-last authors: Silvio Tafuri, MD and Donato Lacedonia PhD, MD

Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

the modified Borg Dyspnoea Scale for severity estimation of Exertion Dyspnoea and the Barthel index for severity estimation of Physical Limitation.

Results. *165 out of 187 patients (88.2%) reported an improvement in dyspnoea, while 116 out 144 patients (80.6%) reported an improvement in both dyspnoea and fatigue. On a total of 118 subjects, a clinically significant improvement in the modified Borg Dyspnoea Scale (i.e. Delta Borg equal or more than -2.0 points) was reached by the 50.8% of patients, while a clinically significant improvement in the Barthel index (i.e. Delta Barthel equal or more than +10.0 points) was reached by the 51.7% of them. The 31.4% of patients reached a minimal clinically important improvement in both the modified Borg Dyspnoea Scale and the Barthel index. No risk factors were associated to a clinically impacting dyspnoea at entry, while a BMI>30 Kg/m^2 was the main risk factor for chronic fatigue. Presence of respiratory comorbidities, obesity and severe acute COVID-19 (phenotype 4) configured risk factors for the lack of improvement of dyspnoea after the treatment, while no risk factors were associated to a lack of improvement for fatigue. Older age, obesity and comorbidities seemed to make more difficult to reach a clinically meaningful improvement in the modified Borg Dyspnoea Scale and the Barthel index after treatment. Female gender may imply more physical limitation at entry, while male patients seem to show less improvement in the Barthel index after treatment.*

Conclusions. *Dyspnoea and fatigue were confirmed to be important post COVID-19 symptoms even in younger subjects of working age and subjects with absent or modest pulmonary alterations at distance from acute COVID-19. A Spa health resort seems to be an effective "low-intensity" setting for a rehabilitation program of such patients. There is a strong relationship in terms of improvement between dyspnoea and fatigue, even if risk factors for their occurrence appear to be different. The improvement in exertion dyspnoea and physical limitation seemed to be less mutually related, probably due to a greater complexity in the assessment questionnaires. Some risk factors may predict a lack of improvement in symptoms after treatment.*

Introduction

At the end of 2020 and in 2021, different authors coined the term of "post-acute COVID-19" to standardize that pattern of symptoms related to SARS-CoV-2 infection that some patients continue to complain even for months after the acute phase and negativization of the nasopharyngeal swab (1, 2). Currently, the World Health Organization (WHO) defines as "post COVID-19 syndrome" a condition characterized by persistent or new onset symptoms beyond 3 months from a probable or confirmed SARS-CoV-2 infection, after excluding other causes (3). The most common symptoms are fatigue and dyspnoea, but a variety of other persistent disturbances are reported, including cough, chest pain, myalgia, joint pain, cognitive impairment, sleep disorders, depression, anxiety, post-traumatic stress disorder, gastrointestinal upset, rashes, and palpitations (4, 5). The percentage frequency of such symptoms is highly variable depending on age, gender and the concomitant presence of other comorbidities. It ranges from 53 to 87% for fatigue and from 43 to 71% for dyspnoea (6-8).

Although the magnitude of the post COVID-19 syndrome is still unknown, its prevalence has been estimated to vary between 10 and 35% of infected individuals, whether treated in intensive or sub-intensive wards or at home (9, 10). Since million of individuals have been and still continue to be infected by SARS-CoV-2 worldwide, the societal impact of this new chronic health condition is likely to become economically relevant in terms of days off from work and utilisation of healthcare resources and treatment.

Post COVID-19 syndrome has been associated with reduced health-related quality of life and poor functional status. However, surprisingly, several studies have reported an apparent discrepancy between presence of symptoms limiting daily activities and lung function tests or chest CT. Indeed, in approximately 35% to 65% of patients exercise intolerance and dyspnoea were present despite normal pulmonary function tests and absence of abnormal chest CT findings (11-13). Based on these evidences, some authors have proposed the possibility of a distinct emerging long COVID-19 phenotype (14).

In order to reduce the possibility of long-term disabling outcomes, a coordinated American Thoracic Society (ATS)/European Respiratory Society (ERS) international task force recommended tailored rehabilitative interventions in all patients hospitalized with COVID-19, not only at the discharge from the hospital, but also after the resolution of the acute infection (15). The American Academy of Physical Medicine and Rehabilitation (AAPM&R) specifically recommended rehabilitation for patients with post

COVID-19 related fatigue and breathing discomfort to promote functional improvement and to facilitate a return to activities of daily living (16, 17). However, to date, evidence from high-quality trials on the effectiveness of rehabilitation programmes in post COVID-19 patients is scarce (18-20). In a systematic review and meta-analysis of the literature, Chen et al. (18) highlighted that effects of pulmonary rehabilitation on lung function and quality of life in post COVID-19 patients should be cautiously interpreted due to conflicting data across studies. Furthermore, data on younger patients (i.e. aged under 55 years), on non-hospitalized patients and on the effects of a rehabilitation treatment undertaken after a longer time (i.e. 6-9 months after the acute phase of COVID-19) are lacking (20). As a result, the same guidelines acknowledge the need for further research investigating the effectiveness of rehabilitation interventions and exercise for individuals with post COVID-19 syndrome (16, 17).

Unfortunately, there are no specific and adequate structures to receive the large number of post COVID-19 patients who need a rehabilitation treatment. To deal with this new health emergency, it is therefore necessary to identify alternative out of-hospital "low-intensity" rehabilitation settings allowing to reduce the pressure on hospital rehabilitation units, which are overworked by acute rehabilitation of COVID-19 patients.

From this perspective, some authors suggested a remotely monitored tele-rehabilitation programme that can be carried out at home (21-23). As another viable option, respiratory rehabilitation in Spa centers have been shown to improve respiratory functions, reduce mucus and chronic inflammation in the airways, ameliorate chest wall kinematics, and increase, not only physical health, but also mental wellbeing in patients with respiratory diseases (24). Already since 2021, almost 700 articles on the effectiveness of Spa treatments in chronic pulmonary diseases had been published and available on Pubmed (25-28). Starting from already existing rehabilitative plans prescribed for work-related respiratory diseases, some authors suggested a Spa-based rehabilitative program also in post-COVID-19 patients (29). Currently, a similar Spa rehabilitation program has been made available for post COVID-19 patients at the "Margherita di Savoia's Baths" (Italy).

On this background, the primary aim of this study was to explore through standardized clinical indices the effectiveness of a Spa respiratory rehabilitation treatment on the improvement of post COVID-19 dyspnoea and fatigue and to explore the relationship between such symptoms. Secondary aims were to assess if different clinical characteristics could predispose patients in experiencing post COVID-19 symptoms or could influence the achievement of the clinical outcomes of effectiveness after Spa intervention.

Materials and methods

Study setting and participants

From July to November 2021, 340 patients who were referred for a Spa rehabilitation protocol of treatment to "Margherita di Savoia's Baths" (Italy) as a result of SARS-CoV2 infection during the first wave of pandemic in Italy were recruited in the study.

Inclusion criteria were: 1) adult patients (aged >18 years); 2) a previous diagnosis of SARS-CoV2 infection from positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay on nasal swabs; 3) a post-COVID-19 syndrome (regarded as persistence of dyspnoea with or without fatigue for at least more than 3 months after the past infection); 4) a written informed consent to participate in the study.

Exclusion criteria were: 1) acute respiratory diseases; 2) signs of cardiovascular instability; 3) cognitive impairment, 4) physical disability.

The study was conducted in accordance to the amended Declaration of Helsinki. The Apulia Region authorized the "Margherita di Savoia's Baths" to provide the day-service package "THERMAL TREATMENTS - REHABILITATION IN POST-COVID PATIENT" with Regional Council Resolution No. 963 of 16/06/2021 supplemented by the Executive Determination of the Department of Health - Health Promotion Department - Strategies and Supply Governance Service (Prot. AOO_183/PROT/10789 OF 06/30/2021).

Patients' assessment

Upon admission in the Baths, the following information were collected for each patient: 1) age; 2) sex; 3) Body Mass Index (BMI); 4) comorbidities; 5) data on the past COVID-19 course and management.

According to the COVID-19 related course and management, patients were classified into four phenotypes:

- Phenotype 1: characterised by patients with no need for oxygen therapy who recovered from COVID-

19 at home;

- Phenotype 2: characterised by patients with hypoxaemia which was possible to correct with oxygen therapy and no need for hospitalization;

- Phenotype 3: characterized by patients with hypoxemia who needed hospitalization and non-invasive mechanical ventilation;

- Phenotype 4: characterised by patients with severe hypoxaemia who required intubation or tracheotomy and hospitalization in intensive care unit (ICU).

Each patient underwent initial and final evaluations with validated questionnaires to determine the degree of patients' symptoms at entry and verify the effects of the rehabilitation treatment. According to the AAPM&R consensus guidance statement on breathing discomfort in in post-acute sequelae of SARS-CoV-2 infection (16) the clinical impact of dyspnoea was assessed using the modified Medical Research Council (mMRC) dyspnoea scale. It consists in a 5-point scale (ranging from 0 to 4) in which higher score correspond to increased dyspnoea. Patients who selected from grade 2 to grade 4 were regarded as affected by clinically important dyspnoea (30). According to the AAPM&R consensus guidance statement on fatigue in post-acute sequelae of SARS-CoV-2 infection (17), "fatigue" was defined as a physical, cognitive or emotional, mild to severe, intermittent to persistent, feeling of weariness, tiredness or lack of energy affecting a person's energy, motivation, and concentration. At the beginning of the Spa treatment, patients were asked whether or not they experienced fatigue. At the end of the treatment, patients were asked to rate the improvement of their dyspnoea and/or fatigue on a 4-point scale as follows: 0 ("unchanged"), 1 ("slight improvement"), 2 ("good improvement") and 3 ("resolution"). Minimal clinically meaningful improvement was considered to be 2 to 3 points. Each patient was also asked to relate the improvement of fatigue to that of dyspnoea as follows: improved more, improved less, improved the same, not improved (in contrast to dyspnoea), both not improved.

In some patient, we also valued the Borg Exertion Dyspnoea (BED) and the Barthel Physical Limitation (BPL). The modified Borg Dyspnoea Scale for exertion dyspnoea consists in a 10-point scale, ranging from 0 ("no exertion dyspnoea at all") to 9 ("maximal exertion dyspnoea"). The minimal clinically important difference (MCID) from the beginning (T_1) to completion (T_2) of the Spa rehabilitation treatment was considered to be -2.0 points (31). The Barthel Index for physical limitation ranges from 0 (maximum level of dependency) to 100 (complete autonomy). A score of 0-20 indicate "total" dependency, 21-60 indicate "severe" dependency, 61-90 indicate "moderate" dependency and 91-99 indicates "slight" dependency (32). The MCID in scores on the BI was considered to be 10 points (33).

At entry, all patients underwent a complete medical examination and functional evaluations. A spirometry, consisting in three reproducible measurements of maximally forced inspiratory and expiratory manoeuvres was used to obtain the forced expiratory volume in the first second (FEV_1) and the forced vital capacity (FVC). A 6 minutes walking test (6MWT) over an incline-free circuit was carried out to evaluate the eventual onset of exercise desaturation. Such functional data were used to plan the rehabilitation treatment but were not taken into consideration in the present preliminary study. Anyhow, we have observed in another study that there is no relationship between functional data and reported symptoms at entry (34).

Effectiveness data were examined one month after the conclusion of the rehabilitation program.

Intervention

The treatment offered to post COVID-19 patients at the "Margherita di Savoia's Baths" was borrowed from the existing ones offered to patients with work-related respiratory diseases (e.g. pulmonary fibrosis due to silicosis and asbestosis) and covered by the Italian public insurance agency called "Istituto nazionale Assicurazione Infortuni sul Lavoro" (INAIL) (35, 36). The post COVID-19 program included a total of 12 therapy sessions, each consisting in about 2-3 hours of daily therapy, disbursed for 12 consecutive days in two weeks (excluding Sundays). Each therapy session aimed at general and respiratory rehabilitation, with the possibility of diversifying treatments according to the comorbidities and symptoms complained by the patient in order to speed up the recovery. The Spa rehabilitation program was started at least 3 months after the COVID-19 acute phase.

Spa treatments provided consisted of:

- Inhalation therapy with mineral water;

- Respiratory physiochinesis of therapy;

- Meccanical pulmonary ventilation with mineral water for rehabilitative purpose;

- Hydrokinesitherapy.

Inhalation treatments consist in the inhalation of a mixture of water vapor and thermal water at a temperature reaching almost 40°C through a mouthpiece. The thermal water of the "Margherita di Savoia's Baths" is a sodium-chloride-bromide-iodide

water with high salinity, rich in chlorides, bromides, iodides and trace elements, such as sulphur. It is particularly effective in determine the reduction of inflammation and congestion of the respiratory system, the fluidification of the mucus and the improvement of the mucociliary clearance in the upper airways.

In patients with chronic bronchitis and bronchiectasis (with or without obstruction), inhalation treatments were associated with controlled pulmonary ventilation with personalized inspiratory and expiratory pressures. Pulmonary ventilations consist in the delivery of thermal aerosol with intermittent positive pressure. This treatment has the dual purpose of allowing the achievement of the beneficial effects of thermal water in the deepest parts of the lungs and of reducing the work of breathing and breathing discomfort, acting as a controlled respiratory gymnastic improving lung functionality and expandability.

Hydrokinesitherapy combines respiratory physiotherapy techniques for breath control (pursed lip breathing, diaphragmatic breathing and secretion mobilization) with the beneficial effects of thermal water in terms of vasodilatation, muscle toning and anti-inflammatory properties.

Study Outcomes

The primary outcome of the study was to assess at the beginning (T_1) and upon completion (T_2) of the Spa rehabilitation treatment the eventual improvement on dyspnoea and fatigue sensation and to explore the relationship between such symptoms.

Secondary outcomes were to assess if different clinical conditions could predispose patients in experiencing a clinically important dyspnoea (mMRC 2-4) and fatigue in the post COVID-19 period or could influence the achievement of the clinical outcomes of effectiveness after Spa intervention.

Statistical analysis

Continuous variables are presented as means and standard deviations, whereas categorical variables are expressed as counts and percentages. Skewness and Kurtosis tests were conducted to evaluate the normality of the continuous variables; in case of a non-normal distribution, a normalization model was established. Student's t-test for independent data (parametric) was used to compare continuous variables between groups. Differences between groups were assessed by χ2-squared test for categorical variables. The strength of the association between patients' conditions and post COVID-19 dyspnoea and fatigue at the start (T1) and upon completion of the treatment (T2) was evaluated through univariate logistic regression analyses; the Odds Ratio (OR) values were indicated together with their 95% confidence intervals (95%CIs).

For all tests, a two-sided p-value<0.05 was considered to indicate statistical significance.

Results

Demographic characteristics of patients

From July to November 2021, 340 patients were referred to the Margherita di Savoia's Baths due to persistent COVID-19 related symptoms. 130 patients were excluded from the study because they didn't meet inclusion criteria (the majority of them didn't complain persistent COVID-19 dyspnoea). Considering a population of 210 subjects with persistent COVID-19 related dyspnoea for the present study, 23 patients were finally excluded because they didn't complete the rehabilitation Spa protocol by undergoing all the 12 scheduled sessions of treatment. Among the remaining 187 participants enrolled, 118 patients also underwent the modified Borg Dyspnoea Scale and the Barthel Index for the assessment of the severity of the daily dyspnoea sensation and the physical limitation, respectively. The study flow chart is summarized in Figure 1.

Demographic descriptive data of the 187 participants who met the inclusion criteria and gave their informed consent to the enrolled in the study are displayed in Table 1.

124 of the 187 patients (66.3%) had at least one comorbidities, while 41 patients had more than one comorbidities. Specifically, a total of 85 patients (45.45%) had at least one cardiovascular disease, of which the most frequently reported was hypertension (38.0%). A total of 30 patients (16.0%) had a chronic respiratory disease; among them, 16 patients (8.6%) had COPD, 13 (7.0%) had asthma and 1 (0.5%) had pulmonary fibrosis. Other most represented comorbidities were type 2 diabetes (7.5%) and thyroid diseases (5.4%).

Among the 187 enrolled patients, 53 patients (28.3%) reported a mMRC grade 1, 82 patients (43.9%) reported a mMRC grade 2, 51 patients (27.3%) a mMRC grade 3 and only 1 patient (0.5%) reported a mMRC grade 4. Therefore, 134 out of 187 patients (71.7%) complained a clinically important dyspnoea according to the mMRC dyspnoea scale. 144 out of 187 patients (77.0%) reported fatigue. 105 out of 134 (55.6%) patients reported either a clinically important dyspnoea and fatigue.

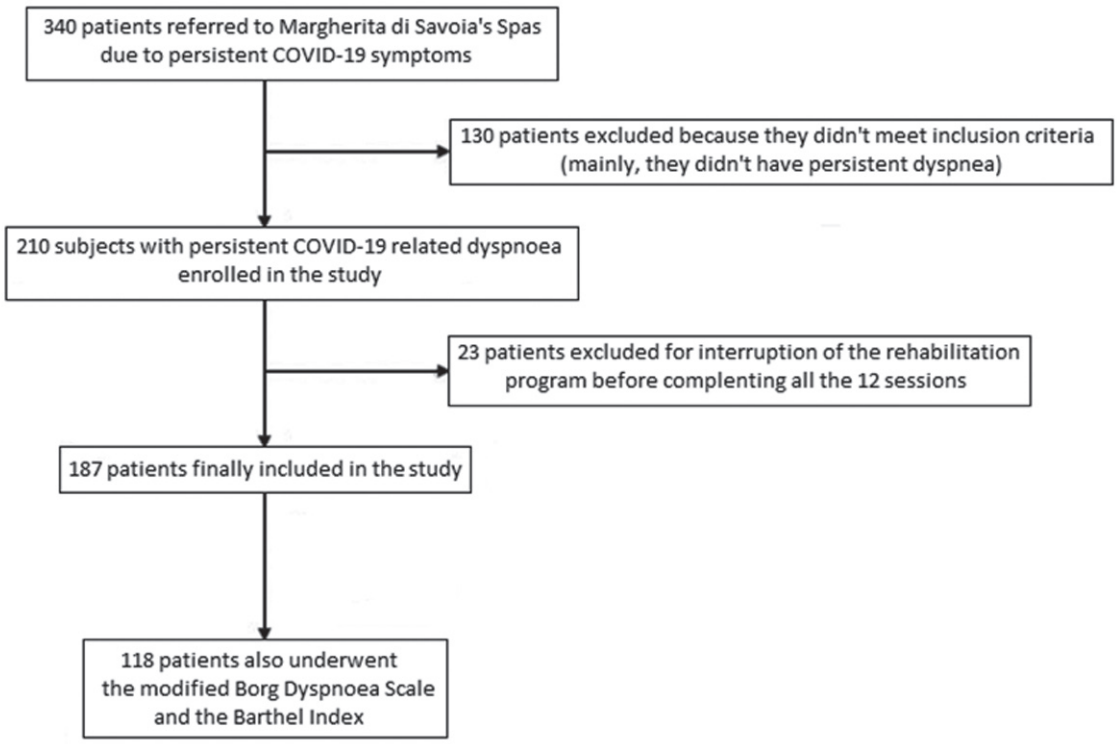

Figure 1 - Study flow chart

Subjective evaluation of the improvement of dyspnoea and fatigue after the treatment

Upon completion of the Spa rehabilitation treatment, 165 out of 187 patients (88.2%) reported an improvement in the dyspnoea sensation, while 116 out 144 patients (80.6%) reported an improvement in the fatigue sensation. The judgment of improvement for dyspnoea and fatigue reported by patients is detailed in Table 2.

Among the 144 patients complaining both the symptoms, 116 subjects (80.6%) reported an improvement in both dyspnoea and fatigue, for 11 subjects (7.6%) fatigue had not improved in contrast to dyspnoea and for 17 subjects (11.8%) both symptoms had not improved. The judgment on the improvement of fatigue compared to that of dyspnoea reported by patients is detailed in Table 3.

A subgroup of 118 patients further underwent the BED and BPL at the beginning (T_1) and the end (T_2) of the treatment. Results are displayed in Table 4.

The mean pre-treatment Borg was 3.60±1.30, while the mean post-treatment Borg was 1.41±0.67. The median Delta Borg was –2.0 points. 60 out of 118 patients (50.8%) reached a clinically significant improvement in BED (i.e. Delta Borg equal or more than -2.0 points).

The mean pre-treatment Barthel was 74.00±13.72, while the mean post-treatment Barthel was 86.55±8.81. The median Delta Barthel was +10 points. 61 out of 118 patients (51.7%) reached a clinically significant improvement in BPL (i.e. Delta Barthel equal or more than +10 points).

37 patients (31.4%) reached a minimal clinically important improvement in both the BED and the BPL, 23 patients (19.5%) reached a minimal clinically important improvement in the BED but no in the BPL, 24 patients (20.3%) reached a minimal clinically important improvement in BPL but no in the BED and 34 (28.9%) didn't reach a minimal clinically important improvement in both the BED and the BPL.

Risk factors for clinically relevant dyspnoea or fatigue at entry and improvement of both symptoms after treatment

No substantial risk factors for clinically relevant dyspnoea were found analyzing differences in clinical characteristics presented by patients who reported a mMRC grade 1 or a mMRC grade 2-4 at entry. However, we unexpectedly recorded a lower likelihood of experiencing important breathlessness in patients with chronic respiratory diseases (OR: 0.42; 95% CI: 0.20-0.87). On the other hand, BMI

Table 1 - Demographic characteristics of the 187 patients enrolled in the study.

Demographic Characteristics	
Age; mean ± SD (range)	58.10 ± 13.54 (18 - 85)
Sex; % male	100 (53.5%)
Sex, % female	87 (46.5%)
BMI; mean ± SD (range)	28.28±3.57
COVID-19 symptoms onset (months); mean ± SD (range)	9.05 ± 3.38 (3 - 15)
COVID-19 phenotype:	
Phenotype 1, n %	67 (35.8%)
Phenotype 2, n %	55 (29.4%)
Phenotype 3, n %	55 (29.4%)
Phenotype 4, n %	10 (5.4%)
Post-COVID-19 symptoms:	
Dyspnoea and asthenia, n %	144 (77.0%)
Dyspnoea mMRC 1, n %	53 (28.3%)
Dyspnoea mMRC 2, n %	82 (43.9%)
Dyspnoea mMRC 3, n %	51 (27.3%)
Dyspnoea mMRC 4, n %	1 (0.5%)
Comorbidities (at least one), n %	124 (66.3%)
Multiple comorbidities (more than one), n %	41 (21.9%)
Comorbidities:	
Hypertension	71 (38.0%)
Left heart failure	18 (4.8%)
COPD	16 (8.6%)
Type 2 diabetes	14 (7.5%)
Asthma	13 (7.0%)
Thyroid disease	10 (5.4%)
Chronic ischaemic heart disease	3 (1.6%)
Arrhythmias	2 (1.1%)
Pulmonary fibrosis	1 (0.5%)
Fibromyalgia	1 (0.5%)
Multiple sclerosis	1 (0.5%)
Ulcerative colitis	1 (0.5%)
Psoriasis	1 (0.5%)
Neoplasm	1 (0.5%)

Table 2. Subjective evaluation of the improvement of dyspnoea and fatigue after the treatment.

Subjective judgment	Dyspnoea (n=187)	Fatigue (n=144)
0 = unchanged	22 (11.8%)	28 (19.4%)
1 = slight improvement	77 (41.2%)	66 (45.8%)
2 = good improvement	70 (37.4%)	36 (25.0%)
3 = resolution	18 (9.6%)	14 (9.7%)
Total improvement	165 (88.2%)	116 (80.6%)

Table 3 - Relationship between the improvement of fatigue compared to that of dyspnoea based on the subjective judgment of patients affected by both the symptoms.

Subjective judgment	Patients (n=144)
"Improved more"	8 (5.6%)
"Improved the same"	90 (62.5%)
"Improved less"	18 (12.5%)
"Not improved" (in contrast to dyspnoea)	11 (7.6%)
"Both not improved"	17 (11.8%)

Table 4 - Pre-treatment (T_1) and post-treatment (T_2) evaluation of exertion dyspnoea and physical limitation.

Exertion dyspnoea		Physical limitation	
Pre-treatment Borg (T_1)	3.60±1.30	Pre-treatment Barthel (T_1)	74.00±13.72
Post-treatment Borg (T_2)	1.41±0.67	Post-treatment Barthel (T_2)	86.55±8.81
Median Delta Borg	-2.0	Median Delta Barthel	+10
Delta Borg >|-2.0|	60 (50.8%)	Delta Barthel >|+10|	61 (51.7%)

Table 5 - Comparison of the frequencies of clinical characteristics between patients without and with clinical impacting dyspnoea at the entry (T_1) and between patients without and with clinical improvement of dyspnoea after treatment (T_2).

Demographic characteristics	Impact of dyspnoea at entry (T_1)			Improvement of dyspnoea (T_2)		
	Not relevant mMRC 1 (n=53)	Relevant mMRC 2-4 (n=134)	p-value	Unchanged or slight 0-1 point (n=99)	Good or resolution 2-3 points (n=88)	p-value
Age > 65 anni (n=60)	16 (30.2%)	44 (32.8%)	0.12	29 (29.3%)	31 (35.2%)	0.39
Male sex (n=100)	32 (60.4%)	68 (50.7%)	0.23	55 (55.6%)	45 (51.1%)	0.55
Female sex (n=87)	21 (39.6%)	66 (49.3%)	0.23	44 (44.4%)	43 (48.9%)	0.55
BMI > 30 (n=53)	12 (22.6%)	41 (30.6%)	0.28	41 (41.4%)	12 (13.6%)	<0.0001*
Phenotype 1 (n=67)	19 (35.8%)	48 (35.8%)	1.00	34 (34.3%)	33 (37.5%)	0.65
Phenotype 2 (n=55)	13 (24.5%)	42 (31.3%)	0.36	26 (26.3%)	29 (33.0%)	0.32
Phenotype 3 (n=55)	16 (30.2%)	39 (29.1%)	0.88	30 (30.3%)	25 (28.4%)	0.78
Phenotype 4 (n=10)	5 (9.4%)	5 (3.7%)	0.12	9 (9.1%)	1 (1.1%)	0.02*
Comorbidities (n=124)	41 (77.4%)	83 (61.9%)	0.04*	68 (68.7%)	56 (63.6%)	0.95
Multiple comorbidities (n=41)	9 (17.0%)	32 (23.9%)	0.30	22 (22.2%)	19 (21.6%)	0.92
Cardiovascular disease (n=85)	17 (32.1%)	58 (43.3%)	0.16	43 (43.4%)	42 (47.7%)	0.56
Respiratory disease (n=39)	17 (32.1%)	22 (16.4%)	0.02*	29 (29.3%)	10 (11.4%)	0.003*

above 30 Kg/m^2 (OR: 0.22; 95% CI: 0.11-0.46), severe phenotype 4 acute COVID-19 (OR: 0.11; 95% CI: 0.01-0.93) and respiratory comorbidities (OR: 0.31, 95% CI: 0.14-0.68; p=0.003) configured risk factors for no significant improvement or lack of improvement in dyspnoea after treatment (Table 5).

Obesity (i.e. BMI above 30 Kg/m^2) configured a risk factor (OR: 3.80, 95% CI: 0.41-10.28) for chronic fatigue at entry, while a lower likelihood of experiencing fatigue was found for patients with chronic respiratory diseases (OR: 0.28, 95% CI: 0.13-0.68). Contrary to dyspnoea, no risk factors were found for no significant improvement or lack of improvement in fatigue after treatment. (Table 6).

Clinical characteristics associated to the lack of improvement of BED and BPL

Patients aged over 65 years, obese patients and patients affected by comorbidies (i.e. one or more than one comorbidites) didn't reach a clinically significant median Delta Borg upon completion of the treatment (Table 7).

Female patients showed a significantly lower pre-treatment BI compared to male patients (70.33±14.40 *vs.* 77.41±12.82; p=0.006). Similarly, patients with a BMI over 30 Kg/m^2 had a significantly lower pre-treatment BI compared patients with a BMI under 30 Kg/m^2 (70.05±13.40 *vs.* 77.24±11.56; p=0.02) and patients with multiple comorbidities had a lower pre-treatment BI compared patients without or with only one comorbidity (65.46±12.97 *vs*. 75.86±11.47; p=0.0002). Patients aged over 65 years, males, obese patients and patients affected by multiple comorbidities didn't reach a clinically meaningful median Delta Barthel (Table 8).

Table 6 - Association between patients' clinical characteristics, presence of fatigue at the entry (T_1) and the improvement of fatigue after treatment (T_2).

Fatigue at entry (T_1)				Improvement of fatigue (T_2)			
Demographic characteristics	Present (n=144)	Not present (n=43)	p-value	Demographic characteristics	Unchanged or slight 0-1 point (n=94)	Good or resolution 2-3 points (n=50)	p-value
Age > 65 years (n=60)	44 (30.6%)	16 (37.2%)	0.41	Age > 65 years (n=44)	31 (33.0%)	13 (26.0%)	0.39
Male sex (n=100)	77 (53.5%)	23 (53.5%)	1.00	Male sex (n=77)	53 (56.4%)	24 (48.0%)	0.34
Female sex (n=87)	67 (46.5%)	20 (46.5%)	1.00	Female sex (n=67)	41 (43.6%)	26 (52.0%)	0.34
BMI > 30 (n=53)	48 (33.3%)	5 (11.6%)	0.006*	BMI > 30 (n=48)	33 (35.1%)	15 (30.0%)	0.54
Phenotype 1 (n=67)	50 (34.7%)	17 (39.5%)	0.56	Phenotype 1 (n=50)	28 (29.8%)	22 (44.0%)	0.09
Phenotype 2 (n=55)	42 (29.2%)	13 (30.2%)	0.89	Phenotype 2 (n=42)	26 (27.7%)	16 (32.0%)	0.59
Phenotype 3 (n=55)	44 (30.5%)	11 (25.6%)	0.53	Phenotype 3 (n=44)	30 (31.9%)	14 (28.0%)	0.63
Phenotype 4 (n=10)	8 (5.6%)	2 (4.7%)	0.82	Phenotype 4 (n=8)	7 (7.4%)	1 (2.0%)	0.17
Comorbidities (n=124)	96 (66.7%)	26 (60.5%)	0.45	Comorbidities (n=96)	60 (63.8%)	36 (27.0%)	0.32
Multiple comorbidities (n=41)	31 (21.5%)	10 (23.3%)	0.81	Multiple comorbidities (n=31)	20 (21.3%)	11 (22.0%)	0.92
Cardiovascular disease (n=85)	67 (46.5%)	18 (41.9%)	0.59	Cardiovascular disease (n=67)	39 (41.5%)	28 (56.0%)	0.10
Respiratory disease (n=39)	22 (15.3%)	17 (39.5%)	0.0006*	Respiratory disease (n=22)	16 (17.0%)	6 (12.0%)	0.43

Table 7 - Evaluation of BED stratified according to patients' clinical characteristics

Age:	> 65 years (n=48)	≤ 65 years (n=70)	p-value
Pre-treatment Borg (T_1)	3.49±1.36	3.67±1.25	0.59
Delta Borg (T_2)	**-1.5**	-2.0	
Sex:	Male (n=62)	Female (n=56)	p-value
Pre-treatment Borg (T_1)	3.36±1.20	3.85±1.44	0.14
Delta Borg (T_2)	-2.0	-2.0	
BMI:	>30 Kg/m^2 (n=24)	≤30 Kg/m^2 (n=94)	p-value
Pre-treatment Borg (T_1)	3.29±1.11	3.51±1.28	0.44
Delta Borg (T_2)	**-1.5**	-2.0	
Comorbidities:	Yes (n=61)	No (n=57)	p-value
Pre-treatment Borg (T_1)	3.62±1.33	3.58±1.28	0.87
Delta Borg (T_2)	**-1.75**	-2.0	
Multiple comorbidities:	Yes (n=24)	No (n=94)	
Pre-treatment Borg (T_1)	3.54±1.37	3.31±1.15	0.40
Delta Borg (T_2)	-1.5	-2.0	
Respiratory Comorbidities:	Yes (n=13)	No (n=105)	
Pre-treatment Borg (T_1)	3.00±0.77	3.67±1.38	0.09
Delta Borg (T_2)	**-1.0**	-2.0	
Cardiovascular Comorbidities:	Yes (n=40)	No (n=78)	
Pre-treatment Borg (T_1)	3.64±1.38	3.58±1.26	0.81
Delta Borg (T_2)	**-1.75**	-2.0	

Discussion

To the best of our knowledge this is the first study evaluating whether Spa health resort is an appropriate "low-intensity" setting to undertake a rehabilitation treatment protocol in a cohort of post COVID-19 patients.

More specifically, our study focused on a respiratory rehabilitation and all the patients complained persistent post COVID-19 dyspnoea at entry. The dyspnoea symptom was reported as "clinically significant" (i.e. mMRC grade 2-4) by 71.7% of patients. The 77% of patients referred also fatigue.

At the end of the intervention, most of the subjects (88.2%) improved their dyspnoea. Such improvement was reported as "good" or "complete" by 47.0% of patients and as "slight" by 41.2% of them. Among patients complaining both the symptoms, the 80.55% reported an improvement in both dyspnoea and fatigue. The improvement in the fatigue sensation was reported as "good" or "complete" by 34.7% of patients and as "slight" by 45.8% of them. In a subgroup of subjects, we also assessed the BED and the BPL. A clinically significant improvement in BED (i.e. Delta Borg equal or more than -2.0 points) was reached by the 50.8% of patients, while a clinically significant improvement in BPL (i.e. Delta Barthel equal or more than +10.0 points) was reached by the 51.7% of them. The 31.4% of patients reached a minimal clinically important improvement in both the BED and the BPL.

Our overall results seem to support the effectiveness of a rehabilitation protocol of treatment in a "low-intensity" Spa setting for post COVID-19 patients. According to the former literature, the percentage frequency of post COVID-19 symptoms ranges from 53 to 87% for fatigue and from 43 to 71% for dyspnoea (6-8). As our study focused more on pulmonary rehabilitation, post COVID-19 symptoms rates reported by our patients are slightly higher than in other case series.

Table 8 - Pre-treatment (T_1) and post-treatment (T_2) evaluation of the physical limitation stratified according to patients' clinical characteristics.

Age:	> 65 years (n=48)	≤ 65 years (n=70)	p-value
Pre-treatment Barthel (T_1)	75.06±13.14	72.44±14.76	0.32
Delta Barthel (T_2)	12.03±7.89	13.33±8.65	0.41
Median Delta Barthel	**9.5**	11	
Sex:	Male (n=62)	Female (n=56)	p-value
Pre-treatment Barthel (T_1)	77.41±12.82	70.33±14.40	0.006*
Delta Barthel (T_2)	11.85±8.05	13.32±8.40	0.33
Median Delta Barthel	**9**	12	
BMI:	>30 Kg/m^2 (n=24)	≤30 Kg/m^2 (n=94)	p-value
Pre-treatment Barthel (T_1)	70.05±13.40	77.24±11.56	0.02*
Delta Barthel (T_2)	13.32±8.29	10.39±7.05	0.11
Median Delta Barthel	**9.5**	11	
Comorbidities:	Yes (n=61)	No (n=57)	p-value
Pre-treatment Barthel (T_1)	73.44±13.35	74.40±14.00	0.70
Delta Barthel (T_2)	12.80±8.71	12.38±7.90	0.78
Median Delta Barthel	11	10	
Multiple comorbidities:	Yes (n=24)	No (n=94)	
Pre-treatment Barthel (T_1)	65.46±12.97	75.86±11.47	0.0002*
Delta Barthel (T_2)	10.62±8.51	13.39±7.86	0.13
Median Delta Barthel	**9.5**	11.5	
Respiratory Comorbidities:	Yes (n=13)	No (n=105)	
Pre-treatment Barthel (T_1)	74.77±10.47	73.90±14.10	0.83
Delta Barthel (T_2)	13.00±7.23	12.50±8.36	0.84
Median Delta Barthel	10	12	
Cardiovascular Comorbidities:	Yes (n=40)	No (n=78)	
Pre-treatment Barthel (T_1)	70.95±13.68	75.44±13.39	0.09
Delta Barthel (T_2)	14.34±9.94	11.71±7.41	0.11
Median Delta Barthel	12	10	

Our study has the strength of being a prospective study enrolling a significant number of post COVID-19 patients of working age (i.e. <65 years). Data on patients aged 18 to 64 years are scarce (37). However, this age range represents the most productive life years of a population. Considering the high healthcare indirect costs deriving from the loss of their productive potential, rehabilitation of subjects aged between 18-65 years developing a long-lasting and debilitating disease assumes fundamental importance. Furthermore, the post COVID-19 population included in our study appears to be more representative of the actual real-world situation. Indeed, 65.2% of the enrolled subjects recovered by mild to moderate SARS-CoV2 infection not requiring hospitalization and/or respiratory support during the acute phase, while 34.7 % of them had severe SARS-CoV2 pneumonia. On the other hand, currently available studies and randomized controlled trial (RCT) evaluating the effectiveness of rehabilitation treatment in post COVID-19 patients are mainly related only to a severe infection requiring mechanical ventilation and/or invasive ICU treatments (21, 38-40). Finally, unlike other "low-intensity" rehabilitation programs that were undertaken at hospital discharge (21-23), our Spa treatment was started at least 3 months after the

acute phase. This allowed us to exclude the possibility of an improvement in symptoms not determined by the treatment but time-related.

Moreover, for the first time, we analyzed the relationship between the two main post COVID-19 symptoms (i.e. dyspnoea and fatigue) at the beginning and at the end of a respiratory rehabilitation treatment. Our results suggested that post COVID-19 dyspnoea and fatigue mostly improve together. On the other hand, BED and BPL were less mutually related. At the basis of this discrepancy, however, there may be the greater complexity of questionnaires, such as the Borg and the Barthel, in assessing exertion symptoms, compared to a "yes" or "no" type assessment used to confirm the presence of dyspnoea or fatigue.

While potential risk factors for the development of a severe COVID-19 are now almost known, studies assessing risk factors for post COVID-19 syndrome are contrasting (41-48). Therefore, in our study we tried to find eventual risk factors associated to the occurrence of post COVID-19 symptoms, as well as risk factors that may predict a lack of improvement in symptoms after treatment. No substantial risk factors were associated to a clinically relevant post COVID-19 dyspnoea, while obesity configured a risk factor for fatigue. Unexpectedly, patients with respiratory comorbidities were less likely for experiencing clinically important dyspnoea and fatigue. A possible explanation is that patients with chronic respiratory diseases are more used to having and chronically enduring the feeling of "short of breath" and related fatigue (49). Obesity, respiratory comorbidities and a previous severe acute COVID-19 (phenotype 4) configured risk factors for the lack of improvement of dyspnoea after treatment, while no risk factors were associated to improvement or lack of improvement of fatigue. Female patients showed a significantly lower pre-treatment BPL compared to male patients. This result agrees with other studies reporting a higher experience of physical limitation in female post COVID-19 patients (4, 50). On the other hand, male patients didn't reach a clinically meaningful improvement in BPL after treatment. As expected, a lower pre-treatment BPL was also recorded in obese patients and in patients with multiple comorbidities. Patients aged over 65 years, patients presenting a BMI>30 Kg/m^2 and patients with comorbidities didn't reach a clinically meaningful improvement in BED and BPL after intervention. Future studies are needed to confirm the possible influence of these clinical differences in post COVID-19 patients.

Although the exact mechanisms of post-COVID-19 fatigue and dyspnoea has yet to be recognized, several hypotheses have been produced. A first hypothesis consists in the presence of residual lung injury after the acute phase (51). However, this explanation fits well only a small percentage of post COVID-19 patients who experienced a severe acute disease and in which exertional dyspnoea can be well explained by persistent residual chest CT abnormalities and restricted pulmonary function (52). On the other hand, in a larger number of patients the causes of dyspnoea and fatigue remains enigmatic due to the absence of abnormalities in pulmonary function tests or chest imaging (11-13). Also in another study of ours we did not find important correlations with functional characterization in post COVID-19 subjects with dyspnoea (34).

A suggestive hypothesis comes from the study by Singh et al (53). This study examined 10 patients who recovered from a mild COVID-19 with invasive cardiopulmonary exercise testing (iCPET). Despite the absence of abnormalities in blood gases or any other pulmonary or cardiovascular parameter, these patients exhibited a condition of severe muscle deconditioning characterized by a peripheral decreased oxygen extraction (EO_2). Additionally, all patients demonstrated an exaggerated hyperventilatory response during exercise. This remarkable finding suggested that dyspnoea in post COVID-19 patients may occur because of an excessive stimulation of the respiratory centres in the brain stem, which, in turn, results from an altered peripheral metabolic situation in skeletal muscles. Several non-mutually exclusive pathobiologic mechanisms may underlie this condition. One of them would be related to a prolonged pro-inflammatory response (hyper-inflammatory cytokine storm) associated with SARS-CoV-2 infection (51, 54). Other hypotheses include clotting/coagulation issues, the establishment of a dysfunctional nerve signalling and a virus-mediated mitochondrial damage (55, 56). To this regard, Lam et al. (14) proposed the existence of a distinct emerging long COVID-19 phenotype with connotations yet to be verified.

On this background, rehabilitation programs including aerobic training, strengthening exercises, diaphragmatic breathing techniques, as well as mindfulness training addressing psychological aspects related to the disease, might represent effective treatment options in patients with persistent symptoms after COVID-19 (57, 58). Thermal waters may have a favourable additive effect to physiotherapy, due to the reduction of inflammation in the early airways

and the positive effect on the vascularisation of large bronchi induced by mineral-rich water inhalations. It is noteworthy to remember that the first damages induced by SARS-CoV_2 occur in the upper airways. The thermal water specifically used at the "Margherita di Savoia's Baths" come directly from the famous local salt deposits, presenting a high saline content, as well as other important substances including iodine and bromine and trace elements, such as sulphur. Treatment with inhaled salt-bromide-iodine thermal water has been shown to have vasodilating activity on the bronchial mucosa and stimulating action on the muco-ciliary clearance, at the same time increasing the production of secretory IgA (28, 59). Sulphur-rich water inhalation has been demonstrated to decrease the synthesis of pro-inflammatory cytokines and the inflammatory mucosal infiltration, and reduce the levels of elastase produced by the neutrophils (28, 60). Assisted breathing creates the conditions for the benefits of thermal water to reach the small airways, as well as promoting better chest expansion thanks also to the use of an end-expiratory pressure. This is important considering the scarring effects induced by COVID-19 affecting the interstitium and resulting in increased traction of the lung. Finally, hydrokinesitherapy combines the rehabilitative effect of physiotherapy on asthenic subjects with the physical effect of the heat of water, leading to an improvement in the vascularisation and tone of the striated muscles. Furthermore, immersions in mineral-rich waters seem to be effective in reducing pro-inflammatory cytokines, including IL-6 levels (28, 59, 60).

We have to acknowledge that the present study has some limitations.

The first limitation could be related to the shorter duration of our rehabilitation program. However, our Spa treatment consisted in about 2-3 hours of daily therapy for a total of 12 sessions disbursed in two weeks. The TERECO study (21) evaluated and remotely monitored the effectiveness of a pulmonary rehabilitation program held at home during 6 weeks, but consisting in about 3-4 weekly sessions, each lasting about 40-60 minutes. De Souza et al. (22) proposed a home-based rehabilitation program for a total duration of 6 weeks, but delivered with only a weekly session by videoconference. Paneroni et al. (23) investigated the efficacy of a one-month telerehabilitation program consisting of one hour of daily exercises monitored by twice a week video calls. Our rehabilitation treatment was, therefore, more intense. Furthermore, effectiveness data in our study were examined one month after the conclusion of the intervention. This allowed us to verify the long-term duration of benefits.

Second, although standardized tools were used for the assessment of dyspnoea and fatigue, all consisted of self-reported questionnaires. This may imply a bias due to the so-called "cognitive dissonance" (61), that is the cognitive need of participants to change the perception of symptoms even if they have not objectively improved after the completion of the rehabilitation program. Anyhow, also other works on rehabilitation treatment in post COVID-19 patients used the same evaluation questionnaires. For example, the TERECO study (21) assessed the post-treatment effectiveness using the mMRC dyspnoea scale, De Souza et al. (22) valued post-treatment patients' exertional dyspnoea using the Borg Dyspnoea Scale et al. (23) analyzed patients' post-treatment physical limitation using the Barthel Index. In this work we have not included functional data (i.e. FEV_1 and FVC values assessed on spirometry, desaturation and meters travelled assessed by 6MWT), but in another work of ours we assessed no correlation between functional parameters and post COVID-19 symptoms (34). Similarly, Lam et al (14) and Huang et al (62) have shown that there is no relationship between imaging, spirometric data and dyspnoea. Functional data would appear to be useful only in the early stages of recovery from COVID-19, when lung damage still persists. Our Spa rehabilitation treatment was started at least 3 months after the acute phase. Patients included in our study had no or only modest lung alterations correlated to previous COVID-19 pneumonia and only one of them was diagnosed with pre-existent pulmonary fibrosis. The functional evaluation at entry was, therefore, performed in our study only for the purpose of planning the rehabilitation intervention.

Third, we did not perform an a priori sample size calculation of participants included in the study. Anyhow, this limit is due to a lack of previously existing data in the literature on a Spa rehabilitation program for post COVID-19 patients.

Another limitation of our study might be a bias related to interventions in the Spa setting, because of the social atmosphere of health resorts producing positive effect on mood and cognitive function through the reduction of stress. To this regard we must add that our study lacks the inclusion of a comparator group that did not have suspected or confirmed SARS-CoV_2 infection. However, the potential presence of psychological confounding factors can also be considered a strength of a Spa rehabilitation treatment, increasing its effectiveness.

In conclusion, dyspnoea and fatigue were confirmed to be important post COVID-19 symptoms even in younger subjects of working age (i.e. <65 years) and subjects with absent or modest pulmonary alterations at distance from the acute episode. Our study suggested that Spa health resorts could be considered as an effective "low intensity" setting for a rehabilitation program of such subjects, allowing to reduce the pressure on "high intensity" hospital rehabilitation units and the economic expenses for the National Health System. Besides the assessment of presence or absence of fatigue and clinically meaningful dyspnoea with the mMRC scale, this work also wanted to evaluate the severity of patients' exertion dyspnoea (BED) and physical limitation (BPL). We found that there is a strong relationship in terms of improvement between dyspnoea and fatigue, even if risk factors for their occurrence appear to be different. The improvement in exertion dyspnoea and physical limitation seemed to be less mutually related. Anyhow, a possible explanation for this discrepancy may be that the Borg and Barthel questionnaires are more complex and articulated. In our study we also tried to verify the factors that predict a lack of improvement in symptoms after treatment. Obesity, respiratory comorbidities and a severe phenotype of acute COVID-19 configured risk factors for the lack of improvement of dyspnoea after treatment, while no risk factors were associated to the lack of improvement of fatigue. Older age, obesity and comorbidities may make a clinically meaningful improvement in BED and BPL after intervention more difficult. Gender differences seem to influence the perceived physical limitation, with women exhibiting worse BPL at entry, but men presenting less improvement in BPL after treatment.

Further studies on the topic are advised to properly investigate beneficial effect of a Spa-based rehabilitative programs in post COVID-19 patients.

Declarations

Ethical approval and Consent to Participate: The study was conducted in accordance to the amended Declaration of Helsinki and all patients signed a written informed consent to participate. Ethical approval was deemed unnecessary according to national regulations because the present study adheres to accepted ethical standards of treatment (Regional Council Resolution No. 963 of 16/06/2021, Apulia Region - Italy, supplemented by the Prot. AOO_183/PROT/10789 OF 06/30/2021, Executive Determination of the Department of Health - Health Promotion Department - Strategies and Supply Governance Service).

Availability of Data and Materials: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for Publication: Not applicable

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests: The authors declare no competing interests

Authors' Contribution: E.R., O.R., M.P.F.B. and D.L. equally contributed to the study conception and design. Data collection were performed by E.R., C.M.I.Q., G.S., E.C., P.T., G.M., E.L., S.S., O.R., M.P.F.B., S.T. and D.L. The analysis was performed by C.M.I.Q. and O.R. The first draft of the manuscript was written by C.M.I.Q., O.R. and S.T. All authors commented on previous versions of the manuscript and contributed to the final version. All authors read and approved the final manuscript

Riassunto

Trattamento riabilitativo "a bassa intensità" per la dispnea persistente post COVID-19: il valore di un centro termale quale setting di cura appropriato

Introduzione. La sindrome post COVID-19 consiste in una frequente e invalidante complicanza che si rende responsabile di un ritardo nel reinserimento sociale e nel ritorno alla vita lavorativa dei pazienti che ne sono affetti.

Disegno dello studio. Quello presentato è stato uno studio prospettico osservazionale di coorte. L'obiettivo principale è stato quello di esplorare l'efficacia di un trattamento riabilitativo termale sul miglioramento della dispnea e della stanchezza post COVID-19, analizzando contemporaneamente la relazione tra tali sintomi. Inoltre, è stato valutata la possibilità che diverse caratteristiche cliniche predispongano i pazienti a manifestare sintomi post COVID-19 o influenzino l'efficacia dell'intervento termale.

Metodi. Da luglio a novembre 2021, sono stati arruolati 187 pazienti con sindrome post COVID-19. Tutti i pazienti lamentavano dispnea persistente, il cui impatto sulle attività quotidiane è stato valutato utilizzando la scala modificata per la dispnea del Medical Research Council. 144 pazienti (77,0%) hanno riferito anche stanchezza persistente. Il trattamento termale è stato iniziato almeno 3 mesi dopo la fase acuta del COVID-19. Alla fine del trattamento, ai pazienti è stato chiesto di valutare il miglioramento nella sensazione di dispnea e di stanchezza. Per 118 pazienti sono stati inoltre impiegati la scala modificata per la Dispnea di Borg per la stima della gravità della dispnea da sforzo e l'indice Barthel per la stima della gravità della limitazione fisica.

Risultati. 165 pazienti su 187 (88,2%) hanno riportato un miglioramento della dispnea, mentre 116 pazienti su 144 (80,6%) hanno riportato un miglioramento sia della dispnea che della stanchezza. Su un totale di 118 soggetti, un miglioramento clinicamente significativo sulla scala modificata per la Dispnea di Borg (inteso come un Delta Borg uguale o superiore a -2,0 punti) è stato raggiunto dal 50,8% dei pazienti, mentre un miglioramento clinicamente significativo per l'indice Barthel (inteso come un Delta Barthel uguale o superiore a +10,0 punti) è stato raggiunto dal 51,7% di essi. Il 31,4% dei pazienti ha raggiunto un miglioramento minimo clinicamente importante sia per la scala modificata per la Dispnea di Borg che per l'indice Barthel. Nessun fattore di rischio è stato associato alla sensazione di dispnea clinicamente rilevante all'ingresso, mentre un BMI>30 Kg/m^2 è risultato il principale fattore di rischio per la stanchezza cronica. La presenza di comorbidità respiratorie, obesità e COVID-

19 acuto grave (fenotipo 4) hanno configurato fattori di rischio per il mancato miglioramento della dispnea dopo il trattamento, mentre nessun fattore di rischio è stato associato a un mancato miglioramento della stanchezza. L'età avanzata, l'obesità e la presenza di comorbidità sembravano rendere più difficile il raggiungimento di un miglioramento clinicamente significativo nella scala modificata per la Dispnea di Borg e nell'indice Barthel dopo il trattamento. Il sesso femminile potrebbe implicare una maggiore limitazione fisica all'ingresso, mentre i pazienti di sesso maschile sembrano mostrare un minore miglioramento nell'indice Barthel dopo il trattamento.

Conclusioni. Dispnea e stanchezza cronica hanno confermato di essere sintomi post COVID-19 importanti anche nei soggetti più giovani in età lavorativa e nei soggetti con alterazioni polmonari assenti o modeste a distanza dal COVID-19 acuto. Un centro termale sembrerebbe essere un ambiente efficace per un programma riabilitativo "a bassa intensità" in tali pazienti. Esiste una forte relazione in termini di miglioramento tra dispnea e stanchezza cronica, anche se i fattori di rischio per la loro insorgenza sembrano essere diversi. Il miglioramento della dispnea da sforzo e della limitazione fisica sembravano essere meno correlati tra loro, probabilmente a causa di una maggiore complessità nei questionari di valutazione. Alcuni fattori di rischio possono predire la mancanza di miglioramento dei sintomi dopo il trattamento.

References

1. Alwan NA, Johnson L. Defining long COVID: Going back to the start. Med. 2021 May; **2**(5):501-4. doi:10.1016/j.medj.2021.03.003. Epub 2021 Mar 25.
2. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021 Apr; **27**(4): 601-15. doi:10.1038/S41591-021-01283-Z. Epub 2021 Mar 22.
3. World Health Organization (WHO). A clinical case definition of post COVID-19 condition by a Delphi consensus. Last updated October 6, 2021. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1 [Last accessed: 2024 Feb 21].
4. Jacobs LG, Paleoudis EG, Lesky-Di Bari D, Nyirenda T, Friedman T, Gupta A, et al. Persistence of symptoms and quality of life at 35 days after hospitalization for COVID-19 infection. PLoS One. 2020 Dec 11; **15**(12): e0243882. doi:10.1371/JOURNAL.PONE.0243882.
5. Fernández-De-las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Palacios-Ceña M, Rodríguez-Jiménez J, de-la-Llave-Rincón AI, et al. Fatigue and Dyspnoea as Main Persistent Post-COVID-19 Symptoms in Previously Hospitalized Patients: Related Functional Limitations and Disability. Respiration. 2022; **101**(2): 132-41. doi: 10.1159/000518854. Epub 2021 Sep 21.
6. Goërtz YMJ, Herck M Van, Delbressine JM, Vaes AW, Meys R, Machado FVC, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ Open Res. 2020 Oct 26; **6**(4): 00542-02020. doi: 10.1183/23120541.00542-2020.
7. Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020 Aug 11; **324**(6): 603-5. doi: 10.1001/JAMA.2020.12603.
8. Parker AM, Brigham E, Connolly B, McPeake J, Agranovich AV, Kenes MT, et al. Addressing the post-acute sequelae of SARS-CoV-2 infection: a multidisciplinary model of care. Lancet Respir Med. 2021 Nov; **9**(11): 1328-41. doi: 10.1016/S2213-2600(21)00385-4. Epub 2021 Oct 19.
9. Office for National Statistics. Updated estimates of the prevalence of long COVID symptoms: Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/adhocs/12788updatedestimatesoftheprevalenceoflongcovidsymptoms [Last accessed: 2024 Feb 21].
10. Pavli A, Theodoridou M, Maltezou HC. Post-COVID Syndrome: Incidence, Clinical Spectrum, and Challenges for Primary Healthcare Professionals. Arch Med Res. 2021 Aug; **52**(6): 575-81. doi: 10.1016/J.ARCMED.2021.03.010. Epub 2021 May 4.
11. Froidure A, Mahsouli A, Liistro G, De Greef J, Belkhir L, Gérard L, et al. Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae. Respir Med. 2021 May; **181**: 106383. doi: 10.1016/j.rmed.2021.106383. Epub 2021 Apr 4.
12. Lerum TV, Aaløkken TM, Brønstad E, Aarli B, Ikdahl E, Lund KMA, et al. Dyspnoea, lung function and CT findings 3 months after hospital admission for COVID-19. Eur Respir J. 2021 Apr 29; **57**(4): 2003448. doi: 10.1183/13993003.03448-2020.
13. Wu X, Liu X, Zhou Y, Yu H, Li R, Zhan Q, et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. Lancet Respir Med. 2021 Jul; **9**(7): 747-54. doi: 10.1016/S2213-2600(21)00174-0. Epub 2021 May 5.
14. Lam GY, Befus AD, Damant RW, Ferrara G, Fuhr DP, Stickland MK, et al. Exertional intolerance and dyspnea with preserved lung function: an emerging long COVID phenotype? Respir Res. 2021 Aug 6; **22**(1): 222. doi: 10.1186/S12931-021-01814-9.
15. Spruit MA, Holland AE, Singh SJ, Tonia T, Wilson KC, Troosters T. COVID-19: interim guidance on rehabilitation in the hospital and post-hospital phase from a European Respiratory Society- and American Thoracic Society-coordinated international task force. Eur Respir J. 2020 Aug 13; **56**(6): 2002197. doi: 10.1183/13993003.02197-2020.
16. Maley JH, Alba GA, Barry JT, Bartels MN, Fleming TK, Oleson CV, et al. Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of breathing discomfort and respiratory sequelae in patients with post-acute sequelae of SARS-CoV-2 infection (PASC). PM R. 2022 Jan; **14**(1): 77-95. doi: 10.1002/PMRJ.12744.
17. Herrera JE, Niehaus WN, Whiteson J, Azola A, Baratta JM, Fleming TK, et al. Multidisciplinary collaborative consensus guidance statement on the assessment and treatment of fatigue in postacute sequelae of SARS-CoV-2 infection (PASC) patients. PM R. 2021 Sep; **13**(9): 1027. doi: 10.1002/PMRJ.12684. Epub 2021 Aug 24.

18. Chen H, Shi H, Liu X, Sun T, Wu J, Liu Z. Effect of Pulmonary Rehabilitation for Patients With Post-COVID-19: A Systematic Review and Meta-Analysis. Front Med (Lausanne). 2022 Feb 21; **9**: 837420. doi: 10.3389/FMED.2022.837420.
19. Fugazzaro S, Contri A, Esseroukh O, Kaleci S, Croci S, Massari M, et al. Rehabilitation Interventions for Post-Acute COVID-19 Syndrome: A Systematic Review. Int J Environ Res Public Health. 2022 Apr 24; **19**(9): 5185. doi: 10.3390/IJERPH19095185/S1.
20. Soril LJJ, Damant RW, Lam GY, Smith MP, Weatherald J, Bourbeau J, et al. The effectiveness of pulmonary rehabilitation for Post-COVID symptoms: A rapid review of the literature. Respir Med. 2022 Mar 2; **195**: 106782. doi: 10.1016/j.rmed.2022.106782. Epub ahead of print.
21. Li J, Xia W, Zhan C, Liu S, Yin Z, Wang J, et al. A telerehabilitation programme in post-discharge COVID-19 patients (TERECO): a randomised controlled trial Rehabilitation. Thorax. 2022 Jul; **77**(7): 697-706. doi: 10.1136/thoraxjnl-2021-217382. Epub 2021 Jul 26.
22. De Souza Y, MacEdo J, Nascimento R, Alves AA, Medeiros S, Leal L, et al. Low-Intensity Pulmonary Rehabilitation Through Videoconference for Post-Acute COVID-19 Patients. Am J Respir Crit Care Med. 2021; **203**: A4124. https://doi.org/10.1164/ajrccm-conference.2021.203.1_MeetingAbstracts.A4124.
23. Paneroni M, Vitacca M, Bernocchi P, Bertacchini L, Scalvini S. Feasibility of tele-rehabilitation in survivors of COVID-19 pneumonia. Pulmonology. 2022 Mar-Apr; **28**(2): 152-4. doi: 10.1016/J.PULMOE.2021.03.009. Epub 2021 Apr 14.
24. Maccarone MC, Masiero S. Spa therapy interventions for post respiratory rehabilitation in COVID-19 subjects: does the review of recent evidence suggest a role? Environ Sci Pollut Res. 2021Sep; **28**(33): 46063-6. doi: 10.1007/S11356-021-15443-8. Epub 2021 Jul 17.
25. Vu K, Mitsunobu F. Spa Therapy for Chronic Obstructive Pulmonary Disease: Studies at the Misasa Medical Center. Altern Complement Ther. 2005 Apr 20; **11**(2): 89-93. http://doi.org/10.1089/act.2005.11.89.
26. Martín-Valero R, Cuesta-Vargas AI, Labajos-Manzanares MT. Evidence-Based Review of Hydrotherapy Studies on Chronic Obstructive Pulmonary Disease Patients. Int J Aquat Res Educ. 2012; **6**(3): 8. doi: https://doi.org/10.25035/ijare.06.03.08.
27. Khaltaev N, Solimene U, Vitale F, Zanasi A. Balneotherapy and hydrotherapy in chronic respiratory disease. J Thorac Dis. 2020 Aug; **12**(8): 4459-68. doi: 10.21037/jtd-gard-2019-009.
28. Zajac D. Inhalations with thermal waters in respiratory diseases. J Ethnopharmacol. 2021 Dec 5; **281**: 114505. doi: 10.1016/J.JEP.2021.114505. Epub 2021 Aug 8.
29. Antonelli M, Donelli D. Respiratory rehabilitation for post-COVID19 patients in spa centers: first steps from theory to practice. Int J Biometeorol. 2020 Oct; **64**(10): 1811-3. doi: 10.1007/S00484-020-01962-5. Epub 2020 Jul 24.
30. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Analysis of Clinical Methods Used to Evaluate Dyspnea in Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 1998 Oct; **158**(4): 1185-9. doi: 10.1164/AJRCCM.158.4.9802091.
31. Saracino A. Review of dyspnoea quantification in the emergency department: Is a rating scale for breathlessness suitable for use as an admission prediction tool? Emerg Med Australas. 2007 Oct; **19**(5): 394-404. doi: 10.1111/J.1742-6723.2007.00999.X.
32. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. J Clin Epidemiol. 1989; **42**(8): 703-9. doi: 10.1016/0895-4356(89)90065-6.
33. Mendelow A, Grotta J, Albers G. Stroke: Patophysiology, Diagnosis and Management. (Grotta J, ed.). Elsevier; 2015.
34. Resta E, Cuscianna E, Pierucci P, Custodero C, Solfrizzi V, Sabbà C et al. Significant burden of post-COVID exertional dyspnoea in a South-Italy region: knowledge of risk factors might prevent further critical overload on the healthcare system. Front Public Health. 2023;**11**:1273853. doi:10.3389/FPUBH.2023.1273853.
35. Italian Republic. Law 323/2000; art. 5, para. 1 [Reordering of the spa sector]. Available from: https://www.parlamento.it/parlam/leggi/00323l.htm [Last accessed: 2024 Feb 21].
36. Italian Republic. Law 208/2015, para. 301-302. Available from: https://www.gazzettaufficiale.it/eli/id/2015/12/30/15G00222/sg [Last accessed: 2024 Feb 21].
37. Chen H, Shi H, Liu X, Sun T, Wu J, Liu Z. Effect of Pulmonary Rehabilitation for Patients With Post-COVID-19: A Systematic Review and Meta-Analysis. Front Med (Lausanne). 2022 Feb 21; **9**: 837420. doi: 10.3389/FMED.2022.837420.
38. Berentschot JC, Heijenbrok-Kal MH, Bek LM, Huijts SM, van Bommel J, van Genderen ME, et al. Physical recovery across care pathways up to 12 months after hospitalization for COVID-19: A multicenter prospective cohort study (CO-FLOW). Lancet Reg Health Eur. 2022 Aug 24; **22**: 100485. doi: 10.1016/J.LANEPE.2022.100485.
39. Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study. Complement Ther Clin Pract. 2020 May; **39**: 101166. doi: 10.1016/J.CTCP.2020.101166. Epub 2020 Apr 1.
40. Spielmanns M, Pekacka-Egli AM, Schoendorf S, Windisch W, Hermann M. Effects of a Comprehensive Pulmonary Rehabilitation in Severe Post-COVID-19 Patients. Int J Environ Res Public Health 2021 Mar 7; **18**(5): 2695. doi: 10.3390/IJERPH18052695.
41. Nguyen NN, Hoang VT, Dao TL, Meddeb L, Lagier JC, Million M, et al. Long-term persistence of symptoms of dyspnoea in COVID-19 patients. Int J Infect Dis. 2022 Feb; **115**: 17-23. doi: 10.1016/J.IJID.2021.11.035. Epub 2021 Nov 27.
42. Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis (Lond). 2021 Oct; **53**(10): 737-54. doi:

10.1080/23744235.2021.1924397. Epub 2021 May 22.
43. Nittas V, Gao M, West EA, Ballouz T, Menges D, Wulf Hanson S, et al. Long COVID Through a Public Health Lens: An Umbrella Review. Public Health Rev. 2022 Mar 15; **43**: 1604501. doi: 10.3389/PHRS.2022.1604501.
44. Fumagalli C, Zocchi C, Tassetti L, Silverii MV, Amato C, Livi L, et al. Factors associated with persistence of symptoms 1 year after COVID-19: A longitudinal, prospective phone-based interview follow-up cohort study. Eur J Intern Med. 2022 Mar; **97**: 36-41. doi: 10.1016/J.EJIM.2021.11.018. Epub 2021 Dec 7.
45. Loosen SH, Jensen BEO, Tanislav C, Luedde T, Roderburg C, Kostev K. Obesity and lipid metabolism disorders determine the risk for development of long COVID syndrome: a cross-sectional study from 50,402 COVID-19 patients. Infection. 2022 Oct; **50**(5): 1165-70. doi: 10.1007/S15010-022-01784-0. Epub 2022 Mar 30.
46. Vimercati L, De Maria L, Quarato M, Caputi A, Gesualdo L, Migliore G, et al. Association between Long COVID and Overweight/Obesity. J Clin Med. 2021 Sep 14; **10**(18): 4143. doi: 10.3390/JCM10184143.
47. Chan Sui Ko A, Candellier A, Mercier M, Joseph C, Schmit JL, Lanoix JP, et al. Number of initial symptoms is more related to long COVID-19 than acute severity of infection: a prospective cohort of hospitalized patients. Int J Infect Dis. 2022 May; **118**: 220-3. doi: 10.1016/J.IJID.2022.03.006. Epub 2022 Mar 5.
48. Crankson S, Pokhrel S, Anokye NK. Determinants of COVID-19-Related Length of Hospital Stays and Long COVID in Ghana: A Cross-Sectional Analysis. Int J Environ Res Public Health. 2022 Jan 4; **19**(1): 527. doi: 10.3390/IJERPH19010527.
49. von Leupoldt A, Dahme B. Psychological aspects in the perception of dyspnea in obstructive pulmonary diseases. Respir Med. 2007 Mar; ***101***(3): 411-22. doi: 10.1016/J.RMED.2006.06.011. Epub 2006 Aug 8.
50. Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLoS One. 2020 Nov 9; **15**(11): e0240784. doi: 10.1371/JOURNAL.PONE.0240784.
51. Maltezou HC, Pavli A, Tsakris A. Post-COVID Syndrome: An Insight on Its Pathogenesis. Vaccines (Basel). 2021 May 12; **9**(5): 497. doi: 10.3390/VACCINES9050497.
52. So M, Kabata H, Fukunaga K, Takagi H, Kuno T. Radiological and functional lung sequelae of COVID-19: a systematic review and meta-analysis. BMC Pulm Med. 2021 Mar 22; **21**(1): 97. doi: 10.1186/S12890-021-01463-0.
53. Singh I, Joseph P, Heerdt PM, Cullinan M, Lutchmansingh DD, Gulati M, et al. Persistent Exertional Intolerance After COVID-19: Insights From Invasive Cardiopulmonary Exercise Testing. Chest. 2022 Jan; **161**(1): 54-63. doi: 10.1016/J.CHEST.2021.08.010. Epub 2021 Aug 11.
54. Afrin LB, Weinstock LB, Molderings GJ. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. Int J Infect Dis. 2020 Nov; **100**: 327-32. doi: 10.1016/j.ijid.2020.09.016. Epub 2020 Sep 10.
55. Proal AD, VanElzakker MB. Long COVID or Post-acute Sequelae of COVID-19 (PASC): An Overview of Biological Factors That May Contribute to Persistent Symptoms. Front Microbiol. 2021 Jun 23; **12**: 698169. doi: 10.3389/FMICB.2021.698169.
56. Nunn AVW, Guy GW, Brysch W, Bell JD. Understanding Long COVID; Mitochondrial Health and Adaptation—Old Pathways, New Problems. Biomedicines. 2022 Dec 2; **10**(12): 3113. doi: 10.3390/BIOMEDICINES10123113.
57. Scurati R, Papini N, Giussani P, Alberti G, Tringali C. The Challenge of Long COVID-19 Management: From Disease Molecular Hallmarks to the Proposal of Exercise as Therapy. Int J Mol Sci. 2022 Oct 14; **23**(20): 12311. doi: 10.3390/IJMS232012311.
58. Masiero S, Maccarone MC, Agostini F. Health resort medicine can be a suitable setting to recover disabilities in patients tested negative for COVID-19 discharged from hospital? A challenge for the future. Int J Biometeorol. 2020 Oct;**64**(10):1807-1809. doi: 10.1007/s00484-020-01947-4. Epub 2020 Jun 5. PMID: 32504142; PMCID: PMC7272594.
59. Khaltaev N, Solimene U, Vitale F, Zanasi A. Balneotherapy and hydrotherapy in chronic respiratory disease. J Thorac Dis. 2020 Aug; **12**(8): 4459-68. doi: 10.21037/JTD-GARD-2019-009.
60. Pellegrini M, Fanin D, Nowicki Y, Guarnieri G, Bordin A, Faggian D et al. Effect of inhalation of thermal water on airway inflammation in chronic obstructive pulmonary disease. Respir Med. 2005 Jun; **99**(6): 748-54. doi: 10.1016/j.rmed.2004.11.001. Epub 2004 Dec 13.
61. Festinger L, Carlsmith JM. Cognitive consequences of forced compliance. J Abnorm Soc Psychol. 1959 Mar; **58**(2): 203-10. doi: 10.1037/H0041593.
62. Huang Y, Tan C, Wu J, Chen M, Wang Z, Luo L, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. Respir Res. 2020 Jun 29; **21**(1): 163. doi: 10.1186/S12931-020-01429-6.

Corresponding Author: Carla Maria Irene Quarato, MD, Institute of Respiratory Diseases, Policlinico Universitario "Riuniti" di Foggia, Via degli Aviatori 1, Foggia, Italy
e-mail: carlamariairene.quarato@gmail.com