



Monaldi Archives for Chest Disease

eISSN 2532-5264

<https://www.monaldi-archives.org/>

Publisher's Disclaimer. E-publishing ahead of print is increasingly important for the rapid dissemination of science. The **Early Access** service lets users access peer-reviewed articles well before print / regular issue publication, significantly reducing the time it takes for critical findings to reach the research community.

These articles are searchable and citable by their DOI (Digital Object Identifier).

The **Monaldi Archives for Chest Disease** is, therefore, e-publishing PDF files of an early version of manuscripts that have undergone a regular peer review and have been accepted for publication, but have not been through the typesetting, pagination and proofreading processes, which may lead to differences between this version and the final one.

The final version of the manuscript will then appear in a regular issue of the journal.

E-publishing of this PDF file has been approved by the authors.

All legal disclaimers applicable to the journal apply to this production process as well.

Monaldi Arch Chest Dis 2023 [Online ahead of print]

To cite this Article:

Vigna M, Ceriana P, Santomassimo M, et al. **Effects of pulmonary rehabilitation in survivors of severe acute respiratory syndrome coronavirus 2. Role of vaccination.**

Monaldi Arch Chest Dis doi: 10.4081/monaldi.2023.2738

 ©The Author(s), 2023
Licensee [PAGEPress](#), Italy

Note: The publisher is not responsible for the content or functionality of any supporting information supplied by the authors. Any queries should be directed to the corresponding author for the article.

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.



**Effects of pulmonary rehabilitation in survivors of severe acute respiratory syndrome
coronavirus 2. Role of vaccination**

Matteo Vigna,¹ Piero Ceriana,¹ Mara Santomassimo,¹ Michele Vitacca,² Mauro Maniscalco,³
Nicolino Ambrosino⁴

¹Respiratory Rehabilitation Unit, ICS Maugeri IRCCS, Institute of Pavia;

²Institute of Lumezzane (BS);

³Institute of Telese (BN);

⁴Institute of Montescano (PV), Italy

Corresponding author: Piero Ceriana, Respiratory Rehabilitation Unit, ICS Maugeri IRCCS, Institute of Pavia, Via S. Maugeri 10, 27100 Pavia, Italy. E-mail: piero.ceriana@icsmaugeri.it

Author's contribution:

Matteo Vigna: study design and statistical analysis

Piero Ceriana: selection of patients and preparation of the manuscript

Mara Santomassimo: data collection

Michele Vitacca and Mauro Maniscalco: patient selection and study design

Nicolino Ambrosino: manuscript review

Conflict of interests with the present manuscript: none from any author

Funding: none

Conference presentation: never

Ethics approval: The study was approved by the Istituti Clinici Scientifici (ICS) Maugeri IRCCS Ethics Committee (EC 2629, April the 5th, 2022). As a retrospective study, participants had not provided any specific written informed consent; at admission to ICS Maugeri hospitals, they had given informed consent for the scientific use of their data

Abstract

Survivors of severe COVID-19 requiring hospital admission may suffer from short- and long-term sequelae, including disability and reduced physical performance. Vaccination and pulmonary rehabilitation (PR) are effective tools against COVID-19 effects. While the beneficial effect of each of these treatments is known, there are no data about their combined effect. In people admitted to PR hospitals after severe COVID-19 disease, we retrospectively analyzed whether PR outcome might be influenced by vaccination status. Ninety-six individuals were studied (46 vaccinated, 50 unvaccinated). Unvaccinated individuals were younger and less comorbid than vaccinated ones and had needed more intensive care support during the previous hospitalization. Measures of disability and physical performance did not differ between groups at the beginning and at the end of the PR program. However, each group showed a statistically significant improvement in all outcome measures (6-minute walking test, short physical performance battery, Barthel Index). We conclude that vaccination status does not influence the outcome of in-patient PR programs for survivors of severe COVID-19.

Key words: COVID-19; acute respiratory failure; pulmonary rehabilitation; COVID vaccination.

Introduction

During the past three years, more than six hundred million people have been infected with the severe acute respiratory syndrome coronavirus 2 (COVID-19) and more than six million died [1]. A significant proportion of individuals required hospital admission including intensive care units (ICU) [2]. The administration of billions doses of vaccines worldwide [1] has resulted in significant reductions in hospital admissions, morbidity and mortality [3]. However, in addition to the consequences on lung function [4] a high prevalence of impairment in physical performance may be found in survivors. These individuals may suffer from fatigue and/or muscle weakness, exercise-induced dyspnea, sleep difficulties, anxiety and/or depression up to six months after the acute infection [5,6]. Pulmonary rehabilitation (PR) turned out to be feasible and effective in these individuals [7]. .

Vaccines and PR target different stages of disease: the former prevents severe disease, the latter enhances functional recovery and improves disability. We wondered whether the effects of PR might be influenced by previous vaccination. Therefore, the aims of this retrospective multicenter study were: i) to evaluate physical performance, disability and oxygenation status in survivors of COVID-19 severe acute respiratory failure according to vaccination status, and, ii) to assess the effects of an in-hospital PR program on physical performance and disability in vaccinated and unvaccinated individuals.

Methods

The study was approved by the Istituti Clinici Scientifici (ICS) Maugeri IRCCS Ethics Committee (EC 2629, April the 5th, 2022). As a retrospective study, participants had not provided any specific written informed consent, but, at admission to ICS Maugeri hospitals, they had given – in advance- informed consent for the scientific use of their data. As a retrospective analysis, the study was not registered.

Participants

Participants were selected among individuals consecutively admitted between September 2021 and April 1st 2022 to the Respiratory Units of ICS Maugeri network hospitals of Pavia,

Lumezzane and Telese (Italy), referral institutions for PR, diagnosis, and care of post-acute and chronic conditions, which during the pandemic admitted individuals transferred from acute care hospitals as previously reported [8,9]. These units share the same evaluation, management and PR programs [10].

Inclusion criteria were: i) previous admissions to acute care hospitals for acute respiratory failure due to COVID-19 infection; ii) previous treatment with invasive (IMV) or non-invasive (NIV) mechanical ventilation, continuous positive airway pressure (CPAP), high flow nasal cannula (HFNC), or oxygen supplementation only; c) negative Real-Time PCR (RT-PCR) test for SARS-CoV-2 at the time of transfer from acute care hospital to PR wards. Exclusion criteria were: i) neurological or orthopaedic conditions (either acute or chronic) preventing the performance or the completion of the PR program; ii) denied or withdrawn consent to use the data for scientific purposes.

Measurements

On admission, the following data were collected: demographics, anthropometrics (body mass index (BMI)), number and diagnosis of comorbidities by the Cumulative Illness Rating Scale (CIRS) including the Cumulative Illness Rating Score Comorbidities Index (CI) and the Cumulative Illness Rating Score Severity Index (SI) [11]. Other collected data included: vaccination status (vaccinated with at least two doses of any kind of vaccine [either mRNA or adenoviral vector]), time elapsed from vaccination to acute care hospitalization, length of stay (LoS) in ICU; need for oxygen therapy, HFNC, CPAP, NIV, IMV and/or tracheostomy during the previous acute care hospital stay.

Before and after the PR program, we assessed the following evaluations [12]:

- Oxygenation status (arterial oxygen tension to inspired oxygen fraction ratio: P/F).
- Degree of disability was evaluated with the Barthel Index (BI) [13]; the total BI score ranges from 0 (maximum level of dependency) to 100 (complete autonomy). A score ≤ 70 corresponds to severe dependency.
- Exercise tolerance was assessed by the Six-minute walking test (6MWT) [14] using the predicted values of Enright *et al.* [15]; in case of a bedridden and/or unable to walk

individual, the score was recorded as 0. The minimum clinically important difference (MCID) for this study was considered as an increase by at least 24 meters by analogy with individuals suffering from interstitial lung disease [16].

- Short Physical Performance Battery (SPPB) [17]. The SPPB total score results from the sum of 3 components: standing balance, 4-m walking test and standing from sitting position 5 times. The total SPPB score ranges from 0 to 12: 1-2: severe; 3-8: moderate disability; 9-12: normal. One point is considered as the MCID for SPPB [18].

At discharge the following data were recorded: LoS in the PR ward, need of aids for walking (such as rollator or ankle-foot-orthoses), discharge destination (home or long-term maintenance rehab facility), need of long-term oxygen.

Pulmonary rehabilitation program

Hospitals of ICS Maugeri network share a four-step early mobilization program involving levels of increasing difficulty, as previously described [19]. The steps are defined according to 1) the ability to maintain the sitting position on the edge of the bed and to cycle against resistance in bed; 2) the ability to maintain the sitting position in chair and to stand; 3) the ability of active transfer from bed to chair and to walk with the aid of a rollator and physiotherapists; 4) the achievement of walking autonomy, with or without the aid of a stick and/or a person. Moving from one step to the following one depends on limb muscle strength increase and the ability to sustain higher workloads.

The physiotherapy program in step 1 entails passive arm and leg motion twice per day for six days per week. In particular, it includes flexion and extension, supination and pronation, internal and external rotation, abduction and adduction for each joint.

In step 2, active-assisted and active exercises are maintained, with addition of the sitting position on a chair for 20 min twice per day as well as exercises involving transition from a sitting to a standing position.

Step 3 includes the addition of active transfer to a chair and walking with the aid of a rollator and physiotherapists. Two walking sessions per day are scheduled with the goal of progressively increasing the distance, as tolerated by the individual.

In step 4, scheduled walking sessions are performed with a stick and/or a person by the patient's side.

In addition to physical training, the physiotherapy program includes optimization of airway clearance and humidification, when needed. Nutritional supplementation and psychological counselling were added when necessary.

Statistical analysis

A Shapiro Wilk test was used to assess the normality of distribution in all continuous variables. For clarity purpose, all continuous variables were expressed as mean \pm standard deviation (SD) irrespectively of their distribution. Continuous variables were compared using Mann Withney's test in case of non-normal distribution and Student's *t*-test in case of normal distribution. Categorical variables were expressed with raw number and percentage (%). Categorical variables were compared using the Chi-squared test or the Fisher exact test.

A p-value <0.05 was considered significant. All analyses were performed with IBM SPSS Statistics 24.0 (Armonk, New York, NY, USA).

Results

Figure 1 represents the trial profile of the study with criteria for enrollment. Data of ninety-six individuals were included during the study period, 46 vaccinated and 50 unvaccinated, admitted to three PR hospitals (Pavia 47 [22 vaccinated, 25 unvaccinated], Lumezzane 19 [8 vaccinated, 11 unvaccinated], Telesse 30 [16 vaccinated, 14 unvaccinated] participants). None of the participants in any group needed any form of ventilatory support at admission or during their stay in the PR hospital. All individuals completed the same PR program with no significant difference in duration between vaccinated and unvaccinated. For vaccinated people, the mean time elapsed from second vaccination to acute care hospitalization had been 156 ± 79 days. The mean LoS of previous acute care hospital had been 43 ± 18 and 49 ± 22 days, for vaccinated and unvaccinated people respectively ($p= 0.7$).

Table 1 shows demographics, anthropometrics and data of previous acute care hospitalization. As expected, unvaccinated individuals were significantly younger with a higher prevalence of ICU admission, need of NIV and IMV, longer ICU LoS, and higher prevalence of tracheostomy.

Table 2 shows the pre to post PR intra-group differences in outcome measures according to vaccination status. On admission to the PR hospital, 20 vaccinated (40%) and 30 unvaccinated individuals (60%) had been totally bedridden and unable to perform 6MWT and/or SPPB. At the end of the program all participants had significantly improved measures of disability and physical performance independently of vaccination status: there was a gain of 16 ± 24 and 23 ± 27 points of BI, respectively for vaccinated and unvaccinated ($p < 0.01$), a 121 ± 100 and 146 ± 108 meter gain in 6MWT, for vaccinated and unvaccinated ($p < 0.01$) respectively (Figure 2) and a 1.9 ± 3 and 2.8 ± 2.9 point gain of SPPB, for vaccinated and unvaccinated respectively ($p < 0.01$). Parameters of blood gas exchange (P/F) improved significantly during the PR hospital stay in both groups ($p < 0.01$).

There was no significant between-group difference in any outcome measures either at admission to or at discharge from the PR hospital (Table 3). The MCID of 6MWT, was reached by 17/46 (36.9%) vaccinated and by 23/50 (46.0%) unvaccinated individuals, without any statistical between-group difference ($p = 0.58$). Furthermore 19/46 vaccinated (41.3%) and 24/50 unvaccinated individuals (48.0%) reached the MCID for SPPB without any significant between-group difference ($p = 0.67$). At the end of the program, almost half of the participants in both groups required the use of an aid for ambulation (46.3% and 50.1%, for vaccinated and unvaccinated respectively, $p = 0.6$) and the majority of them still needed home oxygen in any form: rest, night or during exercise (64.3% and 56.5%, for vaccinated and unvaccinated participants, respectively, $p = 0.55$).

Discussion

Our retrospective multicenter observational study did not find any significant difference in outcome measures of PR between vaccinated and unvaccinated individuals who survived severe COVID-19 infection. Our data indicate that also unvaccinated individuals can undergo a post COVID-19 PR program with the same probability of success rate as vaccinated subjects.

Some data, on our opinion, are relevant and deserve a comment. Vaccinated participants were older and had more comorbidities than unvaccinated subjects. This result is not surprising reflecting some issues about vaccination such as personal attitudes, government policies, and media claims [20]. Younger and healthier people were more often closer to the “stereotype” of reluctant to vaccination for self-confidence to avoid the infection, to catch it with few symptoms or to exploit the effect of herd immunity from the vaccinated subjects [21]. On the other hand, vaccinated participants were older and more comorbid, being part of that high-risk category [22] where the adherence to vaccination was nearly maximal. As soon as vaccines against SARS CoV-2 were available during the course of the pandemic, the target of any country was to reach the maximum possible coverage among the general population, in order to achieve the so-called “herd immunity”. Criteria were set in order to decide which group of people should be vaccinated first: occupational risk, age, chronic diseases, then, upon coverage of these frail categories, proceed with the remaining population. In Italy, the vaccine campaign started on January 2021 and by the end of August of the same year more than 92% of citizens older than 12 years of age had received a full cycle of vaccination (two doses of either mRNA or adenoviral vaccine) [23]. The missed target of 100% vaccinations was due to refusal to accept vaccination by a significant number of citizens [22] or presence of contraindications in a few cases (severe allergy, autoimmune or thromboembolic diseases, *etc.*) and not to shortage of doses.

Another result of our study is that, as expected, unvaccinated individuals had suffered a more severe disease as shown by the higher prevalence of ICU admissions, more need of invasive respiratory assistance, including intubation and tracheostomy. This association between lack of vaccination and more severe COVID 19 disease is in agreement with other reports from Italy and other European countries [24,25].

The PR program turned out to be highly effective in decreasing disability and improving physical performance, independently of the vaccination status. The program applied has already been validated for high-dependency patients, survived acute respiratory failure of different etiologies [19,26]. It is noteworthy that at admission to the PR hospital, a significant proportion of participants (52%) were totally bedridden and unable to perform the 6MWT and, at the end of the program, there was a mean gain of 133 ± 103 meters for the same test.

Rather interestingly, on admission to the PR ward, the two groups did not differ with respect to functional dependency and physical performance (Table 2). As a matter of fact, in absence of some markers of disease severity recorded at the onset of the disease in the acute care hospital, we can only suppose that unvaccinated people had suffered from a more severe disease. It cannot be excluded that the greater use of ICU resources and invasive respiratory support in unvaccinated people was the result of differences in local availability of hospital beds and familiarity of hospital staff with different respiratory support techniques. The two groups had similar LoS in the acute care setting: if from one side the effect of ICU stay on muscle wasting is well known [27], on the other side similar effects, although to a lesser extent, are reported with hospitalization even outside the ICU [28]. Finally, we must also take into account that the heavier impact of ICU stay on unvaccinated individuals might have been counterbalanced by younger age and less comorbidity leading to lack of differences in disability and physical performance between the two groups.

At discharge from the PR ward, there were no significant between group differences in gain of any PR outcome measure (Table 2). Response to PR represents an important issue for health care professionals since there is a high prevalence of poor responders to PR [29] in individuals with chronic obstructive pulmonary disease (COPD). Our participants showed a similar response to PR independently of the vaccination status and, according to the effect size in outcome measures, they can be defined as “good responders”. This is not surprising since, when clustering COPD patients during PR programs, good responders generally show baseline low levels of exercise performance [29], like our participants.

Limitations

This is a retrospective study with the limitations of such studies. However, it represents a real-life condition in a time when also randomized controlled trials are questioned [30]. The lack of lung function data might be a major flaw. It has been shown that post-COVID-19 individuals show impaired lung function; the most frequently affected lung function test being the diffusion capacity [4].

Given the post-acute condition of participants, a control population not performing the PR program would have clarified whether any improvement in outcome would have been (also)

time-dependent. However, given the recognized benefits of PR and the mission of our hospitals, not performing any program would have been unethical.

Conclusions

Our data show that there was no significant difference in measures of disability and functional performance between vaccinated and unvaccinated survivors of severe COVID-19 infection at the beginning of an in-hospital PR program which was effective in improving functional capacity and disability independently of the vaccination status. In conclusion, our data indicate that also unvaccinated individuals can undergo a post-COVID-19 PR program with the same probability of success as vaccinated people.

References

1. Johns Hopkins University [Internet]. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Accessed April 14, 2023. Available from: <https://coronavirus.jhu.edu/map.html>
2. Attaway AH, Scheraga RG, Bhimraj A, et al. Severe covid-19 pneumonia: pathogenesis and clinical management. *BMJ* 2021;327:n436.
3. Tenforde MW, Self WH, Adams K, et al. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. *JAMA* 2021;326:2043-54.
4. Torres-Castro R, Vasconcello-Castillo L, Alsina-Restoy X, et al. Respiratory function in patients post-infection by COVID-19: a systematic review and meta-analysis. *Pulmonology* 2021;27:328-37.
5. Paneroni M, Simonelli C, Saleri M, et al. Muscle strength and physical performance in patients without previous disabilities recovering from COVID-19 pneumonia. *Am J Phys Med Rehabil* 2021;100:105-9.
6. Huang C, Huang L, Wang Y, et al. 6-Month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021;397:220-32.
7. Zampogna E, Paneroni M, Belli S, et al. Pulmonary rehabilitation in patients recovering from COVID-19. *Respiration* 2021;100:416-22.
8. Vitacca M, Migliori GB, Spanevello A, et al. Management and outcomes of post-acute COVID-19 patients in Northern Italy. *Eur J Intern Med* 2020;78:159-60.
9. Ceriana P, Vitacca M, Paneroni M, et al. Usefulness of step down units to manage survivors of critical Covid-19 patients. *Eur J Intern Med* 2021;88:126-8.
10. Vitacca M, Malovini A, Spanevello A, et al. Clusters of individuals with chronic obstructive pulmonary disease according to baseline characteristics and response to post exacerbation pulmonary rehabilitation. *Pulmonology* 2023;29:230-9.
11. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc* 1968;16:622-6.
12. Simonelli C, Paneroni M, Vitacca M, Ambrosino N. Measures of physical performance in COVID-19 patients: a mapping review. *Pulmonology* 2021;27:518-28.
13. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel index for stroke rehabilitation. *J Clin Epidemiol* 1989;42:703-9.
14. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking test in chronic respiratory disease. *Eur Respir J* 2014;44:1428-46.
15. Enright PL, Sherrill D. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998;158:1384-7.
16. Du Bois RM, Weycker D, Albera C, et al. Six-minute walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. *Am J Respir Crit Care Med* 2011;183:1231-7.

17. Bernabeu-Mora R, Medina-Mirapeix F, Lamazares-Herran E, et al. The short physical performance battery is a discriminative tool for identifying patients with COPD at risk of disability. *Int J Chron Obstruct Pulmon Dis* 2015;10:2619-26.
18. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc* 2006;54:743-9.
19. Schreiber AF, Ceriana P, Ambrosino N, et al. Physiotherapy and weaning from prolonged mechanical ventilation. *Respir Care* 2019;64:17-25.
20. Bucchi M, Fattorini E, Saracino B. Public perception of COVID-19 vaccination in Italy: The role of trust and experts' communication. *Int J Public Health* 2022;67:1604222.
21. Rania N, Coppola I, Brucci M, Lagomarsino F. Attitudes and beliefs of the Italian population towards COVID-19 vaccinations. *Int J Environ Res Public Health* 2022;19:6139.
22. Giuliani M, Ichino A, Bonomi A, et al. Who is willing to get vaccinated? A study into the psychological, socio-demographic, and cultural determinants of COVID-19 vaccination intentions. *Vaccines (Basel)* 2021;9:810.
23. Altobelli E, Marzi F, Angelone AM, et al. Burden of COVID-19 and vaccination coverage in the Italian population as of October 2021. *Int J Environ Res Public Health* 2022;19:496
24. Lorenzoni G, Rosi P, De Rosa S, et al. COVID-19 vaccination status among adults admitted to Intensive Care Units in Veneto, Italy. *JAMA Netw Open* 2022;5:e2213553.
25. Whittaker R, Bråthen Kristofferson A, Valcarcel Salamanca B, et al. Length of hospital stay and risk of intensive care admission and in-hospital death among COVID-19 patients in Norway: a register-based cohort study comparing patients fully vaccinated with an mRNA vaccine to unvaccinated patients. *Clin Microbiol Infect* 2022;28:871-8.
26. Doiron KA, Hoffmann TC, Beller EM. Early intervention (mobilization or active exercise) for critically ill adults in the intensive care unit. *Cochrane Database Syst Rev* 2018;3(3):CD010754.
27. Puthuchery ZA, Rawal J, McPhail M, P et al. Acute skeletal muscle wasting in critical illness. *JAMA* 2013;310:1591-600.
28. Loyd C, Markland AD, Zhang Y, et al. Prevalence of hospital-associated disability in older adults: A Meta-analysis. *J Am Med Dir Assoc* 2020;21:455-61.e5.
29. Spruit MA, Augustin IM, Vanfleteren LE, et al. Differential response to pulmonary rehabilitation in COPD: a multidimensional profiling. *Eur Respir J* 2015;46:1625-35.
30. Duarte-de-Ara Jo AN, Teixeira P, Hespanhol V, Correia-de-Sousa J. COPD: How can evidence from randomised controlled trials apply to patients treated in everyday clinical practice? *Pulmonology* 2022;28:431-9.

Table 1. Demographic, anthropometric, clinical characteristics of study population-

Variable	Overall (n=96)	Vaccinated (n 46)	Unvaccinated (n 50)	p
Age	68±10.3	71±10.5	66±9.8	<0.01
Gender (M/F)	66/30	35/11	31/19	0.13
BMI, Kg/m ²	27.4±5.9	27±6.3	27.7±5.6	0.5
PR LoS (days)	38.5±22.3	39.2±18.5	37.7±20.4	0.77
CIRS (CI)	1.7±0.4	1.9±0.4	1.5±0.3	<0.01
CIRS (SI)	3.7±2.1	4.7±2.1	2.9±1.8	<0.01
Individuals requiring ICU, n (%)	40 (41.6%)	10 (21.7%)	30 (62.5%)	<0.01
ICU LoS (days)	13.9 ±20.3	7.5 ±16.1	20.2±13.5	<0.01
Respiratory support in acute care hospitals, n (%)				
O ₂	87 (90.6%)	42 (91%)	44 (91.7%)	0.95
HFNC	55 (63%)	26 (57.8%)	29 (69%)	0.27
CPAP	48 (53%)	21 (46.7%)	27 (60%)	0.20
NIV	30 (31.3%)	9 (19.6%)	19 (39.6%)	0.03
IMV	26 (27.1%)	5 (10.9%)	21 (41.7%)	<0.01
Tracheostomy	18 (18.6%)	4 (8.7%)	14 (28.6%)	<0.01
Respiratory support at admission to PR Hospitals, n (%)				
HFNC	18 (21.4%)	9 (20.9%)	9 (22%)	0.9
O ₂	60 (48.8%)	28 (60.9%)	32 (64.6%)	0.71
IMV	3 (3.6%)	1 (2.4%)	2 (4.9%)	0.54

ICU, intensive care unit; LoS, length of stay; O₂, oxygen therapy; HFNC, High flow nasal cannula; CPAP, continuous positive airway pressure; NIV, noninvasive ventilation; IMV,= Invasive mechanical ventilation.

Table 2. Intra-group comparison of rehabilitative measures between the beginning (pre) and the end (post) of PR. Values are expressed as mean \pm SD.

Variable	Vaccinated (pre)	Vaccinated (post)	p	Unvaccinated (pre)	Unvaccinated (post)	p
Barthel index	51 \pm 32	71 \pm 31	<0.01	46 \pm 33	73 \pm 33	<0.01
SPPB	3 \pm 3	5.3 \pm 3.5	<0.01	2.5 \pm 3.3	5.2 \pm 3.8	<0.01
6MWT, m	99 \pm 119	226 \pm 135	<0.01	88 \pm 116	239 \pm 123	<0.01
P/F	268 \pm 99	302 \pm 66	<0.01	268 \pm 92	319 \pm 64	<0.01

SPPB, short physical performance battery; 6MWT, six-minute walking test; P/F, ratio between partial pressure of oxygen (PaO₂) and fraction of inspired oxygen (FiO₂).

Table 3. Between-group comparison of outcome measures at the beginning and at the end of PR program.

	1	2	3	4	5	6	7	8
Variable	Overall (pre)	Vaccinated (pre)	Unvaccinated (pre)	p	Overall (post)	Vaccinated (post)	Unvaccinated (post)	p
Barthel Index	49±32	51±32	46±33	0.63	72±32	71±31	73±33	0.58
SPPB	2.7±3.2	3±3	2.5±3.3	0.23	5.2±3.6	5.3±3.5	5.2±3.8	0.93
6MWT, m	93±116	99±119	88±116	0.41	231±128	226±135	239±123	0.67
P/F	268±95	268±99	268±92	0.9	309±66	302±66	319±64	0.2

SPPB, Short physical performance battery; 6MWT, six-minute walking test; P/F, arterial oxygen tension to inspired oxygen fraction ration. Columns 1,2,3 = values of Barthel, SPPB, 6MWT and P/F at the beginning of PR program (overall and according to vaccination status). Column 4: statistical significance of between-group difference (vaccinated VS unvaccinated) at the beginning of PR program; Columns 5,6,7 = values of Barthel, SPPB, 6MWT and P/F at the end of PR program (overall and according to vaccination status). Column 8 = statistical significance of between-group difference (vaccinated vs unvaccinated) at the end of PR program.