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

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## 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.

## Introduction

During the past 3 years, more than 600 million people have been infected with the severe acute respiratory syndrome coronavirus 2 (COVID-19), and more than 6 million died [1]. A significant proportion of individuals required hospital admission, including intensive care units (ICU) [2]. The administration of billions of doses of vaccines worldwide has resulted in significant reductions in hospital admissions, morbidity, and mortality [1,3]. 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 6 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 the disease: the former prevents severe disease, and the latter enhances functional recovery and improves disability. We wondered whether the effects of PR might be influenced by a 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.

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Ethics approval and consent to participate: the study was approved by the Istituti Clinici Scientifici (ICS) Maugeri IRCCS Ethics Committee (EC 2629, April 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.

Informed consent: 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.

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## Materials and Methods

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### Participants

Participants were selected among individuals consecutively admitted between September 2021 and April 1st, 2022, to the respiratory units of the 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 polymerase chain reaction test for COVID-19 at the time of transfer from acute care hospital to PR wards. Exclusion criteria were: i) neurological or orthopedic 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, number and diagnosis of comorbidities by the Cumulative Illness Rating Scale, including the Cumulative Illness Rating Score Comorbidities Index and the Cumulative Illness Rating Score Severity Index) [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]: i) oxygenation status (arterial oxygen tension to inspired oxygen fraction ratio: P/F); ii) 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; iii) exercise tolerance was assessed by the 6-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]; iv) 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), and need of long-term oxygen.

### Pulmonary rehabilitation program

Hospitals of the 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 a 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 next 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 6 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 the addition of the sitting position on a chair for 20 min twice per day, as well as exercises involving the 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 counseling were added when necessary.

### Statistical analysis

A Shapiro-Wilk test was used to assess the normality of distribution in all continuous variables. For clarity purposes, all continuous variables were expressed as mean ± standard deviation, irrespective of their distribution. Continuous variables were compared using Mann-Whitney's test in case of non-normal distribution and Student's *t*-test in case of normal distribution. Categorical variables were expressed with raw numbers and percentages (%). Categorical variables were compared using the Chi-squared test or the Fisher exact test. A p-value of <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 96 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), Telese 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 the second vaccination to acute care hospitalization had been 156±79 days. The mean LoS of previous acute care hospitals 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 for 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 m gain in 6MWT, for vaccinated and unvaccinated (p<0.01) (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 the 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, in 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 being 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,



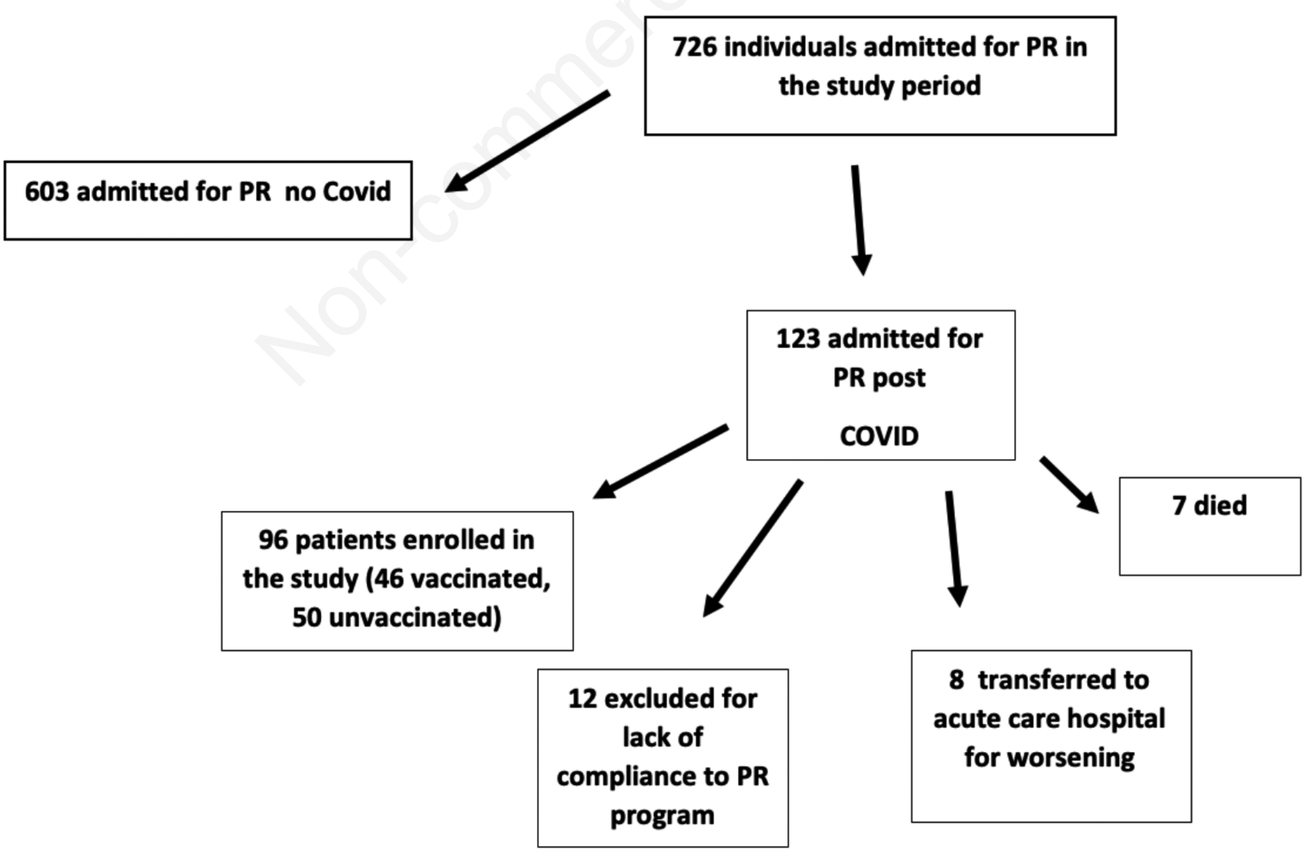


**Figure 1.** Trial profile with criteria for selection of patients enrolled in the study. PR, pulmonary rehabilitation.

being part of that high-risk category [22], where the adherence to vaccination was nearly maximal. As soon as vaccines against COVID-19 were available during the pandemic, the target of any country was to reach the maximum possible coverage among the general population to achieve the so-called "herd immunity". Criteria were set to decide which group of people should be vaccinated first: occupational risk, age, and chronic diseases, then, upon coverage of these frail categories, proceed with the remaining population. In Italy, the vaccine campaign started in 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 the presence

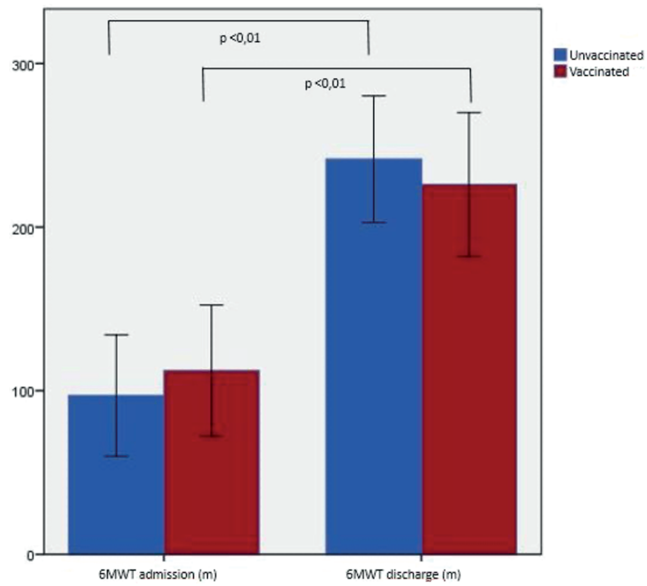


**Figure 2.** Changes in the 6-minute walking test (6MWT) at the beginning (left columns) and at the end (right columns) of the pulmonary rehabilitation program. Data are expressed in meters. There is a statistically significant difference (0.01) for both vaccinated and unvaccinated subjects.

**Table 1.** Demographic, anthropometric, and clinical characteristics of the 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 |

M/F, male/female; BMI, body mass index; PR, pulmonary rehabilitation; 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; CIRS (CI), Cumulative Illness Rating Score Comorbidities Index; CIRS (SI), Cumulative Illness Rating Score Severity Index.

**Table 2.** Intra-group comparison of rehabilitative measures between the beginning (pre) and the end (post) of the pulmonary rehabilitation. Values are expressed as mean ± standard deviation.

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

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

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

| Variable | 1<br>Overall<br>(pre) | 2<br>Vaccinated<br>(pre) | 3<br>Unvaccinated<br>(pre) | 4<br>p | 5<br>Overall<br>(post) | 6<br>Vaccinated<br>(post) | 7<br>Unvaccinated<br>(post) | 8<br>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, 6-minute walking test; P/F, arterial oxygen tension to inspired oxygen fraction ratio. Columns 1,2,3 = values of Barthel index, SPPB, 6MWT and P/F at the beginning of the pulmonary rehabilitation (PR) program (overall and according to vaccination status). Column 4 = statistical significance of between-group difference (vaccinated vs. unvaccinated) at the beginning of the PR program. Columns 5,6,7 = values of Barthel index, SPPB, 6MWT and P/F at the end of the PR program (overall and according to vaccination status). Column 8 = statistical significance of between-group difference (vaccinated vs. unvaccinated) at the end of the PR program.

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 suffered a more severe disease, as shown by the higher prevalence of ICU admissions and higher need for 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 who 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 the 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 consider that the heavier impact of ICU stay on unvaccinated individuals might have been counterbalanced by younger age and less comorbidity, leading to a 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 healthcare 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.

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