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Efficacy of early pulmonary rehabilitation in severe and critically ill COVID-19 patients: a retrospective cohort study

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Abstract

Background Respiratory sequelae, induced by lung injury, reduced muscle strength, and nutritional disturbance, are common in hospitalized patients with coronavirus disease 2019 (COVID-19). Therefore, optimal treatment is essential for reducing the mortality in severe forms of the disease and critically ill patients. Pulmonary rehabilitation (PR) has been used in many chronic respiratory diseases, but the role of early PR in severe and critically ill COVID-19 patients remains to be fully understood.

Methods Hospitalized severe to critically ill COVID-19 patients were recruited from Beijing Chaoyang Hospital between December 1, 2022, and June 30, 2023. In all, we recruited 272 patients, with 39 in the PR group and 233 in the control group. The PR intervention consisted of the prone position, airway clearance therapy (ACT), and resistance respiratory training (RRT). The primary outcome was the composite disease progression outcome rate, defined as death or intensive care unit (ICU) admission. Adverse events (AEs) and serious adverse events (SAEs) were recorded in the PR group. Inverse probability of treatment weighting (IPTW) and propensity score matching (PSM) was used to balance confounding bias, generating weighting cohort and matched cohort.

Results The rate of the primary outcome was lower in the PR group (28.2% [11/39] in the PR group vs. 48.9% [114/233] in the control group). Significant differences were observed in both the original and weighting cohorts. Subgroup analyses showed that receiving ≥ 2 types of PR, receiving RRT, length from admission to intervention ≤ 4 days, and baseline P/F ≤ 150 mmHg were associated with lower rates of progression. Total rates of 2.6% (1/39) for AEs and 10.26% (4/39) for SAEs were reported.

Conclusions Early pulmonary rehabilitation may prevent disease progression and reduce mortality in patients with severe COVID-19. These findings may be helpful for formulating an optimal rehabilitation strategy.

Keywords Pulmonary rehabilitation, COVID-19, Disease progression, Mortality

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Background

The global coronavirus disease 2019 (COVID-19) pandemic has persisted for 5 years, and poses a serious health threat in many countries [1]. According to the COVID Data Tracker from the Centers for Disease Control (CDC), approximately 6 million related hospitalizations and 1.1 million COVID-19–associated deaths were reported by April 26, 2023 [2]. Compared with individuals with mild disease, complications related to COVID-19 have been found to be more common in critically ill patients, such as individuals with acute respiratory distress syndrome, sepsis, or multiorgan failure. Thus, even in surviving severe or critically ill COVID-19 patients, persistent respiratory symptoms were very common. After 6 months, Dyspnea was observed in about 35% patients surviving from severe COVID-19 [3–7], emphasizing the urgent need for pulmonary rehabilitation (PR).

PR is a comprehensive intervention strategy involving exercise training, physical therapy, behavior change, and education according to the status of individuals, which aims to resolve persistent symptoms, improve functional capacity, and improve health-related quality of life in multiple chronic respiratory diseases [8–10]. Respiratory sequelae, induced by lung injury, reduced muscle strength, and nutritional disturbance, are common in hospitalized patients with COVID-19 [6, 11]. Consistent pulmonary abnormalities, especially decreased diffusion capacity, and radiographic abnormalities such as ground-glass opacity and fibrotic-like changes, could be observed in 40–50% patients surviving from severe COVID-19 [7, 12, 13]. Previous researches have proved that appropriate in-hospital PR strategy could be an effective resolution for respiratory sequelae [14]. Therefore, similar to chronic respiratory diseases, several guidelines have recommended the implementation of PR in hospitalized patients with COVID-19 to achieve better clinical outcomes and reduce the rate of long-term impairment [15, 16].

However, because of insufficient resources and a lack of awareness about rehabilitation, PR remains underused. Although PR is mainly used in patients with chronic obstructive pulmonary disease (COPD), previous studies reported that less than 5% of COPD patients received PR [8, 17, 18]. A recent meta-analysis indicated that evidence regarding the effect of PR on exercise capacity and respiratory function in patients with mild COVID-19 is uncertain [19]. In addition, current research has mainly focused on the impact of physical, mental and pulmonary rehabilitation in patients with subacute or post-infection COVID-19 patients [20–22]. There is a paucity of available evidence on the benefits of early rehabilitation in hospitalized COVID-19 patients, especially in severe and critically ill patients. Early rehabilitation has been proven to be effective and safe for critically ill patients, accelerating the recovery of functional capacity and quality of life [23–25]. A previous study demonstrated that it was feasible and safe for patients with severe COVID-19 to receive inpatient PR [26, 27]. In addition, inpatient PR was found to be associated with better physical function and quality of life in severe and critically ill COVID-19 patients [28]. However, these studies were limited by the lack of a control group and small sample size. The role of early PR in severe and critically ill COVID-19 patients remains to be fully understood.

We hypothesize that early pulmonary rehabilitation improves respiratory function and reduces mortality and ICU stay duration in this patient population. In this retrospective study, we evaluated the efficacy of early PR in severe and critically ill COVID-19 patients during hospitalization. Specifically, we focused on the clinical differences between the subgroups divided by intervention measures, length from admission to intervention, and severity of hypoxia at baseline, measured by PaO_2/FiO_2 ratio (P/F). The results of this study may provide useful evidence for formulating PR strategies for hospitalized severe and critically ill COVID-19 patients.

Methods

Study design and participants

This study retrospectively included hospitalized severe or critically ill COVID-19 patients at Beijing Chaoyang Hospital from December 1, 2022, to June 30, 2023. Ethical approval was obtained from the Ethics Committee of the Beijing Chaoyang Hospital (number 2021-KE-500) and annually reviewed in October 2022. At enrollment, participants provided written consent for PR intervention, including the use of the awake-prone position, airway clearance therapy (ACT), and respiratory resistance training (RRT).

We recruited severe and critically ill COVID-19 patients for the study. Diagnosis of patients was based on the Diagnosis and Treatment Plan for Novel Coronavirus Infection (Trial Version 10) [29]. Patients who met any of the following criteria and whose condition could not be explained by other reasons were considered to have severe COVID-19: (1) respiratory rate ≥ 30; (2) oxygen saturation ≤ 93% when inhaling air at rest; (3) P/F ≤ 300 mmHg; and (4) progression of symptoms and pulmonary radiology abnormalities (deterioration of more than 50% within 24 to 48 h). Patients were diagnosed as critically ill with COVID-19 if any of the following criteria were met: (1) respiratory failure requiring mechanical ventilation; (2) shock; and (3) combined organ failure and intensive care unit (ICU) care. Exclusion criteria were: (1) mild to moderate COVID-19; (2) presence of psychiatric disorders, such as schizophrenia, major depression, anxiety, dissociative conversion disorder, organic mental illness (dementia, delirium, lethargy, coma); (3) inability

to cooperate with the PR therapist; (4) refusal to provide written consent to receive PR.

The enrolled patients were divided into two groups: the PR group, patients who received PR in combination with conventional treatment, and the control group (patients who received only conventional therapy). A total of 272 patients were included in this study, with 39 and 233 patients included in the PR and control groups, respectively (Fig. 1). The mean age (standard deviation [SD]) of the PR group was 72.44 (9.52), with six (15.4%) females. In the control group, the mean age (SD) was 72.31 (12.03), and 172 (73.8%) patients were female. Age stratification analysis showed that most of patients included were ≥45 years old. More details were shown in Table 1.

Intervention

During hospitalization, COVID-19 patients who met the inclusion criteria received 1–3 types of PR. Our respiratory therapists conducted a systematic clinical evaluation and chose appropriate therapy following the Expert Consensus on Rehabilitation of Coronavirus Disease 2019 [30]. The inclusion criteria for each intervention measure were as follows:

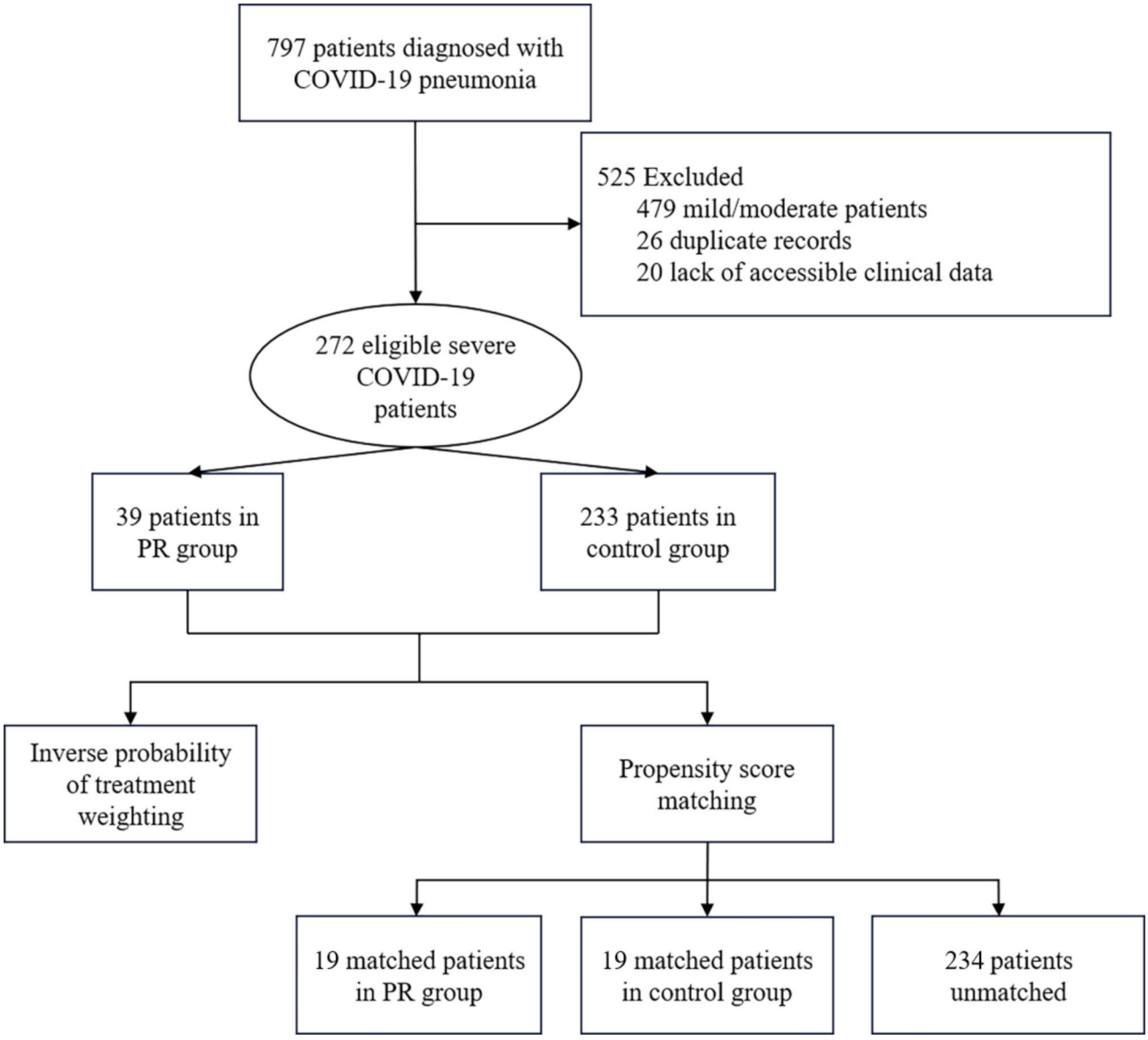

Fig. 1 Flow chart of patient screening. Information regarding 797 COVID-19 patients was extracted from electronic and written records. Two researchers reviewed these records and excluded mild to moderate patients, duplicate records, and patients without accessible clinical data. Finally, data from 272 patients were included in this study (39 in the PR group, and 233 in the control group). IPTW and PSM were conducted to fully evaluate the effects
PR = pulmonary rehabilitation

Table 1 Baseline characteristics of original and weighting cohort. Weighting cohort was calculated by inverse probability of treatment weighting. PR, pulmonary rehabilitation; P/F, PaO_2/FiO_2; SMD, standardized mean difference; SD, standard deviation; IQR, interquartile range; SOFA, sequential organ failure assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; HFNC, high-flow nasal cannula; NIV, noninvasive ventilation; NA, not applicable

Characteristics	Original cohort			Weighting cohort [a]	
	PR group ($n=39$)	Control group ($n=233$)	*P* value	SMD	*P* value
Sex, female, n (%)	6 (15.4%)	172 (73.8%)	< 0.001	0.080	0.763
Age, mean (SD)	72.44 (9.52)	72.31 (12.03)	0.950	0.248	0.228
18–45, n (%) [b]	0 (0.0)	6 (2.6)	0.671	0.226	0.031
45–60, n (%)	3 (7.7)	28 (12.0)	0.607	0.335	0.037
60–75, n (%)	20 (51.3)	94 (40.3)	0.269	0.681	0.009
75+, n (%)	16 (41.0)	105 (45.1)	0.767	0.453	0.073
Comorbidities, n (%)					
Respiratory disease	6 (15.4)	32 (13.7)	0.980	0.049	0.837
Hypertension	22 (56.4)	136 (58.4)	0.957	0.206	0.532
Diabetes	16 (41.0)	86 (36.9)	0.755	0.197	0.532
Coronary heart disease	11 (28.2)	65 (27.9)	1.000	0.098	0.772
Smoking history, n (%)	11 (28.2)	75 (32.2)	0.757	0.515	0.005
Drinking history, n (%)	10 (25.6)	47 (20.2)	0.573	0.320	0.058
Coinfection, n (%)					
Bacteria, n (%)	33 (84.6)	166 (71.2)	0.121	0.453	0.041
Fungi, n (%)	12 (30.8)	51 (21.9)	0.312	0.106	0.735
Body temperature, mean (SD)	36.70 (36.50, 36.90)	36.60 (36.40, 37.00)	0.863	0.169	0.535
Mean arterial pressure, mean (SD)	92.00 (83.50, 101.00)	95.33 (87.67, 103.00)	0.173	0.141	0.524
Heart rate, mean (SD)	87.05 (14.90)	85.29 (16.53)	0.533	0.133	0.446
Respiratory rate, mean (SD)	20.00 (20.00, 21.50)	20.00 (19.00, 23.00)	0.519	0.042	0.821
SOFA scores, median (IQR)	2.00 (2.00, 4.00)	2.00 (2.00, 4.00)	0.196	0.123	0.978
APACHE II scores, median (IQR)	9.00 (7.00, 11.00)	11.00 (9.00, 15.00)	0.001	0.103	0.808
Baseline P/F, median (IQR)	149.09 (96.53, 219.05)	188.00 (108.75, 242.86)	0.081	0.343	0.245
Days from admission to intervention, mean (SD)	5.61 (5.37)	NA	NA	NA	NA
Baseline oxygen inhalation mode, n (%)					
HFNC	7 (17.9)	25 (10.7)	0.305	0.072	0.700
NIV	3 (7.7)	15 (6.4)	1.000	0.175	0.525
Nasal cannula	17 (43.6)	100 (42.9)	1.000	0.313	0.304
Mask	11 (28.2)	59 (25.3)	0.855	0.404	0.199
Invasive mechanical ventilation	1 (2.6)	34 (14.6)	0.069	0.244	0.414
Antiviral drugs	24 (61.5)	137 (58.8)	0.884	0.209	0.520
Systemic steroid	38 (97.4)	203 (87.1)	0.109	0.428	0.008

a. Calculated using inverse probability of treatment weighting. Sex, age, comorbidities, smoking history, drinking history, coinfection, body temperature, mean arterial pressure, heart rate, respiratory rate, SOFA and APACHE II scores, baseline P/F ratio, and baseline oxygen inhalation mode were selected as weighting variables

b. For age stratification, "18–45" means age ≥ 18y and < 45y. The following stratification was similar with this rule. "75+" means age ≥ 75y

* PR, pulmonary rehabilitation; P/F, PaO_2/FiO_2; SMD, standardized mean difference; SD, standard deviation; IQR, interquartile range; SOFA, sequential organ failure assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; HFNC, high-flow nasal cannula; NIV, noninvasive ventilation; NA, not applicable

1) Prone position: refractory hypoxemia, P/F ≤ 200 mmHg or bilateral lower lung lesions on computerized tomography (CT) scan.

2) ACT: pulmonary auscultation showed coarse crackles, sputum ≥ 15 ml per day with positive result for laboratory infectious test, including white blood cell count (WBC) ≥ 10×10^9/ml, C-reactive protein (CRP) ≥ 10 mg/L or procalcitonin (PCT) ≥ 0.05 μg/L, not improving after two days of clinical observation.

3) RRT: chest X ray or CT showed atelectasis or consolidation.

The choice and frequency of treatment was evaluated following the criteria above according to patients' conditions, decided by clinical physicians and respiratory therapists. Each kind of PR intervention was evaluated independently. Patients who met the criteria for two or three types of PR interventions were eligible to receive a combined PR intervention. Critical patients were treated

with PR after their vital signs stabilized. There were 2 patients who performed critically ill and needed intensive care at baseline in the PR group, and the mean time from admission to the stabilization of vital sign in these 2 patients was 7.00 days. The exclusion criteria were mentioned above.

The details for each intervention were as follows:

1) Prone position: Patients were placed in a completely prone position for at least 4 consecutive hours daily. When patients could not tolerate the full-time prone position, rehabilitation was completed multiple times a day and the cumulative prone position time was counted. Electrocardiographic monitoring was performed during intervention.

2) ACT: Two therapies were administered. (a) Vibrating positive pressure ventilation: This therapy used an Acapella PEP machine (27-7000, Smith, USA) to provide positive end-expiratory pressure and generate oscillations in the airway. This treatment was conducted twice per day with and 6–12 breathing cycles each time. (b) Extra-airway oscillation: A vibrating expectoration machine (G5 THERASSIST, General Electric Company, USA) was used to provide high-frequency oscillations through the thoracic wall to promote expectoration in the peripheral airway.

3) RRT: Incentive spirometry (L25913000, Leventon, Spanish) was used to conduct a lung recruitment maneuver, performing five sets of 20 repetitions per day.

All patients underwent routine treatment under the guidance of clinicians, including oxygen inhalation, antiviral drugs, and nebulizer therapy.

Outcomes

The primary outcome was a composite outcome of disease progression including ICU admission and all-cause mortality. The secondary outcomes included all-cause mortality during hospitalization, ICU admission, and changes in P/F ratio. The change in P/F was measured on the basis of differences in arterial blood gas analysis between admission and discharge.

Subgroup analysis was performed for the primary outcome:

(1) age: ≥ 75 years or < 75 years; (2) sex: female or male; (3) baseline P/F: ≤ 150 mmHg or > 150 mmHg; (4) the different PR measures, including the prone position, ACT, and RRT; (5) the number of PR measures received, < 2 or ≥ 2 types; (6) time of receiving intervention, defined as the length from admission to intervention: ≤ 4 days or > 4 days.

Safety

Adverse events (AEs) and serious adverse events (SAEs) were recorded for the PR group. AEs were defined as new onset symptoms or exacerbation of the original symptoms during PR intervention. SAEs were defined as the occurrence of any clinical manifestation since the PR intervention started: (1) SpO2 ≤ 90% or 4% decrease compared with baseline characteristics; (2) respiratory rate ≥ 40; (3) systolic pressure ≤ 90 mmHg or ≥ 180 mmHg, mean arterial pressure (MAP) < 65 mmHg or > 110 mmHg, or more than 20% change compared with baseline characteristics; (4) heart rate < 40 or > 120; (5) new arrhythmia or myocardial ischemia; and (6) change of consciousness, hypnesthesia, or dysphoria. When AEs occurred, we would suspend the PR intervention and reevaluated in the next day. If patients were found suitable for PR in this follow-up assessment, the intervention would resume; however, any AEs arose during the suspension period without active PR intervention would be recorded. In cases where SAEs occurred, the PR intervention would be permanently terminated. The causal relationship between SAEs and PR interventions was evaluated by a physician.

Data collection

Data were obtained from the written and electronic medical records of Beijing Chaoyang Hospital. The covariates included age, sex, comorbidities, smoking and drinking history, bacterial coinfection, fungal coinfection, vital signs, baseline P/F, sequential organ failure assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score and the use of antiviral drugs and systemic steroid.

Data analysis

The baseline characteristics were summarized as categorical or continuous variables, and descriptive statistics were used to present the results. The Wilcoxon test, χ^2 test, and Fisher's exact test were used to compare the differences in primary and secondary outcomes, as appropriate. Odds ratios (OR) and 95% confidence intervals (95% CI) were used for categorical outcomes, and the mean difference (MD) for continuous outcomes was calculated to express the effect of PR intervention on each outcome.

We performed inverse probability of treatment weighting (IPTW) to generate a weighted cohort. Propensity score matching (PSM) was used to balance the differences in baseline data. Sex, age, SOFA score, APACHE II score, baseline P/F, comorbidities, smoking, drinking history and the use of antiviral drugs and systemic steroid were selected as matching variables, with a caliper value of 0.02 and a matched ratio of 1:1. Standardized mean difference (SMD) was used to investigate the balance between groups. When the SMD was < 0.1, the groups were considered balanced.

Multiple logistic regression analysis was used to estimate the risk factors for the primary outcome. The

variables included in the model were based on clinical judgement. The related covariates included age, sex, pre-existing respiratory diseases, bacterial coinfection, fungal coinfection, smoking history, drinking history, baseline P/F ratio, baseline respiratory rate, SOFA score, and APACHE II score.

Statistical significance was defined as a two-sided *P*-value < 0.05. All statistical analyses were performed using R software version 4.3.1.

Results

Participants

Demographics data has been demonstrated above. The median APACHE II score in the control group was 11.00 (9.00,15.00) and that in the PR group was 9.00 (7.00,11.00). The mean duration of PR intervention was 5.86 days during hospitalization. In the original cohort, sex and APACHE II scores were imbalanced between the two groups. There was no significant difference in baseline features between the two groups after adjusting for features using IPTW or PSM (Table 1 and Additional Table 1).

Primary outcome

The rate of composite disease progression was 28.2% (11/39) in the PR group and 48.9% (114/233) in the control group. Significant differences were observed in the original cohort (OR 0.41, 95% CI 0.20–0.86, *P* = 0.016) and weighting cohorts (OR 0.21, 95% CI 0.07–0.66, *P* = 0.005), while the result in the matched cohort was not significant (OR 0.30, 95% CI 0.07–1.23, *P* = 0.087) (Table 2 and Additional Table 2). To assess the factors associated with the composite disease progression outcomes, multiple logistic regression was applied in the weighting cohort, which demonstrated that age ≤ 75 years, P/F > 150 mmHg, and respiratory rate < 24 at admission were associated with a lower risk of disease progression, whereas SOFA scores ≥ 5 and pre-existing respiratory diseases were associated with a higher risk of disease progression. Other variables, including sex, smoking history, drinking history, bacterial coinfection, fungal coinfection, and APACHE II scores, showed no impact on the primary outcome (Table 3).

Subgroup analysis of the primary outcome

The association between PR and composite disease progression outcomes was stronger among the subgroups of patients who received ≥ 2 types of PR intervention (OR 0.28, 95% CI 0.08–1.05, *P* = 0.045), received RRT (OR 0.15, 95% CI 0.03–0.67, *P* = 0.005), had a length from admission to intervention ≤ 4 days (OR 0.35, 95% CI 0.13–0.91, *P* = 0.025), and those with baseline P/F ≤ 150 mmHg (OR 0.21, 95% CI 0.07–0.59, *P* = 0.002) (Fig. 2).

Secondary outcome

The incidence of all-cause mortality during hospitalization was 17.9% (7/39) in the PR group and 35.2% (82/233) in the control group, which was significantly different between the two groups (OR 0.40, 95% CI 0.17–0.95, *P* = 0.034). Similar results were observed after IPTW analysis (OR 0.26, 95% CI 0.07–0.98, *P* = 0.038). The rate of ICU admission was 12.8% (5/39) in the PR group and

Table 2 Primary and secondary outcomes of original and weighting cohort. Results were presented as odds ratio (OR) or mean difference (MD) with 95% confidence interval (CI). Significance was defined as *P* < 0.05. PR, pulmonary rehabilitation; P/F, PaO_2/FiO_2; OR, odds ratio; MD, mean difference; 95% CI = 95% confidence interval; IQR, interquartile range

Outcomes	Original cohort				Weighting cohort [a]			
	PR group (*n* = 39)	Control group (*n* = 233)	OR/MD (95% CI) [b]	*P* value [b]	PR group (*n* = 245.7)	Control group (*n* = 269.4)	OR/MD (95% CI) [b]	*P* value [b]
Primary outcome								
Composite disease progression outcome, n (%)	11 (28.2)	114 (48.9)	0.41 (0.20, 0.86)	0.016	40.5 (16.5)	131.4 (48.8)	0.21 (0.07, 0.66)	0.005
Secondary outcome								
All-cause mortality during hospitalization, n (%)	7 (17.9)	82 (35.2)	0.4 (0.17, 0.95)	0.034	31.9 (13.0)	97.3 (36.1)	0.26 (0.07, 0.98)	0.038
Intensive care unit admission, n (%)	5 (12.8)	59 (25.3)	0.43 (0.16, 1.16)	0.088	23.6 (9.6)	63.1 (23.4)	0.34 (0.08, 1.55)	0.154
Change of P/F, median (IQR) [c]	142.1 (56.9, 223.7)	107.6 (51.8, 178.8)	18.94 (-28.37, 66.26)	0.322	88.1 (45.2, 260.0)	112.5 (51.7, 175.3)	21.2 (-50.39, 92.79)	0.444

a. Sample size of weighting cohort was calculated by inverse probability of treatment weighting

b Chi-square test or Fisher's exact test was used to calculate *P* values for categorical variables, and univariate logistic regression was used to calculate OR (95% CI) for categorical variables. The change in P/F was consistent with a skewed distribution; therefore, the Wilcoxon rank sum test was used to calculate *P* values. Linear regression was used to calculate the MD and 95% CI

c. Outcomes of change in P/F in the original cohort were reported in 95 patients, 29 in the PR group, and 66 in the control group

PR, pulmonary rehabilitation; P/F, PaO_2/FiO_2; OR, odds ratio; MD, mean difference; 95% CI, 95% confidence interval; IQR, interquartile range

Table 3 Multiple logistic regression of primary outcome. Weighting cohort was calculated by inverse probability of treatment weighting. aOR, adjusted odds ratio; 95% CI, 95% confidence interval; SOFA, sequential organ failure assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; PR, pulmonary rehabilitation; P/F, PaO_2/FiO_2

	Original cohort		Weighting cohort [a]	
	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value
Age ≤ 75 years	0.63 (0.33–1.17)	0.146	0.42 (0.20, 0.88)	0.022
Female	1.07 (0.52–2.20)	0.860	0.60 (0.25, 1.41)	0.238
Pre-existing respiratory diseases	1.42 (0.59–3.41)	0.432	4.90 (1.06, 22.63)	0.042
Smoking history	0.67 (0.28–1.55)	0.356	0.37 (0.11, 1.29)	0.120
Drinking history	1.76 (0.68–4.59)	0.247	3.42 (0.85, 13.78)	0.084
Bacteria coinfection	0.83 (0.42–1.62)	0.575	0.99 (0.48, 2.06)	0.982
Fungi coinfection	1.10 (0.52–2.29)	0.800	1.16 (0.42, 3.25)	0.775
Respiratory rate < 24	0.32 (0.15–0.69)	0.005	0.33 (0.12, 0.92)	0.034
SOFA scores ≥ 5	11.17 (4.42–33.03)	< 0.001	4.67 (1.35, 16.16)	0.015
APACHE II scores ≥ 10	1.38 (0.70–2.72)	0.352	1.17 (0.48, 2.89)	0.728
Baseline P/F > 150	0.37 (0.18–0.73)	0.005	0.33 (0.16, 0.70)	0.004
PR intervention	0.45 (0.16–1.16)	0.10	0.10 (0.04, 0.30)	< 0.001

a. Sample of weighting cohort was calculated by inverse probability of treatment weighting

aOR, adjusted odds ratio; 95% CI, 95% confidence interval; SOFA, sequential organ failure assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; PR, pulmonary rehabilitation; P/F, PaO_2/FiO_2

25.3% (59/233) in the control group, which was not significant in the crude analysis (OR 0.43, 95% CI 0.16–1.16, $P = 0.088$). After adjusting for covariates by IPTW and PSM, the results of ICU admission remained negative. Although a trend of improvement in P/F was observed in the PR group, there was no significant difference between the two groups (Table 2 and Additional Table 2).

Safety

AE occurred in 2.6% (1/39) of patients throughout the intervention. One patient had persistent dyspnea in the prone position. 10.26% (4/39) of patients experienced cardiovascular related SAEs, including three patients with heart rate exceeding 120 and one patient who suffered a new myocardial infarction. Following consultation with a cardiology physician, it was determined that the patient's new myocardial infarction was primarily attributed to pneumonia-associated microinfarction, which was the blood vessel damage mediated by COVID-19 infection. Additionally, the other three cases of elevated heart rate may be related to rehabilitation, due to the increase of cardiorespiratory burden during the intervention. Overall, 7.7% (3/39) of the patients experienced PR-related SAEs.

Discussion

Exploring optimal treatment is essential for reducing the mortality associated with severe COVID-19. In addition to drug treatment, PR has been recommended as a useful therapy for COVID-19 patients [6, 30]. However, the efficacy of early PR in severely and critically ill patients remains unclear. In this study, the results revealed that early PR could significantly prevent disease progression and evaluated clinical outcomes in different subgroups. These findings provide further evidence to prove the feasibility and guide PR in patients with severe and critically ill COVID-19, and shed light on specific subgroups that could benefit from PR.

Previous studies have reported lower mortality [31], higher discharge rate [32, 33], better performance on 6-min walking distance (6-MWD) and lung functional tests in acute and sub-acute COVID-19 patients who received hospitalized PR [34]. However, none of these studies focused on severe and critically ill cases of COVID-19. A retrospective cohort study of 51 patients with COVID-19 and 51 patients with common pneumonia found that PR intervention could bring improvements in physical function and quality of life in patients with COVID-19. However, no significant difference was detected between critical ($n = 23$) and severe COVID-19 patients ($n = 14$) [28]. In a cohort of 30 patients with severe COVID-19, inpatient rehabilitation after severe COVID-19 was found to be safe and feasible [26]. Stutz et al. retrospectively analyzed 116 COVID-19 patients in the ICU, which indicated the feasibility of rehabilitation in the ICU. However, the study lacked a control group and did not assess the effects of rehabilitation on clinical outcomes [27]. To the best of our knowledge, few studies have elucidated the effect of early PR on clinical outcomes. In the current study, we enrolled 272 patients, which included 39 patients in the PR group and 233 patients in the control group. PR was associated with a lower rate of disease progression in both the original and weighted cohorts. However, no significant difference was observed after PSM, possibly because of the reduced sample size in the matched cohort. Further studies will be needed to elucidate the effectiveness of PR in severe and critically ill COVID-19 patients.

Next, we explored the risk factors associated with the disease progression. The results revealed that age ≤ 75 years, P/F > 150 mmHg, and respiratory rate < 24 at admission were associated with a lower risk of disease progression, whereas SOFA scores ≥ 5 were associated with a higher risk of disease progression. These results are consistent with the findings of several recent studies, which found that old age, low P/F, elevated respiratory rate, and high SOFA scores were associated with a high risk of death [35–37]. There is also evidence that high body mass index (BMI) is associated with increased

Original cohort

Subgroup	PR	Control	P value	OR (95% CI)
Age				
≥ 75y	5/16	55/105	0.115	0.41 (0.13 to 1.27)
< 75y	7/30	79/165	0.074	0.41 (0.15 to 1.11)
Sex				
Female	1/6	84/172	0.121	0.21 (0.02 to 1.83)
Male	10/33	30/61	0.077	0.45 (0.18 to 1.10)
Baseline P/F				
> 150	4/15	55/151	0.185	0.47 (0.15 to 1.47)
≤ 150	7/20	59/82	0.002	0.21 (0.07 to 0.59)
Different kinds of Intervention				
Prone position	8/27	114/233	0.057	0.44 (0.19 to 1.04)
ACT	4/11	114/233	0.415	0.60 (0.17 to 2.09)
RRT	2/16	114/233	0.005	0.15 (0.03 to 0.67)
Number of intervention				
≥ 2	3/14	114/233	0.045	0.28 (0.08 to 1.05)
< 2	8/25	114/233	0.107	0.49 (0.20 to 1.18)
Length from admission to intervention				
≤ 4 days	6/24	114/233	0.025	0.35 (0.13 to 0.91)
> 4 days	5/15	114/233	0.241	0.52 (0.17 to 1.57)

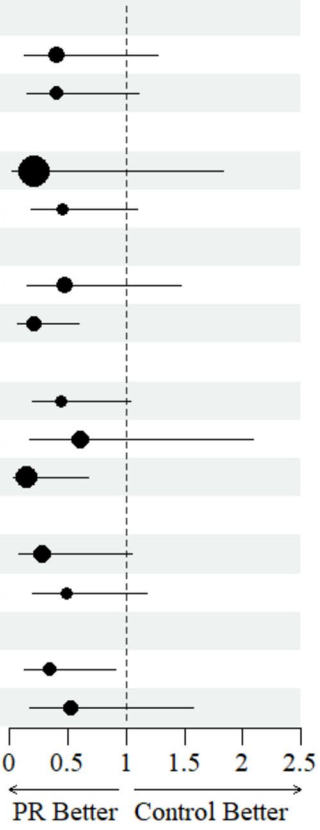

Fig. 2 Forest plot of subgroup analyses. *P*-values were calculated using Chi-square or Fisher's exact test. Univariate logistic regression was used to calculate the odds ratio and 95% confidence interval. The forest plot was generated from the statistics shown on the left

PR, pulmonary rehabilitation; OR, odds ratio; 95% CI, 95% confidence interval; ACT, airway clearance therapy; RRT, respiratory resistance training; P/F, PaO_2/FiO_2

mortality in severe COVID-19 [35]. However, most BMI values were missing. Therefore, we did not analyze them in our study.

The PR group exhibited significantly lower all-cause mortality than the control group in both the original and weighted cohorts, and there was a trend toward lower ICU admission rates in the PR group, but no significant difference was observed. These outcomes were only assessed at discharge, and the follow-up time should be extended in future studies to elucidate the impact of early PR on long-term outcomes. One recent randomized trial confirmed that PR could significantly increase the values of PaO_2 and SpO_2 in patients with severe COVID-19 compared with the control group [38]. The current study revealed that the PR group showed a trend toward P/F improvement, but this difference was not significant. This may be because of incomplete values and a relatively small sample size.

The results of subgroup analyses detected a significant association among those who received PR within 4 days of admission, with a reduction in the rate of disease progression, emphasizing the need for early rehabilitation. Although the concept of early physical rehabilitation in patients with severe COVID-19 has been recommended by clinical management guidelines [30, 39], whether early PR could prevent disease progression and provide survival benefits remains unclear. Evidence regarding the optimal time to initiate PR is limited. A randomized clinical trial showed that hospitalized early PR (starting PR within 3 days after admission) could not significantly reduce 1-month and 3-month mortality in severely intubated patients [38]. However, the study had a small sample size (19 in the intervention group and 18 in the control group), and did not include critically ill patients. These results remain to be verified in large randomized controlled trials (RCTs). Considering safety and clinical feasibility, we selected 4 days as the threshold for early PR based on three reasons. First, previous clinical trials involving rehabilitation in severe to critically ill patients have not established a definitive of "early" PR. The cutoff values ranged from 2 to 4 days after admission across various studies, indicating that

"4 days" is an reasonable threshold for initiating early intervention [40–42]. Second, there are limited studies examining hospitalized PR during the acute phase of pulmonary diseases. Evidences regarding PR in the context of COPD exacerbation remains controversial, with arguments both supporting and opposing the implementation of in-hospital PR being reported [43, 44]. To prioritize patient safety, we chose a relatively conservative threshold to define early PR. Third, before PR intervention, several assessments, including lung CT scans and laboratory tests, need to be performed. A threshold of 4 days allows sufficient time to gather necessary clinical characteristics required for pre-PR evaluation. Consequently, we established "4 days" as the threshold for early PR intervention; our findings indicate that commencing PR within this timeframe may mitigate disease progression.

In the current study, we investigated the impact of each of these individual PR measures and the number of interventions on disease progression. The results indicated that, compared with the control group, patients receiving ≥ 2 kinds of intervention had significantly lower rates of disease progression, while receiving one kind of intervention did not show a protective effect. This finding suggests that applying comprehensive intervention may provide better benefits for severe COVID-19 patients. However, because of the small sample size, the results of the confidence interval showed that the protective effect of receiving ≥ 2 types of intervention was not stable. Further studies will be needed to confirm this effect. Several studies have evaluated the effect of individual PR measures, such as the awake-prone position [45–47], and inspiratory muscle training [48]. To assess the potential different impacts of each PR intervention in the current study, we conducted subgroup analysis. The subgroup analysis results revealed that RRT reduced the rate of composite disease progression outcomes, while the prone position and ACT did not. There is evidence that the prone position is effective for reducing intubation [49]. However, whether this method can prevent disease progression remains controversial. Both positive and negative results were reported in previous multicenter RCTs [46, 50]. The current findings indicated a negative effect. However, because of the small sample size and study design, the actual effect of the prone position on disease progression requires further validation. A negative result was observed for ACT in the present study. We speculate that this may have occurred primarily because COVID-19 patients did not experience difficulties related to sputum production as the primary symptom. According to a previous study, approximately 33% of COVID-19 patients produced sputum [51]. Therefore, ACT may be more effective in patients with coinfection and increased sputum production. For RRT, this treatment was mainly conducted to improve physical function, symptoms, and quality of life in the post-acute phase [21, 52–54]. To the best of our knowledge, no recent studies explored the effects of RRT on disease progression in patients with acute severe COVID-19. However, respiratory muscle weakness was observed in severe COVID-19 patients, and has been reported to be a risk factor for COVID-19 severity in previous studies [55], which may explain the positive effects of RRT in severe to critically ill COVID-19 patients.

As for the mechanisms, there were some studies that reported the improvement of respiratory muscle strength and the reduction of neural respiratory drive could be the potential reasons why PR could improve clinical outcomes [21]. To our knowledge, there have been no studies that comprehensively investigate the detailed mechanisms of implementing PR during the acute phase to improve the prognosis of COVID-19 patients. Therefore, we refer to the mechanism of PR in other respiratory diseases for further discussion. Previous studies have proved that in-hospital PR could significantly reduce dyspnea, improve health-related life quality and confer survival benefit in patients with various respiratory diseases, such as community-acquired pneumonia (CAP), exacerbation of COPD and interstitial lung disease [43, 56, 57]. The mechanisms underlying the efficacy of PR in these patients could be generalized into two main points. First, muscle strength impairment has been observed in patients with COVID-19, COPD and other respiratory diseases [58]. Recent studies have reported that in-hospital rehabilitation could significantly enhance the muscle strength in CAP and COPD patients, which might lead to improved clinical outcomes [43, 56, 59]. Second, there is evidences suggesting that continuous inflammation is closely associated with poor prognosis in patients suffering from severe pulmonary disease [60]. PR may help modulate inflammation level in these individuals, as reported by a recent study including severe COPD patients [61]. Further research is needed to evaluate the mechanism behind the positive effect of PR intervention on clinical prognosis comprehensively. These findings may bring inspiration for further studies to explore the mechanisms of the efficacy of PR in COVID-19 patients.

Regarding safety during PR, the current results revealed that AEs were reported in only one patient and SAEs were reported in four patients, suggesting that PR was relatively safe and well tolerated in severe-to-critically ill patients. Recent studies of patients with severe COVID-19 reported similar results [26, 38]. However, one single-arm retrospective study reported the characteristics of critically ill COVID-19 patients receiving PR in the ICU, and found that 53.4% (62/116) of patients had severe adverse events, with 34% exhibiting $SpO_2 < 80\%$ and 2% exhibiting systolic blood pressure < 90 mmHg

[27]. These findings suggest that the safety of PR in critically ill patients requires further evaluation.

PR could perform positive effect on the improvement of clinical outcomes in severe and critically ill patients, especially for those patients who received the interventions within 4 days of admission. Meanwhile, our safety outcomes showed that PR was a safe approach to conduct in clinical cases. These results recommended that severe COVID-19 patients with relatively stable vital sign should start PR as early as possible. Besides, the cardiovascular events were the most common AEs, which inferred that electrocardiogram monitoring was indispensable during PR intervention, and patients with heart disease should be carefully evaluated before receiving PR, such as electrocardiograph, myocardial enzyme, troponin and 24 h dynamic electrocardiogram. As a safe and effective intervention approach, we suggest that PR could be considered for integration into COVID-19 care protocols.

To the best of our knowledge, the current study is the largest retrospective cohort study to perform early PR in severe and critically ill COVID-19 patients. However, this study involved several limitations that should be considered. First, the study was retrospectively designed, which may have introduced an inherent bias. We did not perform follow-up visits to investigate the impact of early PR on the long-term outcomes in hospitalized patients with COVID-19. Prospective and randomized clinical trials will be required to verify the current results. Second, the sample size in this study was relatively small; therefore, the interpretation of the subgroup analysis was limited by insufficient data. Third, the enrolled patients were mainly older individuals, with a mean age of >70 years in both groups. The effects on young and middle-aged patients need to be assessed further. Fourth, combinations of PR measures, such as use of the prone position combined with ACT and use of the prone position combined with RRT, were not evaluated because of the small sample size. Fifth, because of a shortage of resources during the pandemic period, some research data, including BMI and length of intervention for each patient, were not available. Despite our efforts to balance covariates using IPTW and PSM during statistical analysis, some confounding biases remained unaddressed due to insufficient data, including BMI and vaccine status, potentially affecting the causal inference of our findings. Finally, the effects of other rehabilitation methods, such as physical therapy and progressive resistance exercise, were not analyzed in this study.

Conclusions

In conclusion, early PR could significantly prevent disease progression in severe and critically ill COVID-19 patients, especially patients with higher P/F values, a lower respiratory rate, and lower SOFA scores at admission. Early pulmonary rehabilitation in severe and critically ill COVID-19 patients is associated with improved respiratory function, reduced mortality, and significantly improved patient outcomes. These findings support the integration of early pulmonary rehabilitation into COVID-19 care protocols. Further studies will be needed to determine the safety and effectiveness of PR in specific patient populations to formulate an optimal rehabilitation strategy.

List of Abbreviations

Abbreviation	Full Name
ACT	Airway clearance therapy
aOR	Adjusted odds ratio
APACHE II	Acute physiology and chronic health evaluation
BMI	Body mass index
CAP	Community-acquired pneumonia
CDC	Centers for Disease Control
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CT	Computerized tomography
DLCO	Diffusing capacity of the lung for carbon monoxide
FVC	Forced vital capacity
HFNC	High flow nasal cannula
ICU	Intensive care unit
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
MD	Mean difference
OR	Odds ratio
P/F	PaO_2/FiO_2
PCT	Procalcitonin
PEP	Positive expiratory pressure
PR	Pulmonary rehabilitation
PSM	Propensity score matching
RCT	Randomized controlled trial
RRT	Respiratory resistance training
SD	Standard deviation
SMD	Standardized mean difference
SOFA	Sequential organ failure assessment
WBC	White blood cell count
6-MWD	6-min walking distance
95% CI	95% confidence interval

Supplementary Information

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Supplementary Material 1: Additional Table 1. Baseline characteristics of original and matched cohort. Patients were 1:1 matched with a caliper of 0.02. PR, pulmonary rehabilitation; P/F, PaO_2/FiO_2; SMD, standard mean difference; SD, standard deviation; IQR, interquartile range; SOFA, sequential organ failure assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; HFNC, high-flow nasal cannula; NIV, noninvasive ventilation.

Supplementary Material 2: Additional Table 2. Primary and secondary outcomes of original and matched cohort. Patients were 1:1 matched with a caliper of 0.02. Results were presented as odds ratio (OR) or mean difference (MD) with 95% confidence interval (CI). Significance was defined as $P<0.05$. PR, pulmonary rehabilitation; P/F, PaO_2/FiO_2; OR, odds ratio; MD, mean difference; 95% CI = 95% confidence interval; IQR, interquartile range

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Author contributions
ZHT and HQY designed this study. XW, HMM, XYH, XMG and YR conducted data acquisition, analysis, and interpretation. XW, HMM, and XYH drafted the manuscript. All authors reviewed the manuscript.

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Data availability
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Ethics Committee of the Beijing Chaoyang Hospital (number 2021-KE-500) and annually reviewed in October 2022. Informed consent to participate was obtained from all of the participants in the study. This study adhered to the declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

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