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ORIGINAL ARTICLE

Exercise capacity, dyspnea, and quality of life 6 months after exercise-based rehabilitation in patients with persistent dyspnea following pulmonary embolism

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Abstract

Background: Exercise is safe and effective in the short-term following pulmonary embolism. To date, little is known about the long-term effects.

Objectives: The aim of the study was to investigate whether the effects of exercise-based rehabilitation are maintained 6 months after completion in patients with persistent dyspnea following pulmonary embolism when compared with usual care.

Methods: A 2-center, randomized controlled trial compared 8 weeks of exercise-based rehabilitation with usual care. Patients were reassessed postintervention and 6 months later. Exercise capacity was measured with the incremental shuttle walk test (ISWT).

Dyspnea was assessed with the Shortness of Breath Questionnaire, and health-related quality of life was assessed with disease-specific (Pulmonary Embolism Quality of Life Questionnaire) and generic questionnaires.

Results: In total, 159 of 211 randomized patients attended follow-up 6 months post-intervention. The significant improvement on the ISWT in the rehabilitation group was maintained at the 6-month follow-up (96 m; SE: 15 m; 95% CI: 66, 127). There were no changes on the ISWT in the control group at either time point. From postintervention to 6×-month follow-up, the rehabilitation group had further improvements in dyspnea compared with the control group (−3 points; SE: 1.4; 95% CI: −6, −1; P = .02). Health-related quality of life improved in both groups although superior improvements were seen in the rehabilitation group.

Conclusion: The improvement in exercise capacity after 8 weeks of exercise-based rehabilitation in patients with pulmonary embolism and persistent dyspnea was maintained at the 6-month follow-up, while no improvement was observed in the control group, highlighting the relevance of offering rehabilitation to these patients.

KEYWORDS
dyspnea, exercise capacity, pulmonary embolism, rehabilitation, venous thromboembolism

Essentials

- There is scarce evidence of the long-term effect of exercise in patients with pulmonary embolism (PE).
- We have previously shown that an exercise-based program improves exercise capacity after PE.
- This study showed that the improved exercise capacity was maintained at 6 months.
- Exercise appears to have long-term benefits for people who have experienced PE.

1 | INTRODUCTION

Many pulmonary embolism (PE) survivors report persistent dyspnea, reduced exercise capacity, functional limitations, and an impaired health-related quality of life (HRQoL) more than 6 months following the acute event [1–5]. The loss of physical capacity is, at least partly, due to symptom-induced physical inactivity and may contribute to ongoing persistent symptoms. Therefore, exercise training as part of a rehabilitation program is a potential treatment for this patient group [4,6]. Indeed, exercise training is a safe and effective short-term intervention following PE [7–13]. However, evidence regarding the effects of outpatient, supervised exercise training beyond the immediate intervention phase in this patient group, is scarce.

The overall aim of rehabilitation is to achieve long-term, sustainable benefits [14]. Findings in other patient groups with cardiorespiratory disease suggest that the beneficial effects of rehabilitation diminish with time when no maintenance intervention is provided [15–20]. Our previous work demonstrated positive effects in exercise capacity on completion of an exercise-based rehabilitation program in patients with persistent dyspnea after PE [7]. However, it is currently unclear whether and to what extent an exercise training program can have effects beyond the intervention period in this patient group. Therefore, the main aim of this preplanned 6-month follow-up of the PE-rehabilitation study was to investigate whether the effects of the previously studied 8-week exercise-based rehabilitation program on exercise capacity was maintained 6 months after completion in patients with persistent dyspnea following PE when compared with those of usual care. Other aims were to determine the effects on self-reported dyspnea scores and HRQoL at the 6-month follow-up.

2 | METHOD

2.1 | Study design

This is the preplanned 6-month follow-up of the PE-rehabilitation study, a 2-center single-blinded randomized controlled trial (RCT) performed at the outpatient departments of Østfold Hospital Trust and Akershus University Hospital in Norway [21]. Ethical approval was obtained from The Regional Committee for Medical and Health Research Ethics (2017/1940/REK South-East D), and all participants provided written informed consent. The study was registered in ClinicalTrials.gov (NCT03405480) and followed the tenets of the Helsinki declaration. The baseline and short-term results have been published previously [7,22].

2.2 | Participants, randomization, and blinding

Based on an improvement of 60 m on the incremental shuttle walk test (ISWT), the sample size calculations performed for the previously published primary short-term analysis of the PE-rehabilitation study showed that 190 patients were required [7,21]. Inclusion criteria for participation were as follows: (1) age 18 to 75 years, (2) PE greater than isolated subsegmental emboli diagnosed by computed tomography pulmonary angiogram 6 to 72 months before inclusion, and (3) dyspnea grade ≥1 on the modified Medical Research Council (mMRC) dyspnea scale occurring or worsening at the time of PE diagnosis. The mMRC is a short questionnaire that evaluates the limitation of activities due to dyspnea. Scores range from 0 (not troubled by breathlessness except on strenuous exercise) to 4 (too breathless to leave the house or breathless when dressing or undressing) [23].

Exclusion criteria were previously known pulmonary diseases (such as chronic obstructive pulmonary disease [COPD] GOLD stage of ≥2 or restrictive pulmonary diseases), heart failure and significant valvular heart disease, chronic thromboembolic pulmonary hypertension, active malignancy, life expectancy less than 3 months, and/or pregnancy.

Patients were randomized to either the rehabilitation group or the control group in a 1:1 ratio using a computer-generated allocation sequence in blocks of 10 to ensure balanced recruitment. Randomization was performed separately at each hospital, and allocation codes were stored in sealed, opaque envelopes. To prevent bias, the investigators conducting the follow-up assessments were blinded to group allocation, and patients were encouraged not to discuss their allocation with the investigator at assessment. Inclusion and follow-up occurred from 2018 to 2023.

2.3 | Intervention

2.3.1 | Rehabilitation group

The intervention arm consisted of an exercise-based rehabilitation program similar to current programs for patients with cardiopulmonary disease [14]. Supervised, outpatient exercise sessions were provided for 1 hour twice weekly for 8 weeks, either at the respective hospitals or at local physiotherapy clinics. Participants received individually tailored exercise programs including both endurance and resistance training as prescribed by experienced physiotherapists based on the exercise protocol. Endurance training was performed on a treadmill or exercise bike using intervals at moderate intensity (as guided by patients' self-reported dyspnea levels of 6-7 on the 0-10 Borg scale) for 4 to 8 work bouts lasting for 30 seconds to 4 minutes depending on the patients' capacity [24,25]. The average duration of endurance training sessions was 25 to 30 minutes, with the physiotherapist assisting progression during the intervention period by increasing intensity, duration, and/or frequency of work bouts. The resistance training was performed using 2 to 4 sets of 5 repetitions at 70% to 95% of 1 repetition maximum for lower limbs, such as leg press and squats, and 2 to 3 sets of 10 to 12 repetitions at 65% to 75% of 1 repetition maximum for the upper limbs, such as bicep curls and shoulder press [26]. The physiotherapist assisted progression of the resistance training during the intervention period by increasing load, repetitions, or sets or by providing alternative exercises. In addition, patients were given a simple home-based exercise program to be performed once to twice weekly consisting of resistance exercises that could be performed without equipment.

Participants attended 1 educational session provided by a medical doctor and physiotherapist. The session covered topics such as normal anatomy and physiology of the respiratory and circulatory system, PE, breathing strategies, and benefits of exercise/physical activity.

Attendance was recorded by the supervising physiotherapist, and adherence was defined as attendance to at least 80% of the exercise sessions. The maximal extension of the intervention period was 2 weeks. Minimal actions (1 telephone call following more than 2 unattended sessions) were made to improve adherence.

Rehabilitation group participants received no active intervention in the period between completion of the 8-week intervention and follow-up 6 months later. They were encouraged to continue with regular exercise and to increase their daily physical activity levels, but participants had no contact with the physiotherapist after completion of the rehabilitation program. No record of participants' exercise and physical activity behavior following completion of the RCT was made.

2.3.2 | Control group

Participants randomized to the control group received usual care pathways including use of any medications, but no active intervention was provided between baseline and the follow-up at 6 months. Control group participants were encouraged to continue their normal lifestyle, without specific instructions to exercise. No record of their exercise and physical activity behavior was made.

2.4 | Outcomes

All outcomes were assessed at baseline, after the intervention period and 6 months after completion of the intervention period.

2.4.1 | Incremental shuttle walk test

As according to standardized guidelines as described in the study protocol [21], exercise capacity was assessed by the ISWT. During the ISWT, the patient walks between 2 shuttles along a 10-m track in at speeds guided by audible signals. Walking speed is gradually increased and reaches the maximal speed after 12 minutes. Participants performed the ISWT twice at baseline, unless they reached the maximal incremental shuttle walk distance (ISWD) of 1020 m on the initial test. The minimal clinically important difference (MCID) for the ISWT is 70

m for cardiac patients and 48 to 79 m for patients with COPD [27,28]. The MCID has not been verified for the PE population.

2.4.2 | Endurance shuttle walk test

The endurance shuttle walk test (ESWT) is a derivative of the ISWT where the patient walks at 1 predefined speed, usually 85% of the maximum speed achieved on the ISWT. Results are reported as time in seconds with maximum score being 1200 seconds. The MCID for the ESWT is reported to be 174 to 279 seconds for patients with COPD who have attended rehabilitation [29–31].

2.4.3 | The Shortness of Breath Questionnaire

The Shortness of Breath Questionnaire (SOBQ) assesses dyspnea associated with activities of daily living [32]. SOBQ includes 24 items, with total scores ranging from 0 to 120 points. A higher score indicates a higher degree of dyspnea, and the MCID is considered to be a reduction of 5 points [33,34].

2.4.4 | The Pulmonary Embolism Quality of Life Questionnaire

The Pulmonary Embolism Quality of Life Questionnaire (PEMB-QOL) is a disease-specific patient-reported outcome measure used to assess HRQoL following PE [35]. PEMB-QOL has 40 items over 6 domains (frequency of complaints, intensity of complaints, social limitations, activities of daily living limitations, work-related problems, and emotional complaints). Scores for each domain were standardized to a 0 to 1 scale, with higher scores indicating poorer HRQoL. The MCID for the PEMB-QOL is reported to be 15 points (equivalent to 15%) [36] and is validated in Norwegian [37].

2.4.5 | EQ-5D-5L

The EQ-5D-5L is a generic measure of HRQoL with 5 different dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each scored on a 5-point ordinal scale. Higher scores indicate more problems [38]. In addition, the instrument includes a visual analog scale (VAS) of overall general health (EQ-VAS) from 0 (worst imaginable health) to 100 (best imaginable health) [38]. The 5-dimension scores are also aggregated to a cardinal utility score, EQ-5D index, on a scale from −0.59 to 1 (maximal health). Death is anchored at 0, and negative values indicate conditions that are considered to be worse than death. The transformation of individual dimension scores to EQ-5D index values was performed using crosswalk to the UK EQ-5D-3L value set [39,40]. The MCID in pulmonary rehabilitation in COPD has been suggested to be 0.05 for the EQ-5D index and 8 points for the EQ-VAS [41,42].

2.5 | Statistical analysis

Categorical variables are presented as number (percentages) and continuous variables as mean, SD, and range. Due to data not being normally distributed, a nonparametric Mann–Whitney *U*-test was used to test for differences in demographic variables between the 2 arms for continuous variables, and chi-squared test was used for categorical variables.

Our aim was to assess the change in mean ISWD from baseline to postintervention and the further course to 6 months in the intervention and control groups. Notably, many participants reached the maximum possible ISWD of 1020 m and were censored. We do not know the walking distance these participants could have achieved if they were allowed to continue. A Tobit regression model was used to model the mean ISWD. This model accounts for the bias otherwise induced by the censoring [43]. The correlation induced by each patient having multiple measurements was accounted for by applying a mixed-effects variant of the model. The initial model included age, sex (sex assigned at birth), time points, randomization groups, and site allocation as fixed effects, as well as an interaction between time and group to allow for independent courses over time for the 2 groups. Baseline, control groups, men, and Østfold Hospital were reference categories for the time, group, sex, and hospital categorical variables, respectively. As they are strong predictors of walking distance, we further adjusted for age and sex [44,45]. The model used both baseline ISWDs, 1 ISWD following the 8-week intervention period and 1 at the 6-month follow-up. The model was reduced using backward elimination until all remaining variables were significant ($P < .05$). The final model was subsequently used for predicting mean differences in ISWD with 95% confidence limits between groups at time points and between time points within groups.

Subgroup analyses were performed to investigate the effect on exercise capacity based on dyspnea levels at baseline (0-1 vs ≥2 on the mMRC) and time since PE diagnosis (<12 and ≥12 months). Dyspnea and HRQoL outcomes were analyzed with a mixed linear regression analysis and adjusted for age, sex, and hospital allocation. The model included SOBQ, PEMB-QOL, EQ-5D-5L index, EQ-VAS, time points, randomization groups, and the time point–group interaction, age, sex, and site allocation. The models were reduced by backward elimination similarly to the Tobit regression for the ISWT.

The significance level was set at 0.05. Normality of the residuals was assessed and confirmed using Shapiro–Wilk test and quantile-quantile plots. All analyses were performed using Stata version 17.0.

3 | RESULTS

3.1 | Observed baseline characteristics in the study population

The 6-month follow-up was attended by 159 (75%) participants (80 from the rehabilitation group and 79 from the control group) (Figure 1), with a mean age at baseline of 58 years (SD, 11 years; range, 21-75

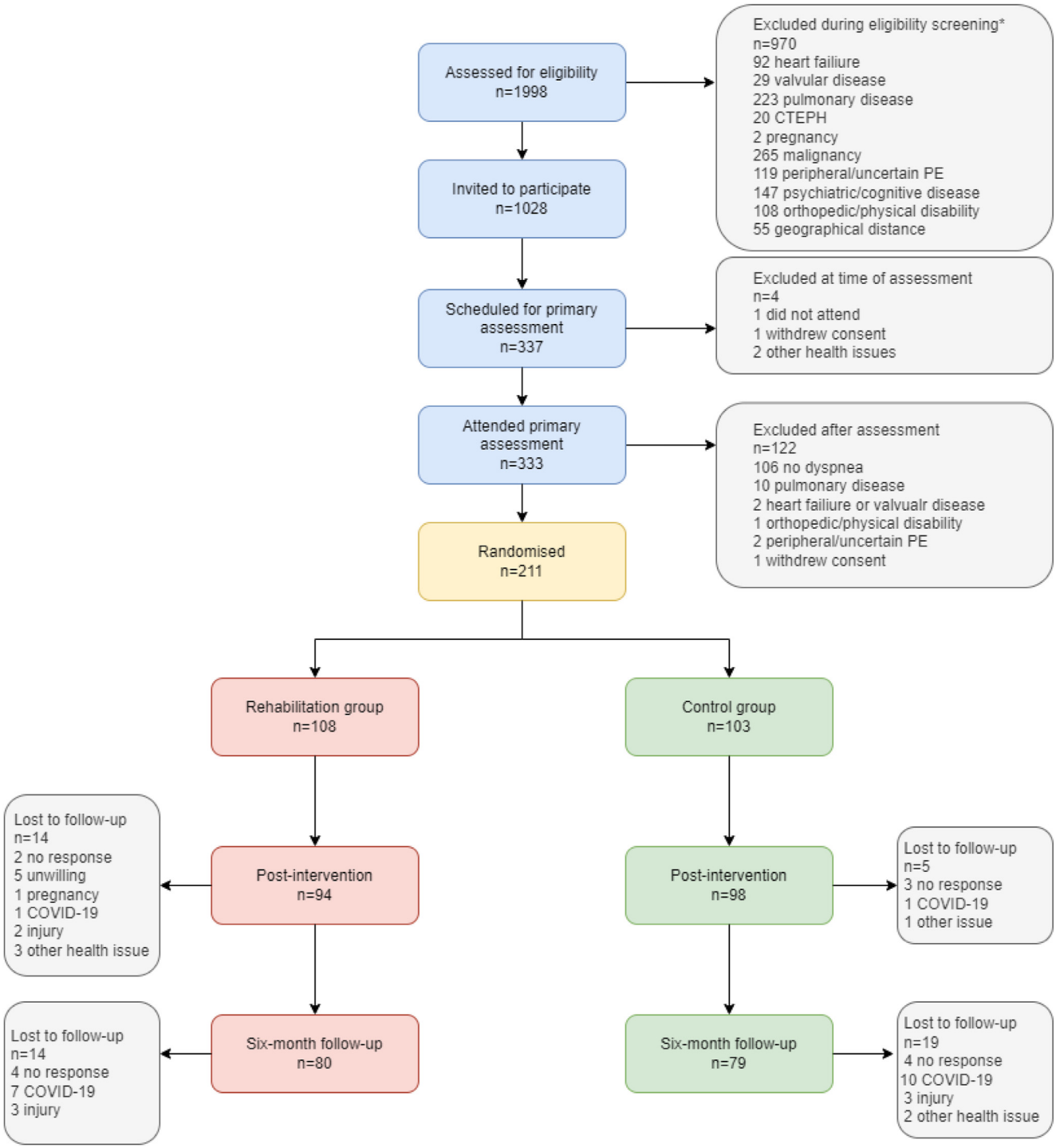

FIGURE 1 Study recruitment and follow-up *Some participants were excluded for multiple reasons. CTEPH, chronic thromboembolic pulmonary hypertension; PE, pulmonary embolism.

years), and 55% were men. The mean time since PE diagnosis was 17 months (SD, 15 months; range, 6-72 months). At inclusion, the majority of participants reported mMRC dyspnea grade 1 (76%) and no comorbidities (75%). No participants reported mMRC grade 4, and only 5% had ≥3 comorbidities. Nonattendees of the 6-month follow-up (n = 52) were significantly younger, had fewer comorbidities, less severe PE at diagnosis, and worse generic HRQoL, whereas attendees had used anticoagulants for a shorter period and had lower self-reported dyspnea scores (Table 1). Of the 80 rehabilitation group participants who attended the 6-month follow-up, 86% (n = 69) adhered to the protocol and attended all exercise sessions during the intervention period (data not shown).

TABLE 1 Baseline characteristics for participants who attended the 6-month follow-up (n = 159) by randomization groups and attendance status at 6-month follow-up (n = 211).

Characteristic	Rehabilitation group, n = 80	Control group, n = 79	Attendees: 6-mo follow-up, n = 159	Nonattendees: 6-mo follow-up, n = 52
Randomization, rehabilitation	—	—	80 (50)	28 (54)
Age (y)	57 (11) [31, 75]	60 (11) [21, 75]	58 (11) [21, 75]	52 (13) [24, 74][a]
Sex, men	45 (56)	42 (53)	87 (55)	30 (58)
Body mass index (kg/m^2)	30.7 (6.2) [21.9, 51.4]	29.8 (5.2) [19.6, 46.3]	30.3 (5.7) [19.6, 51.4]	30.8 (6.0) [20.2, 44.0]
Smoking status				
Never smoked	31 (39)	31 (39)	62 (38)	16 (31)
Former smoker	45 (56)	42 (53)	87 (55)	30 (58)
Current smoker	4 (5)	2 (3)	6 (4)	6 (12)
Missing data	0 (0)	4 (5)	4 (3)	0 (0)
Employment status				
Employed/student	41 (51)	36 (46)	77 (48)	28 (54)
Unemployed	7 (9)	12 (15)	19 (12)	5 (10)
Retired	23 (29)	23 (29)	46 (29)	9 (17)
Sick leave	9 (11)	7 (9)	16 (10)	9 (17)
Missing data	0 (0)	1 (1)	1 (1)	1 (2)
Charlson comorbidity index				
0	58 (73)	56 (71)	114 (72)	45 (87)[a]
1-2	18 (23)	17 (22)	35 (22)	7 (13)
≥3	4 (4)	6 (7)	10 (6)	0 (0)
Time since PE (mo)	18 (16) [6, 72]	15 (13) [6, 60]	17 (15) [6, 72]	16 (10) [6, 60]
<12	44 (55)	50 (63)	94 (59)	26 (50)
≥12	36 (45)	29 (37)	65 (41)	26 (50)
Residual pulmonary vascular obstruction	20 (25)	18 (23)	38 (24)	14 (27)
Missing	11 (14)	12 (15)	23 (14)	10 (19)
PESI score	67 (22) [35, 149]	70 (18) [25, 130]	68 (20) [25, 149]	62 (18) [24, 117][a]
Missing data	8 (10)	9 (11)	17 (11)	8 (15)
Previous VTE	14 (18)	13 (16)	27 (17)	12 (23)
Missing data	0 (0)	1 (1)	1 (1)	2 (4)
Current anticoagulant use	57 (71)	60 (76)	117 (74)	41 (79)
Time anticoagulant used (mo)	8 (4) [3, 29]	9 (4) [3, 25]	8 (4) [3, 29]	11 (6) [3, 28][a]
Missing data	22 (28)	17 (22)	39 (25)	7 (13)
mMRC (range, 0-4)				
1	59 (74)	62 (78)	121 (76)	**27 (52)**[a]
2	20 (25)	14 (18)	34 (21)	22 (42)
3	1 (1)	3 (4)	4 (3)	3 (6)
4	0 (0)	0 (0)	0 (0)	0 (0)
SOBQ	22 (18) [0, 96]	21 (14) [0, 64]	21 (16) [0, 96]	28 (17) [2, 64][a]
Missing data	2 (3)	1 (1)	3 (2)	9 (17)
PEMB-QOL	0.32 (0.08) [0.13, 0.52]	0.33 (0.08) [0.13, 0.56]	0.32 (0.08) [0.13, 0.56]	0.34 (0.09) [−0.01, 0.49]
Missing data	1 (1)	2 (3)	3 (2)	8 (15)

(Continues)

TABLE 1 (Continued)

Characteristic	Rehabilitation group, *n* = 80	Control group, *n* = 79	Attendees: 6-mo follow-up, *n* = 159	Nonattendees: 6-mo follow-up, *n* = 52
EQ-5D-5L				
EQ-5D index (range, −0.594 to 1.0)	0.78 (0.14) [0.30, 1.0]	0.78 (0.15) [0.48, 1.0]	0.78 (0.14) [0.30, 1.0]	0.70 (0.18) [0.11, 1.0][a]
Missing data	3 (4)	2 (3)	5 (3)	11 (21)
EQ-VAS (range 0-100)	66 (17) [15, 100]	63 (15) [30, 95]	65 (17) [15, 100]	56 (19) [20, 95][a]
Missing data	2 (3)	2 (2)	4 (3)	8 (15)
Hospital allocation				
Østfold Hospital Trust	59 (74)	56 (71)	115 (72)	32 (62)
Akershus University Hospital	21 (26)	23 (29)	44 (28)	20 (38)
Regular exercise at inclusion	25 (31)	28 (35)	53 (33)	12 (23)
Missing data	8 (10)	8 (10)	16 (10)	15 (29)

Results are presented as mean (SD) [range] or n (%).

mMRC, modified Medical Research Council dyspnea score; PE, pulmonary embolism; PEMB-QOL, The Pulmonary Embolism Quality of Life Questionnaire; PESI, Pulmonary Embolism Severity Index; SOBQ, The Shortness of Breath Questionnaire; VAS, visual analog scale; VTE, venous thromboembolism.

[a]$P < .05$.

3.2 | Observed exercise capacity at the 6-month follow-up

Of the 159 attendees at the 6-month follow-up, 132 performed the ISWT (Table 2). In total, 32 participants (20%) achieved the maximal ISWD at baseline and 43 (33%) at the 6-month follow-up (Table 2). Compared with baseline, more patients in the rehabilitation group achieved the maximal ISWD at the 6-month follow-up (20% to 37% vs 20% to 28% in the control group) (Table 2). The ESWT was not included in the analyses due to a substantial ceiling effect with 45% of participants achieving the maximal distance at baseline and 65% in the rehabilitation group and 63% in the control group achieving the maximal distance at the 6-month follow-up (Table 2).

3.3 | Estimated exercise capacity at the 6-month follow-up

The initial Tobit mixed-effects model allowed for independent effects of the 2 groups at all 3 time points while adjusting for potential effects of age, sex, and site allocation. After reduction by backward elimination, the ISWD was estimated to improve by 96 m (SE, 15 m; 95% CI: 66, 127) from baseline to postintervention for patients subjected to rehabilitation (Table 3). No significant changes were found in ISWD between postintervention and 6-month follow-up, indicating that the improvement was maintained. In the control group, no significant differences in ISWD could be detected among the 3 time points. The estimates of the final model are listed in Table 3.

Figure 2 presents the predicted ISWDs for the 2 groups at the 3 time points from the mixed Tobit model. CIs for the predicted ISWDs based on the estimates in Table 3 are presented in Supplementary Table. As no significant changes in the control group over the 3 time points could be detected, this is represented by a constant straight line in Figure 2. The rehabilitation group had a significant improvement from baseline to postintervention, which was maintained at the 6-month follow-up. At postintervention and the 6-month follow-up, we found no significant differences, and the 2 groups coincided. In conclusion, the rehabilitation group showed a significant improvement at postintervention, which was maintained at the 6-month follow-up and no change could be detected for the control group throughout the course of the study. Significant differences do not imply nonoverlapping 95% CIs [46]. The only other significant effects in the model were age, sex, and the intercept term (Table 3).

3.4 | Patient-reported outcome measures

All 4 outcomes showed significant dependence of age ($P < .01$), and none of them showed significant dependence on sex (Table 4).

3.4.1 | Shortness of Breath Questionnaire

The control group showed a reduction of symptoms at postintervention relative to baseline of 3 points ($P < .001$) and maintained this at 6-month follow-up ($P = .001$). The rehabilitation group was not significantly different from the control group at postintervention, but showed an additional reduction of −3 points at 6-month follow-up ($P = 016$).

TABLE 2 Observed data for the ISWT, ESWT, and patient-reported outcome measures for attendees at the 6-month follow-up (n = 159) by intervention groups.

	Baseline		Postintervention		6-mo follow-up	
Observed data	**Rehabilitation, n = 108**	**Control, n = 103**	**Rehabilitation, n = 94**	**Control, n = 98**	**Rehabilitation, n = 80**	**Control, n = 79**
ISWT[a] (m)	701 (233) [150, 1020]	716 (248) [140, 1020]	758 (243) [180, 1020]	715 (266) [140, 1020]	783 (231) [310, 1020]	727 (254) [140, 1020]
Missing	0 (0)	1 (1)	4 (5)	10	12 (15)	15 (19)
Maximal ISWT	16 (20)	16 (20)	26 (34)	20 (29)	25 (37)	18 (28)
ESWT (s)	763 (427) [120, 1200]	786 (431) [78, 1200]	831 (437) [42, 1200]	855 (421) [65, 1200]	934 (400) [85, 1200]	914 (406) [47, 1200]
Missing	4 (5)	1 (1)	10 (11)	18 (18)	17 (21)	20 (25)
Maximal ESWT	44 (44)	46 (46)	45 (54)	45 (56)	41 (65)	37 (63)
SOBQ	24 (18) [0, 96]	21 (14) [0, 64]	20 (19) [0, 89]	19 (15) [0, 63]	15 (17) [0, 75]	17 (16) [0, 72]
Missing	7 (6)	5 (5)	6 (6)	7 (7)	6 (8)	2 (3)
PEMB-QOL	0.33 (0.08) [0.13, 0.52]	0.32 (0.08) [0.13, 0.56]	0.31 (0.08) [0.17, 0.58]	0.32 (0.08) [0.14, 0.55]	0.29 (0.08) [0.18, 0.58]	0.29 (0.08) [0.13, 0.55]
Missing	6 (6)	5 (5)	8 (9)	7 (7)	5 (6)	3 (4)
EQ-5D index	0.75 (0.17) [0.11, 1.0]	0.77 (0.14) [0.45, 1.0]	0.80 (0.16) [0.30, 1.0]	0.78 (0.16) [0.19, 1.0]	0.80 (0.17) [−0.002, 1.0]	0.81 (0.19) [0.20, 1.0]
Missing	9 (8)	7 (7)	9 (10)	7 (7)	5 (6)	4 (5)
EQ-5D VAS	63 (19) [15, 100]	63 (16) [25, 90]	70 (17) [20, 100]	65 (17) [25, 95]	71 (18) [5, 100]	70 (15) [40, 100]
Missing	7 (6)	5 (5)	9 (10)	7 (7)	5 (6)	6 (8)

Results are presented as mean (SD) [range] or n (%).

ESWT, endurance shuttle walk test (range, 0-1200 s); ISWT, incremental shuttle walk test (range, 0-1020 m); PEMB-QOL, Pulmonary Embolism Quality of Life Questionnaire; SOBQ: Shortness of Breath Questionnaire; VAS, visual analog scale.

[a]Best performance on ISWT.

TABLE 3 Mixed-effects Tobit model for the incremental shuttle walk test.

Outcome	Predictors	β-Coefficient	SE	95% CI	P
ISWT	Intercept	1555	114	1332, 1778	<.001[a]
	Rehabilitation at baseline	−96	15	−127, −66	<.001[a]
	Age (y)	−12	2	−15, −8	<.001[a]
	Sex: women	−229	43	−313, −145	<.001[a]

Adjusted for age, sex, and site allocation. Final model after backward elimination of nonsignificant terms (n = 132). The β-coefficients are the estimated effect of predictors that remained significant in the final mixed-effects Tobit model. The intercept term represents the predicted ISWT baseline value (in meters) for males at age 0 in the control group. The rehabilitation at baseline term represents the group difference at baseline (in meters), irrespective of age and sex. The age (y) term represent predicted change in ISWT by 1-y increase in age and the sex: women, the predicted difference in ISWT between men and women.

ISWT, incremental shuttle walk test.

[a]$P < .05$.

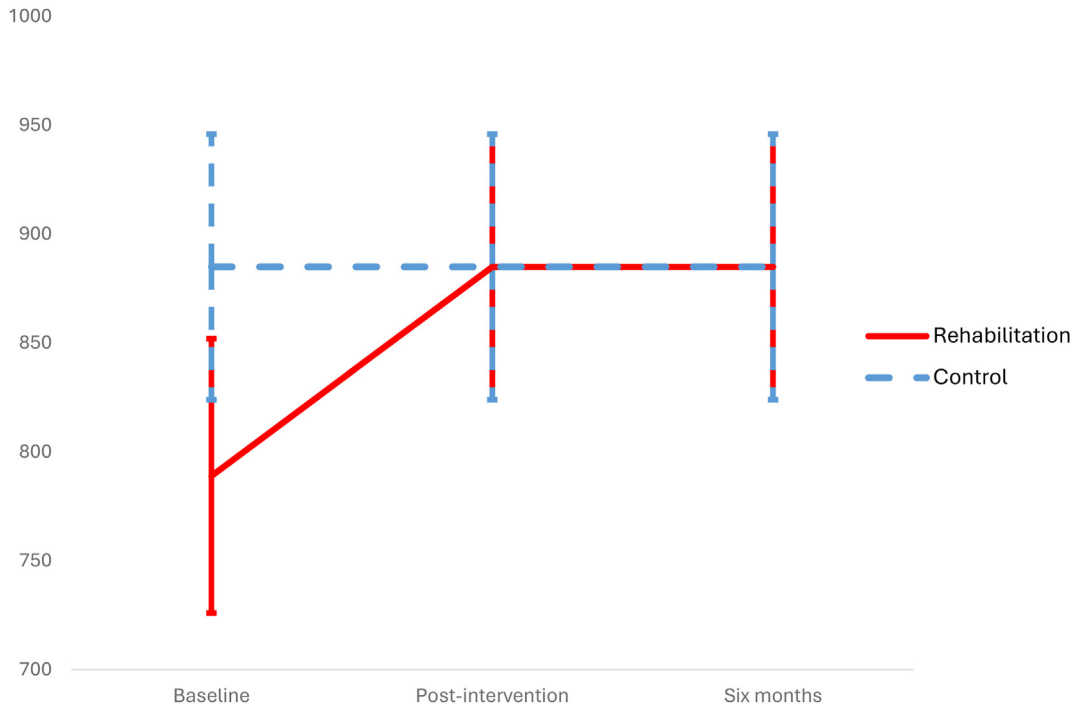

FIGURE 2 The predicted mean performance on the incremental shuttle walk test (in meters) at baseline, postintervention, and 6-month follow-up by group (for men at the age of 58 years). Predicted values of incremental shuttle walk distance for men aged 58 years (mean age among the sample) are shown. Other ages will merely imply vertical shifts of the graphs, while the structure would remain unchanged. Vertical lines represent 95% CIs.

3.4.2 | Pulmonary Embolism Quality of Life Questionnaire

The control group showed no significant change at postintervention relative to baseline, but a reduction of 0.02 points was seen at the 6-month follow-up as compared with that at baseline ($P < .001$). The rehabilitation group showed a borderline significant reduction of 0.01 from baseline to postintervention ($P = .052$). The groups shared the same reduction at the 6-month follow-up.

3.4.3 | EQ-5D index

The control group showed no significant change at postintervention relative to baseline, but an increase of 0.02 points at the 6-month follow-up ($P = .004$). The rehabilitation group showed an increase of 0.03 at postintervention ($P = .002$). The groups shared the same increase at the 6-month follow-up.

3.4.4 | EQ visual analog scale

The control group showed a borderline significant increase in scores of 2.2 points at postintervention ($P = .062$) and an increase of 5.6 points on the EQ-VAS at the 6-month follow-up ($P < .001$). The rehabilitation group showed an additional improvement of 3.6 points ($P = .027$) relative to the control group at postintervention. At the 6-month follow-up, the rehabilitation group did not differ from the control group.

3.4.5 | Subgroup analyses

Subgroup analyses were performed comparing the improvement in exercise capacity based on dyspnea levels at baseline (0-1 vs ≥2 on the mMRC) and time since PE diagnosis (<12 vs ≥12 months). No significant differences were observed between the subgroups (data not shown).

4 | DISCUSSION

In this study, our main finding was that the significant improvement in exercise capacity after an 8-week exercise-based rehabilitation program was maintained at the 6-month follow-up, whereas no significant changes were seen in the control group throughout the course of time. Furthermore, there was an improvement in self-reported dyspnea at the 6-month follow-up only in the rehabilitation group. Both groups had significantly improved HRQoL at the 6-month follow-up, but no between-group differences were detected.

This is, to the best of our knowledge, the first study to report on effects of an outpatient, supervised program beyond the intervention

TABLE 4 Mixed-model linear regression for patient-reported outcome measures.

Outcome	Predictors	β-Coefficient	SE	95% CI	*P*
Shortness of Breath Questionnaire	Intercept	43	5	32, 53	<.001[a]
	Postintervention[b]	−3.0	0.7	−4, −1	<.001[a]
	6 mo[b]	−3.0	1.0	−5, −1	.001[a]
	Rehabilitation at 6 mo[c]	−3.0	1.4	−6, −1	.016[a]
	Age (y)	−0.3	0.1	−0.5, −0.2	<.001[a]
PE Quality of Life Questionnaire	Intercept	0.41	0.03	0.36, 0.46	<.001[a]
	6 mo[b]	−0.02	0.01	−0.03, −0.02	<.001[a]
	Rehabilitation at postintervention[c]	−0.01	0.01	−0.02, 0.01	.052
	Age (y)	−0.01	0.01	−0.01, −0.01	.001[a]
EQ-5D index	Intercept	0.62	0.05	0.52, 0.72	<.001[a]
	6 mo[b]	0.02	0.01	0.01, 0.04	.004[a]
	Rehabilitation at postintervention[c]	0.03	0.01	0.01, 0.05	.002[a]
	Age (y)	0.01	0.1	0.01, 0.01	.006[a]
EQ-VAS	Intercept	48	5.5	37, 59	<.001[a]
	Postintervention[b]	2.2	1.2	−0.1, 4.5	.062
	6 mo[b]	5.6	0.9	3.7, 7.4	<.001[a]
	Rehabilitation at postintervention[c]	3.6	1.6	0.4, 6.8	.027[a]
	Age (y)	0.3	0.1	0.1, 0.4	.007[a]

Adjusted for age, sex and site allocation. Final model after backward elimination of nonsignificant terms (n = 159). The term intercept represents the control group at baseline for a male aged 0 y.

PE, pulmonary embolism; VAS, visual analog scale.

[a]$P < .05$.

[b]Estimated change in response of time points for both groups relative to baseline.

[c]Estimated additional change in response of being allocated to the rehabilitation group at the given time point.

period in this patient group. Despite no maintenance intervention being provided after completion of the intervention period, the improvement on the ISWT in the rehabilitation group (96 m) was higher than the postrehabilitation MCID in similar patient groups, such as cardiac rehabilitation (70 m) and COPD (48-79 m) [27,28]. This is consistent with previous studies in chronically ill patient groups, showing that the effects of rehabilitation may be preserved for 6 to 12 months [19,47,48]. A previous RCT by Rolving et al. [13] compared the effect of an 8-week home-based exercise program following PE in combination with nursing consultations vs nursing consultations alone. At 6 months, both groups had improvements in exercise capacity and HRQoL on the ISWT, and PEMB-QOL and EQ-5D-5L, respectively. However, there were no significant differences between the groups. Rolving et al. [13] also experienced a substantial ceiling effect on the ISWT, and their findings were not fully conclusive. In comparison with this study, Rolving et al. [13] enrolled patients within 2 to 3 weeks following the acute PE and included those with and without dyspnea.

The improvements in dyspnea scores on the SOBQ in the rehabilitation group were small, but greater than the reported MCID [33,34]. Our findings support previous suggestions that physical deconditioning may at least partly be responsible for post-PE dyspnea. Reassurance and increased confidence regarding the safety of performing exercise and physical activity among patients in the rehabilitation group may further explain the improvements in dyspnea scores [49]. Previous reports show that patients experience worrisome thoughts following PE, leading to uncertainty and avoidance of exercise and physical activities [50–52]. Moreover, a large proportion of patients attending cardiopulmonary rehabilitation programs report fear of exercise, which provokes their dyspnea [53]. Rehabilitation may have improved confidence in performing physical activity, both through attendance to supervised exercise sessions and information received in the education session. Consequently, this may alter exercise and physical activity behaviors on completion of the intervention period. The improvements in SOBQ scores observed at the 6-month follow-up in the rehabilitation group were not seen directly following rehabilitation [7]. This may be related to the natural history of the illness with time positively affecting dyspnea. However, due to the large variation in time since PE diagnosis, some participants had already experienced persistent dyspnea for several years before recruitment to this study, suggesting that time alone was not responsible for the improvements in dyspnea observed 6 months following rehabilitation.

We observed small but significant changes in disease-specific and generic HRQoL at 6-month follow-up in both groups when compared with baseline and postintervention. Participants recruited to the study

generally had low symptom burden and good HRQoL at baseline, thus the potential of detecting change following the intervention period may have been limited. Other factors such as patients' coping mechanisms, self-efficacy, illness perceptions, anxiety, and self-management behavior may play a greater role in improving HRQoL than exercise training [54–56]. Therefore, including more educational sessions and individualized interventions focusing more on behavioral change in the rehabilitation program may be more effective at increasing HRQoL than the current intervention [14,57].

While preparing this analysis, we faced several challenges, mainly considerable loss-to-follow-up due to the COVID-19 pandemic, missing data from the ISWT in some patients and a ceiling effect on the ISWT. It is very unlikely that both the pandemic-related dropout and patients achieving a maximal ISWD are random occurrences, so simple comparisons of between or within groups are inappropriate. We handled the ceiling effect issue by applying a Tobit model and adjusted for all relevant determinants, allowing us to estimate ISWD differences between the relevant time points in both groups. In addition, the randomization process in the study was stratified by site allocation only. However, as age and sex are known factors to affect exercise capacity [58,59], stratifying by these factors may have been more optimal given the age range in our study population.

4.1 | Strengths and limitations

The main limitation in this study is the use of the ISWT as the primary outcome measure. There is currently no consensus regarding objective measures of exercise capacity in the post-PE population [60]. However, field walking tests have known clinical transfer, are commonly used in studies measuring the effect of rehabilitation, and allow for comparison with previous studies. Similar to recent reports, we found a considerable ceiling effect at all time points [61]. Therefore, using the ISWT most likely underestimated the effect size and may have limited our ability to measure improvements in exercise capacity among the relatively young and healthy participants in this study. The ESWT had an even more substantial ceiling effect and was therefore excluded from the final analyses. The ISWT may be appropriate in studies including multimorbid patients or those with more severe dyspnea and lower exercise tolerance following PE. However, in this study, alternative outcome measures may have been more appropriate, such as the modified ISWT [62,63], including 3 extra levels of increased walking speed. However, using a cardiopulmonary exercise test, the gold standard for measuring cardiorespiratory fitness [64], may be preferable in further studies in this patient group.

The post-PE population with persistent dyspnea is heterogeneous. Compared with previous reports [2–4], the participants in this study had lower dyspnea levels, fewer comorbidities, and better physical function and HRQoL than expected. This difference was possibly related to the exclusion of patients with conditions such as COPD and cardiac disease, which may contribute to persistent dyspnea. Considering that these comorbidities are common in the PE population [65–67], this may reduce the generalizability of our findings. In addition, although baseline values were similar, a subgroup analysis based on time since PE diagnosis showed that patients included at 6 to 12 months after the acute event achieved greater improvements in exercise capacity compared with those diagnosed more than 1 year before inclusion. However, the differences between the subgroups were not significantly different (data not shown). This suggests that time may affect the response to rehabilitation, and further studies may consider exploring the optimal timing for rehabilitation.

Adherence to the protocol was very good, with 86% of the rehabilitation group participants attending more than 80% of the exercise sessions. The dropout rate, partly due to the COVID-19 pandemic, was similar in both groups and considered acceptable at 25% [68,69]. There were small, but statistically significant differences in age, PE severity, comorbidities, dyspnea grades, and generic HRQoL between participants who did and did not attend the 6-month follow-up. Moreover, the 7-point difference in mean SOBQ scores between participants who did and did not attend the 6-month follow-up is higher than the MCID for the SOBQ [34] and may suggest that dyspnea affected compliance.

Furthermore, previous studies in other patient groups suggest that the effect of rehabilitation diminishes after 1 to 2 years [15,17,70,71]. As our follow-up was 6 months postintervention only, we do not know whether the effects of rehabilitation would be maintained for longer periods than currently investigated or whether maintenance programs may be required for sustained benefits [72,73]. No data were collected on patients' exercise habits between postintervention and the 6-month follow-up, and we do not know how and to what degree they engaged in exercise and physical activity during this period. This knowledge would have been useful for understanding the sustained improvements in the rehabilitation groups to guide future rehabilitation interventions and research. In addition, data were not collected regarding race and ethnicity, which may affect the generalizability of our findings as we are unable to consider the sociocultural determinants of health.

5 | CONCLUSION

We demonstrated that the improved exercise capacity achieved by a standardized rehabilitation program was maintained over time in patients with PE and persistent dyspnea, highlighting the relevance of offering rehabilitation to this patient group. In addition, the outcome measures used in our study bring relevant methodologic challenges to the analysis of the study outcomes. Future studies should therefore explore the optimal timing, exercise regime, and training intensities for patients after PE, using more appropriate measures of functional capacity, as well as the inclusion of the more general PE population including patients with more severe symptoms and comorbidities.

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AUTHOR CONTRIBUTIONS

All authors were responsible for the design of the study. S.H.-P. and Ø.J. were responsible for data collection. S.H.-P. and R.H. performed the statistical analyses. S.H.-P. drafted the manuscript. All authors have contributed to the interpretation of the results and revision of the text and approved the final version of the manuscript.

RELATIONSHIP DISCLOSURE

W.G. reports fees for participation in Advisory board from Amgen, Novartis, Pfizer, Principia Biopharma—a Sanofi Company, Sanofi, SOBI, Grifols, UCB, Argenx, Cellphire, Alpine, Kedrion, HiBio, and Hutchmed; lecture honoraria from Amgen, Novartis, Pfizer, Bristol Myers Squibb, SOBI, Grifols, Sanofi, and Bayer; research grants from Bayer, BMS/Pfizer, and UCB. M.A.S. reports grants from Lung Foundation Netherlands, Stichting Astma Bestrijding, Boehringer Ingelheim, AstraZeneca, TEVA, Chiesi, and Sanofi and fees from Boehringer Ingelheim, AstraZeneca, TEVA, and Chiesi, all outside the submitted work. All payments were made to M.A.S.'s employer. M.A.S. is the founder of Care2Know BV. K.S. reports consulting fees from Merck Sharp and Dohme, outside the submitted work. F.A.K. has received research support from Bayer, BMS, BSCI, AstraZeneca, MSD, Leo Pharma, Actelion, Farm-X, The Netherlands Organisation for Health Research and Development, The Dutch Thrombosis Foundation, The Dutch Heart Foundation, and the Horizon Europe Program, all outside this work and paid to his institution. M.T. has received lecture honoraria from Viatris. The remaining authors declare that they have no conflict of interests.

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REFERENCES

[1] Klok FA, Tijmensen JE, Haeck ML, van Kralingen KW, Huisman MV. Persistent dyspnea complaints at long-term follow-up after an episode of acute pulmonary embolism: results of a questionnaire. *Eur J Intern Med*. 2008;19:625–9.
[2] Tavoly M, Utne KK, Jelsness-Jorgensen LP, Wik HS, Klok FA, Sandset PM, et al. Health-related quality of life after pulmonary embolism: a cross-sectional study. *BMJ Open*. 2016;6:e013086. https://doi.org/10.1136/bmjopen-2016-013086
[3] Ghanima W, Wik HS, Tavoly M, Enden T, Jelsness-Jorgensen LP. Late consequences of venous thromboembolism: measuring quality of life after deep vein thrombosis and pulmonary embolism. *Thromb Res*. 2018;164:170–6.
[4] Kahn SR, Hirsch AM, Akaberi A, Hernandez P, Anderson DR, Wells PS, et al. Functional and exercise limitations after a first episode of pulmonary embolism: results of the ELOPE prospective cohort study. *Chest*. 2017;151:1058–68.
[5] Steiner D, Nopp S, Heinze G, Kraemmer D, Schlager O, Barco S, et al. Functional limitations 3 and 12 months after venous thromboembolism: a cohort study. *Res Pract Thromb Haemost*. 2024;8:102464. https://doi.org/10.1016/j.rpth.2024.102464
[6] Klok FA, Barco S. Follow-up after acute pulmonary embolism. *Hamostaseologie*. 2018;38:22–32.
[7] Jervan Ø, Haukeland-Parker S, Gleditsch J, Tavoly M, Klok FA, Steine K, et al. The effects of exercise training in patients with persistent dyspnea following pulmonary embolism: a randomized controlled trial. *Chest*. 2023;164:981–91.
[8] Lakoski SG, Savage PD, Berkman AM, Penalosa L, Crocker A, Ades PA, et al. The safety and efficacy of early-initiation exercise training after acute venous thromboembolism: a randomized clinical trial. *J Thromb Haemost*. 2015;13:1238–44.
[9] Cires-Drouet RS, Mayorga-Carlin M, Toursavadkohi S, White R, Redding E, Durham F, et al. Safety of exercise therapy after acute pulmonary embolism. *Phlebology*. 2020;35:824–32.
[10] Boon G, Janssen SMJ, Barco S, Bogaard HJ, Ghanima W, Kroft LJM, et al. Efficacy and safety of a 12-week outpatient pulmonary rehabilitation program in Post-PE Syndrome. *Thromb Res*. 2021;206:66–75.
[11] Ghram A, Jenab Y, Soori R, Choobineh S, Hosseinsabet A, Niyazi S, et al. High-intensity interval training in patients with pulmonary embolism: a randomized controlled trial. *Med Sci Sports Exerc*. 2021;53:2037–44.
[12] Nopp S, Klok FA, Moik F, Petrovic M, Derka I, Ay C, et al. Outpatient pulmonary rehabilitation in patients with persisting symptoms after pulmonary embolism. *J Clin Med*. 2020;9:1811.
[13] Rolving N, Brocki BC, Bloch-Nielsen JR, Larsen TB, Jensen FL, Mikkelsen HR, et al. Effect of a physiotherapist-guided home-based exercise intervention on physical capacity and patient-reported outcomes among patients with acute pulmonary embolism: a randomized clinical trial. *JAMA Netw Open*. 2020;3:e200064. https://doi.org/10.1001/jamanetworkopen.2020.0064
[14] Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188:e13–64.
[15] Foglio K, Bianchi L, Bruletti G, Battista L, Pagani M, Ambrosino N. Long-term effectiveness of pulmonary rehabilitation in patients with chronic airway obstruction. *Eur Respir J*. 1999;13:125–32.
[16] Brooks D, Krip B, Mangovski-Alzamora S, Goldstein RS. The effect of postrehabilitation programmes among individuals with chronic obstructive pulmonary disease. *Eur Respir J*. 2002;20:20–9.
[17] Yohannes AM, Dryden S, Casaburi R, Hanania NA. Long-term benefits of pulmonary rehabilitation in patients with COPD: a 2-year follow-up study. *Chest*. 2021;159:967–74.

[18] Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42:3227–337.

[19] Kataoka K, Nishiyama O, Ogura T, Mori Y, Kozu R, Arizono S, et al. Long-term effect of pulmonary rehabilitation in idiopathic pulmonary fibrosis: a randomised controlled trial. *Thorax*. 2023;78:784–91.

[20] Şahin ME, Satar S, Ergün P. Long-term efficiency of pulmonary rehabilitation in patients with chronic obstructive pulmonary disease, bronchiectasis, and asthma: does it differ? *Turk J Med Sci*. 2023;53:814–23.

[21] Haukeland-Parker S, Jervan Ø, Johannessen HH, Gleditsch J, Stavem K, Steine K, et al. Pulmonary rehabilitation to improve physical capacity, dyspnea, and quality of life following pulmonary embolism (the PeRehab study): study protocol for a two-center randomized controlled trial. *Trials*. 2021;22:22.

[22] Haukeland-Parker S, Jervan Ø, Ghanima W, Spruit MA, Holst R, Tavoly M, et al. Physical activity following pulmonary embolism and clinical correlates in selected patients: a cross-sectional study. *Res Pract Thromb Haemost*. 2024;8:102366. https://doi.org/10.1016/j.rpth.2024.102366

[23] Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest*. 1988;93:580–6.

[24] Kortianou EA, Nasis IG, Spetsioti ST, Daskalakis AM, Vogiatzis I. Effectiveness of interval exercise training in patients with COPD. *Cardiopulm Phys Ther J*. 2010;21:12–9.

[25] Vogiatzis I, Nanas S, Roussos C. Interval training as an alternative modality to continuous exercise in patients with COPD. *Eur Respir J*. 2002;20:12–9.

[26] Campos GE, Luecke TJ, Wendeln HK, Toma K, Hagerman FC, Murray TF, et al. Muscular adaptations in response to three different resistance-training regimens: specificity of repetition maximum training zones. *Eur J Appl Physiol*. 2002;88:50–60.

[27] Houchen-Wolloff L, Boyce S, Singh S. The minimum clinically important improvement in the incremental shuttle walk test following cardiac rehabilitation. *Eur J Prev Cardiol*. 2015;22:972–8.

[28] Singh SJ, Jones PW, Evans R, Morgan MD. Minimum clinically important improvement for the incremental shuttle walking test. *Thorax*. 2008;63:775–7.

[29] Revill SM, Morgan MD, Singh SJ, Williams J, Hardman AE. The endurance shuttle walk: a new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. *Thorax*. 1999;54:213–22.

[30] Zatloukal J, Ward S, Houchen-Wolloff L, Harvey-Dunstan T, Singh S. The minimal important difference for the endurance shuttle walk test in individuals with chronic obstructive pulmonary disease following a course of pulmonary rehabilitation. *Chron Respir Dis*. 2019;16:1479973119853828. https://doi.org/10.1177/1479973119853828

[31] Eaton T, Young P, Nicol K, Kolbe J. The endurance shuttle walking test: a responsive measure in pulmonary rehabilitation for COPD patients. *Chron Respir Dis*. 2006;3:3–9.

[32] Eakin EG, Resnikoff PM, Prewitt LM, Ries AL, Kaplan RM. Validation of a new dyspnea measure: the UCSD Shortness of Breath Questionnaire. University of California, San Diego. *Chest*. 1998;113:619–24.

[33] Ries AL. Minimally clinically important difference for the UCSD Shortness of Breath Questionnaire, Borg Scale, and Visual Analog Scale. *COPD*. 2005;2:105–10.

[34] Kupferberg DH, Kaplan RM, Slymen DJ, Ries AL. Minimal clinically important difference for the UCSD Shortness of Breath Questionnaire. *J Cardiopulm Rehabil*. 2005;25:370–7.

[35] Klok FA, Cohn DM, Middeldorp S, Scharloo M, Buller HR, van Kralingen KW, et al. Quality of life after pulmonary embolism: validation of the PEmb-QoL Questionnaire. *J Thromb Haemost*. 2010;8:523–32.

[36] Akaberi A, Klok FA, Cohn DM, Hirsch A, Granton J, Kahn SR. Determining the minimal clinically important difference for the PEmbQoL questionnaire, a measure of pulmonary embolism-specific quality of life. *J Thromb Haemost*. 2018;16:2454–61.

[37] Tavoly M, Jelsness-Jørgensen LP, Wik HS, Roaldsnes C, Sandset PM, Ghanima W. Quality of life after pulmonary embolism: first cross-cultural evaluation of the pulmonary embolism quality-of-life (PEmb-QoL) questionnaire in a Norwegian cohort. *Qual Life Res*. 2015;24:417–25.

[38] Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20:1727–36.

[39] Dolan P. Modeling valuations for EuroQol health states. *Med Care*. 1997;35:1095–108.

[40] van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. 2012;15:708–15.

[41] Nolan CM, Longworth L, Lord J, Canavan JL, Jones SE, Kon SS, et al. The EQ-5D-5L health status questionnaire in COPD: validity, responsiveness and minimum important difference. *Thorax*. 2016;71:493–500.

[42] Zanini A, Aiello M, Adamo D, Casale S, Cherubino F, Della Patrona S, et al. Estimation of minimal clinically important difference in EQ-5D visual analog scale score after pulmonary rehabilitation in subjects with COPD. *Respir Care*. 2015;60:88–95.

[43] McBee M. Modeling outcomes with floor or ceiling effects: an introduction to the Tobit model. *Gift Child Q*. 2010;54:314–20.

[44] Holmberg MJ, Andersen LW. Adjustment for baseline characteristics in randomized clinical trials. *JAMA*. 2022;328:2155–6.

[45] Lydersen S. Adjustment for baseline value in longitudinal randomised trials. *Tidsskr Nor Laegeforen*. 2022;142. https://doi.org/10.4045/tidsskr.21.0824

[46] Knol MJ, Pestman WR, Grobbee DE. The (mis)use of overlap of confidence intervals to assess effect modification. *Eur J Epidemiol*. 2011;26:253–4.

[47] Jácome C, Marques A. Short- and long-term effects of pulmonary rehabilitation in patients with mild COPD: a comparison with patients with moderate to severe COPD. *J Cardiopulm Rehabil Prev*. 2016;36:445–53.

[48] Spencer LM, Alison JA, McKeough ZJ. Maintaining benefits following pulmonary rehabilitation: a randomised controlled trial. *Eur Respir J*. 2010;35:571–7.

[49] Danielsbacka JS, Hansson PO, Mannerkorpi K, Olsén MF. Physical activity and respiratory symptoms after pulmonary embolism. A longitudinal observational study. *Thromb Res*. 2020;189:55–60.

[50] Ingemann-Molden S, Caspersen CK, Rolving N, Højen AA, Klok FA, Grove EL, et al. Comparison of important factors to patients recovering from pulmonary embolism and items covered in patient-reported outcome measures: a mixed-methods systematic review. *Thromb Res*. 2024;233:69–81.

[51] Rolving N, Bloch-Nielsen JR, Brocki BC, Andreasen J. Perspectives of patients and health professionals on important factors influencing rehabilitation following acute pulmonary embolism: a multi-method study. *Thromb Res*. 2020;196:283–90.

[52] Rolving N, Brocki BC, Andreasen J. Coping with everyday life and physical activity in the aftermath of an acute pulmonary embolism: a qualitative study exploring patients' perceptions and coping strategies. *Thromb Res*. 2019;182:185–91.

[53] Farris SG, Abrantes AM, Bond DS, Stabile LM, Wu WC. Anxiety and fear of exercise in cardiopulmonary rehabilitation: patient and practitioner perspectives. *J Cardiopulm Rehabil Prev*. 2019;39:e9–13.

[54] Ratneswaran C, Weinman J, Hart N. Effect of psychological factors on exercise capacity (EC) and health-related quality of life (HRQL) in COPD undergoing pulmonary rehabilitation (PR). *Eur Respir J*.

2015;46:PA550. https://doi.org/10.1183/13993003.congress-2015.PA550

[55] Camp PG, Appleton J, Reid WD. Quality of life after pulmonary rehabilitation: assessing change using quantitative and qualitative methods. *Phys Ther*. 2000;80:986–95.

[56] Bentsen SB, Wentzel-Larsen T, Henriksen AH, Rokne B, Wahl AK. Self-efficacy as a predictor of improvement in health status and overall quality of life in pulmonary rehabilitation—an exploratory study. *Patient Educ Couns*. 2010;81:5–13.

[57] Hug S, Cavalheri V, Lawson-Smith H, Gucciardi DF, Hill K. Interventions with a clear focus on achieving behaviour change are important for maintaining training-related gains in people with chronic obstructive pulmonary disease: a systematic review. *J Physiother*. 2024;70:193–207.

[58] Woo JS, Derleth C, Stratton JR, Levy WC. The influence of age, gender, and training on exercise efficiency. *J Am Coll Cardiol*. 2006;47:1049–57.

[59] Maestri R, Vitacca M, Paneroni M, Zampogna E, Ambrosino N. Gender and age as determinants of success of pulmonary rehabilitation in individuals with chronic obstructive pulmonary disease. *Arch Bronconeumol*. 2023;59:174–7.

[60] Caspersen CK, Ingemann-Molden S, Grove EL, Højen AA, Andreasen J, Klok FA, et al. Performance-based outcome measures for assessing physical capacity in patients with pulmonary embolism: a scoping review. *Thromb Res*. 2024;235:52–67.

[61] Rolving N, Brocki BC, Mikkelsen HR, Ravn P, Bloch-Nielsen JR, Frost L. Does an 8-week home-based exercise program affect physical capacity, quality of life, sick leave, and use of psychotropic drugs in patients with pulmonary embolism? Study protocol for a multicenter randomized clinical trial. *Trials*. 2017;18:245.

[62] Bradley J, Howard J, Wallace E, Elborn S. Validity of a modified shuttle test in adult cystic fibrosis. *Thorax*. 1999;54:437–9.

[63] Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax*. 1992;47:1019–24.

[64] Ferrazza AM, Martolini D, Valli G, Palange P. Cardiopulmonary exercise testing in the functional and prognostic evaluation of patients with pulmonary diseases. *Respiration*. 2009;77:3–17.

[65] Glise Sandblad K, Rosengren A, Sörbo J, Jern S, Hansson PO. Pulmonary embolism and deep vein thrombosis-comorbidities and temporary provoking factors in a register-based study of 1.48 million people. *Res Pract Thromb Haemost*. 2022;6:e12714. https://doi.org/10.1002/rth2.12714

[66] Jareño Esteban JJ, de Miguel Díez J, Fernández Bermejo LA. Pulmonary embolism and comorbidity. *Open Respir Arch*. 2022;4:100188. https://doi.org/10.1016/j.opresp.2022.100188

[67] Mameli A, Palmas MA, Antonelli A, Contu P, Prandoni P, Marongiu F. A retrospective cohort study of patients with pulmonary embolism: the impact of comorbidities on patient's outcome. *Eur Respir J*. 2016;48:555–7.

[68] Fischer MJ, Scharloo M, Abbink JJ, van't Hul AJ, van Ranst D, Rudolphus A, et al. Drop-out and attendance in pulmonary rehabilitation: the role of clinical and psychosocial variables. *Respir Med*. 2009;103:1564–71.

[69] Almadana Pacheco V, Pavón Masa M, Gómez-Bastero Fernández AP, Muñiz Rodríguez AM, Tallón Moreno R, Montemayor Rubio T. Patient profile of drop-outs from a pulmonary rehabilitation program. *Arch Bronconeumol*. 2017;53:257–62.

[70] Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med*. 1995;122:823–32.

[71] Wedzicha JA, Bestall JC, Garrod R, Garnham R, Paul EA, Jones PW. Randomized controlled trial of pulmonary rehabilitation in severe chronic obstructive pulmonary disease patients, stratified with the MRC dyspnoea scale. *Eur Respir J*. 1998;12:363–9.

[72] Beauchamp MK, Francella S, Romano JM, Goldstein RS, Brooks D. A novel approach to long-term respiratory care: results of a community-based post-rehabilitation maintenance program in COPD. *Respir Med*. 2013;107:1210–6.

[73] Blervaque L, Préfaut C, Forthin H, Maffre F, Bourrelier M, Héraud N, et al. Efficacy of a long-term pulmonary rehabilitation maintenance program for COPD patients in a real-life setting: a 5-year cohort study. *Respir Res*. 2021;22:79.

SUPPLEMENTARY MATERIAL

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