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Original Research

Pulmonary rehabilitation in minimal versus high resource settings in COPD: a non-inferiority and economic evaluation

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ABSTRACT

Background: Comparison of results and associated costs of pulmonary rehabilitation (PR) conducted with minimal resources (MR) versus specialised centres (SC) for people with chronic obstructive pulmonary disease (COPD) remains uncertain.

Objectives: We assessed the effects, non-inferiority and associated costs in Portugal of PR with MR compared to PR in SC for COPD.

Methods: PR was conducted with MR and in SC. The functional assessment of chronic illness therapy–fatigue scale-FACIT-FS, hospital anxiety and depression scale-HADS, COPD assessment test-CAT, St. George's Respiratory Questionnaire-SGRQ, quadriceps maximum voluntary contraction-QMVC, Brief-Balance Evaluation Systems Test-Brief-BESTest, 6-min walk test-6MWT and 1-min sit-to-stand-test-1minSTS were assessed pre-post PR. Effects were explored with robust/linear mixed effects model. Costs of PR implementation and intervention were estimated.

Results: 158 people with COPD (69±8years; 79.7 % male; FEV_1 49.0[40.0; 65.8]%predicted) participated, 72 in MR and 86 in SC. No Time*Group interaction was observed, except for the SGRQ. Improvements were significant for all measures in both settings. Non-inferiority was demonstrated for FACIT-FS, HADS-D, QMVC, Brief-BESTest and 1minSTS but inconclusive for HADS-A, CAT, SGRQ and 6MWT. PR implementation costs were 8384€ with

Abbreviations: BMI, Body mass index; Brief-BESTest, Brief-Balance Evaluation Systems Test; CAT, COPD assessment test; CCI, Charlson Comorbidity Index; CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; CRQ, Chronic respiratory disease questionnaire; FACIT-FS, Functional assessment of chronic illness therapy–fatigue scale; FEV_1 %predicted, percent of predicted forced expiratory volume in the first second; HADS-A, Hospital Anxiety and Depression Scale - Anxiety score; HADS-D, Hospital Anxiety and - Depression Scale Depression score; ICER, Incremental cost-effectiveness ratio; ISWT, Incremental shuttle walk test; MCID, Minimal clinically important difference; mMRC, modified Medical Research Council; MR, Minimal resources; PR, Pulmonary rehabilitation; QMVC, Quadriceps maximum voluntary contraction; SC, Specialised centres; SGRQ, St. George's Respiratory Questionnaire; 1minSTS, 1-min sit-to-stand-test; 6MWD, 6-min walk distance; 6MWT, 6-min walk test.

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MR vs. 33,123€ in SC. Intervention costs were 5168€ and 9803€/program including non-emergency medical transportation (646€ vs. 1225€/person) in MR and SC, respectively.
Conclusion: PR with MR has multiple benefits for people with COPD at a lower cost than in SC. However, its non-inferiority compared to SC remains inconclusive for core outcomes. PR with MR could be an effective alternative to increase access to this essential intervention when SC are unavailable.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and morbidity worldwide [1]. Despite pharmacological optimisation, most people with COPD remain symptomatic [2] and live with enormous daily physical, emotional and social disability [3], often resulting in dependence on others and health care, even in the early stages of the disease [4].

Pulmonary rehabilitation (PR) is a comprehensive intervention consisting of, but not limited to, exercise training, education, psychosocial support and behaviour change [5]. PR benefits people with COPD across physical (e.g., exercise intolerance, muscle dysfunction), emotional (e.g., symptoms of anxiety and depression) and social domains (e.g., social isolation), empowering them and their informal carers to better manage the disease (e.g., control of symptoms and adoption of healthy lifestyles) [5,6]. PR programmes have also been associated with higher rates of survival [7].

Despite all these evidence-based benefits, PR is only available to $\leq$5 % of individuals with COPD [5]. Most PR programmes are run in urban hospital outpatient centres [8,9], leading to significant shortages and disparities in access to PR. This situation is aggravated by the limited knowledge of what PR entails and its benefits among individuals, their families/social networks and healthcare professionals [10,11]. Such unawareness leads to a subsequent devaluation of this fundamental intervention. PR programmes conducted in the local communities (e.g., primary healthcare centres), close to people's homes, could be an inclusive, effective and sustainable option to increase the availability of this intervention [12], even considering their often limited infrastructure and equipment.

Recent evidence has shown PR with minimal resources (MR) is cost-effective [13] and leads to similar improvements in functional capacity, peripheral muscle strength and health-related quality of life in people with COPD as PR in specialised centres (SC) [14,15]. Nevertheless, these findings are based on a limited number of studies, and only a few outcomes have been explored, thus, the effectiveness of PR with MR remains uncertain and data on other important outcomes (e.g., symptoms, balance) are lacking. In addition, economic evaluations of PR in different health systems are country-specific and have been poorly reported [13]. Evidence on PR in resource-limited settings and associated costs is crucial for benchmarking.

This study, therefore, aimed to assess the effects, non-inferiority, and associated costs in Portugal of PR with MR compared to PR in SC for COPD.

2. Materials and methods

2.1. Study design and ethics

This observational study was a secondary analysis of data collected prospectively between 2017 and 2022 in people with COPD. Ethical approval was obtained from the Ethics Committees of the Administração Regional de Saúde do Centro, I.P. (December 3, 2016:64/2016/16/2020), Centro Hospitalar do Baixo Vouga (March 22, 2017:777638/15-05-2019), Unidade Local de Saúde de Matosinhos (February 17, 2017:10/CE/JAS), Centro Hospitalar do Médio Ave (August 27, 2018) and Hospital Distrital da Figueira da Foz (July 18, 2017). Approval was also obtained from the Comissão Nacional de Proteção de Dados (8828/2016). Partnerships were established between the University of Aveiro, the institutions mentioned above and four city councils in the country's central region. All participants signed an informed consent before data collection.

This study was reported following the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology [16] and Consolidated Health Economic Evaluation Reporting Standards 2022 [17].

2.2. Participants

Participants were included in this study if they had a diagnosis of stable COPD [6] (i.e., no changes in medication or respiratory exacerbations in the last four weeks) and participated in PR with MR or SC. Those who dropped out from PR were excluded.

2.3. Intervention

Participants were offered PR in SC (Lab3R-ESSUA or in a hospital setting) and centres with MR (city council infrastructures or primary healthcare centres, with limited access to equipment, such as treadmills, cycle ergometers or fixed-weight machines). They were allowed to choose the setting they wished to enrol according to their preference. A detailed list of available equipment/material in each setting is presented in the supplementary material Tables S1 and S2.

All participants underwent a 12-week face-to-face PR programme delivered in group which included twice-weekly exercise training (with endurance, resistance and functional training) and fortnightly education and psychosocial support sessions. Recommendations for home-based physical activity were also provided and monitored every week, and inspiratory muscle training and airway clearance techniques were added as needed. Each session lasted approximately 60–90 min. A interdisciplinary team was involved in the delivery of the education and psychosocial support sessions and included a physiotherapist, a nurse and a medical doctor as minimum [18]. Additionally, the collaboration of a psychologist, a nutritionist and a social worker was obtained in both settings. In these sessions open discussion on common topics and the sharing of experiences were encouraged. Detailed description of the intervention and of the available equipment/material in each setting is provided in the supplementary material I and II.

2.4. Data collection

Two assessment sessions – before and after PR – were conducted, lasting approximately 90 min/person each. Sociodemographic (age, sex), anthropometric (weight and height, to calculate body mass index – BMI) and clinical (lung function, self-reported number of exacerbations and hospitalisations in the past year, smoking habits, self-reported medication and comorbidities) data were collected for sample characterisation. Lung function was retrieved from medical records or assessed with a portable spirometer (MicroLab 3535, CareFusion, Kent, UK) according to guidelines. The values from the percentage of predicted forced expiratory volume in the first second (FEV_1 %predicted) were used to classify people with COPD according to their airflow obstruction in GOLD grades [6]. GOLD groups were determined using the number of exacerbations and hospitalisations in the previous year and the COPD Assessment Test (CAT) [6]. The severity of comorbid diseases was

recorded and scored according to the Charlson Comorbidity Index (CCI) as mild (scores of 1–2), moderate (scores of 3–4) or severe (scores ≥5) [19]. Dyspnoea during activity was characterised with the modified Medical Research Council (mMRC) dyspnoea scale [20]. Outcomes of interest were assessed as described below.

- Fatigue was assessed with the Functional Assessment of Chronic Illness Therapy – fatigue subscale (FACIT-FS). The FACIT-FS assesses physical, functional and emotional fatigue and its social consequences [21]. The total score ranges from 0 to 52, higher scores indicate less fatigue [21]. An increase of 5 points was defined as the minimal clinically important difference (MCID) [22].
- Symptoms of anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS). The HADS has 14 items: 7 measuring symptoms of anxiety (HADS-A) and another 7 measuring symptoms of depression (HADS-D) [23]. Score ranges from 0 (minimum symptom overload) to 21 (maximum symptom overload) for the HADS-A and HADS-D [23]. A reduction of 1 point was defined as the MCID for the HADS-A and 2 points for the HADS-D [24].
- The impact of the disease was measured with the CAT. The CAT is an 8-item questionnaire that assesses the overall impact of COPD on health status. The score ranges from 0 to 40, and higher values indicate a more severe impact of the disease. A reduction of 2 points has been defined as the MCID [25].
- Health-related quality of life was assessed with the St. George's Respiratory Questionnaire (SGRQ). The SGRQ is a 50-item questionnaire that measures the impact of chronic respiratory disease on quality of life [26]. The total score ranges from 0 to 100, and higher values indicate poorer quality of life. A reduction of 4 points was defined as the MCID [26].
- Quadriceps maximal voluntary contraction (QMVC) was measured during a maximum isometric voluntary contraction with a digital dynamometer (microFET2, Hoggan Health, Salt Lake City, Utah) in kilograms-force (KgF) on the dominant side [27]. The percentage predicted values were calculated using the reference equations [27]. A change of 5.2 KgF was defined as the MCID [28].
- Balance was assessed with the Brief-Balance Evaluation Systems Test (Brief-BESTest). The Brief-BESTest is an 8-item balance assessment instrument. The total score ranges from 0 to 24 points, where higher values indicate better balance [29]. An increase of 3 points has been defined as the MCID [30].
- Functional capacity was measured with the 6-min walk test (6MWT) and the 1-min sit-to-stand (1minSTS) test. The 6MWT is a submaximal test that assesses functional exercise tolerance [31]. Participants were instructed to walk as far as possible in a 30-m flat corridor for 6 min [31]. A difference of 25 m was defined as the MCID [31]. The 1minSTS also assesses functional capacity, focusing on a different activity of daily living – sitting and standing from a chair. Participants were instructed to stand up and sit down as many times as possible in 1 min [32]. The MCID used was three repetitions [32]. The percentage of predicted values of both tests was determined using the Portuguese reference equations [33,34].

Participants who met or exceeded the specified MCID were identified as responders, while non-responders were those who did not meet the MCID or had their scores worsened.

2.5. Economic evaluation

A health economic plan was not established a priori, and patient and public involvement was not ensured for economic evaluation purposes. Implementation and intervention costs of PR [35] were estimated in 2024 euro (€) for the worst-case scenario, i.e., which considers conducting a single PR programme with eight people every 12 weeks in each setting with the minimal required equipment/consumables and staff and assuming the MR were nearer individuals' homes. Detailed information on economic evaluation and costs is provided in supplementary materials.

2.6. Implementation costs

The implementation costs were calculated by summing the prices of the required minimum material/equipment/consumables, including Portuguese VAT, and staff costs for each setting. Staff costs included salary at the hourly rate at public institution entry-level defined by the Portuguese Government as well as staff training for delivering the PR (Supplementary materials). If more specialised staff are hired salary costs need to be further adjusted.

2.7. Intervention costs

Associated costs of running PR included: i) the depreciation rates of each material/equipment according to the Portuguese Ministry of Finance; ii) consumables; iii) staff time and training; iv) transportation of individuals covered by the health system; and v) overheads (20 %). The only costs calculated from a personal/societal (indirect) perspective were out-of-pocket expenses related to the transportation to PR in individuals' vehicles. The costs of transportation, price/km, were calculated using a non-emergency medical transport and an individual typical vehicle, considering a mean geographical distance of 15 km to the minimal resource facility and 30 km to the specialised centre. Unit costs (per participant) were estimated by dividing the total cost of each setting by eight (average number of people per PR programme). Costs were calculated per PR programme, per week and per person.

2.8. A cost-effectiveness evaluation approach

The incremental cost-effectiveness ratio (ICER) was calculated by dividing the cost difference between the two settings (intervention costs excluding transportation) by the difference in outcome changes. For outcomes whose higher scores are worse than lower scores, the direction of the incremental effect was inverted to ensure consistency. The bootstrap 95 % confidence interval (CI) of ICER (reflecting uncertainty) was estimated using the percentile method with 1000 resamples. The estimates for each outcome were interpreted based on the four quadrants: greater cost and greater effect, greater cost and less effect, lower cost and less effect or lower cost and greater effect [36]. Missing data in this analysis were handled by pairwise deletion.

2.9. Data analysis

Data were analysed using R version 4.4.0. Normally distributed variables were presented as mean ± standard deviation. Ordinal and non-normally distributed data were reported as median [1st quartile; 3rd quartile]. The absolute and relative frequencies were reported for categorical variables. The baseline characteristics of participants in both settings were compared using the independent samples *t*-test, the Mann-Whitney *U* test, and the Pearson chi-square test or Fisher exact test. The normality assumption was verified using the Shapiro-Wilk test and visual inspection of the quantile-quantile plot. The homogeneity of variances was assessed using the Levene test. The number of responders in each outcome was also compared between settings using the Pearson chi-square test. Linear mixed-effects models with random intercepts were used to evaluate the effects of setting, time and their interaction, adjusting for age, sex, BMI, FEV_1 %predicted, smoking status, GOLD group and baseline value of the 6-min walk distance, as these may influence response to PR. Model assumptions of linearity, normality, constant variance and multicollinearity were assessed by visual inspection. If the assumptions were not met, robust linear mixed effects were fitted. Non-inferiority (alpha = 0.025) of PR with MR was established when the two-sided 95 %CI, using the estimated marginal means,

of the difference in changes after PR between settings lied entirely within the non-inferiority region. The lower bound of the CI was used for positive outcomes, and the upper bound for negative outcomes. Non-inferiority margins were determined using the available MCIDs. For the non-inferiority analysis, individuals were included if they had at least one valid assessment for the specific outcome being analysed. The significance level was set at 0.05.

3. Results

A sample of 158 participants with COPD were included in the analysis (Fig. 1).

Seventy-two people with COPD participated in PR with MR (68.5 ± 7.7years; 61 [84.7 %] men; FEV_1 = 54.5 [41.3; 69.0]%predicted) and 86 in SC (69.5 ± 9.1years; 65 [75.6 %] men; FEV_1 = 49.0 [40.0; 65.8]% predicted). Most participants had moderate-severe airflow obstruction, pertained to GOLD group B and were moderately comorbid. Differences between groups were only found in the GOLD groups and the frequency of exacerbations in the past year, with participants who experienced more exacerbations preferring to integrate PR in SC (Table 1). No adverse events occurred in either setting.

There were no significant time*setting interactions (Table 2), except for the SGRQ. For the SGRQ, a greater improvement was found for PR in SC (Δ_{SC}−8.9 [−11.2, −6.6], p < 0.001) compared with MR (Δ_{MR}−4.6 [−7.1, −2], p < 0.001). Significant improvements within each setting were observed after PR for all outcome measures (FACIT-FS Δ_{MR}2.3 [0.7, 3.8], p = 0.004 *vs.* Δ_{SC}3.1 [1.7, 4.6], p < 0.001; HADS-A Δ_{MR}−0.8 [−1.5, −0.1], p = 0.023 *vs.* Δ_{SC}−0.9 [−1.6, −0.3], p = 0.007; HADS-D Δ_{MR}−0.8 [−1.5, −0.1], p = 0.020 *vs.* Δ_{SC}−0.7 [−1.5, 0], p = 0.040; CAT Δ_{MR}−2 [−3.4, −0.6], p = 0.004 *vs.* Δ_{SC}−3.2 [−4.5, −2], p < 0.001; QMVC Δ_{MR}2.9 [1.3, 4.4], p < 0.001 *vs.* Δ_{SC}2.4 [1.1, 3.8], p < 0.001; Brief-BESTest Δ_{MR}1.8 [1.1, 2.5], p < 0.001 *vs.* Δ_{SC}2.2 [1.6, 2.8], p < 0.001; 6MWT Δ_{MR}29.8 [16.1, 43.4], p < 0.001 *vs.* Δ_{SC}47 [34.5, 59.5], p < 0.001; 1minSTS Δ_{MR}3.3 [2.1, 4.5], p < 0.001 *vs.* Δ_{SC}3.2 [2.1, 4.2], p < 0.001). Mean changes exceed the established MCID in the CAT, SGRQ, 6MWT and 1minSTS in each setting (Table 2). The percentage of responders between settings differed significantly only for the SGRQ (Supplementary material I - Table S1).

The non-inferiority of PR with MR was demonstrated for FACIT-FS, HADS-D, QMVC, Brief-BESTest and 1minSTS. For the remaining outcome measures, the 95 % CIs of change between settings crossed the non-inferiority margin, hence, the non-inferiority of PR with MR compared with SC was inconclusive (Fig. 2).

The costs for the implementation of PR were 8384€ with MR and 33,123€ in SC (Table 3). Intervention costs, with and without paid non-emergency medical transportation, were 5168€ and 3234€/programme (646€ or 404€/person) for PR with MR and 9803€ and 6247€/programme (1225€ or 781€/person) in SC, respectively. If transportation was in own vehicle, intervention costs increased to €5729.35 for MR and €11,238.61 for SC (Supplementary material II - Tables S3 and S4). The

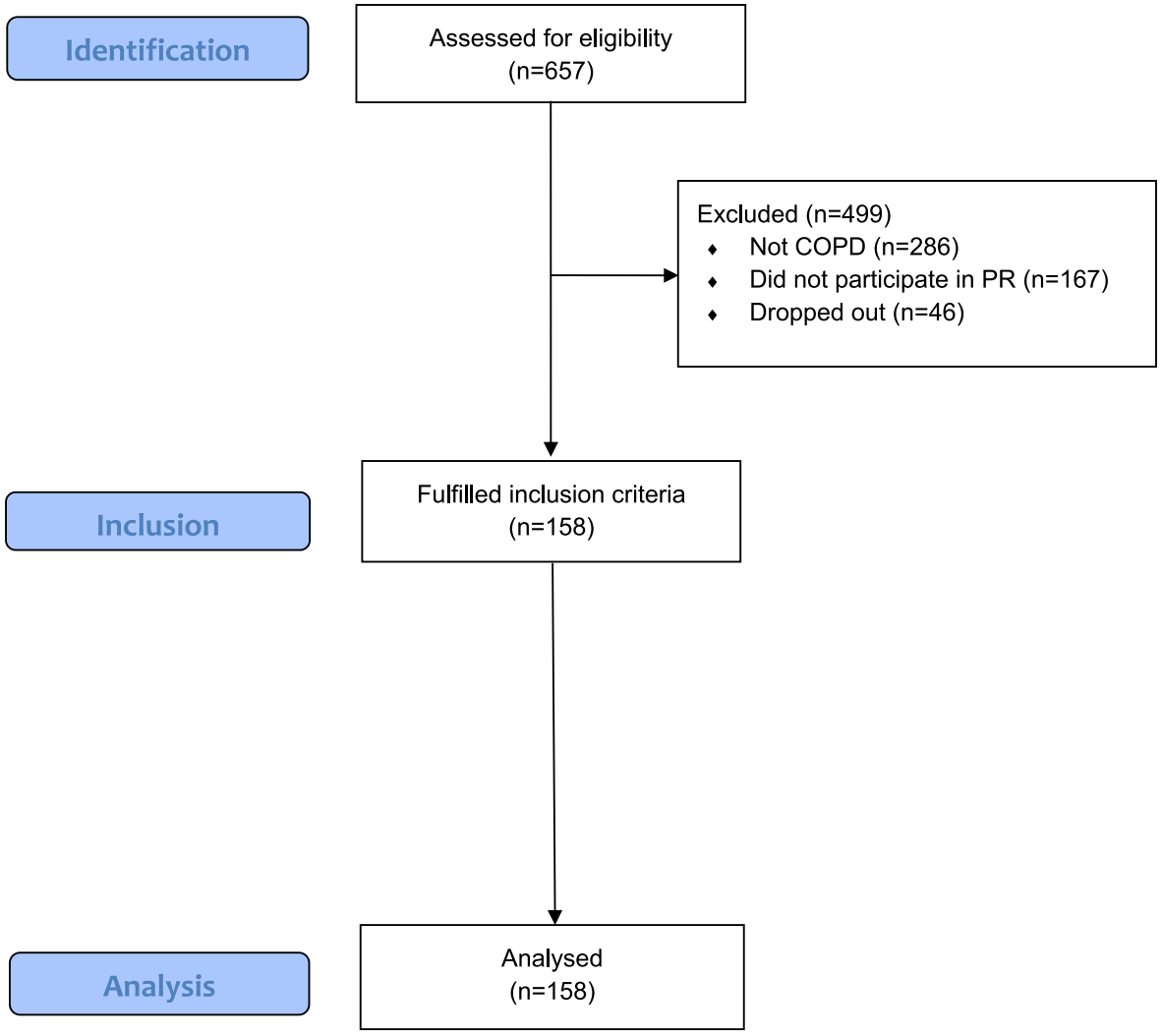

Fig. 1. Flow diagram of the eligibility screening of the study population.

Table 1
Characteristics of people with chronic obstructive pulmonary disease (COPD) who participated in pulmonary rehabilitation conducted with minimal resources or in specialised centres (N = 158).

	All participants (N = 158)	PR with minimal resources (N = 72)	PR in specialised centres (N = 86)	p-value
Attendance rate, %	83.0 [71.0, 92.0]	85.5 [67.0, 96.0]	83.0 [72.0, 92.0]	0.585
Age, years	69.0 ± 8.3	68.5 ± 7.7	69.5 ± 9.1	0.666
Sex (male), n (%)	126 (79.7)	61 (84.7)	65 (75.6)	0.154
BMI, kg/m^2	26.2 [22.6; 30.4]	27.4 [23.4; 31.3]	25.5 [22.2; 28.7]	**0.023***
Lung function				
FEV_1, L	1.2 [1.0; 1.7]	1.4 [1.1; 1.8]	1.2 [0.9; 1.5]	0.067
FEV_1, %predicted	49.0 [40.0; 65.8]	54.5 [41.3; 69.0]	49.0 [40.0; 65.8]	0.120
FVC, L	2.6 [2.1; 3.1]	2.7 [2.1; 3.2]	2.5 [2.1; 3.0]	0.510
FVC, %predicted	79.5 ± 17.7	76.4 ± 19.4	79.5 ± 17.7	0.563
No. ECOPD in the past year	0 [0; 8][a]	0 [0; 4][a]	0 [0; 8][a]	**0.005***
≥2, n (%)	24 (15.2)	7 (9.7)	17 (19.8)	0.080
No. Respiratory-related hospitalisations in the past year	0 [0; 0]	0 [0; 0]	0 [0; 0]	0.092
≥1, n (%)	13 (8.2)	3 (4.2)	10 (11.6)	0.089
Long-term oxygen therapy, yes, n (%)	16 (10.1)	5 (6.9)	11 (12.8)	0.225
Non-invasive ventilation, yes, n (%)	23 (14.6)	10 (13.9)	13 (15.1)	0.828
GOLD grade, 1/2/3/4, n (%)	13 (8.2)/68 (43.0)/65 (41.1)/12 (7.6)	7 (9.7)/36 (50.0)/24 (33.3)/5 (6.9)	6 (7)/32 (37.2)/41 (47.7)/7 (8.1)	0.274
GOLD group, A/B/E, n (%)	37 (23.4)/92 (58.2)/29 (18.4)	23 (31.9)/42 (58.3)/7 (9.7)	14 (16.3)/50 (58.1)/22 (25.6)	**0.009***
Smoking status, Current/Former/Never, n (%)	22 (13.9)/101 (63.9)/35 (22.2)	13 (18.1)/40 (55.6)/19 (26.4)	9 (10.5)/61 (70.9)/16 (18.6)	0.126
Medication, n (%) (N = 156)				
SABA	21 (13.5)	6 (8.5)	15 (17.6)	0.150
SAMA	10 (6.4)	3 (4.2)	7 (8.2)	0.490
LABA	20 (12.8)	7 (9.9)	13 (15.3)	0.441
LAMA	44 (28.2)	14 (19.7)	30 (35.3)	**0.048***
LAMA + LABA	49 (31.4)	23 (32.4)	26 (30.6)	0.945
ICS	18 (11.5)	7 (9.9)	11 (12.9)	0.728
ICS + LABA	60 (38.5)	26 (36.6)	34 (40.0)	0.789
ICS + LABA + LAMA	14 (9.0)	6 (8.5)	8 (9.4)	1
Xanthines	12 (7.7)	6 (8.5)	6 (7.1)	0.982
Expectorants	16 (10.3)	7 (9.9)	9 (10.6)	1
CCI, total score	4.0 [3.0; 5.0]	4.0 [3.0; 5.0]	4.0 [3.0; 5.0]	0.789
Mild/Moderate/Severe	17 (10.8)/95 (60.1)/46 (29.1)	8 (11.1)/44 (61.1)/20 (27.8)	9 (10.5)/51 (59.3)/26 (30.2)	0.943
mMRC, grade	2 [1; 3]	2 [1; 3]	2 [1; 3]	0.647
≥2, n (%)	90 (57.0)	37 (51.4)	53 (61.6)	0.195
FACIT-FS, total score (n = 148)	39.0 [31.0; 44.0]	39.5 [30.0; 44.0]	38.0 [32.0; 43.0]	0.534
HADS, Anxiety score (n = 139)	5.0 [3.0; 9.0]	5.0 [3.0; 8.0]	6.0 [3.0; 9.0]	0.193
HADS, Depression score (n = 139)	6.0 [3.0; 9.0]	6.0 [3.25; 9.0]	6.0 [3.0; 9.0]	0.854
CAT, total score	14.5 ± 8.2	14.4 ± 8.4	15.0 ± 8.0	0.642
SGRQ, total score	43.7 ± 19.4	42.8 ± 21.0	45.4 ± 17.5	0.085
QMVC, KgF (n = 157)	30.7 ± 7.8	30.1 ± 7.8	31.6 ± 7.8	0.418
QMVC, % predicted (n = 157)	88.3 ± 24.3	82.2 ± 23.3	94.8 ± 24.1	0.07
Brief-BESTest, total score (n = 150)	18.0 [15.0; 22.0]	19.0 [14.3; 22.0]	18.0 [15.0; 22.0]	0.504
6MWD, m	411.2 ± 121.3	420.0 ± 119.0	402.3 ± 125.9	0.560
6MWD, % predicted	71.4 ± 20.4	73.1 ± 20.1	69.7 ± 21.1	0.441
1minSTS, repetitions (n = 153)	22.0 [18.0; 27.0]	21.5 [18.0; 28.0]	22.0 [19.0; 25.0]	0.924
1minSTS % predicted (n = 153)	73.5 [63.4; 87.5]	74.2 [60.7; 93.0]	72.3 [64.2; 85.6]	0.654

Data are presented as mean ± standard deviation, median [1st quartile; 3rd quartile] or number (percentage), except for the number of exacerbations of COPD, which is reported as median [minimum; maximum].
Legend: BMI: Body mass index; Brief-BESTest: Brief-Balance evaluation systems test; CCI: Charlson comorbidity index; CAT: COPD assessment test; ECOPD: exacerbations of COPD; FACIT-FS: functional assessment of chronic illness therapy fatigue subscale; FEV_1: Forced expiratory volume in the first second; GOLD: Global initiative for chronic obstructive lung disease; HADS: hospital anxiety and depression scale; HRQoL: Health-related quality of life; ICS: inhaled corticosteroid; LABA: long-acting beta-agonists; LAMA: long-acting muscarinic antagonist; mMRC: modified Medical research council dyspnoea scale; No.: Number; PR, pulmonary rehabilitation; QMVC: quadriceps maximal voluntary contraction; SABA: short-acting beta-agonists; SAMA: short-acting muscarinic antagonist; SGRQ: St. George's respiratory questionnaire; 1minSTS: 1-min sit-to-stand test; 6MWD: 6-min walking distance; 1–4: Severity of airflow limitation, 1 – $FEV_1 \geq 80$ % predicted, 2–50 % ≤ $FEV_1 < 80$ % predicted, 3–30 % ≤ $FEV_1 < 50$ % predicted, 4 - $FEV_1 < 30$ % predicted; A-E: A – CAT <10 points and 0–1 moderate-to-severe exacerbations (not leading to hospitalisation), B – CAT ≥10 points and 0–1 moderate exacerbations (not leading to hospitalisation), E – ≥ 2 moderate exacerbations or ≥ 1 exacerbations leading to hospitalisation.
[a] Median [minimum; maximum].

ICER analysis showed that PR with MR was 'more effective and less costly' for HADS-D, QMVC and 1minSTS (Supplementary material I - Table S2). However, for FACIT-FS, HADS-A, CAT, SGRQ, Brief BESTest, and 6MWD, PR with MR was 'less effective and less costly'.

4. Discussion

This study found no differences between groups for changes across all PR outcomes, except for the SGRQ. Significant pre-post changes were found in each setting for all outcome measures, with clinically relevant improvements for the CAT, SGRQ, 6MWT and 1minSTS. The non-inferiority of PR with MR for the FACIT-FS, HADS-D, QMVC, Brief-BESTest, and 1minSTS was established but was inconclusive for the HADS-A, CAT, SGRQ, and 6MWT compared to PR in SC in people with COPD. Implementation costs were about four times lower in PR delivered with MR than PR in SC, with costs of €8384 for MR and €33,123 for SC. Similarly, intervention costs were approximately twice as high for PR in SC than with MR, ranging from €5168 to €3234/programme (€646 or €404/person) with MR, and from €9803 to €6247 (€1225 or €781/person) in SC, with or without paid non-emergency medical transportation, respectively.

Previous studies have also found no differences between PR with MR and in SC in changes in functional capacity (measured with the incremental shuttle walk test - ISWT [14] or 6MWT [15]) and peripheral muscle strength [14,15]. Our study corroborates these findings and provides new evidence for other meaningful outcomes, including fatigue, symptoms of anxiety and depression, impact of the disease, balance, functional capacity in activities other than walking, and health-related quality of life (measured with the SGRQ). However, in contrast to earlier findings that found comparable benefits in health-related quality of life using the chronic respiratory disease

Table 2
Estimated marginal means with 95 % confidence intervals of the fitted (robust) linear mixed models for each outcome measure assessed in pulmonary rehabilitation conducted with minimal resources and in specialised centres in people with chronic obstructive pulmonary disease.

	PR conducted with minimal resources (N = 72)		PR conducted in specialised centres (N = 86)		Between-group changes 95 % CI	P-value Time[c]Setting interaction
	Baseline	Post	Baseline	Post		
FACIT-FS, total score[a] (n = 149)	36.5 [34.4, 38.6] [b] 2.3 [0.7, 3.8][c]	38.8 [36.7, 40.9]	38.3 [36.3, 40.3] [b] 3.1 [1.7, 4.6][c]	41.4 [39.4, 43.5]	−0.9 [−3, 1.3]	0.424
HADS-Anxiety, score (n = 145)	6 [4.9, 7] [b] −0.8 [−1.4, −0.1][c]	5.2 [4.2, 6.2]	6.1 [5, 7.1] [b] −0.9 [−1.6, −0.3][c]	5.1 [4.1, 6.2]	0.1 [−0.8, 1.1]	0.757
HADS-Depression, score[a] (n = 145)	7 [6.1, 7.9] [b] −0.8 [−1.5, −0.1][c]	6.2 [5.3, 7.1]	5.9 [5, 6.8] [b] −0.7 [−1.5, 0][c]	5.2 [4.3, 6.1]	−0.1 [−1.1, 0.9]	0.853
CAT, total score[a] (n = 158)	14.8 [13.1; 16.5] [b] −2 [−3.4, −0.6][c]	12.8 [11.1; 14.5]	13.4 [11.8; 15.0] [b] −3.2 [−4.5, −2][c]	10.2 [8.6; 11.8]	1.2 [−0.6, 3.1]	0.196
SGRQ, total score[a] (n = 158)	43.1 [39.1, 47.1] [b] −4.6 [−7.1, −2][c]	38.5 [34.5, 42.5]	43.6 [39.9, 47.4] [b] −8.9 [−11.2, −6.6][c]	34.7 [30.9, 38.5]	4.3 [0.9, 7.8][c]	**0.014**[c]
QMVC, KgF (n = 158)	26.5 [24.4, 28.5] [b] 2.9 [1.3, 4.4][c]	29.3 [27.3, 31.4]	29 [27.1, 31] [b] 2.4 [1.1, 3.8][c]	31.5 [29.5, 33.4]	0.4 [−1.6, 2.5]	0.689
Brief-BESTest, total score[a] (n = 154)	17 [16, 17.9] [b] 1.8 [1.1, 2.5][c]	18.8 [17.8, 19.7]	17.4 [16.4, 18.3] [b] 2.2 [1.6, 2.8][c]	19.5 [18.6, 20.5]	−0.4 [−1.3, 0.5]	0.417
6MWD, m[a] (n = 158)	423.4 [393.4, 453.4] [b] 29.8 [16.1, 43.4][c]	453.1 [423.1, 483.1]	414.4 [385.8, 443] [b] 47 [34.5, 59.5][c]	461.4 [432.8, 490]	−17.2 [−35.8, 1.3]	0.069
1minSTS, repetitions (n = 157)	23 [20.9, 25.1] [b] 3.3 [2.1, 4.5][c]	26.3 [24.2, 28.4]	22.7 [20.7, 24.7] [b] 3.2 [2.1, 4.2][c]	25.9 [23.9, 27.9]	0.2 [−1.5, 1.8]	0.848

Legend: Brief-BESTest: Brief-Balance Evaluation Systems Test; CAT: COPD assessment test; FACIT-FS: fatigue with the functional assessment of chronic illness therapy fatigue subscale; HADS: hospital anxiety and depression scale; PR: pulmonary rehabilitation; QMVC: quadriceps maximal voluntary contraction; SGRQ: Saint George's respiratory questionnaire; 1minSTS: 1-min sit-to-stand test; 6MWD: 6-min walking distance.

[a] Robust linear mixed-effects model.

[b] Change post-pre pulmonary rehabilitation.

[c] P-value<0.05.

questionnaire (CRQ) [15] in people with COPD, greater improvements in health-related quality of life (measured with the SGRQ) were observed in PR in SC compared with MR. This difference could be attributed to the higher proportion of people experiencing exacerbations in SC compared to MR. It is likely that the devastating impact that exacerbations have on people's lives, even when they do not require hospitalisation, influences not only the choice of setting (i.e., perceived safety), but also their perception of health-related quality of life, "valuing" more the improvements after receiving an interdisciplinary intervention such as PR [37]. Additional research is, however, needed to better understand these findings.

Non-inferiority of PR with MR compared with PR in SC was established for several outcomes, however, it could not be ruled out for core outcomes such as functional capacity (6MWT) and health-related quality of life (SGRQ). Studies for functional capacity (ISWT [14,38] and 6MWT [39]) and health-related quality of life (CRQ) [14,38,39] demonstrated either non-inferiority or inconclusive findings. The small number of studies and sample sizes, the heterogeneity of interventions (e.g., home-based or minimal equipment *vs.* SC) and outcome measures (e.g., 6MWT, ISWT, CRQ) [14,15,38,39], as well as the comparator failing to exceed the MCID [15] may justify the current uncertainty of the evidence and emphasises the need for further non-inferiority trials.

Our data and the existing literature support that PR in SC should remain the standard of care for people with COPD. Nevertheless, as increasing the availability of PR is a top priority, and significant improvements without adverse effects were observed regardless of the setting, PR with MR may be a viable intervention when access to the standard of care is unavailable or limited. It can decentralise this fundamental intervention from the main urban hospitals and outpatient settings and promote adherence [14,15], reducing inequalities in access to this gold-standard intervention. More importantly, it may meet individual needs and preferences. Careful consideration of disease burden, treatable traits, social factors, and personal preferences and needs should therefore guide the choice of PR setting - the right setting for the right person [12].

The present study also provides data on the implementation and intervention of PR associated costs in Portugal, following previous recommendations [35]. PR with MR was a less expensive option, as previously acknowledged [13,40]. Nevertheless, the estimated costs per person for PR with MR were significantly higher (646€) than previously reported (198€) [40] as we included an interdisciplinary team, equipment and its depreciation, and paid transportation of people to PR to ensure a minimum level of quality and safety for all individuals. However, this cost reduction also meant that non-inferiority could not be established when compared to SC. Thus, investing in PR equipment is of value across settings to improve access to this intervention and maximise its benefits.

Several strengths and limitations of this study need to be acknowledged. Firstly, the study explored the effects and non-inferiority of PR with MR compared to SC on multiple patient-centred outcomes for COPD. Secondly, PR implementation and intervention costs were estimated for Portugal. This study contributes to the overall assessment of PR costs across the European Union, informing different stakeholders to benchmark PR and potentially influencing health policies in the region. Finally, PR was shown to be a value-based healthcare intervention independent of the setting. Nevertheless, our sample consisted mostly of men and individuals with moderate-to-severe COPD, which may limit the generalisability of findings. Secondly, our results come from an observational study and therefore, selection bias may have influenced the results, even though efforts were made to control for possible confounders. Thirdly, both settings had similar staff specialisation delivering PR, and therefore results and cost estimates may not hold if the staff is more specialised. A health economic plan was also not established in advance, as this was not the original aim of the multiple studies gathered in this research. In addition, the implementation and intervention costs were calculated assuming that the entry-level staff would carry out a single PR programme with eight people every 12 weeks. Therefore, the costs presented may not be transferable to other scenarios where more specialised staff are deployed and/or a different number of PR programmes per year are conducted with a different number of

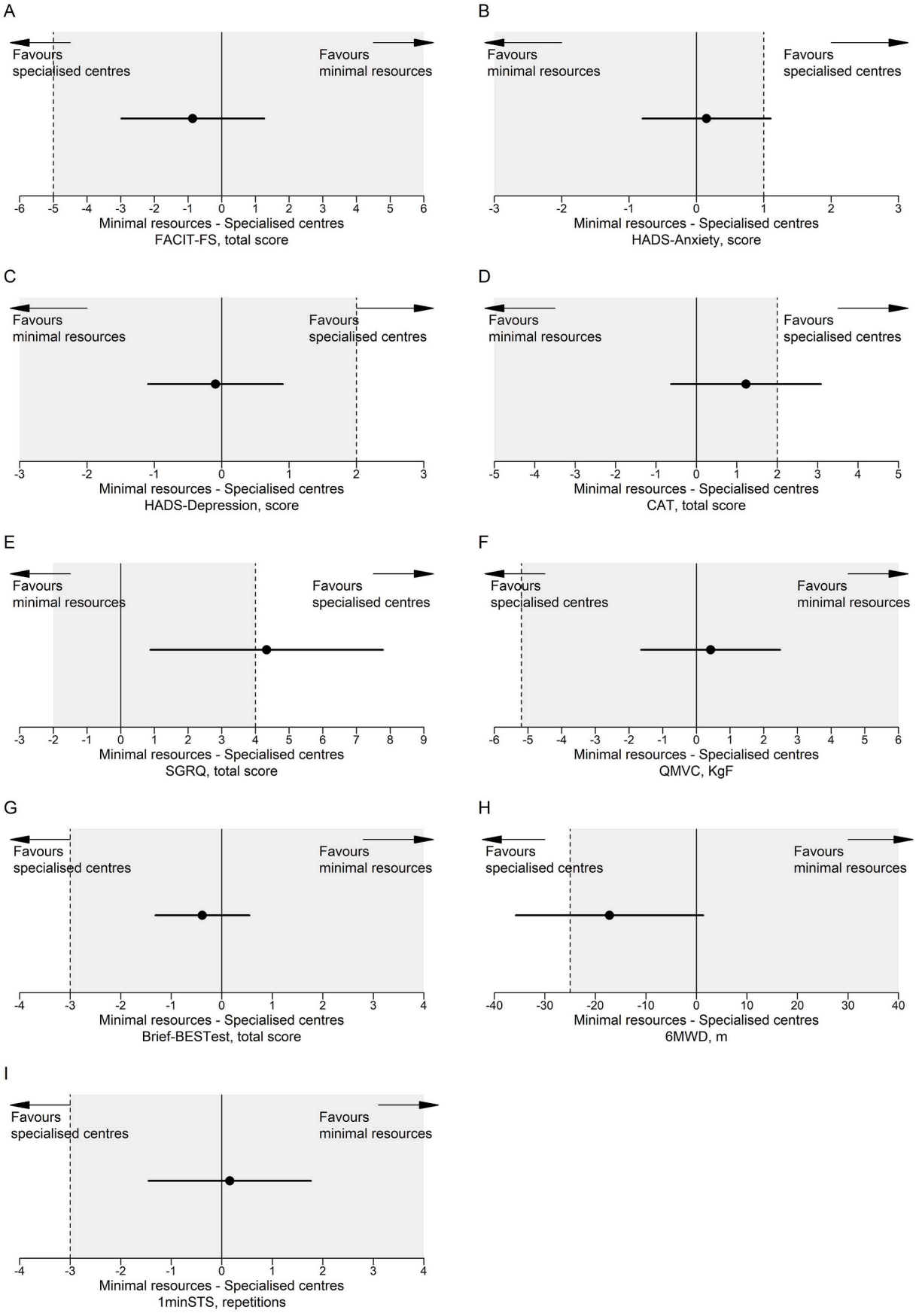

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Fig. 2. Between-group changes and non-inferiority margins for the **A** - fatigue - Functional Assessment of Chronic Illness Therapy - fatigue scale (FACIT-FS), **B** – symptoms of anxiety - Hospital Anxiety and Depression Scale - Anxiety score (HADS-A), **C** – symptoms of depression - Hospital Anxiety and Depression Scale – Depression score (HADS-D), **D** - impact of the disease - COPD Assessment Test (CAT), **E** - health-related quality of life - St. George's Respiratory Questionnaire (SGRQ), **F** - quadriceps maximal voluntary contraction (QMVC), **G** - Brief-Balance Evaluation Systems Test (Brief-BESTest), **H** - 6-min walk distance (6MWD) and **I** - 1-min stand and sit test (1minSTS); assessed in pulmonary rehabilitation conducted with minimal resources and in specialised centres in people with chronic obstructive pulmonary disease. Data are presented as marginal means and 95 % confidence intervals (CI). The dashed vertical lines represent the non-inferiority margin which corresponds to the established minimal clinically important difference (MCID) per outcome measure: FACIT-F, 5 points; HADS-A, −1 point; HADS-D, −2 points; CAT, −2 points; SGRQ, −4 points; QMVC, 5.2kgF; Brief-BESTest, 3 points; 6MWD, 25m and 1minSTS, 3 repetitions. The solid vertical lines represent the null effect.

Table 3
Implementation and intervention costs of pulmonary rehabilitation conducted with minimal resources and specialised centres in people with chronic obstructive pulmonary disease.

Direct costs components	Costing approach	Costs of PR with minimal resources (€)				Costs of PR in specialised centres (€)			
		PR programme	PR programme/ person	Week	Week/ person	PR programme	PR programme/ person	Week	Week/ person
Implementation costs									
Equipment/ material	Minimum required to start the programme in both settings. including VAT	6743.62	–	–	–	29,972.82	–	–	–
Consumables	Minimum required to start the programme in both settings. including VAT	93.80	–	–	–	1603.80	–	–	–
Staff timing and training	Salary costs and price/hour associated with the interdisciplinary team delivering the PR at entry level values	1546.25	–	–	–	1546.25	–	–	–
Total cost		**8383.67**	**-**	**-**	**-**	**33,122.87**	–	–	–
Intervention costs									
Equipment/ material	Depreciation rates applied to the prices with VAT	1054.41	131.80	81.11	10.14	2055.46	256.93	158.11	19.76
Consumables	Minimum required to start the programme in both settings. including VAT	93.80	11.72	7.82	0,98	1603.80	200.48	133.65	16.71
Staff timing and training	Salary costs and price/hour associated with the interdisciplinary team delivering the PR at entry level values	1546.25	193.28	128.85	16.11	1546.25	193.28	128.85	16.11
Overheads (20 %)	Applied to the costs above	538.89	67.36	43.56	5.45	1041.10	130.14	84,12	10.52
Total cost without transportation		**3233.35**	**404.16**	**261.34**	**32.67**	**6246.61**	**780.83**	**504,73**	**63.09**
Transportation	Non-emergency medical transport	1934.4	241.8	161.20	20.15	3556.8	444.6	296.40	37.05
Total cost with transportation		**5167.75**	**645.96**	**422.54**	**52.82**	**9803.41**	**1225.43**	**801.13**	**100.14**

Note: Costs of pulmonary rehabilitation (PR) were calculated considering the worst (more expensive) scenario, i.e., that in one year only four PR programmes with 8 people each are delivered.

people treated. However, we filled an important gap as this study was the first to estimate PR associated costs in Portugal. Future studies should aim to establish the cost-effectiveness of these interventions including direct costs (e.g., medication and healthcare utilisation), and indirect costs from the patient and societal perspectives (e.g., productivity losses). Lastly, other core outcomes, such as problematic activities of daily living, health behaviours, knowledge about the disease and personal goals should be further explored in future non-inferiority PR trials.

5. Conclusion

PR with MR was safe, successfully improved multiple health domains and was non-inferior to PR in SC in improving symptoms of fatigue and depression, quadriceps muscle strength, balance, and functional capacity (1minSTS), at a lower cost. However, it was inconclusive for symptoms of anxiety, impact of the disease, health-related quality of life and functional capacity (6MWT). Consequently, traditional centre-based programmes should continue to be the standard of care. PR with MR may, however, be an effective alternative to increase access to PR when SC are unavailable or satisfactorily target an individual's treatable traits and accommodate their social context, personal preferences and needs - "the right setting for that person".

CRediT authorship contribution statement

Alda Marques: Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Joana Antão:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Guilherme Rodrigues:** Writing – review & editing, Visualization, Resources, Methodology. **Cátia Paixão:** Writing – review & editing, Visualization, Resources, Methodology. **Patrícia Rebelo:** Writing – review & editing, Visualization, Resources, Methodology. **Ana Machado:** Writing – review & editing, Visualization, Resources, Methodology. **Sara Souto-Miranda:** Writing – review & editing, Visualization, Resources, Methodology. **Ana Sofia Grave:** Writing – review & editing, Visualization, Resources, Methodology. **Cíntia Dias:** Writing – review & editing, Visualization, Resources, Methodology. **Raquel Marinho:** Writing – review & editing, Visualization, Resources, Methodology. **Maria Aurora Mendes:** Writing – review & editing, Visualization, Resources, Methodology. **Ana Oliveira:** Writing – review & editing, Visualization, Resources, Methodology. **José Joaquim Alvarelhão:** Writing – review & editing, Visualization, Methodology, Formal analysis.

Ethics approval

Ethical approval was obtained from the Ethics Committees of the Administração Regional de Saúde do Centro, I.P. (December 3, 2016:64/2016/16/2020), Centro Hospitalar do Baixo Vouga (March 22, 2017:777638/15-05-2019), Unidade Local de Saúde de Matosinhos (February 17, 2017:10/CE/JAS), Centro Hospitalar do Médio Ave (August 27, 2018) and Hospital Distrital da Figueira da Foz (July 18, 2017). Approval was also obtained from the Comissão Nacional de Proteção de Dados (8828/2016). Partnerships were established between the University of Aveiro, the institutions mentioned above and four city councils in the country's central region. All participants signed an informed consent before data collection.

Data sharing

The data that support the findings of this study are available on request from the corresponding author, AM.

Previous presentations

Part of this work has been presented at the European Respiratory Society Congress 2023 as an oral communication.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2025.108229.

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