The Effect of Pulmonary Rehabilitation on Mortality, Balance, and Risk of Fall in Stable Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review

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Abstract

Objectives: To evaluate the impact of pulmonary rehabilitation on survival and fall (including balance) in patients with chronic obstructive pulmonary disease (COPD) at stability.

Design: Systematic Review.

Methods: OVID, MEDLINE, EMBASE, and Cochrane Collaboration Library were searched for literature dating from January 1980 up to November 2014 as well as an update in October 2015. Two reviewers screened titles, abstracts and full text records, extracted data and assessed studies for risk of bias; any disagreements were resolved by a third member of the team, and consensus was always sought.

Results: Initial searches yielded 3216 records but after review, only 7 studies were included and no studies focused solely on falls. Two cohort studies found some positive benefits of pulmonary rehabilitation on balance but the results were inconsistent across the studies. Regarding survival, two randomised controlled trials were conducted; one study showed significant survival benefit at 1 year while the other one showed non-significant survival benefit at 3 years. Neither were adequately powered and in both, survival was a secondary outcome.

Conclusions: There was only limited inconclusive evidence to show that pulmonary rehabilitation has a significant beneficial effect on balance or survival.

Keywords: COPD, Pulmonary Rehabilitation, Survival, Mortality, Fall, Balance
Words: 191

Abbreviations	Description
ABC	Activities-Specific Balance Confidence-Scale
BBS	Berg Balance Scale
BESTtest	Balance Evaluation Systems Test
COPD	Chronic Obstructive Pulmonary Disease
FEV_1	Forced Expiratory Volume in the First Second
MCID	Minimum Clinically Important Difference
MDC	Minimum Detectable Change
NOS	Newcastle-Ottawa Scale
PR	Pulmonary Rehabilitation
RCT	Randomized Control Trial
TUG	Time Up and Go-Test

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous inflammatory lung disease characterized by progressive airway obstruction. It is the third leading cause of death worldwide.[1] Comorbidities include cardiovascular disease, diabetes mellitus, osteoporosis, increased risk of fall, and depression. [2] In general, impaired mobility, muscle weakness, and impairment of balance due to chronic diseases are strong predictors of fall in adults;[3] recent studies have found that balance is impaired in patients with COPD.[4] A recent Cochrane systematic review showed evidence that falls in elderly can be prevented with exercise.[5] Exercise, with balance training, has been recommended in the guidelines for prevention of falls in older people with grade B evidence. [6]

Pulmonary rehabilitation (PR) is an important part in the clinical management of COPD, and it includes education, exercise training, and psychological support [7]. There are demonstrable improvements in exercise tolerance, muscle strength, dyspnoea, quality of life in patients with COPD after PR, cemented in a Cochrane review[8] and the BTS guidelines[9]. Improving muscle strength and exercise tolerance through PR as well as the opportunity for educational support and improving confidence may well therefore improve risk of future falls. Given patients with COPD have a high prevalence of osteoporosis;[2] an increased risk of falls is of even more concern. Further quality of life in the older population as a whole is associated with falls.

Whilst a systematic review of six clinical trials has shown survival benefit in those undergoing pulmonary rehabilitation in patients with COPD after an acute exacerbation, [10] the situation in stable patients undergoing standard PR is uncertain. The BTS pulmonary rehabilitation guidelines document research recommendations and include need for research on comorbidities, preserving health, personalisation of PR and extending the outcomes used.[9] The aim of this study is to conduct a systematic review of published studies that evaluate the effect of a PR programme on stable patients with COPD to determine if there is benefit with regard to balance or falls, and survival.

Method

Searches were conducted through OVID on Medline, EMBASE, Cochrane Collaboration Library and the register of controlled trials from January 1980 until November 2014, and through an update in October 2015. The search yielded adult human studies on patients with COPD who have had standard PR not less than four weeks; the outcome measures were balance, fall, survival, and mortality. The search was conducted with the University library services who approved the search terms and methodology structure. The search was limited to articles in "English" and "humans".

Using the PICOS (The population, intervention, comparison, outcome, and setting) model, the criteria were:

1. The population: Stable adult patients with COPD.

2. The intervention: Standard multidisciplinary PR of not less four weeks.

3. The comparator/control: Other patients with COPD did not have PR.

4. The outcome: balance, fall, survival, mortality.

5. The study design: Either cohort or clinical trials from 1980 onward.

The following key words were used: “Pulmonary Rehabilitation”; “COPD” or “chronic obstructive pulmonary disease”, “chronic obstructive lung disease”, “Chronic bronchitis”, “emphysema”, “bronchitis”; “mortality” or “death”, “survival”, “survive”, “fall”, “faller”, “falling”, “accidental fall”, “balance”, “imbalance”. We conducted this review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[11] [Online Supplement Table E1]

Two reviewers independently assessed the titles and abstracts; they evaluated the full text studies based on outcome and type of rehabilitation program for at least 4 weeks. These studies were evaluated and selected independently for inclusion in the systematic review. Any disagreements were resolved by a third member of the team, and consensus was always sought. Additional studies were searched for the bibliographies and relevance of the retrieved articles. Studies that did not fulfil the selection criteria were excluded.

Two reviewers independently extracted the full text of the included articles and recorded details on authorship, year of publication, study design, interventions, patient and outcome measures. Risk of bias was assessed using the Cochrane Collaboration’s ‘Cochrane risk of bias tool (modified) for quality assessment of the randomized control trial (RCT)’ for sequence generation, allocation concealment, and blinding.[12] The

Newcastle-Ottawa scale (NOS) was used to assess the methodology and quality of the cohort studies; the scale awards 4 points for selection, 2 points for comparability, and 3 points for outcome - a score of 9 is the highest.[13]

Results

3216 citations were identified from the databases in the original search; seven studies that met the eligibility criteria of the review, of which 2 were randomized control trials and 5 were cohort studies, were selected.[14-20] **[**Figure 1**]** The quality of the cohort studies, as assessed by the NOS with a mean score of 6 out of 9, with points loss due to sampling method or inadequate time for follow-up.[13] For the two randomized trials, the quality of the included studies' reporting was high; allocation concealment and sequence generation were clearly described in both trials. But one trial did not use blinding while the other was only single-blinded. No quantitative analysis was performed due to the lack of data to comparable outcome data to combine. In general, the studies did not show major problems of bias, for detailed characteristics of the included studies and quality assessment for risk of bias, see Online Supplement Table E2-E8.

[Figure 1]

Fall / Balance

There were no studies that report of the impact of PR on falls directly, while two cohort studies evaluated the effect of standard PR on balance in patients with COPD. **[**Table 1**]** Both studies assessed the balance tests using Minimum Detectable Change (MDC) as the

true change in the balance. The first cohort study by Beauchamp *et al.* [15] studied 29 patients with COPD (pre- and post-PR), and found significant improvement in measures of balance, the Berg Balance Scale (BBS) [BBS mean difference=2.8 points; 95% CI (1.7 to 3.8); P<0.001], and the Time Up and Go test (TUG), [TUG mean difference=-1.5s; 95% CI (-2.4 to -0.5); P=0.003], but not for self-assessed balance confidence score as measured by Activities-Specific Balance Confidence Scale (ABC) [mean difference=4.8; 95% CI (-1.0 to 10.7), p=0.1]. In the second study by the same authors [14], they conducted a randomized clinical trial comparing standard PR with PR + balance training. Based on our inclusion criteria we have taken only the control arm of this trial (PR) and treated as a cohort study. Here, patient inclusion criteria also included a self-reported decline in balance, fall in the last 5 years or a near fall. Within this control arm, 17 patients (pre- and post-PR program) were studied and this time the results showed no significant improvement in the BBS [mean difference=1.6 points; 95% CI (-0.26 to 3.46), p=0.07]; but there was significant improvement in ABC confidence [mean difference=13; 95% CI (3.72 to 22.27), p=0.014]. Here, the Balance Evaluation Systems Test (BESTtest) showed significant improvement as well [mean difference=6; 95% CI (3.39 to 8.60), p=0.0003].

[Table 1]

Survival

Three cohort studies [16-18] **[Table 2]** and two randomized controlled trials [19, 20] (Table 3) contributed to the mortality data with pulmonary rehabilitation. In 1996, a

cohort study by Gerardi [18] investigated survival in 158 patients (of which 87% had COPD) who had completed the PR program, and the survival rate was 80% at 3 years after rehabilitation. In another cohort study by Bowen [16] in 2000 (of which 89% had COPD) the survival rate in 149 patients who completed the PR program was 95% at 1 year, 92% at 2 years, 85% at 3 years, and 73% at 4 years after rehabilitation. In the third cohort study by Connor [17] in 2001 on 170 patients, the 1-year survival rate was slightly lower than Bowen's study at 91%.

Two randomized control trials [19, 20] compared the survival rate between PR and control groups **[**Table 2**]**, where survival was a secondary outcome in both cases. In 1995, Ries *et al*. [20] studied two groups of patients; 57 patients (rehab) received the standard PR program and 62 patients (control) received only the PR education component. They found at 3 years that 85% survived in the rehab group compared to 74% amongst the control group; and at 6 years, 67% in rehab and 56% in the control group survived. Although the PR survival was better, there was no significant difference in survival rate (Hazard ratio=0.74 [95% CI, 0.41 to 1.34; P = 0.32]). In the second trial in 2000, Griffiths *et al*. [19] compared a standard rehab group (92 patients) with a control group (90 patients); survival was reported as a supplementary result of their study. By year 1 of the study, 94.5% survived in the rehab group compared to 90% in the control group, (P value=0.032).

[Table 2]

[Table 3]

Discussion

This systematic review identified a paucity of studies that focus on the effect of PR on falls, balance or survival. In the 2 studies that examined any potential benefit of PR on balance, the results were not consistent across the two studies even though each of them demonstrated a significant improvement in at least one of the balance scores. The survival in patients with COPD who had PR at clinical stability appeared to show some benefit however this was not always statistically significant.

The identified studies on balance [14, 15] have small sample size and they have excluded patients with many comorbidities that could influence their balance. Small statistical differences in some of the balance tests were found but these were not consistent across the studies. Previous research have shown that patients with COPD have worse balance score on their BBS test compared to healthy individuals.[21, 22] . The balance tests used in the studies (BBS, TUG, and BESTest) and the ABC balance confidence are important as they have shown reliable and valid results for determining balance and fall risk in adults [23-26]. In addition, they have been used to evaluate the ability to maintain balance and quantify patients with COPD at risk of falling.[3, 27] Both cohorts used Minimum Detectable Change (MDC) instead of the Minimum Clinically Important Difference (MCID). “Statistically significant difference” does not necessarily mean “clinically important” in terms of a clinically demonstrable change. Recently,

Beauchamp carried out a secondary analysis to determine the MCID of the BBS, BESTest, and ABC.[28]

Previous evidence has shown that exercise reduces falls in the elderly.[5] Furthermore, studies have found that standard PR with adding balance training component had a better effect on functional balance and muscle strength in patients with COPD which should, in turn lead to reduced falls.[29, 30] On the current evidence therefore, patients at risk of falls, undergoing PR should have a personalised balance training.

Pulmonary rehabilitation has been associated with improved survival in patients with COPD after an acute exacerbation.[31] However, the evidence that PR is associated with improved survival in stable patients with COPD is not as clear. The RCTs included in this review were underpowered to show a difference in survival. They both showed improved survival but they were not both statistically significant. [19, 20] In addition to the RCT's we identified the three cohort studies that showed survival following PR, though it is difficult to then compare with other reports of survival in patients with COPD generally. The four year survival in a general cohort of patients with COPD was 81%,[32] in one study and as expected, varied according to severity of COPD in another study.[33] When assessed according to airflow obstruction alone, survival at 52 months was 75% for patients with stage I (FEV_1> 50) and II (FEV_1 36-50), and 48% for stage III (FEV_1<

35).[33] Overall, although evidence on PR has shown significant improvement in the quality of life and dyspnoea, the outcomes of balance, fall, and survival are less clear.

The main strength of this review was in the rigorous study selection process, and therefore it is unlikely to have missed any research in this area. The main limitation of this review was the lack of studies and evidence for evaluating the desired outcomes. Moreover, Gerardi[18] and Bowen[16] have included patients with diagnoses other than COPD, although the majority did have COPD. It was not possible to look at survival in those with COPD alone.

In conclusion, this systematic review is unable to demonstrate sufficient evidence of the role of pulmonary rehabilitation in improving balance or survival in patients with COPD. Further studies with alternative strategies may need to be employed to determine the benefits of pulmonary rehabilitation particularly on survival as the short term benefits are from pulmonary are well established, and therefore unethical to with hold from patients.

Declaration of Conflicting Interests

The authors declare that there is not conflict of interest.

Funding

Ali Hakamy has carried out this study as part of his PhD program at University of Nottingham. He has received scholarship award from Ministry of Education (Saudi Arabia). No other support from any other organization for the submitted work.

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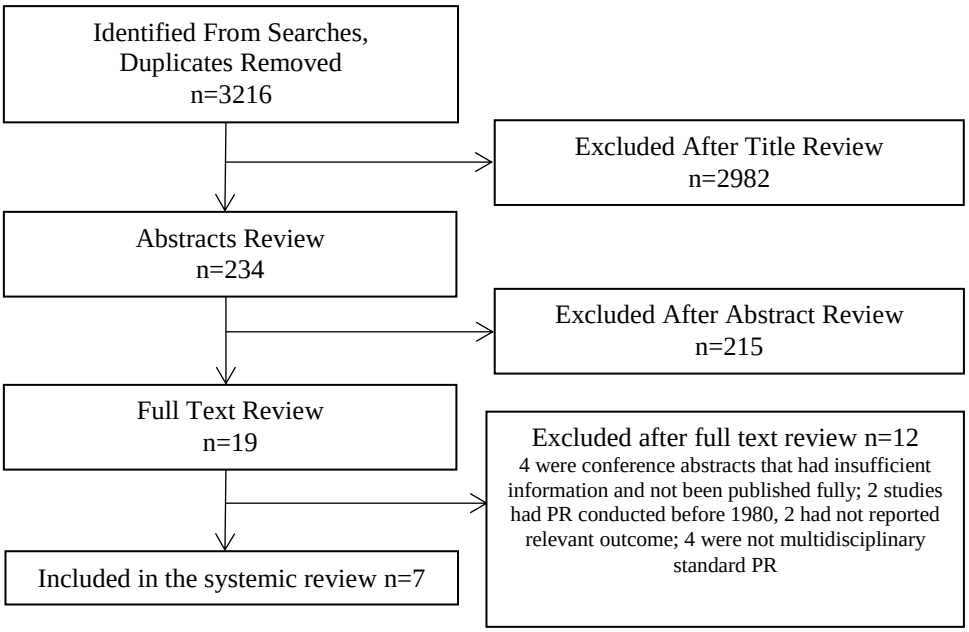

Figure 1. Flow diagram of the selection process of studies included in the systematic review.

Table 1. Two cohort studies assessing the impact of pulmonary rehabilitation on fall/balance

Author/ Year	PR site	Inclusion	Exclusion	PR weeks	PR Education	PR Breath Tech	PR Exercise Train	Total No /Lost to follow up /Final No of patients	Quality score*	Outcome	Mean difference (95% CI)	P- value
Beauchamp 2010 [15]	Inpatient	COPD (FEV1 <80% predicted and FEV1/forced vital capacity <70% predicted), smoking history >20 pack/year	Cognitive impairment, symptomatic cardiovascular disease, musculoskeletal condition that limited mobility	6	2/wk /30min	Daily	4-5 times/ week	33 / 4 / 29	6 out of 9	BBS	2.8 (1.7 to 3.8)	P<0.001
										TUG	-1.5 (-2.4 to -0.5)	P=0.003
										ABC	4.8 (-1.0 to 10.7)	P=0.10
Beauchamp 2013 [14]	Inpatient	patients with COPD who reported decline in balance or fall in last 5 years or a recent near-fall	Inability to communicate, comorbidity that influenced balance, musculoskeletal condition that severely limited mobility and balance	6	2/wk /30min	Daily	4-5 times/ week	18 / 1 / 17	7 out of 9	BBS	1.6 (-0.26 to 3.46)	P=0.07
										BESTest	6 (3.39 to 8.60)	P=0.0003
										ABC	13 (3.72 to 22.27)	P=0.014

* Studies' quality assessed by Newcastle-Ottawa scale. Characteristics of the studies [Appendix]
Abb i: PR: pulmonary rehabilitation, wk: week, BBS: Berg Balance Scale, BESTest: Balance Evaluation Systems Test, ABC: Activities-Specific Balance Confidence scale, TUG: Timed Up and Go test.

Table 2. Cohort studies assessing the impact of pulmonary rehabilitation on mortality

Author/ Year	PR site	Inclusion	Exclusion	PR weeks	PR Education	PR Breath Tech	PR Exercise Train	Total No / Lost follow up / Final No of patients	Quality score*	Duration of follow-up	Survival Rate
Gerardi 1996 [18]	Outpatient	Pt. completed PR from Nov1989 to Mar1993	Not mentioned	6	Included	Included	3 h/ twice /wk	158 / 0 / 158 (87% COPD)	7 out of 9	3 years	80% at 3 years
Bowen 2000 [16]	10 programs inpatient + 1 outpatient	Symptomatic lung disease (89% COPD)	Not mentioned	4-12	1-3 wk	1-3 wk	1-3 wk *inpatient 7-9days	164 / 15 / 149	6 out of 9	44 ± 12 months	95% at 1 year 92% at 2 years 85% at 3 years 73% at 4 years
Connor 2001 [17]	1st week inpatient, and the rest is outpatient	All patients with COPD	Not mentioned	8	1st wk	Not included	Circuit of mobility twice/wk. endurance exercise 3-6 days/wk	170 / 0 / 170	6 out of 9	1 year	91% at 1 year

* Studies' quality assessed by Newcastle-Ottawa scale**.** Characteristics of the studies [Appendix]
Abb ii: PR: pulmonary rehabilitation, wk: week

Table 3. Randomized control trials assessing the impact of pulmonary rehabilitation on mortality

Author/ Year	PR site	Inclusion	Exclusion	PR weeks	PR Education	PR Breath Tech	PR Exercise Train	Total No of patients / Lost follow up / Final No of patients	Quality score*	Duration of follow-up	Survival Rate
Ries 1995	Inpatient	COPD, asthmatic bronchitis, stable, no heart problem or disabilities	Reversible asthma, current smokers don't want to quit	8 weeks and monthly visit for 1 year	Control group 8 weeks, rehab group 8wk+1year	Included in only rehab group	Included in only rehab group	Rehab 63 / 6 / 57 Control 65 / 3 / 62	5 Yes, 2 No	6 year	At 3 years: rehab 85% and control 74%. At 6 years: rehab 67% and control 56%. P=0.32
Griffiths 2000	Outpatient	Stable patient with FEV1 <60%, with less than 20% reversibility	Pt. can't walk, cognitive impairment, symptomatic heart disease	6 weeks for rehab group	Third of the PR time in the rehab group	Included in rehab group only	3 half days /wk for rehab group	Rehab 99 (83% COPD) / 7 / 92	6 Yes, 1 No	1 year	At 1 year: rehab 94.5% and control 90%. P=0.032

* Studies' quality assessed by the Cochrane Collaboration risk of bias tool. Characteristics of the studies [Appendix]

Online Supplements

Table E1. PRISMA Checklist [11]

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTARCT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	-

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	-
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	17
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	23
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	23
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	23
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	23
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

CHARACTERISTICS OF THE INCLUDED STUDIES

Table E2. Beauchamp 2010[15]

Methods	Cohort study
Participants	29 diagnosed COPD patients (mean ±SD age, 69.8±10.3y; forced expiratory volume in 1 second, 46.3%± 22.3% predicted; 59% men[n=17]).
Pulmonary rehabilitation	6-week inpatient PR which includes: Supervised endurance exercise training 4 to 5 times a week, Lower- and upper-extremity strength training 3 times a week, Breathing exercises daily. Self-management education and psychological and social support were provided through lectures, relaxation classes, and recreational activities at least twice a week for 30 minutes.
Outcome	BBS, TUG, ABC
Risk of bias	
NOS selection	***
NOS comparability	*
NOS ascertainment	**

NOS: selection, comparability and ascertainment asterisks (*) with a maximum score of 4, 2, and 3, respectively.

Table E3. Beauchamp 2013[14]

Methods	Cohort study. (this was a clinical trial on PR vs PR with balance training, for the purpose of the systematic review we have taken only PR only and treated it as cohort study)
Participants	17 COPD patients (mean ±SD age, 67.1±9.4y; forced expiratory volume in 1 second, 35.4%± 17.5% predicted; 52% women [n=9]).
Pulmonary rehabilitation (duration, frequency, in or out-patient, and what it did include)	6-week inpatient PR which includes: Supervised endurance exercise training 4 to 5 times a week, Lower- and upper-extremity strength training 3 times a week, Breathing exercises daily. Self-management education and psychological and social support were provided through lectures, relaxation classes, and recreational activities at least twice a week for 30 minutes.
Outcome	BBS, BESTest, ABC
Risk of bias	
NOS selection	***
NOS comparability	*
NOS ascertainment	***

NOS: selection, comparability and ascertainment asterisks (*) with a maximum score of 4, 2, and 3, respectively.

Table E4. Gerardi 1996[18]

Methods	Cohort study
Participants	Records from 158 patients who completed outpatient pulmonary rehabilitation from Nov1989 to Mar1993 [COPD (87%), asthma (8%), restrictive disease (2.5%), and bronchiectasis (2.5%)]; (mean ±SD age 67±10y)
Pulmonary rehabilitation (duration, frequency, in or out-patient, and what it did include)	Outpatient 3 h/ twice weekly/ 6 weeks. Educational, with topics including symptom management, medications, compliance, breathing retraining, pacing, nutrition, and stress reduction. The remainder of the time was spent on exercise conditioning. Exercise included upper extremity training with weights and elastic bands, inspiratory resistive exercise, and lower extremity training with a treadmill and stationary bicycle.
Outcome	Survival
Risk of bias	
NOS selection	***
NOS comparability	*
NOS ascertainment	***

NOS: selection, comparability and ascertainment asterisks (*) with a maximum score of 4, 2, and 3, respectively.

Table E5. Bowen 2000[16]

Methods	Cohort study
Participants	149 patients with symptomatic lung disease (89% COPD; mean ±SD age 69±9y; forced expiratory volume in 1 second, 39%± 19% predicted; 55% women [n=82]).
Pulmonary rehabilitation (duration, frequency, in or out-patient, and what it did include)	Connecticut Pulmonary Rehabilitation Consortium program. 10 programs gave outpatient PR; 1 of them had both out and inpatient PR. PR includes education, breathing exercise, and exercise training. Duration and visit varies, [visits per week X program weeks, 1(2X5) 2(1X10-12) 3(2X6-8) 4(1-3X8-12) 5(3X6) 6(2X8) 7(2X6) 8 inpat(7-9X4) outpat(2X4) 9(3X12) 10(2X8)]
Outcome	Survival
Risk of bias	
NOS selection	****
NOS comparability	
NOS ascertainment	**

NOS: selection, comparability, and ascertainment asterisks (*) with a maximum score of 4, 2, and 3, respectively.

Table E6. Connor 2001[17]

Methods	Cohort study
Participants	170 COPD patients (mean ±SD age 68.5±8.3y; forced expiratory volume in 1 second, 43.8%± 17.6% predicted; 59% men [n=100]).
Pulmonary rehabilitation (duration, frequency, in or out-patient, and what it did include)	8 weeks. The first week of this programme consisted of in-patient stay of 5 days and 4 nights, followed by twice weekly attendances of 2 hours each. Education was during an in-patient stay and utilises a multidisciplinary team. There were 2 types of exercise practised. A circuit of mobility and strength exercises was performed twice weekly according to an individual prescription time and the patient was also encouraged to perform this circuit at home. Endurance exercise, in the form of continuous walking, was performed by the patient at home for a minimum of 3 and maximum of 6 days per week and a diary was completed.
Outcome	Survival
Risk of bias	
NOS selection	***
NOS comparability	
NOS ascertainment	***

NOS: selection, comparability, and ascertainment asterisks (*) with a maximum score of 4, 2, and 3, respectively.

Table E7. Ries 1995[20]

Methods	Randomized Control trial		
Participants	119 stable COPD patients, rehabilitation group (n=57, mean ±SD age 61.5±8y; forced expiratory volume in 1 second, 1.21L± 0.55L predicted; 74% men [n=42]) education group (n=62, mean ±SD age 63.6±6.3y; forced expiratory volume in 1 second, 1.24L± 0.56L predicted; 73% men [n=45]).		
Pulmonary rehabilitation (duration, frequency, and what it did include)	8-week, 2-phase comprehensive rehabilitation program; 1st phase involved education, physical and respiratory care instruction, psychosocial support, supervised exercise training. 2nd phase involved monthly follow-up visits for 1 year; this visit included a supervised period of exercise, group sessions to discuss progress and problems, and the introduction of maintenance techniques.		
Outcome	Survival		
Risk of bias			
Based on Cochrane Risk of Bias Tool:	Yes*	No	Unclear
Was the allocation sequence adequately generated?	✓		
Was the sequence generation adequately concealed before group assignments?	✓		
Was knowledge of the allocated interventions adequately hidden from the participants and personnel after participants were assigned to respective groups?		✓	
Was knowledge of the allocated interventions adequately hidden from the outcome assessors after participants were assigned to respective groups?		✓	

Were incomplete outcome data adequately addressed?	✓		
Are study reports free from suggestion of selective outcome reporting?	✓		
Was the study apparently free of other problems that could put it at risk of bias?	✓		

*"Yes" indicates low risk of bias; "no" indicates high risk of bias; and "unclear" indicates an unclear risk of bias for that specific entry.

Table E8. Griffiths 2000[19]

Methods	Randomized Control Trial		
Participants	200 COPD patients, rehabilitation group (n=99, mean ±SD age 68.2±8.2y; forced expiratory volume in 1 second, 39.7%± 16.2% predicted; 62% men [n=61]) control group (n=101, mean ±SD age 68.3±8.1y; forced expiratory volume in 1 second, 39.4%± 16.4% predicted; 58% men [n=59]).		
Pulmonary rehabilitation (duration, frequency, in or out-patient, and what it did include)	Multidisciplinary outpatient PR, 3 half days per week for 6 weeks. Each session was about 2 hours long. The first third of the time was spent in educational activities; an exercise session followed with individually prescribed training programmes: 30 min of exercise for the legs and arms; treadmill; circuit training, individual dietary advice was also given.		
Outcome	Survival		
Risk of bias			
Based on Cochrane Risk of Bias Tool:	Yes*	No	Unclear
Was the allocation sequence adequately generated?	✓		
Was the sequence generation adequately concealed before group assignments?	✓		
Was knowledge of the allocated interventions adequately hidden from the participants and personnel after participants were assigned to respective groups?		✓	
Was knowledge of the allocated interventions adequately hidden from the outcome assessors after participants were assigned to respective groups?	✓		

Were incomplete outcome data adequately addressed?	✓		
Are reports of the study free from suggestion of selective outcome reporting?	✓		
Was the study apparently free of other problems that could put it at risk of bias?	✓		

*"Yes" indicates low risk of bias; "no" indicates high risk of bias; and "unclear" indicates an unclear risk of bias for that specific entry.