SYSTEMATIC REVIEW

Safety and Efficacy of Inpatient Pulmonary Rehabilitation for Patients Hospitalized with an Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Systematic Review and Meta-analyses

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Abstract

Rationale: Pulmonary rehabilitation (PR) during hospitalization for acute exacerbations of chronic obstructive pulmonary disease (AECOPD) occurs during a period of disease instability for the patient, and the safety and efficacy of PR, specifically during the hospitalization period, have not been established.

Objective: The purpose of this review is to determine the safety and efficacy of PR during the hospitalization phase for individuals with AECOPD.

Methods: Scientific databases were searched up to August 2022 for randomized controlled trials that compared in-hospital PR with usual care. PR programs commenced during the hospitalization and included a minimum of two sessions. Titles and abstracts followed by full-text screening and data extraction were conducted independently by two reviewers. The intervention effect estimates were calculated through meta-analysis using a random-effect model.

Results: A total of 27 studies were included ($n = 1{,}317$). The meta-analysis showed that inpatient PR improved the 6-minute-walk distance by 105 m ($P < 0.001$). Inpatient PR improved the performance on the five-repetition sit-to-stand test by −7.02 seconds ($P = 0.03$). Quality of life (QOL), as measured by the 5-level EuroQoL Group-5 dimension version (EQ-ED-5L) and the St. George's Respiratory Questionnaire, was significantly improved by the intervention. Inpatient PR increased lower limb muscle strength by 33.35 N ($P < 0.001$). There was no change in the length of stay. Only one serious adverse event related to the intervention was reported.

Conclusions: This review suggests that it is safe and effective to provide PR during hospitalization for individuals with AECOPD. In-hospital PR improves functional exercise capacity, QOL, and lower limb strength without prolonging the hospital length of stay.

Keywords: respiratory infections; chronic airways disease; rehabilitation medicine

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Acute exacerbations occur regularly for many people with chronic obstructive pulmonary disease (COPD) (1, 2). These acute exacerbations of COPD (AECOPD) can be severe, resulting in hospital admissions and high healthcare costs (3, 4). AECOPD can result in further decreases in quality of life (QOL), lung function, and functional status (1, 2, 5, 6) and can increase the risk of subsequent hospitalization and early mortality (7).

Hospitalized patients with AECOPD are largely sedentary while in the hospital (8), and their activity levels remain low 1 month after discharge (8). As reduced physical activity is a primary risk factor for readmission after discharge from AECOPD (9), an important treatment goal is improving exercise tolerance during or soon after AECOPD via pulmonary rehabilitation (PR) (10).

Several clinical trials have investigated the effect of PR during and after hospitalization for AECOPD. Many of these trials were subsequently analyzed in a systematic review and meta-analyses by the Cochrane Airway Group and published in 2016 (11). The purpose of the Cochrane review was to examine if early PR initiated in the hospital and/or shortly after discharge from AECOPD improved future hospital admissions, mortality, QOL, and exercise capacity outcomes. The Cochrane review investigators reported that early inpatient PR reduced the risk of hospital admissions, decreased mortality, and improved health-related QOL (HRQOL). There was also a marked improvement in exercise capacity (11).

Despite the results of the Cochrane review, there has been some controversy regarding the safety of rehabilitation during the very acute phase of an exacerbation (12), as well as a recommendation by the ERS (European Respiratory Society) to withhold PR during hospitalization (13). This recommendation was on the basis of the study by Greening and colleagues (14), that reported increased mortality rates at 12 months in the rehabilitation group. However, early mobility programs and physical therapy interventions are widely used in critical care and acute care settings without evidence of increased mortality (15, 16). It is important to note that the review on which the ERS recommendation was based (11) included studies in which the PR intervention began in the hospital and continued after discharge. Outcome measurement, including mortality events, occurred after the discharge period when supervision and monitoring of the intervention are typically less than what would occur during the inpatient period. It is not clear if PR delivered during hospital admission is safe and results in changes in health status and physical function before discharge from the hospital. Thus, the purpose of this systematic review is to evaluate the safety and efficacy of pulmonary rehabilitation in the in-hospital period for patients admitted to the hospital for AECOPD.

Methods

Literature Search Strategy

A systematic review of randomized controlled trials that provided PR for individuals hospitalized for AECOPD compared with usual care was conducted. A comprehensive literature search was performed on the following bibliographic databases: MEDLINE, EMBASE, PEDro, CINAHL, CENTRAL, CADTH, and PsychInfo. To capture additional literature, a hand search of meeting abstracts from the American Thoracic Society and the ERS scientific conferences was conducted. The electronic searches were supplemented by scanning the reference lists from all retrieved articles. Databases were searched up to August 15, 2022.

An academic librarian provided assistance with the development of the search strategies. Keyword search terms and medical subject headings were used in MEDLINE and CENTRAL databases. For CINAHL, we used CINAHL headings, and for Embase, we used Emtree terms. A key term search strategy was employed for the PEDro and CADTH databases. A detailed search strategy for MEDLINE is available in Appendix E1 (*see* data supplement) and was adapted for use in other databases. We elected to substantially expand the search strategy used in the Cochrane Review by adding additional terms related to COPD, hospital, and exercise interventions. Although this approach substantially increases the number of titles and abstracts and full texts to screen, because of the concerns about safety, it was important to confirm that any randomized controlled trials (RCTs) investigating the effects of exercise on hospitalized patients with AECOPD were included.

Study Eligibility and Selection

The PICO (Population, Intervention, Comparison, and Outcome) components and eligibility criteria for determining studies to include in the analysis are presented in Table 1. We included both full peer-reviewed articles and conference abstracts.

All retrieved studies were uploaded into Covidence, an online systematic review management system (www.covidence.org, 2019, Veritas Health Innovation Ltd.), and duplicates were removed. The titles and abstracts of articles identified by the search strategy were assessed by two independent reviewers according to the inclusion and exclusion criteria. The full text of the studies that met the inclusion criteria was then independently evaluated by two reviewers. Any discrepancies at any stage were resolved by discussion and/or consultation with a third reviewer. Initially, we attempted to use Google Translate to translate studies written in any language other than English, but because of formatting issues, this was not possible, so we excluded eight papers that were not written in English (17–24).

Data Extraction and Quality Assessment

Two reviewers performed data extraction of all the included studies using a piloted data extraction form. Information on the title, authors, year of publication, country, source of funding, name of the hospital and/or department, study groups characteristics, study design, intervention (including general description, frequency, intensity, time and duration, type number of intervention sessions, and adherence), description of control group, lung function and smoking history, outcomes (e.g., exercise capacity tests, muscle function, HRQOL and/or health status, length of stay, and adverse events) was collected. Any questions or discrepancies regarding these data were resolved through iteration and consensus.

We assessed bias using the Cochrane Risk of Bias tool for RCTs (25). Two reviewers independently assessed each study, with final decisions made via discussion to reach a consensus or by a third party. We also assessed the available protocols for the included studies using the trial registries ClinicalTrials.gov and the World Health Organization trials portal to account for selective reporting. The GRADE (Grading of

Table 1. Population, intervention, comparison, and outcome components

	Inclusion Criteria	Exclusion Criteria
Population	• Aged >19 yr. • Clinical diagnosis of COPD and hospitalized for AECOPD at the time of the study. • Capable of physical activity (patient is capable of initiating some form of active movement).	• Individuals with stable COPD who have been admitted to the hospital to participate in an inpatient pulmonary rehabilitation program. • The population is a mixed medical ward population or mixed respiratory disease population, and data for those with AECOPD is not presented separately, or patients with AECOPD represent ⩽75% of the cases.
Intervention	• Any rehabilitation program that involves mobilization, exercise, or ambulation that started while the patient was hospitalized for AECOPD. • The rehabilitation program must include a minimum of two sessions. • Studies that include a subsequent outpatient rehabilitation program after inpatient intervention are included only if there are pre- and postintervention measurements for the duration of the hospitalization.	• Programs initiated after discharge. • Respiratory/inspiratory muscle training programs as opposed to programs that incorporate whole-body movement. • Neuromuscular stimulation that does not include any active movement on the part of the patient.
Comparison	• Control • Usual care • Other interventions that may include some mobility intervention (e.g., physiotherapy routine care) but are different from the formal exercise training that the experimental group receives.	• None
Outcome	• Any outcomes were accepted.	• The outcome assessment only occurred after discharge.
Study Design	• Randomized controlled trials	• Participants are allocated to groups nonrandomly or on the basis of some other characteristic.

Definition of abbreviations: AECOPD = acute exacerbation of chronic obstructive pulmonary disease; COPD = chronic obstructive pulmonary disease.

Recommendations, Assessment, Development, and Evaluations) framework was used to present the certainty of the evidence for each of the main outcomes, and the bias ratings for each outcome in the studies reviewed can be found in the data supplement (Appendix E2).

Data Synthesis and Analysis

Data were synthesized by calculating mean differences and pooled odds ratios using random-effects models with Review Manager 5.4 software (RevMan, 2020) (26). The 95% confidence interval (CI) was calculated for each outcome. Heterogeneity was assessed by analyzing forest plots, the Q statistic, and the I^2 statistic. I^2 values more than 50% and *P* values greater than 0.1 for the Q statistic indicated significant heterogeneity (27). When possible, we determined whether estimates and 95% confidence limits between study groups exceeded the minimal clinically important difference (MCID) for each outcome. Sensitivity analysis was undertaken to estimate the consistency of the results by removing each study separately (Appendix E3).

Review Procedures

The protocol for this systematic review was registered (CRD42021198877) with PROSPERO (the International Prospective Register of Systematic Reviews) (28). The review was exempted from formal ethics approval because it was a review of existing published literature. Reporting of the findings of this review followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (29).

Results

Description of Studies

Results of the search. A total of 61,774 citations were identified through searches of electronic databases, and 19,938 duplicates were excluded. After screening for titles and abstracts, 393 papers were retrieved for detailed evaluation, and 27 records were included in this review (14, 30–55). The study flow diagram is shown in Figure 1.

Twenty-six studies (14, 30–37, 39–48, 50–55) were RCTs published in peer-reviewed journals, and two studies were published as conference abstracts (38, 49). Studies were conducted in 11 different countries, but the greatest single proportion (33%) was conducted in Spain (41–44, 46, 49, 51–53). The year of publication ranged from 1998 to 2022, and 48% were published within the last 5 years (32, 37, 38, 40–44, 46, 47, 52, 53, 55). The general characteristics of the included studies can be found in Appendix E4.

Characteristics of participants. The 27 studies involved a total of 1,317 participants who were hospitalized because of AECOPD. Twenty-six of the studies recruited patients with a primary diagnosis of AECOPD. One study included people with a variety of chronic respiratory conditions (COPD, chronic asthma, bronchiectasis, or interstitial lung disease), but they provided separate data for those with AECOPD; therefore, we were able to include this study in our analysis (14).

Study design. Most studies (74%) randomly assigned participants to two groups (i.e., intervention and usual care) (14, 30, 31, 33–40, 45–49, 51, 52, 54, 55). Six studies used two intervention groups compared with usual care (41–44, 50, 53). One study had three intervention groups compared with usual care, but only two of

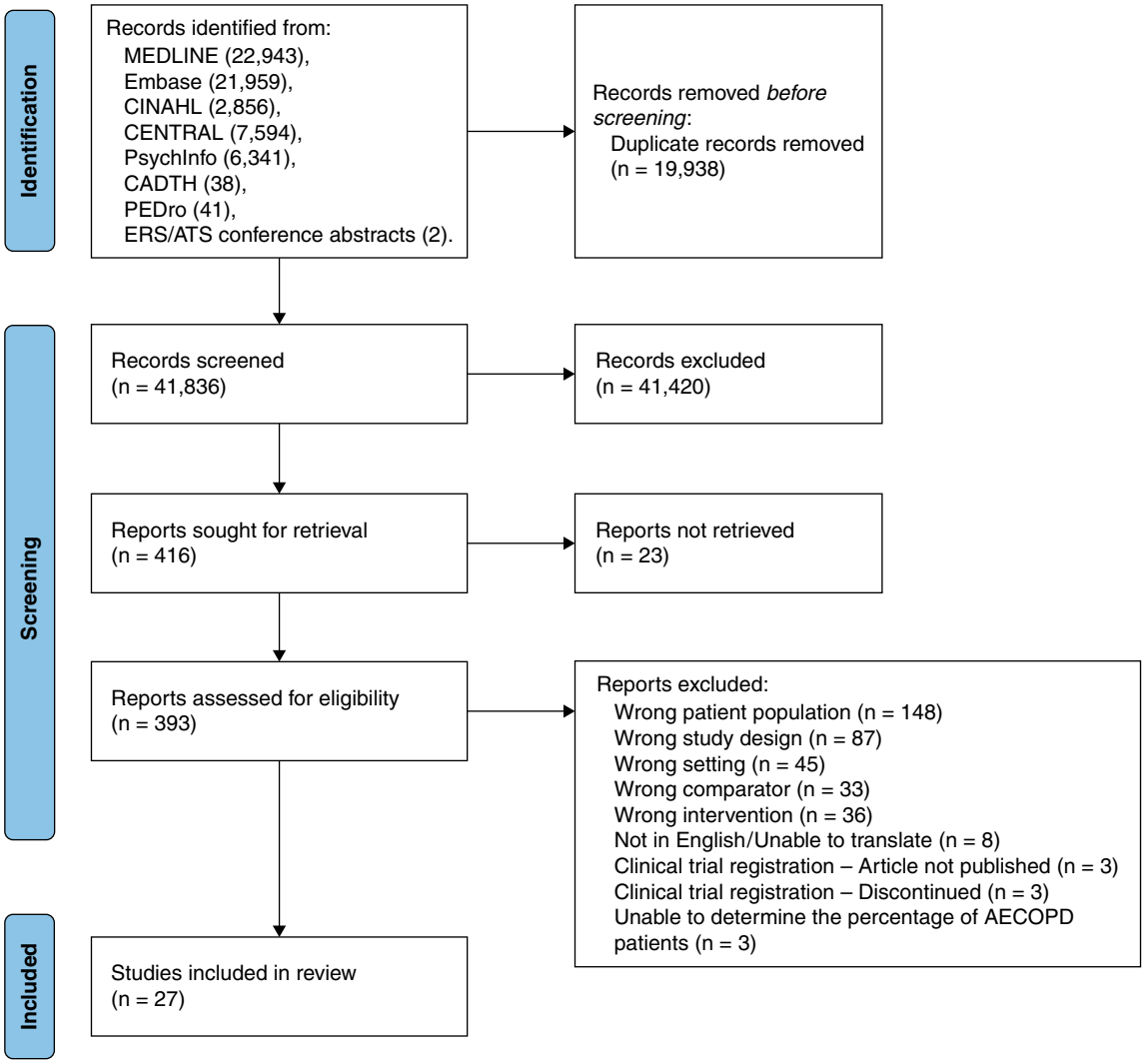


Figure 1. PRISMA flowchart of identification and selection of studies process. AECOPD = acute exacerbation of chronic obstructive pulmonary disease; ATS/ERS = American Thoracic Society/European Respiratory Society; CADTH = canadian agency for drugs & technologies in health; CENTRAL = cochrane central register of controlled trials; CINAHL = cumulative index to nursing and allied health literature; Embase = Excerpta Medica dataBASE; MEDLINE = medical literature analysis and retrieval system online; PEDro = physiotherapy evidence database; PRISMA = preferred reporting items for systematic reviews and meta-analyses.

the intervention groups met our eligibility criteria and were included in this review (32). The majority of studies (59%) started the exercise intervention within the first and the third day of hospitalization (14, 31, 32, 34, 35, 37, 38, 41–43, 45, 47, 49, 50, 52, 53). As per our inclusion criteria, all studies assessed outcomes at discharge. Thirteen studies then performed a follow-up assessment after hospital discharge (14, 30–33, 37, 38, 42, 45, 46, 49, 54, 55), and six studies continued to provide a PR intervention (14, 30, 32, 33, 40, 45). Eight trials delivered aerobic training interventions (30, 32, 36, 37, 39, 49, 55), 5 studies evaluated resistance training interventions (31, 38, 42, 53, 54), 10 studies evaluated mixed interventions (combining aerobic and resistance strength training) (14, 33, 35, 41, 43, 44, 46–48, 50), and 4 studies were not specific about the exercise type (34, 40, 45, 51).

Risk of bias. As anticipated, because of the nature of the intervention, it was not possible to blind the participants and PR personnel, which is demonstrated by a high risk of performance bias across all studies. Two papers were evaluated as having a high risk of selection and detection bias (35, 54), and two papers as having a high risk for reporting bias (41, 52). Several of the included studies provided insufficient information to inform judgments. Figures 2 and 3 present a detailed assessment of the risk of bias across studies.

Effects of Interventions

Functional exercise capacity. Twelve studies used the 6-minute-walk test distance (6MWD) to assess exercise capacity (30–37, 39, 45, 48, 54). Although these studies met the inclusion criteria for this review, five studies could not be included in a meta-analysis for the 6MWD outcome. Specifically, two studies only provided baseline and postdischarge follow-up results with no predischarge assessment (33, 37), one study only reported data after intervention with no baseline assessment

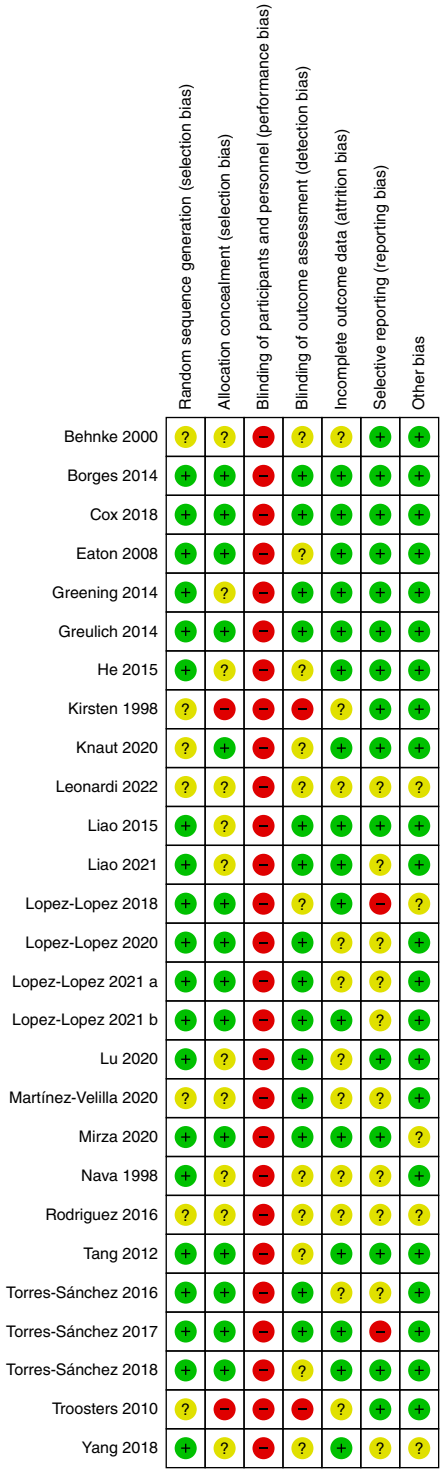


Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. + = high; − = low; ? = unclear.

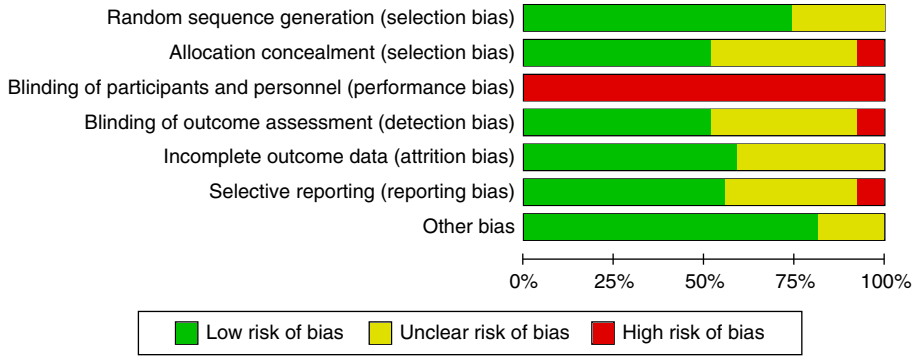


Figure 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

(32), one study only presented *P* values and graphical representations without the 6MWD values (48), and one study used median and range because of nonparametric results (39). Therefore, seven studies involving 330 participants were included in the 6MWD meta-analysis. High-quality evidence shows that inpatient PR significantly improved the 6MWD by 105.41 m (95% CI, 42.80–168.03; $P < 0.001$) (Figure 4), which exceeded the MCID of 30 m (56). The analysis showed significant heterogeneity between the studies ($I^2 = 99\%$), but all favored a positive effect of the intervention. This heterogeneity is likely partially explained by studies showing very large effect sizes, whereas others showed smaller but still significant effect sizes.

Three studies involving 135 participants used the five-repetition sit-to-stand test (5STST), which is a functional measure commonly used in acute care settings (34, 41, 42). One study used this test, but the data provided was unsuitable for the analysis (44). Moderate quality evidence shows that inpatient PR improved the performance on 5STST on average by −7.02 seconds (95% CI, −13.41 to −0.63; $P = 0.03$) (Figure 5). This effect size is greater than the MCID of 1.7 seconds (57).

Two studies involving 90 participants used the 30-second sit-to-stand test (30-sec STST) (47, 52), a field exercise test that has been accepted as an indicator of functional status for elderly people. There was no significant treatment effect on the 30-sec STST (Mean difference = 2.82; 95% CI, −2.67 to −8.31; $P = 0.31$) (Figure 6).

Other outcome measures were used to assess functional capacity, such as the shuttle walk test (14), the 2-minute walk test (47), the 3-minute walk test (50), the Short Physical Performance Battery (46), and the 2-minute step-in-place test (51). However, because of the small number of trials providing data for these outcomes, these findings were not included in the meta-analysis.

HRQOL. Four studies used the 5-level EuroQoL Group-5 dimension version (EQ-ED-5L) to evaluate HRQOL and included 247 participants (42, 43, 51, 53). Moderate quality evidence showed a significant treatment effect on mobility (MD = −0.25; 95% CI, −0.40 to −0.10; $P = 0.001$), self-care (MD = −0.27; 95% CI, −0.45 to −0.08; $P = 0.004$), and usual activities subscores (MD = −0.41; 95% CI, −0.61 to −0.22; $P < 0.001$). Effects were not statistically significant for pain/discomfort (MD = −0.18; 95% CI, −0.79 to 0.43; $P = 0.57$) or anxiety/depression (MD = −0.27; 95% CI, −0.45 to −0.09; $P = 0.004$) (Figure 7A). The overall effect size still significantly favored inpatient PR (MD = −0.41; 95% CI, −0.61 to −0.22; $P < 0.001$), but there was significant heterogeneity ($I^2 = 81\%$). In addition, a significant treatment effect of 12.86 points was observed on the visual analog scale (VAS) (95% CI, 7.93–17.78; $P < 0.001$), which was above the MCID of eight points (58) (Figure 7B).

Five studies used the SGRQ (Saint George's Respiratory Questionnaire) to measure HRQOL (14, 31, 34, 37, 52). However, one study only reported the baseline data (52), and two studies reported baseline and follow-up data (no predischarge assessment) (14, 37). Therefore, two studies involving 69 participants were included in this meta-analysis. Moderate quality evidence shows that participants allocated to inpatient PR groups had, on average, significantly greater changes in SGRQ total score when compared with participants allocated to control groups (MD = −10.51; 95% CI, −18.25 to −2.77; $P = 0.008$). The common effect exceeded the MCID of four points (59); however, the lower limit of its CI did not (Figure 8).

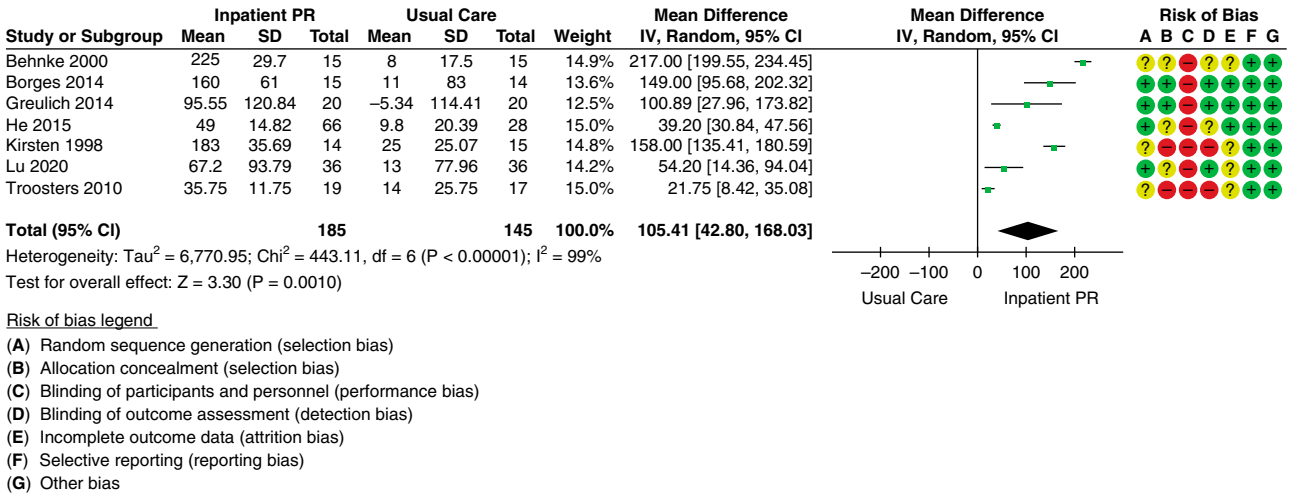


Figure 4. Change from baseline in the 6-minute-walk test distance (inpatient PR vs. usual care). CI = confidence interval; IV = inverse variance; PR = pulmonary rehabilitation; SD = standard deviation.

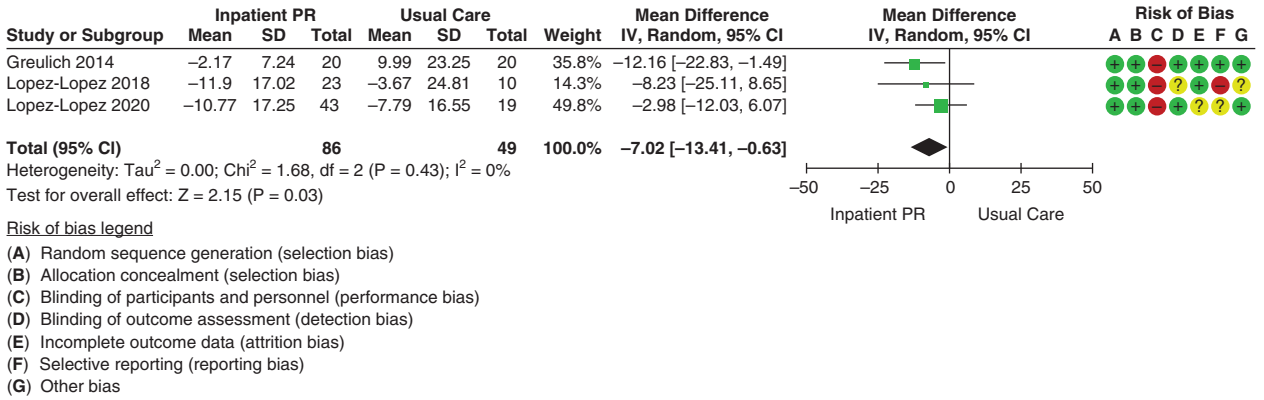


Figure 5. Change from baseline in the five-repetition sit-to-stand test (inpatient PR vs. usual care). CI = confidence interval; IV = inverse variance; PR = pulmonary rehabilitation; SD = standard deviation.

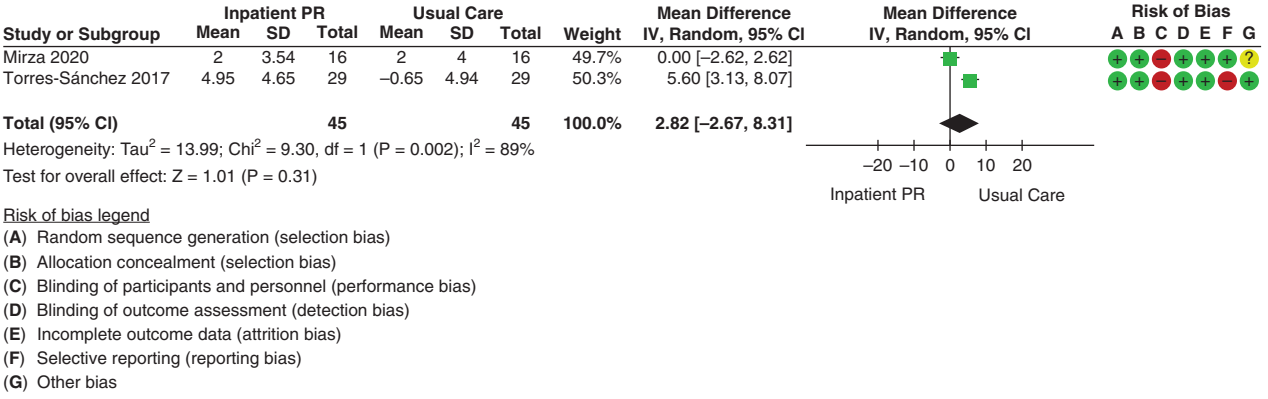
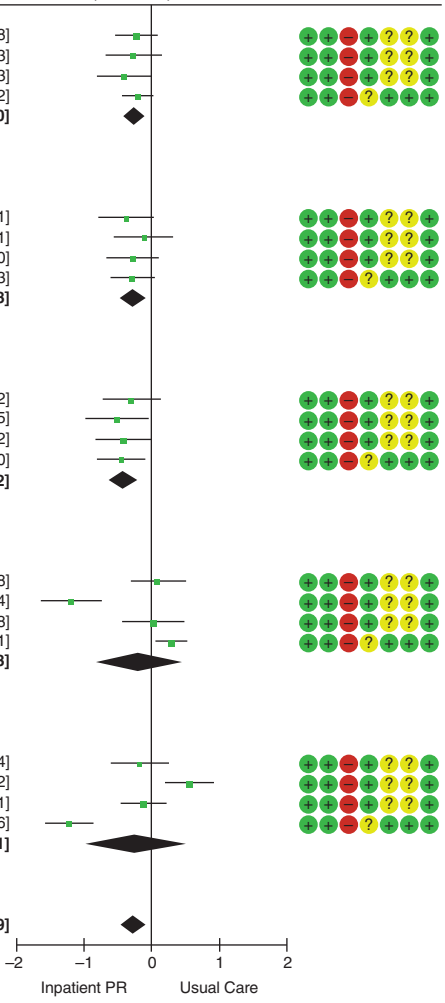


Figure 6. Change from baseline in the 30-second sit-to-stand test (inpatient PR vs. usual care). CI = confidence interval; IV = inverse variance; PR = pulmonary rehabilitation; SD = standard deviation.

A

Study or Subgroup	Inpatient PR Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.5.1 EQ-5D: Mobility								
Lopez-Lopez 2020	−0.56	0.6	44	−0.34	0.58	22	5.4%	−0.22 [−0.52, 0.08]
Lopez-Lopez 2021 a	−0.6	0.52	27	−0.33	0.69	15	4.8%	−0.27 [−0.67, 0.13]
Torres-Sánchez 2016	−0.71	0.72	24	−0.3	0.65	25	4.9%	−0.41 [−0.79, −0.03]
Torres-Sánchez 2018	−0.53	0.46	60	−0.33	0.53	30	5.8%	−0.20 [−0.42, 0.02]
Subtotal (95% CI)			**155**			**92**	**20.9%**	**−0.25 [−0.40, −0.10]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.91$, df = 3 (P = 0.82); $I^2 = 0\%$								
Test for overall effect: Z = 3.22 (P = 0.001)								
1.5.2 EQ-5D: Self-Care								
Lopez-Lopez 2020	−0.65	0.73	44	−0.27	0.78	22	4.9%	−0.38 [−0.77, 0.01]
Lopez-Lopez 2021 a	−0.52	0.59	27	−0.41	0.71	15	4.7%	−0.11 [−0.53, 0.31]
Torres-Sánchez 2016	−0.57	0.81	24	−0.3	0.47	25	5.0%	−0.27 [−0.64, 0.10]
Torres-Sánchez 2018	−0.7	0.62	60	−0.42	0.74	30	5.3%	−0.28 [−0.59, 0.03]
Subtotal (95% CI)			**155**			**92**	**19.9%**	**−0.27 [−0.45, −0.08]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.86$, df = 3 (P = 0.84); $I^2 = 0\%$								
Test for overall effect: Z = 2.87 (P = 0.004)								
1.5.3 EQ-5D: Usual Activities								
Lopez-Lopez 2020	−0.69	0.83	44	−0.39	0.81	22	4.7%	−0.30 [−0.72, 0.12]
Lopez-Lopez 2021 a	−0.89	0.71	27	−0.38	0.74	15	4.5%	−0.51 [−0.97, −0.05]
Torres-Sánchez 2016	−0.71	0.75	24	−0.3	0.65	25	4.9%	−0.41 [−0.80, −0.02]
Torres-Sánchez 2018	−0.8	0.82	60	−0.36	0.76	30	5.1%	−0.44 [−0.78, −0.10]
Subtotal (95% CI)			**155**			**92**	**19.2%**	**−0.41 [−0.61, −0.22]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.48$, df = 3 (P = 0.92); $I^2 = 0\%$								
Test for overall effect: Z = 4.09 (P < 0.0001)								
1.5.4 EQ-5D: Pain/Discomfort								
Lopez-Lopez 2020	−0.35	0.73	44	−0.44	0.79	22	4.9%	0.09 [−0.30, 0.48]
Lopez-Lopez 2021 a	−1.15	0.61	27	0.03	0.74	15	4.6%	−1.18 [−1.62, −0.74]
Torres-Sánchez 2016	−0.47	0.9	24	−0.5	0.68	25	4.6%	0.03 [−0.42, 0.48]
Torres-Sánchez 2018	−0.15	0.52	60	−0.44	0.48	30	5.8%	0.29 [0.07, 0.51]
Subtotal (95% CI)			**155**			**92**	**19.8%**	**−0.18 [−0.79, 0.43]**
Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 34.74$, df = 3 (P < 0.00001); $I^2 = 91\%$								
Test for overall effect: Z = 0.57 (P = 0.57)								
1.5.5 EQ-5D: Anxiety/Depression								
Lopez-Lopez 2020	−0.6	0.8	44	−0.43	0.8	22	4.8%	−0.17 [−0.58, 0.24]
Lopez-Lopez 2021 a	0.09	0.64	27	−0.48	0.49	15	5.1%	0.57 [0.22, 0.92]
Torres-Sánchez 2016	−0.62	0.65	24	−0.5	0.51	25	5.2%	−0.12 [−0.45, 0.21]
Torres-Sánchez 2018	−1.17	0.81	60	0.04	0.78	30	5.1%	−1.21 [−1.56, −0.86]
Subtotal (95% CI)			**155**			**92**	**20.2%**	**−0.23 [−0.97, 0.51]**
Heterogeneity: $Tau^2 = 0.53$; $Chi^2 = 51.81$, df = 3 (P < 0.00001); $I^2 = 94\%$								
Test for overall effect: Z = 0.62 (P = 0.54)								
Total (95% CI)			**155**			**92**	**100.0%**	**−0.27 [−0.45, −0.09]**
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 101.34$, df = 19 (P < 0.00001); $I^2 = 81\%$								
Test for overall effect: Z = 2.89 (P = 0.004)								
Test for subgroup differences: $Chi^2 = 2.02$, df = 4 (P = 0.73), $I^2 = 0\%$								

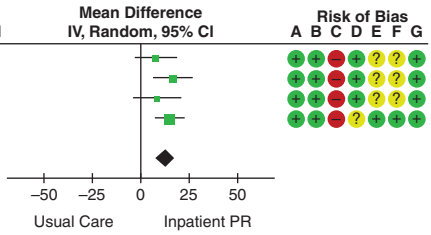


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

B

Study or Subgroup	Inpatient PR Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Lopez-Lopez 2020	17.45	19.98	44	9.63	22.01	22	20.3%	7.82 [−3.11, 18.75]
Lopez-Lopez 2021 a	29.03	12.37	27	12.47	18.05	15	23.1%	16.56 [6.30, 26.82]
Torres-Sánchez 2016	17.45	23.51	24	9	20.87	25	15.6%	8.45 [−4.02, 20.92]
Torres-Sánchez 2018	28.72	13.09	60	13.77	19.39	30	41.0%	14.95 [7.26, 22.64]
Total (95% CI)			**155**			**92**	**100.0%**	**12.86 [7.93, 17.78]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.08$, df = 3 (P = 0.56); $I^2 = 0\%$								
Test for overall effect: Z = 5.12 (P < 0.00001)								



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 7. (*A*) Change from baseline in the 5-level EuroQoL Group-5 dimension version (EQ-ED-5L) subscores (inpatient pulmnonary rehabilitation [PR] vs. usual care). (*B*) Change from baseline in the EQ-5D-5L visual analog scale (inpatient PR vs. usual care). CI = confidence interval; IV = inverse variance; EQ-5D = EuroQoL group 5 dimension version; SD = standard deviation.

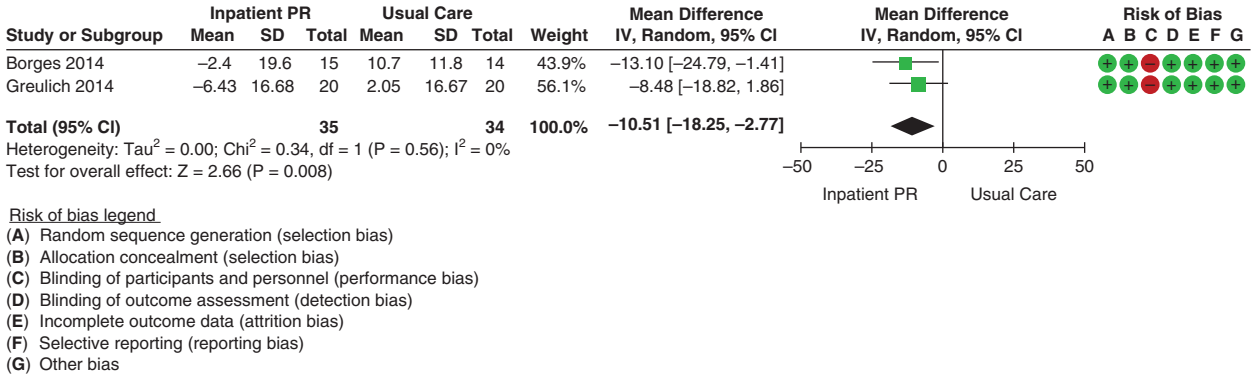


Figure 8. Change from baseline in the Saint George's Respiratory Questionnaire (inpatient PR vs. usual care). CI = confidence interval; IV = inverse variance; PR = pulmonary rehabilitation; SD = standard deviation.

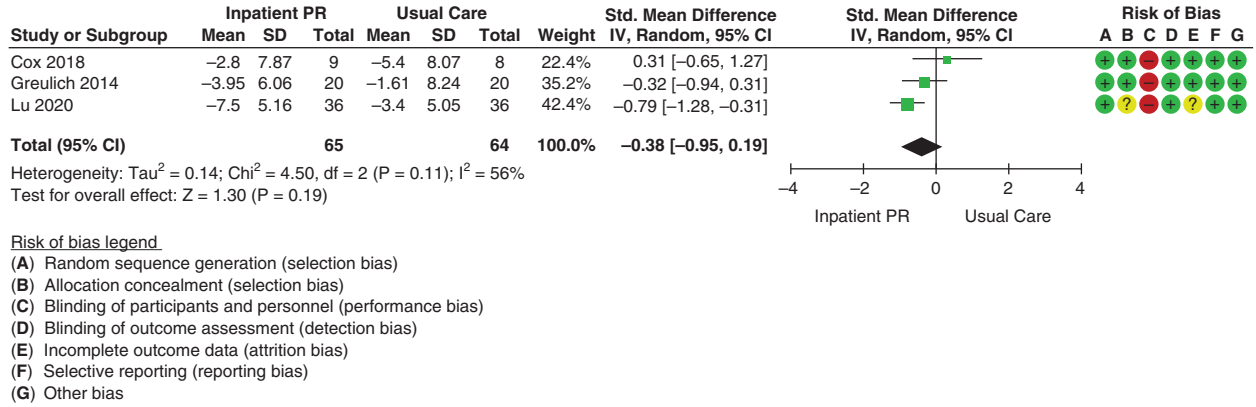


Figure 9. Change from baseline in the chronic obstructive pulmonary disease assessment test (inpatient PR vs. usual care). CI = confidence interval; IV = inverse variance; PR = pulmonary rehabilitation; SD = standard deviation.

Three studies involving 129 participants used CAT (COPD Assessment Test) to measure HRQOL (32, 34, 45). There was no significant treatment effect in the CAT score (MD = −0.38; 95% CI, −0.95 to 0.19) (Figure 9). High heterogeneity was identified ($P > 0.01$; $I^2 = 56\%$).

Other outcome measures were used to assess HRQOL, such as the 36-Item Short Form Survey (33) and the Chronic Respiratory Questionnaire (30, 33, 35). However, the data provided was not suitable for inclusion in the meta-analysis.

Lower limb strength. Five studies assessed quadriceps strength (43, 46, 47, 51, 52).

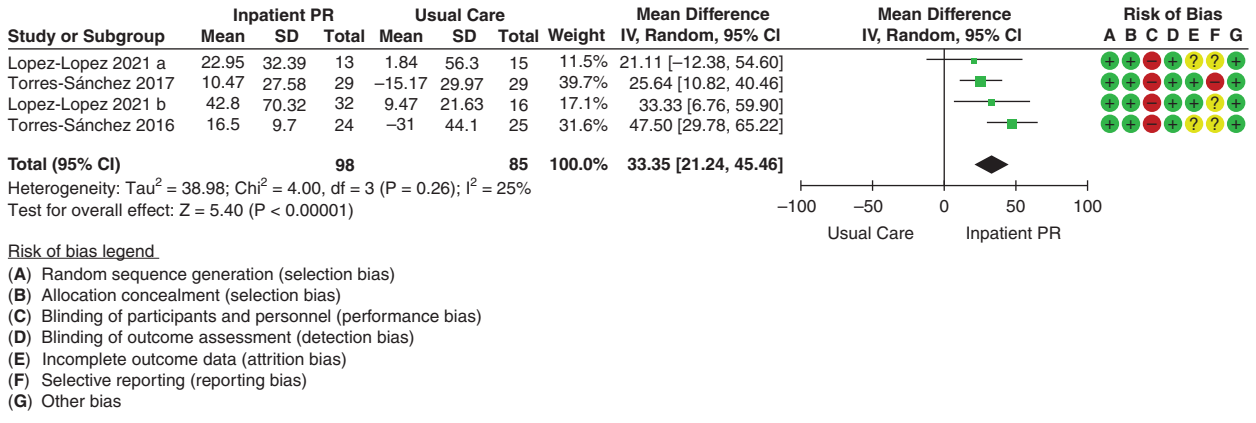


Figure 10. Change from baseline in lower limb strength (inpatient PR vs. usual care). CI = confidence interval; IV = inverse variance; PR = pulmonary rehabilitation; SD = standard deviation.

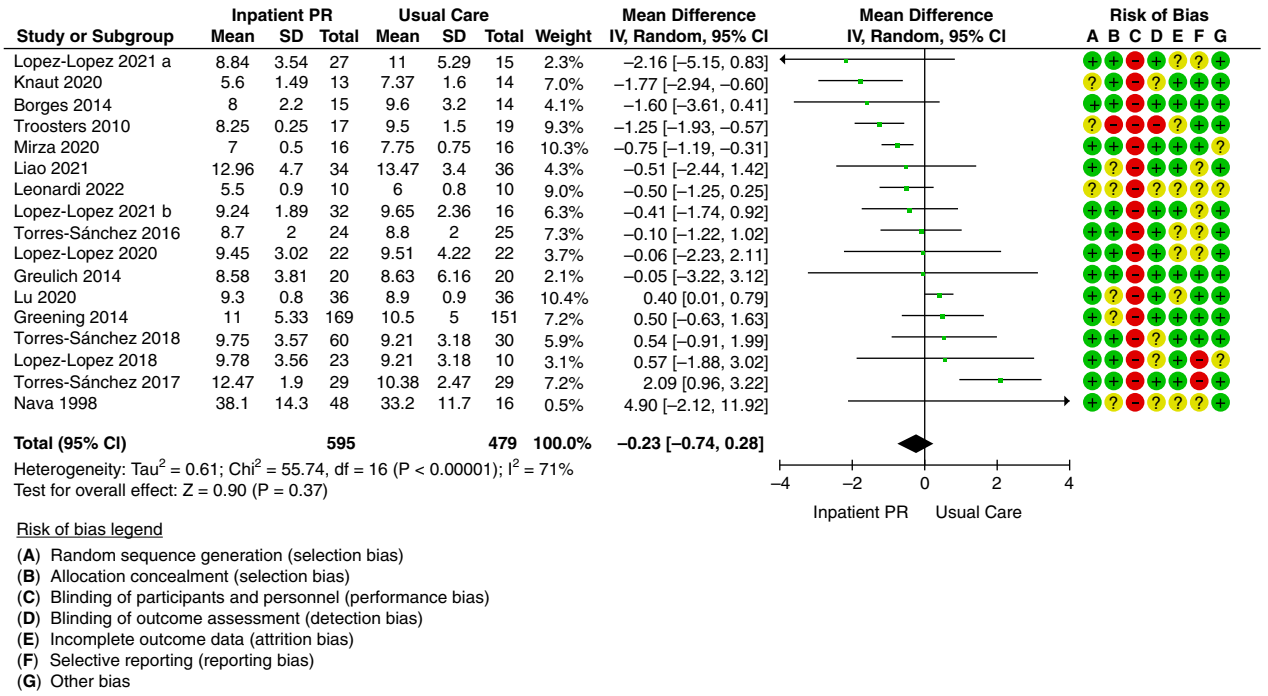


Figure 11. Change from baseline in the length of stay (inpatient PR vs. usual care). CI = confidence interval; IV = inverse variance; PR = pulmonary rehabilitation; SD = standard deviation.

One study used the one repetition maximum leg press test (kg) (46), whereas another study measured the peak quadriceps muscle force generated during an isometric maximum voluntary contraction using a chair-mounted force transducer (kg) (47). Both these studies showed significant improvements favoring inpatient PR compared with the control groups (MD = 2.8 kg, 95% CI, 0.3–5.3; MD = 19 kg, 95% CI, 26.2–11.9, respectively), but they were not included in the meta-analysis because of the evaluation method and unit of measurement applied. Four studies ($n = 183$) that used a portable hand-held dynamometer to measure quadriceps strength during 5 seconds of maximal muscle contractions with resistance applied to the anterior tibia (patient in a seated position) were included (43, 44, 51, 52). Moderate quality evidence shows that inpatient PR increased quadriceps muscle strength by, on average, 33.35 N (95% CI, 21.24–45.56; $P < 0.001$) (Figure 10).

Length of stay (LOS) in the hospital. Seventeen studies including 1,074 participants provided data on the LOS that were suitable for the meta-analysis (14, 31, 34, 37, 38, 40–45, 47, 48, 51–54). Thirteen studies reported LOS in mean and standard deviation (SD) (31, 34, 38, 40–45, 48, 51–53), and four studies used median and range or interquartile range (14, 37, 47, 54), allowing for an estimation of the mean and SD (60). Moderate quality evidence showed no statistically significant difference in the LOS in the days between inpatient PR and usual care (MD = 0.17; 95% CI −0.83 to 0.79) (Figure 11). High heterogeneity was identified ($I^2 = 76\%$). Four studies did not report on the LOS (30, 32, 36, 55), two studies reported the mean LOS (d) without SD (39, 49), and the other four studies provided data that was insufficient or presented in a way that was not suitable for inclusion in the meta-analysis (33, 35, 46, 50). Among all the papers that reported on LOS but were not included in the meta-analysis, there was no significant between-group difference in the LOS.

Adverse events. Fifteen of the included studies ($n = 797$) assessed adverse events (14, 31–35, 40, 43–47, 50, 52, 54), and only one reported a serious adverse event related to the intervention (50). Of the 32 patients included in the trial by Tang and colleagues (50), one experienced a serious, study-related, adverse event of arrhythmia that completely resolved within an hour after cessation of the intervention without any additional medical treatment, nor an increase in LOS. The study by Greening and colleagues (14) assessed mortality, and although they reported increased mortality in the early rehabilitation group at 12 months, there was no difference in mortality rates between the early rehabilitation and control groups during the hospitalization period.

Sensitivity Analysis

Each article was removed individually, and then sensitivity analysis was conducted to ascertain the stability of the results. Most of the outcomes did not change; however, by removing the trial by Lopez-Lopez and colleagues (43) from the EQ-5D-5L subgroup meta-analysis for pain/discomfort, the results favor usual care, and heterogeneity no longer exists. When deleting the Cox and colleagues (32) trial from the CAT meta-analysis, the results significantly favor the intervention, and there is no heterogeneity among the included studies. Finally, by removing either trial by Greulich and colleagues (34) or Lopez-Lopez and colleagues (41) from the 5STST meta-analysis, the positive treatment effect was not sustained (Appendix E3).

Discussion

Our review focuses on in-hospital PR, a clinical setting in which patients are typically closely supervised. The main findings of this review demonstrate that in-hospital PR for

patients with AECOPD is safe and efficacious. We report a positive effect of PR in the in-hospital period for patients with AECOPD on functional exercise capacity, HRQOL, and lower limb strength. Results show benefits that exceed the MCID for the 6MWD, the 5STST, the 5Q-5D-5L VAS, and the SGRQ total score. Significant effects were not found for the 30-sec STST, CAT, and LOS.

On the basis of the findings from this systematic review, in-hospital PR for patients admitted for AECOPD is safe and efficacious, and we believe this intervention should be recommended as part of the in-hospital acute care treatment plan. We also recommend that future systematic reviews, guidelines, and recommendations that examine the safety and efficacy of PR for AECOPD should separately analyze trials that provide inpatient acute-care PR from those that provide PR for AECOPD outside of an acute care hospital setting, such as in an outpatient hospital department, community setting, via telehealth, or home-based. The reasons for this recommendation are: *1*) the in-hospital AECOPD patient is in a setting with high degrees of monitoring by staff and devices in which adverse events can be quickly detected or even anticipated and mitigated; *2*) the intervention in the in-hospital setting can be very structured (for example, offering one or two rehab sessions per day with individualized exercise prescriptions); and *3*) there is a high likelihood the in-hospital PR exercise will be directly supervised by a physical therapist, rehabilitation aide, or nurse. These characteristics may not be easily achieved in the variety of outpatient rehabilitation settings. The heterogeneity of the monitoring, intervention, and supervision may make it difficult to provide recommendations on the safety and efficacy of PR for AECOPD if PR from in-hospital and outpatient settings are analyzed together. Similarly, we also recommend that investigators that conduct clinical trials of PR for AECOPD that is initiated in the hospital and continues after discharge ensure they measure outcomes at hospital discharge to allow for analysis of the in-hospital phase and postdischarge phase separately.

The results of functional exercise capacity and HRQOL outcomes are in agreement with previous high-quality meta-analytical evidence supporting the beneficial effect of PR programs for patients with COPD after an exacerbation (11). However, the improvements in the 6MWD are greater than previously reported, suggesting that initiating PR during hospitalization may optimize the gains in exercise capacity for patients with AECOPD. A potential explanation for the remarkable improvement in the 6MWD may be attributed to two studies (30, 36) in which the participants in the training group completed a 10-day walking training program in the hospital. The intervention lasted longer than most other included studies, and improvements may be related to this lengthy intervention. High heterogeneity was identified in the 6MWD, which has not impacted the quality of evidence, as all studies showed a positive effect favoring the intervention. We hypothesize that this heterogeneity could be partially explained by the significant differences in the effect sizes. There were differences in the number of supervised exercise sessions provided, the adherence to the proposed intervention, and the components of exercise prescription (frequency, intensity, time, and type), which all may have influenced the effect size of each study.

The 30-sec STST is a field exercise test that was initially created to evaluate the functional performance of older adults (61), and it is a feasible and sensitive tool to assess PR efficacy in patients with COPD (62). Two trials used this test to assess the effects of in-patient PR on the functional performance of patients with AECOPD (47, 52), but no differences were found in our meta-analysis. This result needs to be interpreted with caution because of the small sample size across the studies, but a potential explanation is that the trial by Mirza and colleagues (47) did not find a between-group difference in this outcome because participants did not present a significant impairment in their baseline measure. The reference value for older adults (>60 yr old) is 12 chair stands for women and 13 for men (61). In this study, in which the participant mean age was 64 years, and 97% were men, the 30-sec STST baseline values in the control group were 11, and in the exercise group were 12 STS repetitions (47). Furthermore, to improve one's 30-sec STST, a participant needs to increase the speed of their movement. The exercise protocol in the study by Mirza and colleagues was not designed for participants to increase their speed of sit-to-stand movements but rather the number of repetitions overall (47). Therefore, the test may not have captured gains in functional performance in that study.

Although the EQ-5D-5L is not a disease-specific tool, it is a valid and responsive measure of HRQOL in COPD (63). Both the EQ-5D-5L VAS and the SGRQ total score showed positive and clinically important effects of in-patient PR programs compared with usual care, but no differences were seen in the CAT (64, 65). First, the limited sample size across the three included studies on the CAT meta-analysis impacted the quality of evidence. Moreover, sensitivity analysis showed that the trial by Cox and colleagues (32) is responsible for introducing heterogeneity in the results and that there would be a significant treatment effect if this study were removed from the analysis. There was an imbalance in the CAT scores at baseline in this study, with the control group presenting higher scores than the intervention groups (29.4 ± 7.7 and 25 ± 8.1, respectively), which may have impacted the between-group difference in changes from baseline. Taken together, our findings support that in-patient PR can significantly improve HRQOL for patients with AECOPD.

Skeletal muscle dysfunction is a predictor of mortality in COPD (66, 67), but few trials focused on muscle function as an outcome after PR for AECOPD. Hospitalized patients often present a decline in muscle strength, and the quadriceps cross-sectional area has been observed to decrease by up to 5% over 5 days of hospitalization (68). Among studies that presented data suitable for our meta-analysis (43, 51, 52), evidence supports a positive effect of in-patient PR on lower limb muscle strength. Other trials not included in the meta-analysis corroborate this finding, such as Troosters and colleagues (54), who demonstrated an increase of 10% in quadriceps force after daily quadriceps resistance training for 7 days on a knee-extension chair, in comparison with −1% in the control group. Borges and colleagues (31) also showed that whole-body resistance training for an average of 5.6 sessions significantly increased strength in the hip and knee flexors, whereas the control group lost more than 10% of these muscles' strength.

Acute exacerbations that require hospitalization are recognized as a major event in the natural history of COPD because of its association with survival and a substantial decline in lung function, functional status, and HRQOL (6, 69–71).

During hospitalization, patients are often physically inactive, and physical inactivity after AECOPD has been associated with an increased susceptibility for subsequent readmissions (9). A prolonged LOS may also result in increased frailty and patients that will require more medical attention after discharge (72). Our findings, similar to previous reviews, suggest that in-patient PR may not reduce the LOS in the hospital, but it also does not prolong hospitalization for patients with AECOPD (73).

Although previous reviews reported the benefits of PR for AECOPD (11), current guidelines and recommendations discourage initiating PR during hospitalization for AECOPD (13, 74). These guidelines are informed by data with intervention timelines that extend long past the acute in-hospital phase. The negative recommendations appear to be primarily on the basis of findings from an RCT (14) that compared an early rehabilitation strategy with usual care during and after admission to the hospital for an exacerbation of chronic respiratory diseases. That trial did report an increased mortality rate at 12 months in the early rehabilitation group, but importantly there was no increase in mortality during the hospitalization phase. The reason for the higher mortality after discharge in the intervention group is not understood, but there have been concerns (75–77) about the nature of rehabilitation provided in the outpatient phase, including the fact that the exercise portion after discharge was not supervised, not on the basis of an accurate exercise prescription, was not progressed according to accepted standards of PR, and had poor adherence from the participants. However, it should be reinforced that in that trial, there were no safety concerns or increased mortality during the hospitalization period. Indeed, of the 15 studies ($n = 797$) that reported adverse events, only one serious, yet temporary, adverse event related to the intervention was reported. Although we recognized this one adverse event could be coincidental, we assumed it was causally related to the training on the basis of the author's categorization and description of the case (50).

Study Limitations

As many of the meta-analyses included a limited number of studies, it was not always possible to assess publication bias using funnel plots. Although we only selected papers that included exercise training as part of their PR programs, there are differences in the type of intervention (e.g., aerobic and resistance training) and in the details of exercise protocols (e.g., frequency, intensity, and duration) that may have impacted the results. We did not evaluate the comprehensiveness of the interventions, and although exercise training is a fundamental component of PR programs, we acknowledge that there are other components that might be missing from some studies, and this potentially could impact our findings. A high risk of performance bias was common in all studies because of the nature of the intervention. We were not able to translate documents that were not written in English. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1418–1422.

2 Miravitlles M, Ferrer M, Pont A, Zalacain R, Alvarez-Sala JL, Masa F, *et al.*; IMPAC Study Group. Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study. *Thorax* 2004;59:387–395.

3 Mittmann N, Kuramoto L, Seung SJ, Haddon JM, Bradley-Kennedy C, Fitzgerald JM. The cost of moderate and severe COPD exacerbations to the Canadian healthcare system. *Respir Med* 2008;102:413–421.

4 Sullivan SD, Ramsey SD, Lee TA. The economic burden of COPD. *Chest* 2000;117:5S–9S.

5 Hoogendoorn M, Feenstra TL, Hoogenveen RT, Al M, Mölken MR. Association between lung function and exacerbation frequency in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2010;5: 435–444.

6 van der Schaaf M, Dettling DS, Beelen A, Lucas C, Dongelmans DA, Nollet F. Poor functional status immediately after discharge from an intensive care unit. *Disabil Rehabil* 2008;30:1812–1818.

7 McGhan R, Radcliff T, Fish R, Sutherland ER, Welsh C, Make B. Predictors of rehospitalization and death after a severe exacerbation of COPD. *Chest* 2007;132:1748–1755.

8 Pitta F, Troosters T, Probst VS, Spruit MA, Decramer M, Gosselink R. Physical activity and hospitalization for exacerbation of COPD. *Chest* 2006;129:536–544.

9 Garcia-Aymerich J, Farrero E, Félez MA, Izquierdo J, Marrades RM, Antó JM; Estudi del Factors de Risc d'Agudització de la MPOC investigators. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. *Thorax* 2003;58:100–105.

10 Burtin C, Decramer M, Gosselink R, Janssens W, Troosters T. Rehabilitation and acute exacerbations. *Eur Respir J* 2011;38: 702–712.

11 Puhan MA, Gimeno-Santos E, Cates CJ, Troosters T. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2016;12:CD005305.

12 Wilson KC, Krishnan JA, Sliwinski P, Criner GJ, Miravitlles M, Hurst JR, *et al.* Pulmonary rehabilitation for patients with COPD during and after an exacerbation-related hospitalisation: back to the future? *Eur Respir J* 2018;51:1702577.

13 Wedzicha JA, Miravitlles M, Hurst JR, Calverley PM, Albert RK, Anzueto A, *et al.* Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2017;49: 1600791.

14 Greening NJ, Williams JE, Hussain SF, Harvey-Dunstan TC, Bankart MJ, Chaplin EJ, *et al.* An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial. *BMJ* 2014;349:g4315.

15 Zhang L, Hu W, Cai Z, Liu J, Wu J, Deng Y, *et al.* Early mobilization of critically ill patients in the intensive care unit: a systematic review and meta-analysis. *PLoS One* 2019;14:e0223185.

16 de Morton NA, Keating JL, Jeffs K. Exercise for acutely hospitalised older medical patients. *Cochrane Database Syst Rev* 2007;CD005955.

17 Du S, Ding LM, Wang C, Yang F, Xing B, Liu Z, *et al.* Effect of Taijiquan on exercise tolerance and pulmonary function in chronic obstructive pulmonary patients. *Chinese J. Rehab. Med.* 2013;4:374–376.

18 Schultz K, Schwiersch M, Petro W, Mühlig S, Petermann F. [Individualized, modular structured patient behavioral training in obstructive airway diseases during inpatient rehabilitation]. *Pneumologie* 2000;54:296–305.

19 Zhang L, Wu JJ, Wang ZC. Effect of 24-form tai chi with respiratory rehabilitation training on pulmonary function and quality of life of patients with COPD. *Acta U Trad Med Sine Pharm Shanghai* 2012;26:53–56.

20 Kurihara N, Shirai S. Rehabilitation of patients with chronic obstructive lung diseases. *Kango Gijitsu* 1988;34:1807–1811.

21 Fedechkin V, Struchkov PV. A complex of respiratory exercises in the rehabilitation of patients with chronic obstructive lung diseases. *Med Sestra* 1990;49:27–29.

22 Jin X, Nui M, Han Y, Wu Z. Study progress on safety of exercise intervention in patients at acute exacerbation of chronic obstructive disease. *Chinese Nursing Research* 2020;32:2166–2169.
23 Schultz K, Koczulla AR. [Pulmonary rehabilitation in patients with chronic obstructive airway diseases]. *Pneumologie* 2021;75:457–473.
24 Chunxiang Z, Renjuan S, Ru Z, Jinghua T, Yexia D, Xiaofeng Z, *et al.* Effect of modified Morita therapy combined with motor imagery training on pulmonary rehabilitation of elderly patients with chronic obstructive pulmonary disease. *Chin J Integr Nurs* 2021;7:1.
25 Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
26 Review manager (RevMan). Version 5.4. London: The Cochrane Collaboration; 2020.
27 Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, *et al.* Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev* 2019;10:ED000142.
28 Dissemination CfRa. PROSPERO international prospective register of systematic reviews. York, United Kingdom: University of York; 2015 [accessed 2022 Jun 24]. Available from: https://www.crd.york.ac.uk/prospero/.
29 Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al.*; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
30 Behnke M, Taube C, Kirsten D, Lehnigk B, Jörres RA, Magnussen H. Home-based exercise is capable of preserving hospital-based improvements in severe chronic obstructive pulmonary disease. *Respir Med* 2000;94:1184–1191.
31 Borges RC, Carvalho CR. Impact of resistance training in chronic obstructive pulmonary disease patients during periods of acute exacerbation. *Arch Phys Med Rehabil* 2014;95:1638–1645.
32 Cox M, O'Connor C, Biggs K, Hind D, Bortolami O, Franklin M, *et al.* The feasibility of early pulmonary rehabilitation and activity after COPD exacerbations: external pilot randomised controlled trial, qualitative case study and exploratory economic evaluation. *Health Technol Assess* 2018;22:1–204.
33 Eaton T, Young P, Fergusson W, Moodie L, Zeng I, O'Kane F, *et al.* Does early pulmonary rehabilitation reduce acute health-care utilization in COPD patients admitted with an exacerbation? A randomized controlled study. *Respirology* 2009;14:230–238.
34 Greulich T, Nell C, Koepke J, Fechtel J, Franke M, Schmeck B, *et al.* Benefits of whole body vibration training in patients hospitalised for COPD exacerbations - a randomized clinical trial. *BMC Pulm Med* 2014;14:60.
35 He M, Yu S, Wang L, Lv H, Qiu Z. Efficiency and safety of pulmonary rehabilitation in acute exacerbation of chronic obstructive pulmonary disease. *Med Sci Monit* 2015;21:806–812.
36 Kirsten DK, Taube C, Lehnigk B, Jörres RA, Magnussen H. Exercise training improves recovery in patients with COPD after an acute exacerbation. *Respir Med* 1998;92:1191–1198.
37 Knaut C, Bonfanti Mesquita C, Dourado VZ, de Godoy I, Tanni SE. Evaluation of inflammatory markers in patients undergoing a short-term aerobic exercise program while hospitalized due to acute exacerbation of COPD. *Int J Inflamm* 2020;2020:6492720.
38 Leonardi N, Kabbach E, Schafauser N, Heubel A, Sentanin A, Castello-Simões V, *et al.* Hospital rehabilitation using elastic bands provides early improvements and maintenance of endothelial function in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD): a randomized controlled trial [abstract]. *Am J Respir Crit Care Med* 2022;A4959.
39 Liao LY, Chen KM, Chung WS, Chien JY. Efficacy of a respiratory rehabilitation exercise training package in hospitalized elderly patients with acute exacerbation of COPD: a randomized control trial. *Int J Chron Obstruct Pulmon Dis* 2015;10:1703–1709.
40 Liao S, Wang F, Lin Q, Jian F, Li Y, Zhong Q, *et al.* Effect of sitting and lying Liuzijue exercise for pulmonary rehabilitation in acute exacerbation of chronic obstructive pulmonary disease patients with non-invasive ventilation: a randomized controlled trial. *Ann Palliat Med* 2021;10:9914–9926.
41 Lopez Lopez L, Granados Santiago M, Donaire Galindo M, Torres Sanchez I, Ortiz Rubio A, Valenza MC. Efficacy of combined electrostimulation in patients with acute exacerbation of COPD: randomised clinical trial. *Med Clin (Barc)* 2018;151:323–328.
42 Lopez-Lopez L, Valenza MC, Rodriguez-Torres J, Torres-Sanchez I, Granados-Santiago M, Valenza-Demet G. Results on health-related quality of life and functionality of a patient-centered self-management program in hospitalized COPD: a randomized control trial. *Disabil Rehabil* 2020;42:3687–3695.
43 López-López L, Calvache-Mateo A, Rodríguez-Torres J, Granados-Santiago M, Ortiz-Rubio A, Valenza MC. A feasibility and efficacy randomized controlled trial of two exercise programs in severe AECOPD patients with resting hypoxemia. *Healthcare (Basel)* 2021;9:1102.
44 Lopez-Lopez L, Torres-Sanchez I, Rodriguez-Torres J, Cabrera-Martos I, Cahalin LP, Valenza MC. Randomized feasibility study of twice a day functional electrostimulation in patients with severe chronic obstructive pulmonary disease hospitalized for acute exacerbation. *Physiother Theory Pract* 2021;37:1360–1367.
45 Lu H, Liu N, Hu JY, Wang X, Li Y, Song M, *et al.* The effectiveness, safety and compliance of Zheng's supine rehabilitation exercise as a rehabilitation programme among elderly patients with AECOPD. *Clin Respir J* 2020;14:533–540.
46 Martínez-Velilla N, Valenzuela PL, Zambom-Ferraresi F, Sáez de Asteasu ML, Ramírez-Vélez R, García-Hermoso A, *et al.* Tailored exercise is safe and beneficial for acutely hospitalised older adults with COPD. *Eur Respir J* 2020;56:2001048.
47 Mirza FT, Jenkins S, Harrold M, Othman SK, Ismail R, Tengku Ismail TS, *et al.* Initiating exercise training early during the hospitalisation for an exacerbation of chronic obstructive pulmonary disease improves exercise capacity and quadriceps strength: a randomised controlled trial. *Respir Med X* 2020;2:100024.
48 Nava S. Rehabilitation of patients admitted to a respiratory intensive care unit. *Arch Phys Med Rehabil* 1998;79:849–854.
49 Rodriguez DA, Rodo-Pin A, Guerrero M, Coll R, Huerta A, Soler N, *et al.* Impact of step exercises as an early intervention during COPD exacerbation. *Eur Respir J* 2016;48:PA2061.
50 Tang CY, Blackstock FC, Clarence M, Taylor NF. Early rehabilitation exercise program for inpatients during an acute exacerbation of chronic obstructive pulmonary disease: a randomized controlled trial. *J Cardiopulm Rehabil Prev* 2012;32:163–169.
51 Torres-Sánchez I, Valenza MC, Sáez-Roca G, Cabrera-Martos I, López-Torres I, Rodríguez-Torres J. Results of a multimodal program during hospitalization in obese COPD exacerbated patients. *COPD* 2016;13:19–25.
52 Torres-Sánchez I, Valenza MC, Cabrera-Martos I, López-Torres I, Benítez-Feliponi Á, Conde-Valero A. Effects of an exercise intervention in frail older patients with chronic obstructive pulmonary disease hospitalized due to an exacerbation: a randomized controlled trial. *COPD* 2017;14:37–42.
53 Torres-Sánchez I, Valenza MC, Cebriá I Iranzo MDÀ, López-López L, Moreno-Ramírez MP, Ortíz-Rubio A. Effects of different physical therapy programs on perceived health status in acute exacerbation of chronic obstructive pulmonary disease patients: a randomized clinical trial. *Disabil Rehabil* 2018;40:2025–2031.
54 Troosters T, Probst VS, Crul T, Pitta F, Gayan-Ramirez G, Decramer M, *et al.* Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010;181:1072–1077.
55 Yang S, Liu J, Yang W, Yuan J, Meng S, Liang M, *et al.* [Effect of early mobilization on diaphragmatic function in patients with mechanical ventilation: a prospective randomized controlled study]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2018;30:112–116.
56 Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, *et al.* An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014;44:1428–1446.
57 Jones SE, Kon SS, Canavan JL, Patel MS, Clark AL, Nolan CM, *et al.* The five-repetition sit-to-stand test as a functional outcome measure in COPD. *Thorax* 2013;68:1015–1020.
58 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.
59 Schünemann HJ, Griffith L, Jaeschke R, Goldstein R, Stubbing D, Guyatt GH. Evaluation of the minimal important difference for the feeling thermometer and the St. George's Respiratory Questionnaire in patients with chronic airflow obstruction. *J Clin Epidemiol* 2003;56: 1170–1176.
60 Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; 14:135.
61 Jones CJ, Rikli RE, Beam WCA. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport* 1999;70:113–119.
62 Zanini A, Crisafulli E, D'Andria M, Gregorini C, Cherubino F, Zampogna E, *et al.* Minimum clinically important difference in 30-s sit-to-stand test after pulmonary rehabilitation in subjects with COPD. *Respir Care* 2019; 64:1261–1269.
63 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.
64 Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145: 1321–1327.
65 Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009;34:648–654.
66 Marquis K, Debigaré R, Lacasse Y, LeBlanc P, Jobin J, Carrier G, *et al.* Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002; 166:809–813.
67 Swallow EB, Reyes D, Hopkinson NS, Man WD, Porcher R, Cetti EJ, *et al.* Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax* 2007;62: 115–120.
68 Spruit MA, Gosselink R, Troosters T, Kasran A, Gayan-Ramirez G, Bogaerts P, *et al.* Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. *Thorax* 2003;58:752–756.
69 Schmier JK, Halpern MT, Higashi MK, Bakst A. The quality of life impact of acute exacerbations of chronic bronchitis (AECB): a literature review. *Qual Life Res* 2005;14:329–347.
70 Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005;60: 925–931.
71 Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002;57:847–852.
72 Roche N, Rabbat A, Zureik M, Huchon G. Chronic obstructive pulmonary disease exacerbations in emergency departments: predictors of outcome. *Curr Opin Pulm Med* 2010;16:112–117.
73 Zhang D, Zhang H, Li X, Lei S, Wang L, Guo W, *et al.* Pulmonary rehabilitation programmes within three days of hospitalization for acute exacerbation of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2021;16: 3525–3538.
74 Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. *Eur Respir J* 2019;53:1900164.
75 Hopkinson N. What is and what is not post exacerbation pulmonary rehabilitation? *BMJ* 2014;349:g4315.
76 Spruit M, Rochester CL, Pitta F, Goldstein R, Troosters T, Nici L, *et al.* A 6-week, home-based, unsupervised exercise training program is not effective in patients with chronic respiratory disease directly following a hospital admission. *BMJ* 2014;349:g4315.
77 Man WD, Kon SS, Maddocks M. Rehabilitation after an exacerbation of chronic respiratory disease. *BMJ* 2014;349:g4370.