Pulmonary Rehabilitation for Patients After COPD Exacerbation

Manaka Shibuya, Shuhei Yamamoto, Shuken Kobayashi, Kenichi Nishie, Takayoshi Yamaga, Shohei Kawachi, and Atsuhiko Matsunaga

BACKGROUND: The aim of this study was to clarify the effectiveness of pulmonary rehabilitation in patients after exacerbations of COPD and to explore the initiation timing of pulmonary rehabilitation. METHODS: Systematic review and meta-analysis were performed to assess the effects of pulmonary rehabilitation in subjects with exacerbations of COPD on mortality and readmission compared with usual care. We searched for studies published up to October 2020 in MEDLINE, Embase, Cochrane Library, and other sources. Risk of bias was assessed for the randomization process, deviations from intended interventions, missing outcome data, outcome measurements, and selection of the reported result using the Risk of Bias 2 tool. We pooled mortality and readmission data and performed comparisons between pulmonary rehabilitation and usual care. The subgroup analysis compared pulmonary rehabilitation at different start times (early: ≤ 1 week from admission; and late: > 1 week from admission). RESULTS: We identified 10 randomized trials (1,056 participants). Our meta-analysis showed a clinically relevant reduction in readmission up to 3–6 months after pulmonary rehabilitation in both early group (4 trials, 190 subjects; risk ratio [RR] 0.58, [95% CI 0.34–0.99]) and late group (3 trials, 281 subjects; RR 0.48, [95% CI 0.32–0.71]). However, pulmonary rehabilitation had no significant effect on mortality 1 y later compared with usual care (4 trials, 765 subjects; RR 1.27, [95% CI 0.91–1.79]). CONCLUSIONS: Pulmonary rehabilitation showed short-term effects for subjects with exacerbations of COPD even if initiated within 1 week; however, further study is required to determine its long-term effects. *Key words: chronic obstructive pulmonary disease; exercise; hospitalization; meta-analysis; mortality; rehabilitation.* [Respir Care 2022;67(3):360–369. © 2022 Daedalus Enterprises]

Introduction

Pulmonary rehabilitation is important for managing disease in patients with COPD because it reduces symptoms, increases exercise capacity, improves survival, and reduces hospitalization rates in patients with COPD.[1-3] However, many previous studies have included only subjects with stable COPD, and the effects of pulmonary rehabilitation initiated early after hospital admission for patients with COPD remain unknown. After exacerbations of COPD, meta-analysis has shown that rehabilitation initiation within 4 weeks of hospitalization is effective[4]; but there are no clear results for earlier initiation, particularly during the hospitalization period. In recent years, a large randomized controlled trial (RCT) has shown that starting early rehabilitation within 48 h of hospitalization is associated with higher mortality after 1 y.[5] Even the global guidelines regarding the effects of the timing of pulmonary rehabilitation initiation differ. The 2011 guidelines of the National

Dr Shibuya and Mr Kobayashi are affiliated with Department of Rehabilitation, Kitasato University Hospital, 1-15-1, Kitasato, Minami-ku, Sagamihara, Kanagawa, Japan. Dr Yamamoto is affiliated with Department of Rehabilitation, Shinshu University Hospital, 3-1-1, Asahi, Matsumoto, Nagano, Japan. Dr Nishie is affiliated with The First Department of Internal Medicine, Shinshu University School of Medicine, 3-1-1, Asahi, Matsumoto, Nagano, Japan and Department of Respiratory Medicine, Iida Municipal Hospital, 438, Yawatamachi, Iida, Nagano, Japan. Dr Yamaga is affiliated with Department of Occupational Therapy, Health Science University, 7187 Kodachi, Fujikawaguchiko-machi, minamitsuru-gun, Yamanashi, Japan. Mr Kawachi is affiliated with Department of Biomedical Laboratory Science, Graduate School of Medicine, Shinshu University, 3-1-1, Asahi, Matsumoto, Nagano, Japan and Institute for Biomedical Sciences, Shinshu University, 3-1-1, Asahi, Matsumoto, Nagano, Japan. Dr Matsunaga is affiliated with Department of Rehabilitation, School of Allied Health Sciences, Kitasato University, 1-15-1, Kitasato, Minami-ku, Sagamihara, Kanagawa, Japan and Department of Rehabilitation Sciences, Kitasato University Graduate School of Medical Sciences, 1-15-1, Kitasato, Minami-ku, Sagamihara, Kanagawa, Japan.

Institute for Health and Care Excellence recommend that rehabilitation be initiated for patients hospitalized with COPD exacerbations.[6] However, as per the 2017 guidelines of the European Respiratory Society and the American Thoracic Society, the result of the RCT[5] was considered important; and thus, they suggested that pulmonary rehabilitation should not be initiated for patients hospitalized with COPD exacerbations.[7] As such, there is no clear recommendation on when to start rehabilitation. In particular, a history of exacerbations has been reported to increase the risk of hospitalization, which is an important prognostic factor for decreased survival.[8] COPD exacerbation has also been reported to affect the progression of emphysema.[9] As such, prevention of exacerbations of COPD is an important treatment strategy; and thus, whether pulmonary rehabilitation is associated with readmission and mortality should be examined. In the meta-analysis conducted by Puhan et al,[10] while rehabilitation for subjects with COPD after exacerbation showed a moderate evidence of reducing readmissions, the results obtained were heterogeneous. This meta-analysis did not consider differences in the initiation timing, and the impact of initiation time remained unclear.

Therefore, the current systematic review and meta-analysis were conducted to evaluate the effectiveness of pulmonary rehabilitation in patients after exacerbations of COPD. Then, a subgroup analysis was performed to explore the initiation timing of pulmonary rehabilitation. This study evaluated the effects of rehabilitation on mortality and readmission in patients with COPD.

Methods

Search Methods for Identifying Studies

We performed this study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement for meta-analyses and systematic reviews.[11] We searched for studies published up to October 2020 in the following electronic databases: Cochrane Central Register of Controlled Trials, MEDLINE, Embase, CINAHL, PubMed, and OvidSP. By carrying out discussions with an academic librarian, we finalized the search strategy and modified it appropriately for each database. The search strategy comprised a combination of free-text words; words used in titles; and/or abstracts and medical subject headings, including "lung diseases obstructive OR chronic obstructive lung disease OR chronic obstructive pulmonary disease," "rehabilitation OR exercise OR physical endurance OR muscle training OR resistance training OR exercise therapy OR aerobic training OR endurance training," and "randomized, controlled trial OR randomized" (Appendix A, see related supplemental material at http://www.rcjournal.com). The search strategy was limited to the inclusion of only peer-reviewed publications that involved human participants. In order to ensure that the search strategy covered all the topic-related studies, we included different terms and spellings that are used worldwide. In addition, language restrictions were not applied.

Inclusion and Exclusion Criteria

In this review, we included studies that evaluated the effectiveness of pulmonary rehabilitation on patient prognosis after exacerbation of COPD. The primary outcome was readmission for up to 3–6 months. First, we evaluated readmissions at 3 months; and if 3-month data were not available, we added readmissions at 6 months. The secondary outcomes included readmission within 1 y and mortality 1 y later.

The studies that met all of the following criteria were considered eligible: (1) RCT study design, (2) study involved subjects after experiencing exacerbations of COPD, (3) study compared pulmonary rehabilitation and usual care, (4) study reported on at least one of the above-mentioned outcome measures, (5) pulmonary rehabilitation was initiated during admission for an exacerbation or within 4 weeks of hospital discharge after exacerbation, and (6) pulmonary rehabilitation was provided for more than 1 month. All published and unpublished RCTs were included. Animal and in vitro studies were excluded.

Data Extraction

To determine relevance, titles and abstracts that contained key terms were independently screened by 2 investigators (MS and SK) based on the above inclusion criteria. If a decision could not be made based on the title and abstract alone, it was left for screening. The corresponding full-text articles were subsequently retrieved to assess the eligibility of the articles remaining in the screening, which then determined their inclusion in the study. Disagreements, if any, were resolved by consulting and discussing with a third author (SY). The following data were recorded from each study: the intervention details and comparison method, subjects (number) that were randomly assigned to each group as well as attrition, outcome data, first author's name, publication year,

The authors have declared no conflicts of interest.

The study was performed at Department of Rehabilitation, Kitasato University Hospital, 1–15-1, Kitasato, Minami-ku, Sagamihara, Kanagawa, Japan.

Supplementary material related to this paper is available at http://www.rcjournal.com.

Correspondence: Manaka Shibuya PT PhD, Department of Rehabilitation, Kitasato University Hospital, 1–15-1, Kitasato, Minami-ku, Sagamihara, Kanagawa 252–0375, Japan. E-mail: manaka.s@kitasato-u.ac.jp.

DOI: 10.4187/respcare.09066

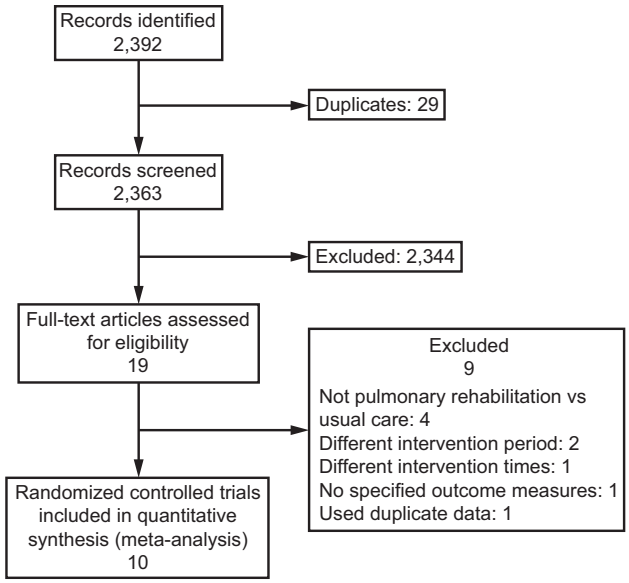

Fig. 1. Flow chart.

blinding, subject age, intervention period and follow-up duration, hospital length of stay, pulmonary rehabilitation program completion rate, and adverse events. When data were insufficient, the authors were contacted and unpublished data were requested. Wherever possible, data were collected on an intention-to-treat basis.

Assessment of Risk of Bias in the Included Studies

The quality of each study was independently assessed by MS and SK using the Risk of Bias 2 tool as per the Cochrane Handbook for Systematic Reviews of Interventions.[12] In cases of differing assessments, the third author (SY) was consulted for a final decision on the assessment.

Meta-Analysis and Subgroup Analysis

We divided subjects into 2 groups: the pulmonary rehabilitation group and the usual-care group. To explore the initiation timing of pulmonary rehabilitation, subgroup analysis was planned for the early ($\leq$ 1 week from admission) and late ($>$ 1 week from admission) groups based on the initiation timing of pulmonary rehabilitation. Data syntheses and analyses were performed using Review Manager version 5.3. For outcomes, pooled risk ratios (RRs) were calculated.

The Tau^2, I^2, and chi-square statistics were used to determine the statistical heterogeneity in each meta-analysis as per the Cochrane Handbook for Systematic Reviews of Interventions.[13] Heterogeneity was regarded as substantial when I^2 was $>$ 50% and the P value for heterogeneity was $<$ .05. To increase the validity of the test results, a sensitivity analysis was performed to determine whether a high risk of bias of some of the included studies affected the study results. When $\geq$ 10 studies were included in a meta-analysis, a funnel plot was created, and its asymmetry was visually examined to explore any publication bias. A high risk of bias was defined as follows: (1) insufficient random sequence generation, (2) insufficient allocation concealment, or (3) many high-risk domains.[12]

Results

According to our search strategy, 2,390 records were identified in the initial search.[11] In addition, 2 other studies were found via hand searching.[14,15] A total of 29 duplicate studies, 254 reviews, and 15 animal or in vitro studies were excluded. The full texts of the remaining 19 studies were retrieved, and finally, 10 RCTs met our inclusion criteria.[5,14-22] Figure 1 shows the screening process and the reasons for excluding studies.

Quality and Bias Assessment in the Included Studies

Table 1 summarizes the risk of bias for each study. The risk of bias was high in 3 (30%) studies with deviations from intended interventions, one (10%) study with missing outcome data, and 3 (30%) studies with overall risk of bias.

Study Characteristics

The characteristics of the included RCTs and participant information are presented in Table 2. Five RCTs[5,15,16,18,19] had started pulmonary rehabilitation $\leq$ 1 week from admission, whereas 5 RCTs[14,17,20-22] had started pulmonary rehabilitation $>$ 1 week from admission. A total of 1,056 participants were included in the 10 RCTs. In one RCT, the intervention groups received 4–8 weeks of pulmonary rehabilitation; in 2 RCTs, the intervention groups received 6 weeks of pulmonary rehabilitation; in one RCT, the intervention group received 7 weeks of pulmonary rehabilitation; and in the remaining RCTs, the intervention groups received 8 or more weeks of pulmonary rehabilitation.

Readmissions for up to 3–6 Months

Seven RCTs with 471 subjects were included in the analysis of readmission for up to 3–6 months. Participants who underwent pulmonary rehabilitation had a significantly lower risk of readmission for up to 3–6 months following the initial admission (RR 0.51, [95% CI 0.37–0.70]; participants = 471; studies = 7; Fig. 2). There was no significant heterogeneity (chi-square = 3.97, P = .68, I^2 = 0%). In subjects who had received pulmonary rehabilitation, significant decreases in readmission for up to 3–6 months were found in both the early (RR 0.58, [95% CI 0.34–0.99]; participants = 190;

Table 1. Risk of Bias

Study	Year	Randomization Process	Deviations From Intended Interventions	Missing Outcome Data	Outcome Measurements	Selection of the Reported Result	Overall
Behnke et al[16]	2000	●	●	●	●	●	●
Manat al[17]	2004	●	●	●	●	●	●
Murphy et al[18]	2005	●	●	●	●	●	●
Eaton et al[19]	2009	●	●	●	●	●	●
Seymour et al[14]	2010	●	●	●	●	●	●
Ko et al[20]	2011	●	●	●	●	●	●
Greening et al[5]	2014	●	●	●	●	●	●
Ko et al[21]	2017	●	●	●	●	●	●
Cox et al[15]	2018	●	●	●	●	●	●
Ko et al[22]	2020	●	●	●	●	●	●

●: Low risk, ●: Some concerns, ●: High risk.

studies = 4; $I^2 = 0\%$) and late subgroups (RR 0.48, [95% CI 0.32–0.71]; participants = 281; studies = 3; $I^2 = 0\%$).

Readmissions within 1 Year

Four RCTs with 765 subjects were included in the analysis of readmission within 1 y. Participants who underwent pulmonary rehabilitation had a significantly lower risk of readmission 1 y following the initial admission (RR 0.89, [95% CI 0.78–1.00]; participants = 765; studies = 4; $I^2 = 83\%$; Fig. 3). In subjects who had received pulmonary rehabilitation, significant decreases in readmissions within 1 y were found in the late subgroup (RR 0.70, [95% CI 0.58–0.85]; participants = 376; studies = 3; $I^2 = 66\%$). The early subgroup included only one RCT, and no significant difference was observed between the participants who received pulmonary rehabilitation and those who received usual care (RR 1.08, [95% CI 0.92–1.27]; participants = 389; study = 1).

Mortality 1 Year Later

Four RCTs with 765 subjects were included in the analysis of mortality 1 y later. The overall results showed that no significant difference was observed between the patients who received pulmonary rehabilitation and those who received usual care (RR 1.27, [95% CI 0.91–1.79]; participants = 765; studies = 4; $I^2 = 17\%$; Fig. 4). The substantial heterogeneity was explained by the subgroup analysis. There was a significant increase in the early subgroup (RR 1.56, [95% CI 1.04–2.33]; participants = 389; study = 1) but no significant difference in the late subgroup (RR 0.77, [95% CI 0.39–1.51]; participants = 376; studies = 3; $I^2 = 0\%$). Heterogeneity was lower after the subgroup analysis compared with the pre-subgroup analysis.

Sensitivity Analysis

The reliability of results was assessed using a sensitivity analysis. The meta-analysis was repeated without the inclusion of studies with many high-risk domains[15] or few events,[16,18,20,22] respectively. In the analysis of readmissions for up to 3–6 months, this omission changed the results such that there was no significant difference between pulmonary rehabilitation and usual care in the early subgroup (Figures B.1–B.3, see related supplemental material at http://www.rcjournal.com.).

Adverse Events

Adverse events in included studies were described in 3 articles, and no intervention-related adverse events were observed.

Discussion

The present study indicated that there was a significant decrease in readmission for up to 3–6 months and within 1 y in the participants who received pulmonary rehabilitation compared with those who received usual care. Furthermore, significant decreases in readmission for up to 3–6 months in pulmonary rehabilitation were found for both the early and late subgroups. The results for mortality 1 y later indicated that there were no significant differences between pulmonary rehabilitation and usual care. Based on the results of the present study, pulmonary rehabilitation had a short-term (3–6 months) beneficial effect in subjects with exacerbations of COPD even if it was initiated within 1 week of admission, similar to after 1 week from admission.

Table 2. Characteristics of the Included Studies

Author	Year	Subjects, *n*	Time to Start Treatment	Intervention Period	Training for Intervention Group	Follow-Up Duration	Age, Mean (SD), Gender (%), %FEV_1 (%)	Hospital LOS	Pulmonary Rehab Completion Rate	Readmissions for up to 3–6 mo	Readmissions Within 1 y	Mortality 1 y Later
Behnke et al[16]	2000	Training: 23 Control: 23	Training: ≤ 1 wk from admission (4–7 d after admission)	6 mo	Type: in hospital: walking, home exercise: walking 3 times per d within 15 min Frequency: 7/wk	6 mo	Training ($n = 15$): age 64.0 (1.9), gender (men) 12 (80%), % FEV_1 34.1 (7.4) Control ($n = 15$): age 68.0 (2.2), gender (men) 11 (73%), % FEV_1 37.5 (6.6)	N/A	N/A	Training: 1/23 Control: 3/23		
Man et al[17]	2004	Early rehab: 21 Usual care: 21	Early rehab: > 1 wk from admission (within 10 d of hospital discharge)	8 wk	Type: aerobic training, strength training, education, home exercise at least 20 min per d Frequency: 2/wk	3 mo	Early rehab: age 69.6 (9.2), gender (men) 9 (43%), %FEV_1 41.7 (18.9) Usual care: age 70.7 (9.3), gender (men) 8 (38%), %FEV_1 36.7 (14.9)	Early rehab: 8.0 (3.9) Usual care: 8.8 (4.3)	The average was 73%; 6 out of 18 subjects were < 50%.	Early rehab: 7/20 Usual care: 12/21		
Murphy et al[18]	2005	Exercise: 16 Control: 15	Exercise: ≤ 1 wk from admission (day of hospital discharge: 3–7 d after admission)	6 wk	Type: aerobic exercises, muscle training Frequency: 2/wk	6 mo	Exercise ($n = 13$): age 67 (9.7), gender (men) 7 (54%), % FEV_1 38 (12) Control ($n = 13$): age 65 (11), gender (men) 10 (77%), %FEV_1 42 (12)	Exercise: 3–7 Control: 2–7	N/A	Exercise: 0/13 Control: 3/13		
Eaton et al[19]	2009	Early pulmonary rehab: 47 Usual care: 50	Early pulmonary rehab: ≤ 1 wk from admission (at a mean of 2.6 d after admission)	8 wk	Type: in-patient: walking, strengthening exercises out-patient: exercise training, education Frequency: 2/wk	3 mo	Early pulmonary rehab: age 70.1 (10.3), gender (men) 21 (45%), %FEV_1 36 (16) Usual care: age 69.7 (9.4), gender (men) 21 (42%), %FEV_1 35 (16)	N/A	19 subjects (40%) were over 75%.	Early pulmonary rehab: 11/47 Usual care: 16/50		
Seymour et al[14]	2010	PEPR: 30 Usual care: 30	PEPR: > 1 wk from admission (within a wk of hospital discharge)	8 wk	Type: strengthening, aerobic activities, education Frequency: 2/wk	3 mo	PEPR: age 67 (10), gender (men) 13 (43%), %FEV_1 52 (20) Usual care: age 65 (10), gender (men) 14 (47%), %FEV_1 52 (22)	PEPR: 6 (4–8) Usual care: 5 (4–8)	77% subjects were over 50%.	PEPR: 2/30 Usual care: 10/30		
Ko et al[20]	2011	Rehab: 30 Usual care: 30	Rehab: > 1 wk from admission (2–3 wk after discharge from hospital)	8 wk Follow-up: once every 3 mo for 1 y	Type: aerobic training, strength training Frequency: 3/wk	12 mo	Rehab: age 73.5 (7.7), gender (men) 30 (100%), %FEV_1 46.2 (19.7) Usual care: age 73.8 (6.4), gender (men) 29 (97%), %FEV_1 40.8 (17.5)	N/A	73.3% (22 out of 30) subjects were at least 70%.		Rehab: 16/30 Usual care: 13/30	Rehab: 0/30 Usual care: 2/30

(Continued)

Table 2. Continued

Author	Year	Subjects, *n*	Time to Start Treatment	Intervention Period	Training for Intervention Group	Follow-Up Duration	Age, Mean (SD), Gender (%), $\%FEV_1$ (%)	Hospital LOS	Pulmonary Rehab Completion Rate	Readmissions for up to 3–6 mo	Readmissions Within 1 y	Mortality 1 y Later
Greening et al[5]	2014	Early rehab: 196 Usual care: 193	Early rehab: ≤ 1 wk from admission (within 48 h of hospital admission)	6 wk	Type: in hospital: aerobic training, strength training, neuromuscular electrical stimulation, education after discharge: walking-based home exercise program, telephone consultation Frequency: 7/wk	12 mo	Early rehab: age 71.1 (9.4), gender (men) 88 (45%), $\%FEV_1$ 51.9 (25.1) Usual care: age 71.2 (10.0), gender (men) 85 (44%), $\%FEV_1$ 57.4 (23.6)	Early rehab: 5 (1–33) Usual care: 5 (1–31)	In hospital: 165 (86%) participants for aerobic training, 176 (90%) for resistance training, and 176 (90%) for neuromuscular electrical stimulation training. After discharge: 54% of participants for aerobic training and 61% for resistance training.		Early rehab: 122/196 Usual care: 111/193	Early rehab: 49/196 Usual care: 31/193
Ko et al[21]	2017	Intervention: 90 Usual care: 90	Intervention: > 1 wk from admission (at about 3–4 wk after hospital discharge)	8 wk Follow-up: once every 3 mo for 1 y	Type: individualized physical training program education Frequency: 3/wk	12 mo	Intervention: age 74.9 (7.9), gender (men) 85 (94%), $\%FEV_1$ 46.7 (18.3) Usual care: age 74.6 (8.6), gender (men) 87 (97%), $\%FEV_1$ 44.2 (14.7)	N/A	64 subjects (71.1%)	Intervention: 17/90 Usual care: 33/90	Intervention: 44/90 Usual care: 63/90	Intervention: 10/90 Usual care: 12/90
Cox et al[15]	2018	Early pulmonary rehab: 14 Usual care:15	Early pulmonary rehab: ≤ 1 wk from admission (within 48 h of admission)	7 wk	Type: in hospital: cycling, resistance training home exercise: aerobic training, strength training, education Frequency: 5 consecutive d and 2/wk	3 mo	Early pulmonary rehab ($n = 10$): age 70 (11), gender (men) 5 (50%), $\%FEV_1$ ($n = 11$) 49.4 (17.9) Usual care ($n = 9$): age 69 (8), gender (men) 5 (56%), $\%FEV_1$ 55.6 (22.7)	Early pulmonary rehab: 5 (7) Usual care: 5 (3)	In hospital: 34.1% of sessions Home exercise: 78.3% of sessions	Early pulmonary rehab: 3/11 Usual care: 5/10		
Ko et al[22]	2020	Intervention: 68 Control: 68	Intervention: > 1 wk from admission (about 2–4 wk posthospital discharge)	4–8 wk	Type: supervised training by a trained physiotherapist: treadmill walking/running training, upper- and lower-limb weight lifting and stretching exercise Home exercise: brisk walking, static	12 mo	Intervention: age 76 (8), gender (men) 67 (99%), $\%FEV_1$ 49 (17) Control: age 74 (7), gender (men) 65 (96%), $\%FEV_1$ 46 (15)	N/A	The average was 7.3 sessions (out of 4–8 sessions).		Intervention: 26/68 Control: 46/68	Intervention: 3/68 Control: 3/68

(Continued)

Table 2. Continued

Author	Year	Subjects, *n*	Time to Start Treatment	Intervention Period	Training for Intervention Group	Follow-Up Duration	Age, Mean (SD), Gender (%), %FEV$_1$ (%)	Hospital LOS	Pulmonary Rehab Completion Rate	Readmissions for up to 3–6 mo	Readmissions Within 1 y	Mortality 1 y Later
					bike cycling, free-weights lifting by upper extremity and stretching exercise Frequency: 1–2/wk							

Values are presented as mean (SD) or *n* (%).
LOS = length of stay
PEPR = post-exacerbation pulmonary rehabilitation

Short-Term Effects

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) reports a high level of evidence indicating that pulmonary rehabilitation improves dyspnea, health status, and exercise tolerance in stable patients.[1,23] Additionally, pulmonary rehabilitation after exacerbations of COPD has been noted, and the initiation of pulmonary rehabilitation within 3 months has been shown to be significantly associated with a reduced risk of death at 1 y.[24] In a recent systematic review, although heterogeneity existed, pulmonary rehabilitation initiated within 3 weeks after discharge reduced the rate of readmission and mortality.[10] Studies reported in GOLD also reported that pulmonary rehabilitation within 4 weeks of prior hospitalization reduced hospitalization among participants who experienced a recent exacerbation.[1,4]

The GOLD also states that the effect of pulmonary rehabilitation before discharge remains unclear. In the present meta-analysis, pulmonary rehabilitation has a short-term (3–6 months) effect on participants with exacerbations of COPD even if it is initiated within 1 week of admission. The meta-analysis about early mobilization among critically ill subjects reported that there were no adverse effects even if pulmonary rehabilitation was initiated within 1 week of ICU admission.[25] This study newly indicated that short-term effects for subjects with exacerbations of COPD were observed in addition to no adverse effects, similar to the previous study.

The findings also indicated that there was no difference in the timing of rehabilitation initiation and that there were no short-term adverse effects from starting early. Several studies have compared differences in the timing of rehabilitation initiation in participants with COPD after exacerbation. Revitt et al[26] compared a group that received rehabilitation within 4 weeks of discharge with a group that received rehabilitation starting at 7 weeks and found that the subjects who received pulmonary rehabilitation sooner after exacerbations of COPD showed better improvements than the delayed group. However, no firm conclusions could be drawn because of the significantly small sample number. In a study that initiated rehabilitation earlier, no significant differences were found by Puhan et al[27] between early pulmonary rehabilitation, which was started within 2 weeks, and late pulmonary rehabilitation, which was started 6 months after randomization and in a stable state. However, their trial indicated that early rehabilitation may lead to a faster recovery of health-related quality of life after exacerbations compared with late rehabilitation. Furthermore, pulmonary rehabilitation within 1 week after discharge led to a faster improvement in physical performance than rehabilitation initiated later in the stable phase; however, it did not decrease the mortality rate or increase the time to hospital readmission.[28] Thus, early rehabilitation has been shown to have a potential for faster recovery of physical function and quality of life, but its effectiveness on mortality and readmission is unclear.[28,29] The reason for the difficulty in

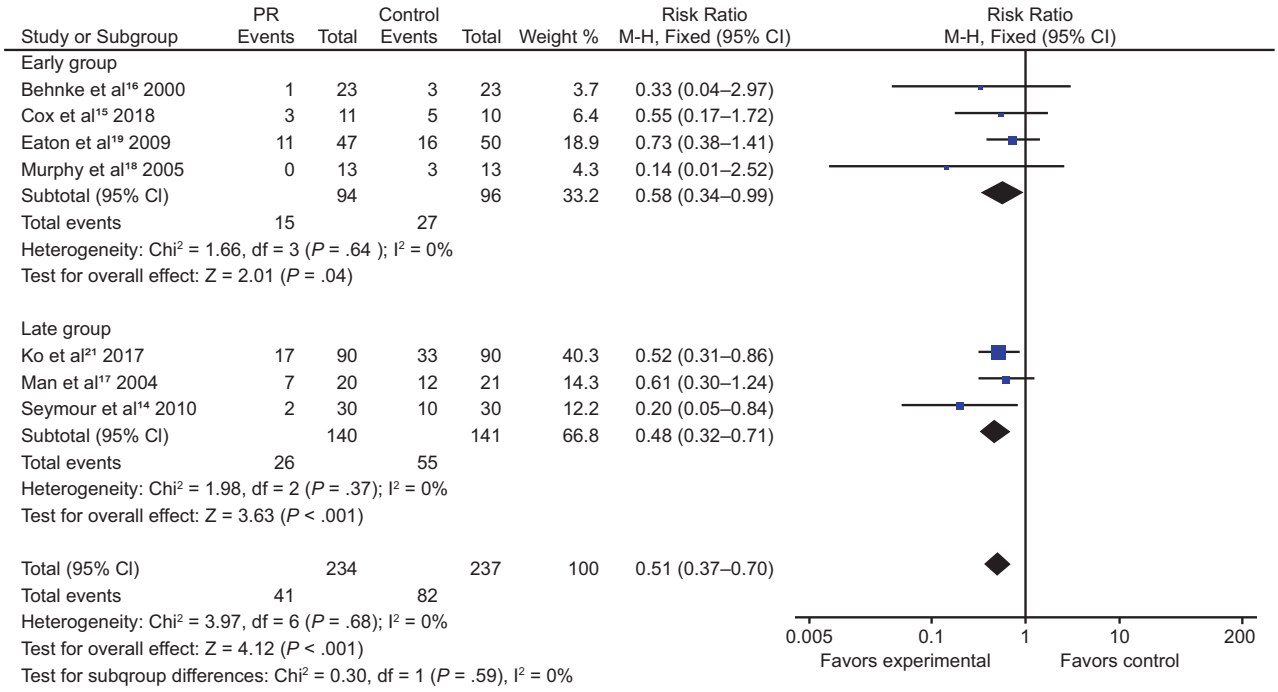

Fig. 2. The effect of pulmonary rehabilitation versus usual care on readmissions for up to 3–6 months. PR = pulmonary rehabilitation.

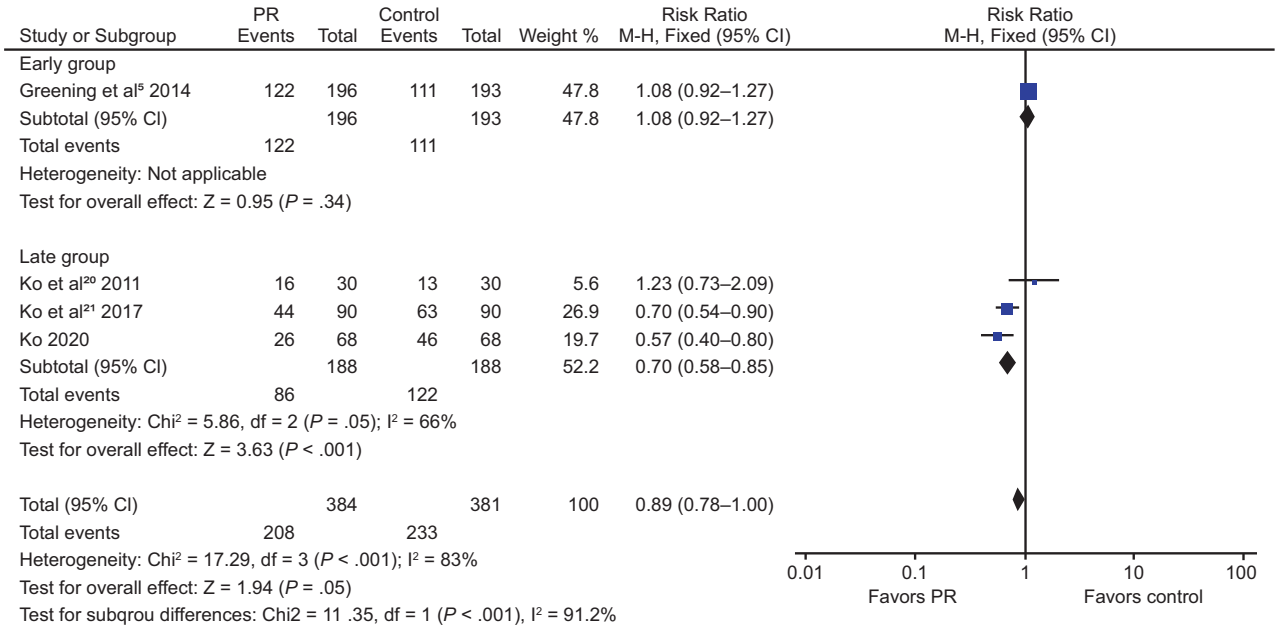

Fig. 3. The effect of pulmonary rehabilitation versus usual care on readmissions within 1 y. PR = pulmonary rehabilitation.

presenting clear results in these studies may be the small number of subjects. The integration of the results of multiple studies in the present meta-analysis indicates that pulmonary rehabilitation has a short-term (3–6 months) effect for subjects with exacerbations of COPD even if it is initiated within 1 week of admission.

Long-Term Effects

However, similar to the guidelines, no significant results were obtained for the long-term (1 y) effects of pulmonary rehabilitation. This result is due to the fact that there are few papers with a long-term follow-up period of

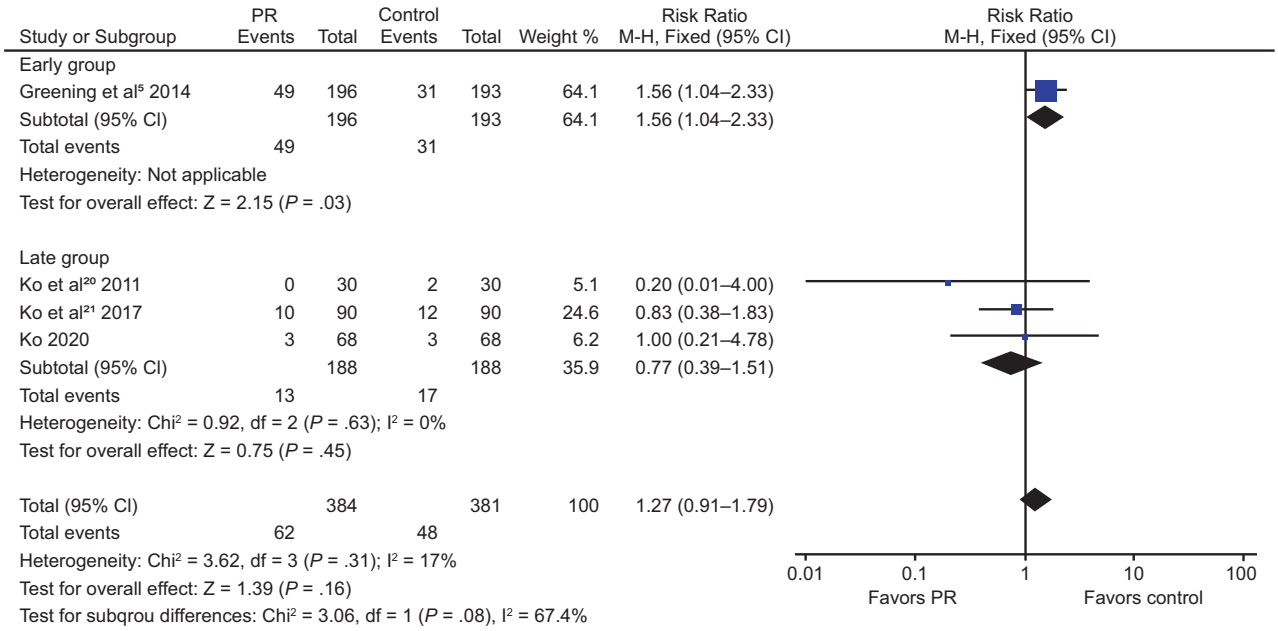

Fig. 4. The effect of pulmonary rehabilitation versus usual care on mortality 1 y later. PR = pulmonary rehabilitation.

1 y. Although early pulmonary rehabilitation was shown to increase mortality at 1 y in one large-scale RCT,[5] no other large RCTs have been reported on this topic. In the present meta-analysis, because few studies were included, especially in the early group, and only one RCT was included, the long-term effects remain unclear. In the meta-analysis on nonpharmacologic therapies in subjects with exacerbation of COPD, risk of readmission was similar in rehabilitation and control groups, but only one study was included in the analysis.[30] RCTs in various populations are necessary to clarify the long-term effects of pulmonary rehabilitation for patients with exacerbations of COPD.

Limitations

This study has several limitations. First, the definition of the intervention was clinically heterogeneous. The training content was not uniform and included articles in which the exercising was unsupervised and for which the exercise content may not have been fully controlled. Second, the program completion rate for early pulmonary rehabilitation after COPD exacerbation has been reported to be associated with the risk of hospital readmissions,[31] but we did not examine the program completion rate in this study. Third, in the sensitivity analysis, different results were shown when omissions were made, so care should be taken in interpreting the results. Fourth, the impact of different initiation timings is a secondary comparison. Since the present results suggest that starting rehabilitation early is not a bad choice, future RCTs comparing the early and late groups will be necessary. These limitations should be considered while interpreting the study results.

Conclusions

For participants with exacerbations of COPD, both early (within 1 week of admission) and late (after 1 week from admission) initiation of pulmonary rehabilitation reduced hospital readmission for up to 3–6 months. Further studies are necessary to confirm the long-term effects of pulmonary rehabilitation, especially to compare the effects of different initiation timings of pulmonary rehabilitation.

ACKNOWLEDGMENTS

The authors thank the rehabilitation staff for their support in this study.

REFERENCES

1. The Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2020 Gold Reports 2020 Global Strategy For Prevention, Diagnosis And Management Of COPD. Available at: https://goldcopd.org/gold-reports. *Accessed June 25, 2020.*
2. Lalmolda C, Coll-Fernández R, Martínez N, Baré M, Teixidó Colet M, Epelde F, Monsó E. Effect of a rehabilitation-based chronic disease management program targeting severe COPD exacerbations on readmission patterns. Int J Chron Obstruct Pulmon Dis 2017;12:2531-2538.
3. van Ranst D, Stoop WA, Meijer JW, Otten HJ, van de Port IG. Reduction of exacerbation frequency in patients with COPD after participation in a comprehensive pulmonary rehabilitation program. Int J Chron Obstruct Pulmon Dis 2014;9:1059-1067.
4. Ryrsø CK, Godtfredsen NS, Kofod LM, Lavesen M, Mogensen L, Tobberup R, et al. Lower mortality after early supervised pulmonary

rehabilitation following COPD-exacerbations: a systematic review and meta-analysis. BMC Pulm Med 2018;18(1):154.
5. 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.
6. National Clinical Guideline Centre. 2010 Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care. London: Royal College of Physicians.
7. Wedzicha JA (Ers Co-Chair), 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(3):1600791.
8. Müllerova H, Maselli DJ, Locantore N, Vestbo J, Hurst JR, Wedzicha JA, et al. Hospitalized exacerbations of COPD: risk factors and outcomes in the ECLIPSE cohort. Chest 2015;147(4):999-1007.
9. Tanabe N, Muro S, Hirai T, Oguma T, Terada K, Marumo S, et al. Impact of exacerbations on emphysema progression in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2011;183 (12):1653-1659.
10. Puhan MA, Gimeno-Santos E, Cates CJ, Troosters T. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2016;12(12):CD005305.
11. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
12. 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.
13. Deeks JJ, Higgins JPT, Altman DG. Chapter 10: analyzing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane handbook for systematic reviews of interventions version 6.1. London: Cochrane; 2020, (updated September 2020).
14. Seymour JM, Moore L, Jolley CJ, Ward K, Creasey J, Steier JS, et al. Outpatient pulmonary rehabilitation following acute exacerbations of COPD. Thorax 2010;65(5):423-428.
15. 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(11):1-204.
16. 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(12):1184-1191.
17. Man WD, Polkey MI, Donaldson N, Gray BJ, Moxham J. Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. BMJ 2004;329(7476):1209.
18. Murphy N, Bell C, Costello RW. Extending a home from hospital care programme for COPD exacerbations to include pulmonary rehabilitation. Respir Med 2005;99(10):1297-1302.
19. 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(2):230-238.
20. Ko FW, Dai DL, Ngai J, Tung A, Ng S, Lai K, et al. Effect of early pulmonary rehabilitation on health care utilization and health status in patients hospitalized with acute exacerbations of COPD. Respirology 2011;16(4):617-624.
21. Ko FW, Cheung NK, Rainer TH, Lum C, Wong I, Hui DS. Comprehensive care programme for patients with chronic obstructive pulmonary disease: a randomised controlled trial. Thorax 2017;72 (2):122-128.
22. Ko FW, Tam W, Siu EHS, Chan KP, Ngai JC, Ng SS, et al. Effect of short-course exercise training on the frequency of exacerbations and physical activity in patients with COPD: a randomized controlled trial. Respirology 2021;26(1):72-79.
23. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2015;2:CD003793.
24. Lindenauer PK, Stefan MS, Pekow PS, Mazor KM, Priya A, Spitzer KA, et al. Association between initiation of pulmonary rehabilitation after hospitalization for COPD and 1-year survival among Medicare beneficiaries. JAMA 2020;323(18):1813-1823.
25. Okada Y, Unoki T, Matsuishi Y, Egawa Y, Hayashida K, Inoue S. Early versus delayed mobilization for in-hospital mortality and health-related quality of life among critically ill patients: a systematic review and meta-analysis. J Intensive Care 2019;7:57.
26. Revitt O, Sewell L, Singh S. Early versus delayed pulmonary rehabilitation: A randomized controlled trial - Can we do it? Chron Respir Dis 2018;15(3):323-326.
27. Puhan MA, Spaar A, Frey M, Turk A, Brändli O, Ritscher D, et al. Early versus late pulmonary rehabilitation in chronic obstructive pulmonary disease patients with acute exacerbations: a randomized trial. Respiration 2012;83(6):499-506.
28. Kjærgaard JL, Juhl CB, Lange P, Wilcke JT. Early pulmonary rehabilitation after acute exacerbation of COPD: a randomised controlled trial. ERJ Open Res 2020;6(1):00173-2019.
29. Maestri R, Bruschi C, Fracchia C, Pinna GD, Fanfulla F, Ambrosino N. Physiological and clinical characteristics of patients with COPD admitted to an inpatient pulmonary rehabilitation program: a real-life study. Pulmonology 2019;25(2):71-78.
30. Dobler CC, Morrow AS, Farah MH, Beuschel B, Majzoub AM, Wilson ME, et al. Nonpharmacologic therapies in patients with exacerbation of chronic obstructive pulmonary disease: a systematic review with meta-analysis. Mayo Clin Proc 2020;95(6):1169-1183.
31. Kjærgaard J, Juhl CB, Lange P, Wilcke T. Adherence to early pulmonary rehabilitation after COPD exacerbation and risk of hospital readmission: a secondary analysis of the COPD-EXA-REHAB study. BMJ Open Respir Res 2020;7(1):e000582.