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ORIGINAL RESEARCH

# Effect of Long-Term Oxygen Therapy on Reducing Rehospitalization of Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis

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## ABSTRACT

***Introduction***: The aim of this work is to evaluate whether the addition of home oxygen therapy (HOT) would reduce readmission in chronic obstructive pulmonary disease (COPD) patients.

***Methods***: PubMed, ScopeMed, Cochrane, Scopus, and Google Scholar databases were searched. The search strategy used the following keywords "chronic obstructive pulmonary disease", the intervention "long-term oxygen therapy", and the outcome "readmission" combined with the AND operator. The Newcastle–Ottawa Scale and Jadad Scale were used for assessing the quality of cohort studies and clinical trials, respectively. A random-effects model was employed in this study after calculating the standard errors by 95% confidence intervals. The I2 statistic and Cochran's *Q*-test were used to measure heterogeneity. To address heterogeneity, subgroup analyses were carried out according to the length of LTOT, which was classified as "over 8 months" and "under 8 months".

***Results***: Seven studies were included in the analysis. In the pooled analysis, the RR [CI95%, *p* value], heterogeneity criteria for readmission reduced by 1.542 [1.284–1.851, $< 0.001$], $I^2 = 60\%$, and 1.693 [1.645–1.744, $< 0.001$], $I^2 = 60\%$ for patients with a length of LTOT treatment under and above 8 months, respectively. A sensitivity analysis was conducted by systematically omitting each study, and it showed no influential studies. Egger's test indicated no publication bias ($p = 0.64$).

***Conclusions***: Based on our results in this systematic review, long-tern oxygen therapy (LTOT) at home was associated with a significantly lower risk ratio of hospital readmission.

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However, the sample sizes in the studies necessitate larger RCTs to evaluate the effect of LTOT on readmission in COPD patients.

**Keywords:** COPD; Readmission; LTOT; Hospitalization

**Key Summary Points**

Chronic obstructive pulmonary disease (COPD) is at a higher level and more advanced staging of spirometricallly confirmed than has been typically reported.

It is associated with increased morbidity, mortality, hospitalization, healthcare burden, substantial societal burden, and impaired quality of life.

In an attempt to combat COPD-related hospitalization, researchers have studied the effects of oxygen therapy. Long-term oxygen therapy (LTOT) has been revealed to improve the survival and life quality of COPD patients and stabilize pulmonary hypertension in these patients.

This systematic review evaluated based on the hypothesis that the addition of HOT would reduce readmission for COPD patients to provide evidence on appropriate indications for HOT.

Based on our results in this systematic review, LTOT at home was associated with a significantly lower risk ratio of hospital readmission in COPD patients.

## INTRODUCTION

Globally, exacerbation is an event of considerable importance in the course of chronic obstructive pulmonary disease (COPD). It is associated with increased morbidity, mortality, hospitalization, impaired quality of life, increased healthcare burden, and substantial societal burden [1, 2]. Hence, it is viewed as a severe public health problem in many countries.

Based on the projection model in 12 Asian countries, it was estimated that 56.6 million people aged 30 years and above were suffering from moderate-to-severe COPD [3]. The World Health Organization (WHO) projects that COPD will be the third main cause of death worldwide by the year 2030, followed by ischemic heart disease and cerebrovascular disease [4].

In an attempt to combat COPD-related hospitalization, researchers have evaluated the results of oxygen therapy in these patients. Long-term oxygen therapy (LTOT) has been shown to improve life quality and survival in COPD patients and stabilize their pulmonary hypertension [5–7].

Home oxygen therapy (HOT) is the at-home administration of oxygen at concentrations greater than the ambient air concentration. Nevertheless, findings regarding the effect of HOT on hospitalization are diverse. While several studies have designated that LTOT reduces hospital admissions [8, 9], one study presented no effect [10]. Most studies indicated that LTOT had an impact on hospital admission, especially since the greatest association has been detected among severely hypoxemic COPD patients [11]. However, in moderately hypoxemic COPD patients, HOT may not lessen hospitalizations [10]. On the other hand, hospital admission is more likely in LTOT users and inappropriate oxygen consumption can impose an additional financial burden on the patient [12]. It would be mentioned that prescriptions for oxygen therapy are circumstances that predispose patients to repeated hospital admissions [13, 14].

This systematic review was evaluated based on the hypothesis that the addition of HOT would reduce readmission for COPD patients to provide evidence on appropriate indications for HOT.

## METHODS

### Search Strategy and Selection

The search strategy for the retrieval of English articles was made by three main concepts and their synonyms, including the problem "chronic obstructive pulmonary disease", the intervention "long-term oxygen therapy", and the outcome "readmission" combined with the AND operator. The synonyms of this concept were extracted from thesauruses like Medical Subject Headings (MeSH) and EMtree. The search strategy used for databases is shown in the supporting information (Table 1).

We searched multiple international scientific databases (PubMed, Medline, ISI-Web of Science-Core Collection, Scopus, Cochrane Central Register of Controlled Trials, and Embase). We did not consider any time limitation and all published studies from inception to September 2020 were included in this study. However, the records are limited to research articles and articles in the English language.

### Study Selection and Eligibility Criteria

Duplicate papers were removed, and the selection of suitable studies was conducted in three phases. In the first and second phases, titles and abstracts of papers were screened, and irrelevant papers were excluded. In the last phase, the full text of identified papers was explored deeply to select only relevant papers. Two independent reviewers did all three screening phases. Discrepancies were resolved by consultation and consensus.

The number of searched articles and articles in each step was defined in the PRISMA diagram (Fig. 1). Prescribing criteria for oxygen therapy was according to $PaO_2 \leq 55$ mmHg (7.3 kPa) or oxygen saturation as measured by pulse oximetry ($SpO_2$) $\leq 88\%$; or $PaO_2 = 56–59$ mmHg (7.5–7.9 kPa) or $SpO_2 = 89\%$ plus one of the following: edema, hematocrit $\geq 55\%$, or P pulmonale on an ECG [15, 16]. LTOT is prescribed for at least 15 h/day. patients' hours of oxygen use [15, 16].

### Quality Assessment

Cohort studies were assessed by the Newcastle–Ottawa and Jaded Scale, which evaluate the description of randomization, blinding, and dropouts used to assess the clinical trial (Tables 2, 3).

### Data Extraction and Abstraction

To extract and summarize the data, we developed an extraction form (Table 4). This form contained several elements including name, country, and period in which the model was operating. Two independent reviewers did all screening phases. Discrepancies were resolved by consultation and consensus.

### Statistical Analysis

For the meta-analysis of case–control studies, RR was transformed to natural logarithms and the 95% confidence intervals (CIs) were used to calculate the standard errors. We assumed that the true effect could vary between studies. Thus, we employed a random-effects model. We used the $I^2$ statistic and Cochran's $Q$-test to measure heterogeneity. A significant $Q$ test ($p$ value $< 0.05$) or $I2 > 50\%$ indicated the presence of heterogeneity [17].

To address heterogeneity, we carried out subgroup analyses using the following comparison groups: length of LTOT; over and under 8 months.

Sensitivity analyses were conducted by omitting each study to test the stability of the results. Finally, publication bias was evaluated using the funnel plot and Egger's test [18].

These analyses were conducted using the software Comprehensive Meta-Analysis version 3.

### Ethics

The Research Committee of Isfahan University of Medical Sciences approved the study protocol, and the Ethics Committee confirmed it (IR.MUI.MED.REC.1399.040). This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

**Table 1** Search strategy according to PICO framework

| | Concept | Synonyms |
|---|---|---|
| Population/ problem | Chronic obstructive pulmonary disease | "Asthma Chronic Obstructive Pulmonary Disease Overlap Syndrome*" or "Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome*" or "Asthma COPD Overlap Syndrome*" or "Asthma-COPD Overlap Syndrome*" or "Centriacinar Emphysema" or "Centriacinar Emphysemas" or "Centrilobular Emphysema" or "Centrilobular Emphysemas" or "chronic airflow obstruction*" or "chronic airway obstruction*" or "chronic lung obstruction*" or "chronic pulmonary obstruction*" or "chronic respiratory tract obstruction*" or "chronic respiratory obstruction*" or "Chronic bronchitis" or "Chronic Obstructive airflow" or "Chronic Obstructive airflow disease*" or "Chronic Obstructive airflow disorder*" or "Chronic Obstructive Airway" or "Chronic Obstructive Airway disease*" or "Chronic Obstructive Airway disorder*" or "chronic obstructive bronchitis" or "chronic obstructive bronchopulmonary disease" or "chronic obstructive lung" or "chronic obstructive lung disease*" or "chronic obstructive lung disorder*" or "chronic obstructive pulmonary " or "chronic obstructive pulmonary disease*" or "chronic obstructive pulmonary disorder*" or "chronic obstructive respiratory " or "chronic obstructive respiratory disease*" or "chronic obstructive respiratory disorder*" or "chronic obstructive respiratory tract disease*" or "chronic obstructive respiratory tract disorder*" or "chronic respiratory failure" or "COAD" or "COLD" or "COPD" or "emphysema" or "Focal Emphysema" or "Focal Emphysemas" or "lung chronic obstructive " or "lung chronic obstructive disease*" or "lung chronic obstructive disorder*" or "obstructive lung disease*" or "obstructive lung disorder*" or "obstructive pulmonary disease*" or "obstructive pulmonary disorder*" or "obstructive respiratory disease*" or "obstructive respiratory disorder*" or "obstructive respiratory tract disease*" or "obstructive respiratory tract disorder*" or "Panacinar Emphysema" or "Panacinar Emphysemas" or "Panlobular Emphysema" or "Panlobular Emphysemas" or "Pulmonary Emphysema" or "Pulmonary Emphysemas" or "Pulmonary chronic obstructive " or "Pulmonary chronic obstructive disease*" or "Pulmonary chronic obstructive disorder*" or "respiratory chronic obstructive " or "respiratory chronic obstructive disease*" or "respiratory chronic obstructive disorder*" or "respiratory tract chronic obstructive disease*" or "respiratory tract chronic obstructive disorder*" |
| Intervention | Long-term oxygen therapy | "Ambulatory oxygen therap*" or "home oxygen therap*" or "long-term oxygen therap*" or "Long-term supplemental oxygen therap*" or "long-term oxygen therap*" or "Long-term supplemental oxygen therap*" or "long-term o2 therap*" or "Long-term supplemental o2 therap*" or "long-term o2 therap*" or "Long-term supplemental o2 therap*" or "LTOT" or "nocturnal oxygen therap*" or "o2 administration" or "o2 therap*" or "oxygen administration" or "oxygen inhalation therap*" or "oxygen insufflation" or "oxygen supplementation" or "oxygen therap*" or "oxygen treatment" or "supplemental oxygen" or "ambulatory oxygen" or "home oxygen" or "long-term oxygen" or "Long-term supplemental oxygen" or "long-term oxygen" or "Long supplemental oxygen" or "long-term o2" or "Long-term supplemental o2" or "long-term o2" or "Long-term supplemental o2" or "LTOT" or "nocturnal oxygen" term |

**Table 1** continued

| | Concept | Synonyms |
|---|---|---|
| Comparison | – | – |
| Outcome | Readmission | "Hospital readmission" or "Hospital Readmissions" or "patient readmission" or "patient readmission*" or "readmission" or "readmission*" or "readmission rate" or "readmissions" or "reducing rehospitalization" or "reducing rehospitalisation" or "reducing readmission" or "rehospitalization" or "rehospitalizations" or "rehospitalisation" or "rehospitalisations" or "hospital re-admission" or "Hospital Re-admissions" or "patient re-admission" or "patient re-admissions" or "re-admission" or "re-admission*" or "re-admission rate" or "re-admissions" or "reducing re-hospitalization" or "reducing re-hospitalisation" or "reducing re-admission" or "re-hospitalization" or "re-hospitalisation" or "re-hospitalizations" or "re-hospitalisations" or "reduces hospital use" or "reduce hospital use" or "reducing hospital use" or "Reduce hospitalization*" or "Reduce hospitalisation*" or "Reduces hospitalization*" or "Reduces hospitalisation*" or "Reducing hospitalization*" or "Reducing hospitalisation*" or "reduces risk of hospitalization*" or "reduces risk of hospitalisation*" or "reducing risk of hospitalization*" or "reducing risk of hospitalisation*" or "reduce risk of hospitalization*" or "reduce risk of hospitalisation*" or "reducing hospital admission*" or "reduce admission*" or "reducing admission*" or "reduces admission*" or "reduce hospital admission*" or "reducing hospital admission*" or "reduces hospital admission*" or "reduce patient admission*" or "reducing patient admission*" or "reduces patient admission*" or "reduce admittance*" or "reducing admittance*" or "reduces admittance*" or "reduce hospital admittance*" or "reducing hospital admittance*" or "reduces hospital admittance*" or "reduce patient admittance*" or "reducing patient admittance*" or "reduces patient admittance*" or "reduce admitting*" or "reducing admitting*" or "reduces admitting*" or "reduce hospital admitting*" or "reducing hospital admitting*" or "reduces hospital admitting*" or "reduce patient admitting*" or "reducing patient admitting*" or "reduces patient admitting*" or "reduce admission to hospital*" or "reduces admission to hospital*" or "reducing admission to hospital*" or "reduce admissions to hospital*" or "reduces admissions to hospital*" or "reducing admissions to hospital*" or "reduce admitting to hospital*" or "reduces admitting to hospital*" or "reducing admitting to hospital*" or "reduce admittance to hospital*" or "reduces admittance to hospital*" or "reducing admittance to hospital*" or "rehospitalisation*" or "rehospitalization*" or "re-hospitalisation*" or "re-hospitalization*" or "readmission*" or "re-admission*" or "reduction in hospital admission*" or "reduction in hospital admitting*" or "reduction in hospital admittance*" or "reduction in patient admission*" or "reduction in patient admitting*" or "reduction in patient admittance*" or "reduction in admission*" or "reduction in admitting*" or "reduction in admittance*" or "reduction of hospital admission*" or "reduction of hospital admitting*" or "reduction of hospital admittance*" or "reduction of patient admission*" or "reduction of patient admitting*" or "reduction of patient admittance*" or "reduction of admission*" or "reduction of admitting*" or "reduction of admittance*" or "frequency of hospitalization*" or "frequency of hospitalization*" or "frequency of admission*" or "frequency of admitting" or "frequency of admittance" or "rate of hospitalization*" or "rate of hospitalization*" or "rate of admission*" or "rate of admitting" or "rate of admittance" or "hospitalization frequenc*" or "hospitalisation frequenc*" or "hospitalizations frequenc*" or "hospitalisations frequenc*" or "admission frequenc*" or "admissions frequenc*" or "admitting frequenc*" or "admittance frequenc*" or "reduces deaths or hospitalization*" or "reduces deaths or hospitalisation*" or "reduce deaths or hospitalization*" or "reduce deaths or hospitalisation*" or "reducing deaths or hospitalization*" or "reducing deaths or hospitalisation*" |

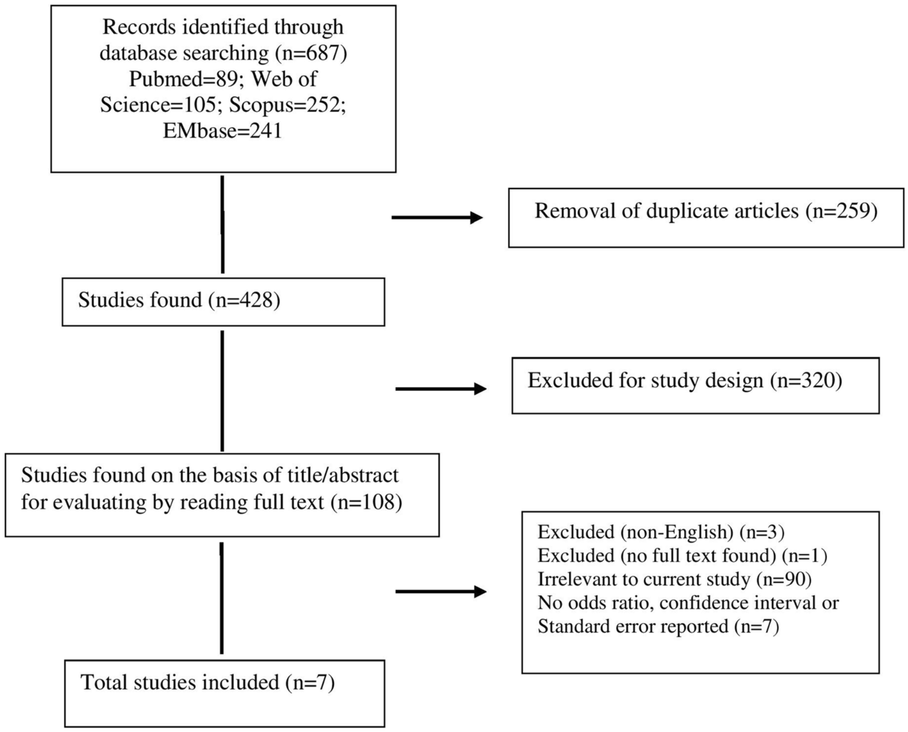



**Fig. 1** Flow diagram of study selection process

# RESULTS

## Literature Search Results

A total of 687 studies were identified using keywords in the initial database search. After the removal of duplicate articles and reviewing 428 titles and abstracts, 108 full-text articles were retrieved and assessed for eligibility. During the processing process, the two reviewers had no disagreement on involving studies and 14 studies met the inclusion criteria in the qualitative analysis. After failing to receive the data required to perform the analysis for one study, seven studies were included in our final quantitative analysis.

Sub-group analysis has been performed based on the length of LTOT; over and under 8 months (Fig. 2). Information on the seven studies that met the eligibility criteria is shown in Table 4. All of the variables such as sex, age, COPD grade, smoking, FEV1, outcome, and length of LTOT treatment were entered systematically and due to the low number of studies in every variable, we could not enter in meta-analysis.

In the pooled analysis, the RR [CI 95%, $p$ value], $I^2$ for readmission reduced 1.542 [1.284–1.851, < 0.001], $I^2 = 60\%$, and 1.693 [1.645–1.744, < 0.001, $I^2 = 60\%$] for patients with length of LTOT treatment under and above 8 months, respectively. A forest plot of the total and subgroup analysis is presented in Fig. 2.

Accordingly, comparing the two subgroups shows that the rate of readmission in COPD patients who have received LTOT for more than 8 months is lower than those who have received LTOT for less than 8 months in comparison with the patients who have not received LTOT. A sensitivity analysis was conducted by systematically omitting each study, and it showed no influential studies. Egger's test indicated no publication bias ($p = 0.64$).

As shown in Table 2, characteristics of included studies have been classified based on countries including the USA, west Malaysia,

**Table 2** Assessment of cohort studies through Newcastle–Ottawa Scale

| Items | Selection | | | | Comparability | Outcome | | | Total score |
|---|---|---|---|---|---|---|---|---|---|
| | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at the start of study | | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | |
| Sana' M.H. Al Aqqad (2015) | * | – | – | * | * | * | * | – | 5 |
| González (2004) | – | * | – | * | ** | * | * | – | 6 |
| Cruz Gonzalez (2008) | – | * | – | * | ** | * | * | – | 6 |
| Kyoung Hee Cho (2015) | * | * | – | * | ** | * | * | – | 7 |
| Alice M Turner (2014) | * | * | – | * | ** | * | * | * | 8 |
| Maurizio Rizzi (2008) | * | * | * | * | ** | * | * | * | 9 |

Table 3 Assessment of clinical trials through Jadad Scale

| | 1. Is this a RCT study? | 2. Reported as randomized | 3. Randomization is appropriate | 4. Double blinding is reported | 5. Double blinding is appropriate | 6. Withdrawals are reported by number and reason per arm | 7. Jadad score (/5) |
|---|---|---|---|---|---|---|---|
| Aboumatar (2019) | Yes | Yes | Yes | No | Not described | Yes | 3 |

Korea, Spain, Italy, and Birmingham East and North, type of studies including a clinical trial, retrospective cohort study, and prospective cohort study, year of study as well as other variables such as age, gender, mortality, ICU admission, COPD grade, smoking, etc.

## DISCUSSION

Based on our results in this systematic review, LTOT at home was associated with a significantly lower risk ratio of hospital readmission.

Recently, the frequency of exacerbations has been considered a noteworthy criterion to be measured in patients suffering from COPD. Frequent exacerbations are attributed to advanced impairment of lung function. Furthermore, as a result of increased disease severity, exacerbations became more frequent and severe [19]. In addition, the frequency of hospital admission is considered a prognostic factor with the higher frequency of hospital admission at any time after discharge but does not rise the risk of mortality [20].

Consistent with our findings in this meta-analysis, an early study from the 1970s and two other studies, all including a small number of patients acting as their control, have indicated that LTOT reduces the number of hospitalizations [16, 21–23]. The first months of LTOT were found to be associated with a noteworthy decrease in the number of days spent in the hospital when compared to the pre-oxygen period [8] and also LTOT is concomitant with a reduction in hospitalization in patients with hypoxemic chronic obstructive pulmonary disease [8, 24]. It seems that any effect of oxygen therapy on hospitalization could have resulted from improving attacks of severe desaturations and alleviating pulmonary hemodynamics [25–27].

Oxygen therapy could reduce dyspnea by decreasing the demanding effort for breathing and preventing anxiety and distress development, consequently avoiding hospitalization of some COPD patients in stable conditions even without permanent hypoxemia [28].

Cho et al. revealed that HOT was associated with a 27% decreased risk of hospitalization only in patients with COPD grade 1 (FEV1 of $\leq$ 25% or a resting PaO2 of $\leq$ 55 mmHg) and a 65% decreased risk after matching. Also, in COPD patients with other grades of COPD, similar results related to HOT treatment were not observed [11]. It was concluded that physicians could prescribe HOT according to the clinical status of patients [11].

Nevertheless, most previous studies have shown a consistent tendency to oxygen therapy in patients with severe hypoxemia in whom HOT was associated with decreased hospital admissions. However, there is a discrepancy between the confirmed documents related to the rule of LTOT treatment in the number of readmissions in COPD patients.

Indeed, a randomized control group that was conducted with Medical Research Council (MRC) study failed to approve this advantage of LTOT [7].

Ringbaek et al. [10] designated that HOT was not effective in lessening the hospitalization rate in patients with moderate hypoxemia. One recent paper recommended that oxygen use outside the National Institute for Health and Care Excellence (NICE) guidance did not seem to prevent admissions [12].

**Table 4** Characteristics and outcomes of included studies

| Source, country, year | Gender | Age | Study type | Study population (number of study and control group) | Number of readmissions | ICU admission number (%) | OR (CI% 95) | Number and/or percent of deaths | COPD grade number (%) | Smoking number (%),P/Y | FEV1% |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hanan Aboumatar et al. USA (2019) | M/F | > 40 years (Mean): LTOT: 63.9 ± 9.6 Non LTOT: 66.0 ± 10.0 | Randomized clinical trial | LTOT: 119 Non LTOT: 120 | LTOT: 202 Non LTOT: 137 | – | 1.400 (1.097–1.786) | LTOT: 8 (6.7%) Non LTOT: 7 (5.8%) | – | LTOT: 49 (40.8%) Non LTOT: 43 (35.8%), > 10 | Mean (SD): LTOT: 33.3 (16.0) Without LTOT: 35.8 (14.2) |
| Sana' M.H. Al Aqqad et al. West Malaysia (2015) | M/F | > 40 years (Median): 70.1 | Retrospective cohort study | 259 patients No control group | Risk of readmission: 34% for 1 year 43.2% for 3 years, 48.6% for 5 years | – | 2.990 (1.505–5.939) | 26.3% for 1 year, 49.8% for 3 years, 59.5% for 5 years | – | Frequency: 123 (47.5%), 20 | – |

**Table 4** continued

| Source, country, year | Gender | Age | Study type | Study population (number of study and control group) | Number of readmissions | ICU admission number (%) | OR (CI% 95) | Number and/or percent of deaths | COPD grade number (%) | Smoking number (%),P/Y | FEV1% |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Kyoung Hee Cho et al. Korea (2015) | M/F | > 40 years<br>Mean (SD):<br>LTOT:<br>67.4 (9.7)<br>Non LTOT:<br>68.0 (9.9) | Retrospective cohort study | LTOT: 1239<br>Non LTOT: 1239 | Grade 1:<br>LTOT: 244<br>Non LTOT: 319<br>Grade 2:<br>LTOT: 291<br>Non LTOT: 128<br>Grade 3:<br>LTOT: 245<br>Non LTOT: 81<br>No Grade:<br>LTOT: 1409<br>Non LTOT: 322 | LTOT: 9 (39.1%)<br>Non LTOT: 12(60.9%) | 1.650 (1.249–2.179) | – | Grade 1:<br>LTOT: 91 (43.1%)<br>Non LTOT: 120 (56.9%)<br>Grade 2:<br>LTOT: 102 (55.7%)<br>Non LTOT: 81 (44.3%)<br>Grade 3:<br>LTOT: 110 (61.1%)<br>Non LTOT: 70 (38.9%)<br>No Grade:<br>LTOT: 936 (49.2%)<br>Non LTOT: 968 (50.8%) | – | – |

**Table 4** continued

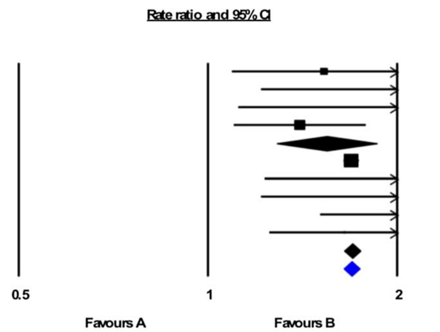
| Source, country, year | Gender | Age | Study type | Study population (number of study and control group) | Number of readmissions | ICU admission number (%) | OR (CI% 95) | Number and/or percent of deaths | COPD grade number (%) | Smoking number (%),P/Y | FEV1% |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dra C. González et al. Spain (2004) | M | Mean (SD): 69.3 (7.5) | Prospective cohort study | LTOT: 30% ($n$ = 27) $N$ = 90 patients | Readmission in LTOT vs. Non LTOT: 66.7 vs. 34.3<br>Readmission in LTOT > 8 m vs. LTOL < 8 m: 68.2 vs. 36.1<br>13 patients (14.4%) were readmitted<br>Total readmissions number in 3-month period was 16 | – | < 8 months: 2.500 (1.213–5.154)<br>> 8 months:2.770 (1.229–6.245) | – | Moderate to severe COPD | 48 (57%), 75.3 | Mean (SD): 43.03 (8.1) |
| Cruz Gonzalez et al. Spain (2008) | M | Mean (SD): 69.3 (7.5) | Cohort study | LTOT: 30% ($n$ = 27) $N$ = 112 patients | Readmission in LTOT vs. Non LTOT: 66.7 vs. 34.3<br>Readmission in LTOT > 8 m vs. LTOL < 8 m: 68.2 vs. 36.1 36 patients (32.1%) for acute exacerbations Total number of hospital readmissions in the group was 73 | – | < 8 months: 2.100 (1.115–3.954)<br>> 8 months:2.500 (1.213–5.154) | – | Moderate to severe COPD | – > 10 | Mean (SD): 43 (12) |

**Table 4** continued

| Source, country, year | Gender | Age | Study type | Study population (number of study and control group) | Number of readmissions | ICU admission number (%) | OR (CI% 95) | Number and/or percent of deaths | COPD grade number (%) | Smoking number (%),P/Y | FEV1% |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Maurizio Rizzi et al. Italy (2008) | M/F | Mean (SD): 70 (6) LTOT: 68 (10) Non LTOT: 66(12) | Prospective two parallel cohorts follow-up | LTOT: 108<br>Non LTOT: 109 | About 2 units lower emergency department visits in "Non LTOT" group<br>Baseline "LTOT-Non LTOT" difference of ordinary admissions:<br>– 0.196<br>10 year "LTOT-non LTOT" difference of the numbers of ordinary admissions: – 0.616 | LTOT patients had a lower number of admissions to the ICU (_0.5unit) | 1.690 (1.641–1.741) | Overall mortality during follow-up: 63% | Severe | – | Mean (SD): LTOT:<br>30 (10)<br>Non LTOT: 29(8) |
| Alice M Turner et al. Birmingham East and North (2014) | M/F | Median (IQR): LTOT: 72.82 (0.72)<br>Non LTOT: 73.95 (65.47–81.00 | Cohort-retrospective study | LTOT: 189<br>Non LTOT: 706 | Median (IQR) of readmission in 895 patients with COPD diagnosis confirmed by spirometry: LTOT: 2 (1–4)<br>Non LTOT: 1 (1–2) Readmission was more likely in LTOT users (3.18 vs. 1.67 readmissions/per patient, $p < 0.001$) considering all 1942 patients identified with COPD | – | 1.530 (1.089–2.149) | 64% ($n$ = 176) of patients who received oxygen died during the follow-up period | – | – | Median (IQR): LTOT: 35 (27–50)<br>Non LTOT: 51 (37–70) |

*LTOT* long-term oxygen therapy, *OR* odds ratio, *CI* confidence interval, and P/Y pack/year

| Group by Subgroup within study | Study name | Subgroup within study | Rate ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|---|
| <8 months | Alice M Turner et al., 2014 | <8 months | 1.530 | 1.089 | 2.149 | 2.454 | 0.014 |
| <8 months | Cruz Gonzalez et al., 2003 (2) | <8 months | 2.500 | 1.213 | 5.154 | 2.482 | 0.013 |
| <8 months | Cruz Gonzalez et al., 2008 (2) | <8 months | 2.100 | 1.115 | 3.954 | 2.298 | 0.022 |
| <8 months | Hanan Aboumatar et al., 2019 | <8 months | 1.400 | 1.097 | 1.786 | 2.709 | 0.007 |
| <8 months | | | 1.542 | 1.284 | 1.851 | 4.644 | 0.000 |
| >8 months | Maurizio Rizzi et al., 2009 | >8 months | 1.690 | 1.641 | 1.741 | 34.751 | 0.000 |
| >8 months | Cruz Gonzalez et al., 2003 (1) | >8 months | 2.770 | 1.229 | 6.245 | 2.456 | 0.014 |
| >8 months | Cruz Gonzalez et al., 2008 (1) | >8 months | 2.500 | 1.213 | 5.154 | 2.482 | 0.013 |
| >8 months | Sana M.H.A Aqqad et al., 2015 | >8 months | 2.990 | 1.505 | 5.939 | 3.128 | 0.002 |
| >8 months | Kyoung Hee Cho et al., 2015 | >8 months | 1.650 | 1.249 | 2.179 | 3.529 | 0.000 |
| >8 months | | | 1.693 | 1.645 | 1.744 | 35.169 | 0.000 |
| Overall | | | 1.690 | 1.641 | 1.739 | 35.461 | 0.000 |




Meta Analysis

**Fig. 2** Forest plot of the total and subgroup analysis (representing odds ratio in patients with length of LTOT treatment under and above 8 months)

Furthermore, in many previous studies, FEV1% could be considered a predictor of acute exacerbation hospitalization [29, 30]. In addition, several studies [14, 20, 31] showed that the risk of readmission was high in LTOT users, especially after adjustment for severity variables such as predicted FEV1 or $PaO_2$ [14].

Indeed, the excess risk of re-admission in patients with COPD associated with medical care-related factors might be partially due to confounding by indication [11]. This discrepancy in the result part may be explained that patients receiving oxygen therapy have chronic respiratory failure and more severe disease [13]. In addition, patients with COPD who treat with constant oxygen therapy at home have inadequate effort and exercise ability, which might affect morbidity and mortality [14].

However, our meta-analysis showed that LTOT at home was associated with a significantly lower risk ratio of readmission in the hospital.

Long-term home oxygen therapy improved survival in severe hypoxemia of COPD patients [32] and several measures of health-related quality of life functional status and gas exchange were improved with LTOT treatment [33].

Patients with oxygen-dependent COPD with impaired exercise tolerance and health-related quality of life [34] usually experience more anxiety and depression leading to social isolation and restrictions in daily life activities, and also a high risk of hospitalizations associated with suffering and high health care costs [14]. Thus, it is critical to explore factors influencing these measurements. In our meta-analysis, it has been shown that LTOT at home was associated with a noteworthy lower risk ratio of readmission in hospitals. There are fairly complex reasons for emergency room visits and hospital admissions in COPD patients [35].

This study has several limitations. Firstly, we were not capable of assessing some factors that could potentially influence hospital admissions. For example, we had no data on smoking history, body mass index, health behaviors, use of systemic corticosteroids, laboratory results, etc. Secondly, due to a lack of sufficient information on systematic review variables, we could not analyze other variables that will be influenced in the result section. Finally, the sample sizes in the studies necessitate larger RCTs to evaluate the effect of LTOT on readmission in COPD patients.

## CONCLUSIONS

Based on our results in this systematic review, LTOT at home was associated with a significantly lower risk ratio of hospital readmission. However, the sample sizes in the studies necessitate larger RCTs to evaluate the effect of LTOT on readmission in COPD patients.

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***Compliance with Ethics Guidelines.*** The Research Committee of Isfahan University of Medical Sciences approved the study protocol, and the Ethics Committee confirmed it (IR.MUI.MED.REC.1399.040). This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the author.

***Data Availability.*** The collection of papers/data used for this review article is available from the corresponding author on reasonable request.



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