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Short communication

Hypoxemia severity and survival in ILD and COPD on long-term oxygen therapy – The population-based DISCOVERY study

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ABSTRACT

Background and aim: Whether long-term oxygen therapy (LTOT) improves survival in interstitial lung disease (ILD) is unclear. A recent study reported similar survival in ILD patients with severe hypoxemia on LTOT vs. moderate hypoxemia without LTOT, and proposed that LTOT could be indicated in ILD already at moderate hypoxemia. The aim of this study was to compare survival by severity of hypoxemia in patients with ILD and COPD, respectively, *treated with LTOT*.

Methods: A population-based, longitudinal study of adults starting LTOT for ILD or COPD 1987–2018. Transplant-free survival was compared between moderate (PaO₂ 7.4–8.7 kPa) and severe (PaO₂ <7.4 kPa) hypoxemia using Cox regression, adjusted for age, sex, BMI, smoking status, WHO performance status, year of starting LTOT, diagnosis of heart failure, ischemic heart disease and diabetes mellitus.

Results: In total, 17,084 patients were included, with ILD and moderate (n = 470) or severe hypoxemia (n = 2,408), and COPD with moderate (n = 2,087) or severe hypoxemia (n = 12,119). Compared with in COPD, ILD patients on LTOT had lower transplant-free survival after one year (41.9 vs. 67.1%) and two years (20.3 vs. 46.5%). In COPD worse hypoxemia was associated with slightly increased risk of death/lung transplantation, aHR 1.07 (1.00–1.14), a difference not shown in ILD, aHR 0.91 (0.80–1.03).

Conclusion: Transplant-free survival did not differ in ILD patients between moderate and severe hypoxia despite LTOT.

1. Introduction

Long-term oxygen therapy (LTOT) improves survival of patients with chronic obstructive pulmonary disease (COPD) and severe resting hypoxemia, but its effect in moderate hypoxemia and in other conditions such as interstitial lung disease (ILD) is unclear [1]. The large Long-Term Oxygen Therapy Trial (LOTT) found no benefit from LTOT in moderate resting hypoxemia, but all evidence to date pertain only to patients with chronic obstructive pulmonary disease (COPD) [2]. Severe ILD such as idiopathic pulmonary fibrosis is characterized by progressive deterioration, hypoxemia and short survival [3], and is the second most common reason for starting LTOT [4].

A recent observational study [5] reported markedly higher mortality in patients with ILD (n = 205) than COPD (n = 38). A key finding was that ILD patients with moderate hypoxemia (PaO₂ 7.4–8.0 kPa without or 8.0–8.7 mmHg with hypoxic organ damage) not treated with LTOT

had similar mortality as patients with severe hypoxemia (PaO₂ <7.4 kPa without or 7.4–8.0 kPa with hypoxic organ damage), whom all received LTOT in accordance to international guidelines [1]. Based on these findings, the authors hypothesized that LTOT might be indicated earlier in ILD than COPD - already in moderate hypoxemia to improve the outcomes in ILD. If true, this hypothesis would be supported by observing improved survival in ILD patients with moderate hypoxemia compared with severe hypoxemia *when receiving LTOT*, but no such data has been available as yet. The aim of this study was to compare transplant-free survival between patients with moderate vs. severe hypoxemia in ILD and COPD *treated with LTOT*.

2. Methods

This was a population-based, longitudinal study of adults starting LTOT for ILD or COPD between 1987 and 2018 in the ‘Course of Disease

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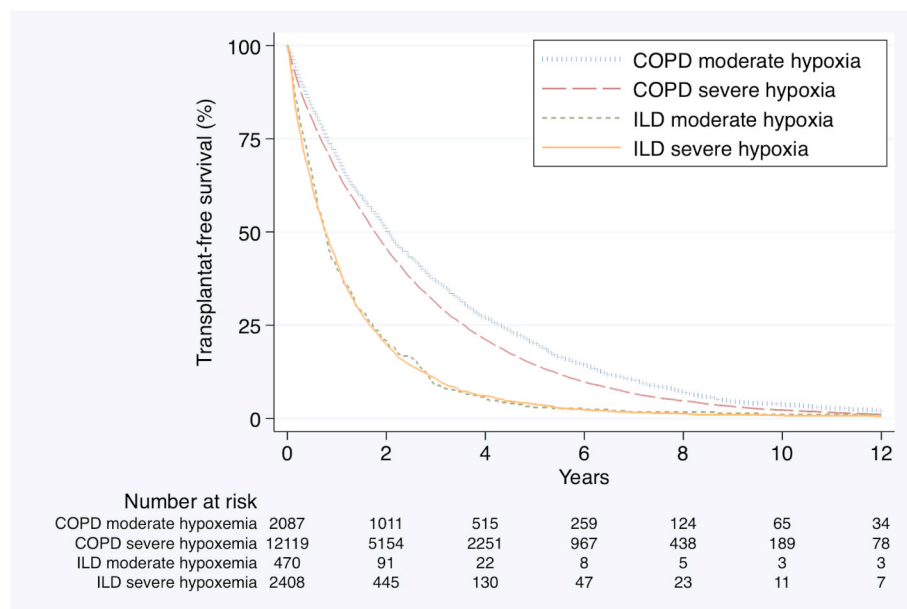


Fig. 1. Kaplan-Meier survival estimates for hypoxemia subgroups of patients with interstitial lung disease (ILD) and chronic obstructive pulmonary disease (COPD) on treatment with long-term oxygen therapy (LTOT). Mortality was higher in patients with ILD than with COPD. There was no difference in transplant-free survival between patients with moderate (PaO_2 7.4–8.7 kPa) and severe hypoxemia ($\text{PaO}_2 < 7.4$ kPa) on air breathing in ILD but in COPD when adjusting for age, sex, smoking history, WHO performance status, year of starting LTOT and comorbidities at baseline (heart failure, ischemic heart disease and diabetes mellitus) in a multivariable Cox regression model.

In patients reported to the Swedish CPAP Oxygen and Ventilator Registry (DISCOVERY) database [6]. The study was approved by the Swedish Ethical Review Board (DNr: 2018/51).

In this study, severe hypoxemia was defined as $\text{PaO}_2 < 7.4$ kPa, and moderate hypoxemia as PaO_2 7.4–8.7 kPa on air breathing. Comorbidity data was obtained from the National Patient Registry [7] and mortality data from the Swedish Causes of Death Registry [8]. Associations with mortality was analysed using Cox regression, adjusted for age, sex, BMI, smoking status (current, former, never smoker), WHO performance status, year of starting LTOT, diagnosis of heart failure, ischemic heart disease and diabetes mellitus. Statistical analyses were conducted using Stata, version 16.0 (StataCorp LP; College Station, TX).

3. Results

Baseline characteristics by diagnosis and hypoxemia severity are presented in [supplementary table 1](#). A total of 17,084 patients were included, comprising ILD patients with moderate ($n = 470$) and severe hypoxemia ($n = 2,408$) and COPD patients with moderate ($n = 2,087$) and severe hypoxemia ($n = 12,119$). Compared to those with COPD, patients with ILD were older (75.2 ± 9.2 vs. 73.3 ± 8.4 years), more often men (62.4 vs. 42.8%), more often never smokers (36.4 vs. 4.4%), had a higher mean BMI (25.5 ± 4.9 vs. 23.7 ± 6.2), more ischemic heart disease (27.4 vs. 23.1%), diabetes (16.9% vs. 10.7%), but less heart failure (33.3 vs. 37.4%) at baseline, $p < 0.001$ for all comparisons. There were no differences between diagnoses in PaO_2 (breathing air) (6.6 ± 1.0 vs. 6.6 ± 0.9 kPa, $p = 0.30$) or WHO performance status ($p = 0.41$).

During the study period 16,004 (92.3%) died and 42 ILD patients (1.4%) compared to 92 COPD patients (0.6%), $p < 0.001$ underwent lung transplantation. Survival by severity of hypoxemia in ILD and COPD is shown in [Fig. 1](#). ILD patients had lower transplant-free survival after one year (41.9 vs. 67.1%) and two years (20.3 vs. 46.5%) on LTOT. Median transplant-free survival time was 0.76 years [95% confidence interval] 0.68–0.84) in ILD with moderate hypoxemia and 0.77 years (0.72–0.83) with severe hypoxemia and 2.03 years (1.93–2.14) in COPD with moderate hypoxemia and 1.77 years (1.72–1.83) with severe hypoxemia. COPD patients with severe hypoxemia had increased risk of death/lung transplantation compared to those with moderate hypoxemia; aHR 1.07 (1.00–1.14), a difference not shown in patients with ILD, aHR 0.91 (0.80–1.03). In sensitivity analysis, there was also a difference in risk of death/lung transplantation in patients with severe hypoxemia

compared with mild hypoxemia at rest (PaO_2 [air] > 8.0 kPa) in patients with COPD ($n = 396$), aHR 1.17 (1.01–1.35) but not in patients with ILD ($n = 109$), aHR 1.09 (0.85–1.41).

4. Discussion

The main finding of this national cohort study was that transplant-free survival did not differ in ILD patients with moderate and severe hypoxemia despite LTOT. Presence of moderate or even mild resting hypoxemia is a strong marker of poor prognosis in ILD and these patients should be optimally treated and monitored and the option of lung transplantation should be considered early. The markedly shorter survival in ILD than COPD likely reflects the more severe and progressive disease trajectory of ILD. This study does not support the previous proposal that LTOT improves survival in patients with ILD and moderate hypoxemia and that indications for LTOT should be redefined [5].

Strengths of the present study are the large, nationwide cohort of patients treated with LTOT, with complete follow-up using mandatory national registries and high internal and external validity of LTOT data [4,9]. With an estimated completeness of 85–90% the study is population-based in regard to patients starting LTOT. Specific diagnoses in the ILD group have been validated to pertain mostly (77%) to idiopathic pulmonary fibrosis [10]. A potential limitation is that patients starting LTOT with moderate hypoxemia may be more likely to have hypoxemia related complications including heart failure (as part of the indication of LTOT at a PaO_2 7.4–8.0 kPa) [1]. Therefore, the analyses were adjusted for diagnosed ischemic heart disease and heart failure at initiation of LTOT. Moreover, findings were similar when analysing patients with mild hypoxemia ($\text{PaO}_2 > 8.0$ kPa).

5. Conclusion

Transplant-free survival did not differ in ILD patients with moderate and severe hypoxemia despite LTOT.

CRediT authorship contribution statement

Andreas Palm: Data curation, Formal analysis, Methodology, Visualization, Writing – review & editing. **Magnus Ekström:** Conceptualization, Methodology, Writing – original draft.

Declaration of competing interest

No conflicts of interest exist for the authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmed.2021.106659>.

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