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Original Research

Breathlessness and exercise performance to predict mortality in long-term oxygen therapy – The population-based DISCOVERY study

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ABSTRACT

Background: Patients with chronic respiratory failure treated with long-term oxygen therapy (LTOT) often have severe breathlessness, impaired exercise performance, and high but variable mortality that is difficult to predict. We aimed to evaluate breathlessness and exercise performance upon starting LTOT as predictors of overall and short-term mortality.

Methods: This was a longitudinal, population-based study of patients who initiated LTOT between 2015 and 2018 in Sweden. Breathlessness was measured using the Dyspnea Exertion Scale, and exercise performance using the 30s-Sit-To-Stand test. Associations with overall and three-month mortality were analyzed using Cox-regression. Subgroup analyses were performed for patients with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) respectively. The predictive capacity of models was assessed using a C-statistic.

Results: A total of 441 patients (57.6% female, aged 75.4 ± 8.3 years) were analyzed, of whom 141 (32%) died during a median follow-up of 260 (IQR 75–460) days. Both breathlessness and exercise performance were independently associated with overall mortality in the crude models, but only exercise performance remained independently associated with overall mortality when models were adjusted for other predictors, when short-term mortality was analyzed, or when breathlessness and exercise capacity were analyzed concurrently. The multivariable model including exercise performance but not breathlessness provided a relatively high predictive capacity for overall mortality, C-statistic 0.756 (95% CI 0.702–0.810). Similar results were seen in the COPD and ILD subgroups.

Conclusion: Exercise performance as measured by the 30s-STS may be useful to identify patients with higher mortality on LTOT for optimized management and follow-up.

1. Introduction

Long-term oxygen therapy (LTOT) improves survival in patients with chronic pulmonary obstructive disease (COPD) and severe resting hypoxemia [1,2]. In clinical practice, LTOT is also prescribed using the same criteria for patients with severe hypoxemia due to other conditions than COPD, such as interstitial lung disease (ILD) [3]. Despite LTOT, mortality remains high among patients with chronic respiratory failure, with more than half of all patients dying within two years after starting treatment [4–6]. Individual survival is however variable, and in one previous study of patients with LTOT due to COPD, 25% of the study population lived for four years or more after treatment initiation [5].

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Known predictors of mortality in LTOT include baseline age, sex, pulmonary function, and comorbidities, but their predictive capacity however remain limited, and no clinically useful model or set of predictors for mortality in LTOT exists today [5–8].

Patients with LTOT often experience severe breathlessness and impaired exercise performance, both factors known to associate with worse outcomes in COPD and ILD [9–13]. Simple and clinically feasible methods exist for assessing these factors, and routine assessment of symptom burden and impairments in functional capacity is recommended in the management of patients across these respiratory conditions [14–17]. However, no study has evaluated the predictive ability of breathlessness or exercise performance for mortality in patients with LTOT. Identifying such predictors is important as it could help clinicians identify vulnerable patients in need of optimized management, including pulmonary rehabilitation, identification and treatment of comorbidities, and intensified follow-up.

The aim of this study was to evaluate breathlessness and exercise performance at starting LTOT as predictors of overall and short-term mortality in patients with chronic respiratory failure.

2. Material and methods

2.1. Study design and population

This was a longitudinal analysis of the population-based, national DISCOVERY (Course of DIsease in patients reported to the Swedish CPAP Oxygen and VEntilator RegistrY) database [18]. DISCOVERY is based on the Swedish National Registry for Respiratory Failure (Swedevox), which covers an estimated 90% of all patients who have started LTOT in Sweden since 1987. The registry has previously been validated against medical records for key variables [19]. Data on breathlessness and exercise performance have been reported since 2015 [20].

In this study, data on patients aged ≥18 years who initiated LTOT due to any cause between January 2015 and March 2018 were cross-linked with data from the Swedish National Patient Registry (NPR) for identification of co-morbidities, and the Swedish Causes of Death Registry for longitudinal mortality data [18,21]. Patients prescribed other types of oxygen therapy such as palliative oxygen or oxygen for exertional desaturation were not included in the database. Patients without data on breathlessness and exercise performance were excluded from analysis. For patients starting LTOT more than once during the study period, only the latest LTOT episode was analyzed. End of follow-up was March 9th, 2018.

3. Ethical considerations

The study protocol was approved by the Ethics Committee at the Medical Faculty at Lund University and the Swedish Ethical Review Authority, Dnr. 2018/51, 2019-01420, 2020–02721, 2021–04984, 2022-00745, and 2022-02012. According to Swedish law, patients entering a national quality registry like Swedevox are informed, can withdraw from registration at any time, but do not sign an informed consent. The study is reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines [22].

3.1. Data and assessments

Baseline data upon initiation of LTOT was retrieved from the Swedevox registry on patient age, sex, body mass index (BMI), spirometric values, arterial blood gas values while breathing room air and supplemental oxygen, and underlying cause for starting LTOT (grouped as COPD, ILD, or other). ILD included diagnoses of idiopathic interstitial pneumonias and sarcoidosis, with a majority of patients having been diagnosed with idiopathic pulmonary fibrosis. Further baseline data included smoking history, and World Health Organization (WHO) performance status. At baseline, data was also collected on breathlessness, and exercise performance.

Breathlessness was assessed using the Dyspnea Exertion Scale (DES), a self-reported scale originally developed from the well-established modified Medical Research Council scale (mMRC) [14]. The DES includes five categories, where the lowest score of one represents lack of breathlessness while walking at own pace, and the highest score of five represents breathlessness at rest. The categories of the DES are shown in Table 1. The DES scale has previously been validated against the mMRC and has shown some advantages over the latter, such as a lower risk of ceiling effects [14]. At baseline, patients included in Swedevox are assessed with a six-degree DES variant, with an additional degree of breathlessness ("I become breathless if I walk more than 100 m on the level at my own pace") as the second to lowest score. The additional DES score used in the Swedevox assessment was in this study merged with the lowest score of one before analysis.

Exercise performance was assessed using the 30s-Sit-To-Stand test (STS), which measures functional capacity by counting how many unaided chair risings the patient can perform in 30 s, in this study using a chair of standardized height with armrests [15]. STS test results have previously been found to strongly correlate with mortality among patients with pulmonary disease, and has advantages including feasibility and ease of completion when used as an alternative to 6-min walking tests (6MWT) or handgrip strength [10,11,23,24]. Previous studies have also indicated that variations of the STS test are useful alternatives to the 6MWT for detecting exertional hypoxemia in COPD and ILD [25,26]. Inter-rater and test-retest reliability has previously been demonstrated for the 30s-STS [27].

Data on baseline comorbidities were obtained from the NPR, a Swedish governmental registry containing, among other information, diagnoses registered by physicians from inpatient (since 1987) and specialized outpatient (since 2001) care, coded according to the International Classification of Disease (ICD) [28]. In this study, heart failure was defined as ICD-10 codes I11.0, I42 or I50; diabetes mellitus as E10-14; cardiovascular disease of any type as I00-99; ischemic heart disease as I20-25; and cerebrovascular disease as I60-69. Patients were followed longitudinally for the primary endpoint of all-cause mortality using the Swedish Causes of Death register, which due to mandatory reporting laws covers all deaths among Swedish residents [29].

3.2. Statistical analyses

Baseline patient characteristics were cross-tabulated between survivors and non-survivors at the end of follow-up. A cross-tabulation was also performed between included and excluded patients to explore potential selection bias due to missing data.

Associations between breathlessness, mortality and exercise performance were analyzed using Kaplan-Meier curves and crude and multivariable Cox proportional-hazards regression [30]. Multivariable models were adjusted for relevant confounders and predictors of mortality in LTOT, based on the previous literature: age, sex, BMI, WHO performance status, blood gas analyses (arterial blood gas tension of oxygen when breathing ambient air at rest; arterial blood gas tension of oxygen when breathing oxygen at rest; arterial blood gas tension of carbon dioxide when breathing ambient air at rest), prescribed oxygen dose, smoking status, main underlying diagnosis (COPD, ILD or other), and comorbidities (diabetes mellitus, heart failure and ischemic heart disease) [5–8]. For the analysis, patients were divided into four quartiles based on their number of performed repetitions during the STS test (zero to five, six to seven, eight to ten, and 11–30 repetitions respectively). The fourth STS quartile was used as reference. A sensitivity analysis with the number of STS repetitions included as a continuous variable was also performed. Associations were analyzed both with breathlessness and exercise performance in separate models and in the same model. Separate analyses were performed for sub-cohorts defined by underlying diagnosis (COPD or ILD), as well as for three-month mortality in all

Table 1
Baseline characteristics of included patients with LTOT (n = 441), by survival status at end of follow-up.

Baseline Characteristic	All Patients n = 441	Survivors n = 300 (68%)	Non-Survivors n = 141 (32%)
Age, years	75.4 (8.3)	74.5 (8.4)	77.5 (7.8)
Female	254 (57.6%)	174 (58.0%)	80 (56.7%)
BMI, kg/m^2	24.7 (5.7)	25.0 (5.8)	24.1 (5.6)
PaO_2 on air, kPa	6.5 (0.8)	6.6 (0.8)	6.3 (0.8)
PaO_2 on oxygen, kPa	8.7 (1.2)	8.7 (1.1)	8.7 (1.2)
$PaCO_2$ on air, kPa	5.7 (1.3)	5.8 (1.3)	5.5 (1.4)
$PaCO_2$ on oxygen, kPa	6.0 (1.3)	6.0 (1.4)	5.8 (1.2)
FEV_1, L	1.2 (0.7)	1.2 (0.7)	1.2 (0.6)
FEV_1, % of predicted	51.9 (23.7)	50.5 (24.7)	54.7 (21.4)
VC, L[a]	2.1 (0.9)	2.1 (0.9)	1.9 (0.7)
FEV_1/VC	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)
Cause for starting LTOT			
COPD	271 (61.5%)	201 (67.0%)	70 (49.6%)
Interstitial Lung Disease	90 (20.4%)	46 (15.3%)	44 (31.2%)
Other[b]	79 (17.9%)	52 (17.3%)	27 (19.1%)
Missing	1 (0.2%)	1 (0.3%)	0 (0.0%)
Comorbidities			
Heart failure	173 (39.2%)	105 (35.0%)	68 (48.2%)
Diabetes mellitus	82 (18.6%)	52 (17.3%)	30 (21.3%)
Cardiovascular disease (any type)	357 (81.0%)	237 (79.0%)	120 (85.1%)
Ischemic heart disease	104 (23.6%)	57 (19.0%)	47 (33.3%)
Cerebrovascular disease	25 (5.7%)	18 (6.0%)	7 (5.0%)
Breathlessness, DES score			
1"I am able to walk at my own pace on the level without getting out of breath" *or* "I become breathless if I walk more than 100 m on the level at my own pace"	104 (23.6%)	79 (26.3%)	25 (17.7%)
1a "I am able to walk at my own pace on the level without getting out of breath"	6 (1.4%)	5 (1.7%)	1 (0.7%)
1 b "I become breathless if I walk more than 100 m on the level at my own pace"	98 (22.2%)	74 (24.7%)	24 (17.0%)
2 "I become breathless if I walk around the house or on the hospital ward on the level at my own pace"	140 (31.7%)	100 (33.3%)	40 (28.4%)
3 "I become breathless if I move around in bed or get out of bed"	89 (20.2%)	56 (18.7%)	33 (23.4%)
4 "I become breathless on talking"	79 (17.9%)	49 (16.3%)	30 (21.3%)
5 "I am breathless at rest"	29 (6.6%)	16 (5.3%)	13 (9.2%)
Exercise performance, STS quartile			
1 (0–5 repetitions)	130 (29.5%)	76 (25.3%)	54 (38.3%)
2 (6–7 repetitions)	100 (22.7%)	61 (20.3%)	39 (27.7%)
3 (8–10 repetitions)	114 (25.9%)	83 (27.7%)	31 (22.0%)
4 (11–30 repetitions)	97 (22.0%)	80 (26.7%)	17 (12.1%)
WHO performance status			
0	34 (7.7%)	25 (8.3%)	9 (6.4%)
1	212 (48.1%)	158 (52.7%)	54 (38.3%)
2	129 (29.3%)	78 (26.0%)	51 (36.2%)
3	36 (8.2%)	17 (5.7%)	19 (13.5%)
4	1 (0.2%)	1 (0.3%)	0 (0.0%)
Missing	29 (6.6%)	21 (7.0%)	8 (5.7%)
Ever-smokers	365 (82.8%)	258 (86.0%)	107 (75.9%)
Missing	14 (3.2%)	9 (3.0%)	5 (3.5%)

Data presented as mean (standard deviation) or n (percentage).
Abbreviations: BMI = Body Mass Index; DES = Dyspnea Exertion Test; FEV_1 = forced expiratory volume in 1 s; FEV1/VC = forced expiratory volume in 1s/vital capacity ratio; LTOT = Long-Term Oxygen Therapy; $PaCO_2$ on air = arterial blood gas tension of carbon dioxide when breathing ambient air at rest; $PaCO_2$ oxygen = arterial blood gas tension of carbon dioxide when breathing oxygen at rest; PaO_2 on air = arterial blood gas tension of oxygen when breathing ambient air at rest; PaO_2 on oxygen = arterial blood gas tension of oxygen when breathing oxygen at rest; STS = Sit-to-Stand test; VC = vital capacity; FVC = forced vital capacity; WHO = The World Health Organization.
[a] Highest of forced vital capacity and slow vital capacity.
[b] Other diagnoses including pulmonary arterial hypertension, thoracic deformities, chronic pulmonary embolism.

patients. Due to an insufficient number of deaths, no subgroup analysis was performed for short-term mortality.

The predictive ability of each model was measured using the C-statistic, with 95% confidence intervals (CIs) generated using a jackknife approach. The C-statistic describes the probability that a randomly selected patient experiencing an outcome (in this study death) had a higher risk score than another randomly selected patient who did not experience the outcome. A C-statistic of 0.800 would thus indicate that 80% of outcomes were correctly predicted by the model. Model calibration (agreement between predicted and observed outcomes) was assessed using calibration plots, generated using the derivation dataset.

Statistical analyses were conducted using Stata, version 17 (StataCorp LP; College Station, TX), with the somersd package used to estimate C-statistics and CIs, and the stcoxcal package used to generate calibration plots [31,32]. 95% CIs were used to describe statistical significance. Continuous variables with normal distributions are presented as mean with standard deviation. Continuous variables with nonnormal distributions are presented as median with interquartile range (IQR).

4. Results

4.1. Patient characteristics

Out of 3591 eligible patients starting LTOT during the study period, a total of 441 patients (57.6% female, aged 75.4 ± 8.3 years) had assessments of both breathlessness and exercise performance at baseline, and were included in analysis. Most baseline characteristics, including anthropometric data, results from blood gas analyses and pulmonary function testing, and distribution of comorbidities were similar between survivors and non-survivors, while underlying ILD and a higher WHO performance status group were more common among non-survivors (Table 1). Included and excluded patients had similar baseline characteristics (Supplemental Table S1).

During a median follow-up of 260 days (IQR 75–460), a total of 141 (32%) patients died. Among those, 39 (8.8%) patients died within the first three months after starting LTOT. No patient was lost to follow-up.

4.2. Overall mortality

In the crude Cox-regression analysis of overall mortality among all patients, higher degrees of breathlessness were significantly associated with increased mortality, as was lower exercise performance (Figs. 1–2). In multivariable analysis including either breathlessness or exercise performance, no significant associations were seen between breathlessness and overall mortality, while lower exercise performance remained associated with an increased mortality, C-statistic 0.756 (95% CI 0.702–0.810) (Table 2). Calibration plots for the multivariable models showed good calibration-in-the-large (Supplemental Figs. S1 and S2). When 30s-STS results were included as a continuous variable in the same adjusted model, the hazard ratio per additional STS repetition was 0.90 (95% CI 0.84–0.96), C-statistic 0.743 (95% CI 0.686–0.799).

When breathlessness and exercise performance was mutually adjusted for each other in the same model, only exercise performance was significantly associated with mortality, regardless of whether other confounding factors were included in the analysis, C-statistic 0.765

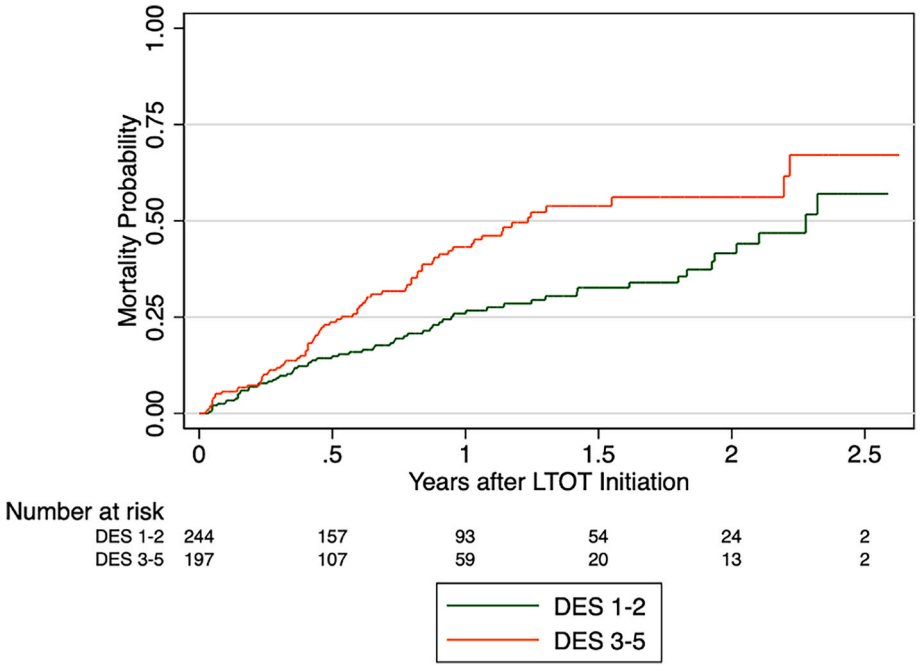

Fig. 1. Kaplan-Meier curve estimating overall crude mortality in patients with LTOT by breathlessness (DES score) at baseline.
Abbreviations: LTOT = Long-Term Oxygen Therapy; DES = Dyspnea Exertion Scale (higher numbers indicate higher degree of breathlessness).

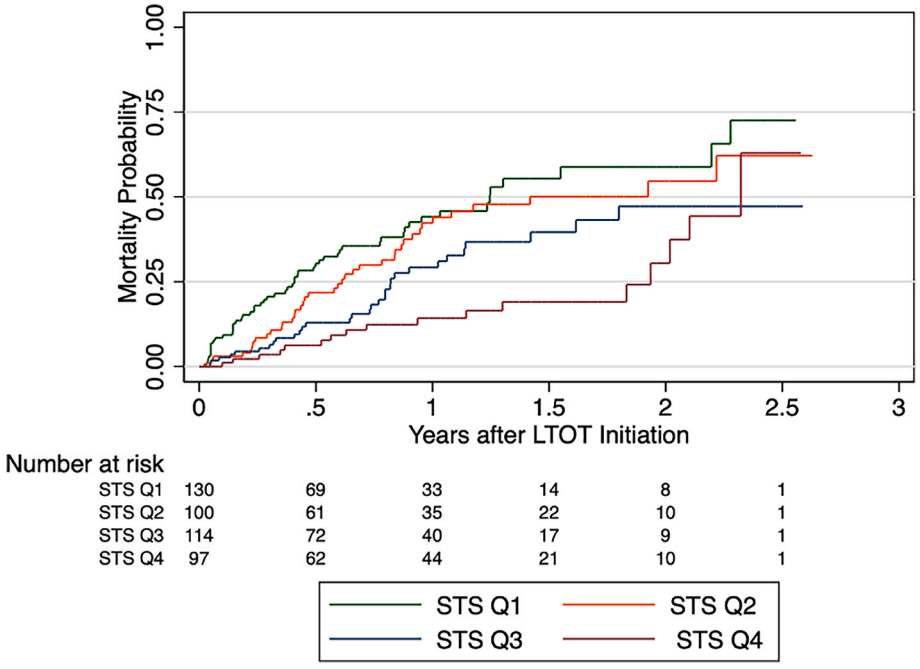

Fig. 2. Kaplan-Meier curve estimating overall crude mortality in patients with LTOT by exercise performance (STS quartile) at baseline.
Abbreviations: LTOT = Long-term Oxygen Therapy; STS = Sit-to-Stand Test quartiles (first quartile is the lowest or most unfavorable STS value); Q = Quartile.

(95% CI 0.712–0.818) (Table 3).

When patient subgroups were analyzed separately based on underlying diagnosis (COPD or ILD) using the crude model, breathlessness significantly associated with overall mortality only in the COPD subgroup, while the association between exercise performance and mortality remained significant in both subgroups. When using the multivariable model, the only association seen was between exercise performance and mortality in the ILD subgroup.

4.3. Short-term mortality

In the analysis of three-month mortality among all patients, significant associations were seen only between exercise performance and mortality, when using both the crude and adjusted models, C-statistic 0.863 (95% CI 0.809–0.915) in the adjusted model (Table 4, Supplemental Figs. S3–S4).

Table 2
Overall mortality risk in relation to breathlessness and exercise performance in patients starting LTOT.

	All patients		COPD		ILD	
	Crude HR (95% CI) n = 441	Adjusted HR (95% CI) n = 281	Crude HR (95% CI) n = 271	Adjusted HR (95% CI) n = 183	Crude HR (95% CI) n = 90	Adjusted HR (95% CI) n = 58
Breathlessness, DES score						
1	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
2	1.2 (0.75–2.0)	0.84 (0.43–1.7)	1.7 (0.77–4.0)	1.3 (0.43–3.7)	0.88 (0.36–2.2)	0.50 (0.11–2.2)
3	2.1 (1.2–3.5)	1.3 (0.60–2.8)	3.4 (1.5–7.7)	1.7 (0.7–4.1)	0.98 (0.35–2.7)	0.38 (0.048–3.0)
4	1.9 (1.1–3.2)	1.3 (0.65–2.8)	2.6 (1.1–6.3)	1.0 (0.37–2.8)	1.4 (0.56–3.4)	1.3 (0.31–5.6)
5	1.9 (0.97–3.7)	0.88 (0.31–2.4)	3.8 (1.4–10)	2.4 (0.75–7.8)	2.0 (0.59–6.8)	5.6 (0.30–100)
C-statistic (95% CI)	0.575 (0.525–0.625)	0.719 (0.660–0.778)	0.615 (0.546–0.686)	0.701 (0.614–0.789)	0.533 (0.436–0.629)	0.787 (0.659–0.915)
Exercise performance, STS quartile						
1 (0–5 repetitions)	3.1 (1.8–5.4)	4.5 (2.1–9.8)	2.5 (1.1–5.6)	2.5 (0.76–8.3)	6.3 (2.1–19.3)	14.9 (1.1–199.2)
2 (6–7 repetitions)	2.4 (1.4–4.2)	2.7 (1.2–6.1)	2.2 (0.99–5.0)	2.1 (0.64–7.1)	6.6 (2.1–21.3)	7.8 (0.59–100)
3 (8–10 repetitions)	1.7 (0.93–3.0)	1.6 (0.67–3.9)	1.7 (0.72–3.9)	1.8 (0.53–6.3)	2.8 (0.87–8.9)	2.6 (0.23–28)
4 (11–30 repetitions)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
C-statistic (95% CI)	0.634 (0.587–0.682)	0.756 (0.702–0.810)	0.590 (0.512–0.659)	0.718 (0.638–0.797)	0.665 (0.585–0.745)	0.818 (0.716–0.919)

Estimates using Cox regression, crude and adjusted for age, sex, body mass index, World Health Organization performance status, blood gas analyses (arterial blood gas tension of oxygen when breathing ambient air at rest; arterial blood gas tension of oxygen when breathing oxygen at rest; arterial blood gas tension of carbon dioxide when breathing ambient air at rest), prescribed oxygen dose, smoking, main diagnosis, and comorbidities (diabetes mellitus, heart failure and ischemic heart disease).
Abbreviations: CI = Confidence Interval; COPD = Chronic Obstructive Pulmonary Disease; DES = Dyspnea Exertion test (higher numbers indicate higher degree of breathlessness); HR = Hazard Ratio; LTOT = Long-Term Oxygen Therapy; STS = Sit-to-Stand test (first quartile is the lowest or most unfavorable STS value).

Table 3
Overall mortality in relation to breathlessness and exercise performance in patients starting LTOT, mutually adjusted models.

All patients		
	Mutually adjusted for DES and STS, without other predictors HR (95% CI) n = 441	Mutually adjusted for DES, STS and other predictors HR (95% CI) n = 281
Breathlessness, DES score		
1	1 (ref)	1 (ref)
2	1.1 (0.68–1.8)	0.62 (0.31–1.2)
3	1.6 (0.93–2.7)	0.78 (0.35–1.7)
4	1.5 (0.85–2.5)	0.70 (0.32–1.5)
5	1.3 (0.64–2.6)	0.39 (0.13–1.1)
C-statistic	0.642 (0.594–0.690)	0.765 (0.712–0.818)
Exercise performance, STS quartile		
1 (0–5 repetitions)	2.7 (1.5–4.8)	5.6 (2.4–13.0)
2 (6–7 repetitions)	2.1 (1.2–3.8)	3.2 (1.4–7.3)
3 (8–10 repetitions)	1.6 (0.86–2.9)	1.8 (0.73–4.4)
4 (11–30 repetitions)	1 (ref)	1 (ref)
C-statistic	0.642 (0.594–0.690)	0.765 (0.712–0.818)

Estimates using Cox regression, other predictors including age, sex, body mass index, World Health Organization performance status, blood gas analyses (arterial blood gas tension of oxygen when breathing ambient air at rest; arterial blood gas tension of oxygen when breathing oxygen at rest; arterial blood gas tension of carbon dioxide when breathing ambient air at rest), prescribed oxygen dose, smoking, main diagnosis, and comorbidities (diabetes mellitus, heart failure and ischemic heart disease).
Abbreviations: CI = Confidence Interval; COPD = Chronic Obstructive Pulmonary Disease; DES = Dyspnea Exertion test (higher numbers indicate higher degree of breathlessness); HR = Hazard Ratio; LTOT = Long-Term Oxygen Therapy; STS = Sit-to-Stand test (first quartile is the lowest or most unfavorable STS value).

Table 4
Three-month mortality in relation to breathlessness and exercise performance in patients starting LTOT.

	Crude HR (CI 95%) n = 441	Adjusted HR (CI 95%) n = 281
DES		
1	1 (ref)	1 (ref)
2	1.3 (0.51–3.3)	0.64 (0.17–2.4)
3	1.5 (0.57–4.1)	0.87 (0.2–3.6)
4	1.3 (0.47–4.1)	0.91 (0.23–3.7)
5	2.1 (0.60–7.0)	[a]
C-statistic	0.552 (0.464–0.639)	0.829 (0.759–0.900)
STS		
1 (0–5 repetitions)	9.8 (2.3–41.4)	11 (1.4–93)
2 (6–7 repetitions)	4.0 (0.84–18.6)	3.8 (0.42–34.3)
3 (8–10 repetitions)	2.2 (0.42–11)	1.7 (0.14–20.4)
4 (11–30 repetitions)	1 (ref)	1 (ref)
C-statistic	0.707 (0.635–0.779)	0.863 (0.809–0.915)

Estimates using Cox regression, crude and adjusted for age, sex, body mass index, World Health Organization performance status, blood gas analyses (arterial blood gas tension of oxygen when breathing ambient air at rest; arterial blood gas tension of oxygen when breathing oxygen at rest; arterial blood gas tension of carbon dioxide when breathing ambient air at rest), prescribed oxygen dose, smoking, main diagnosis, and comorbidities (diabetes mellitus, heart failure and ischemic heart disease).
Abbreviations: CI = Confidence Interval; COPD = Chronic Obstructive Pulmonary Disease; DES = Dyspnea Exertion test (higher numbers indicate higher degree of breathlessness); HR = Hazard Ratio; LTOT = Long-Term Oxygen Therapy; STS = Sit-to-Stand test (first quartile is the lowest or most unfavorable STS value).
[a] Too few cases to allow estimation.

5. Discussion

5.1. Main findings

The main finding of this study was that exercise performance (30s-STS) was significantly associated with both overall and short-term mortality, and had a relatively high predictive ability for overall mortality in multivariable models. Breathlessness (DES) did not associate with mortality in multivariable models or in analyses of short-term mortality. Similar results were seen in subgroup analyses based on underlying diagnosis (COPD or ILD).

This study provides evidence that the 30s-STS may be a useful method of identifying patients on LTOT who have a higher risk of long- and short-term mortality. This finding is consistent with a previous study where the 30s-STS predicted mortality in all stages of COPD [24]. In patients with LTOT, previous research has identified other predictors of mortality, such as age, sex, and performance status, many however with a relatively weak predictive capability [5,7,8]. In contrast, multivariable models including exercise performance provided a relatively strong predictive capacity in our study.

While breathlessness, as measured with the mMRC scale, has previously been shown to predict mortality among patients with different types of pulmonary disease, this was not the case in our study [12,13]. This discrepancy may be caused by our use of the DES instead of the mMRC, or by differences in underlying disease or disease severity. Patients with LTOT are known to report high degrees of breathlessness, which may cause ceiling effects and lack of differentiation despite the use of the DES scale.

5.2. Strengths and limitations

Strengths of this study include the multicenter, population-based sample of patients with chronic respiratory failure, with baseline and longitudinal survival data available from registries with high coverage and validity [19]. During the study period, indications for LTOT initiation remained stable, and no patient was lost to follow-up due to mandatory reporting of mortality data nationwide. The number of included patients allowed multivariable analysis, including several factors previously known to associate with mortality in LTOT, which strengthens the validity of the findings. Available baseline characteristics were similar between included and excluded patients in the DISCOVERY database.

Limitations of this study include primarily the risk of selection bias. Out of 3600 patients, only 441 had registered DES and STS scores, with most lacking a completed STS test. This may be due to unsatisfactory implementation or insufficient time for clinicians to perform DES or STS assessments, but could also be due to patient inability to complete exercise testing or questionnaires, in turn caused by factors such as advanced age or disease progression. As both these factors are likely to associate with higher mortality, results may potentially underestimate the true effects of exercise capacity or breathlessness on mortality. The low portion of registered scores also contributed to statistical inaccuracies and possibly inadequate statistical power in subgroup and short-term analyses.

5.3. Clinical implications

These findings have several implications. For clinical practice, this study provides evidence that exercise performance as measured by the 30s-STS is a useful method of identifying patients with a higher risk of long- and short-term mortality, who may need optimized management in the form of more frequent follow-up and rehabilitation interventions. Further implementation of this easy to apply exercise test could provide beneficial as a part of routine assessment when initiating LTOT. While variations of the STS test have been shown to be useful for detecting exertional hypoxemia, further research is needed to determine whether the 30s-STS could also be used for this purpose when assessing patients for LTOT.

6. Conclusions

Exercise performance as measured by the 30s-STS was an independent predictor for overall and short-term mortality in patients with LTOT, and provided a relatively high predictive ability in multivariable models. Exercise testing can be further implemented in the routine assessment of patients for LTOT.

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CRediT authorship contribution statement

Filip Björklund: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Project administration. **Andreas Palm:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – review & editing. **Jwan Abdulrazak Gorani:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Zainab Ahmadi:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Josefin Sundh:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Jenny Theorell-Haglöw:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Mirjam Ljunggren:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Ludger Grote:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Karin Wadell:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Magnus Ekström:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – review & editing, Visualization, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions: FB takes responsibility for the contents of the manuscript, including data and analysis. All authors made substantial contributions to the study concept and design. FB, JG, and ME performed data analysis, while all authors contributed to data interpretation. All authors contributed significantly to manuscript writing and critical revisions for intellectually important content, and all authors have read and approved the final version of the manuscript. Study sponsors had no role in the design of the study, the collection or analysis of the data, or preparation of the manuscript.

Appendix A. Supplementary data

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