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TRENDS IN CAUSE-SPECIFIC MORTALITY IN OXYGEN-DEPENDENT COPD

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At a Glance Commentary: *Scientific Knowledge on the Subject:* Although the proportion of women and age of patients starting long-term oxygen therapy for COPD has increased markedly, it is not known whether mortality and causes of death have changed over time. *What This Study Adds to the Field:* In oxygen-dependent COPD, mortality has decreased for respiratory disease and increased for non-respiratory causes, such as cardiovascular disease. This supports the importance of treating co-morbidity to improve survival in severe COPD.

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ABSTRACT

Rationale: Since the introduction of long-term oxygen treatment (LTOT) in COPD with chronic hypoxia, the proportion of women and the age of patients starting LTOT has increased markedly. We hypothesize that this might have led to shifts in the causes of death over time.

Objectives: To test for time trends in cause-specific mortality in COPD with LTOT.

Methods: Patients starting LTOT for COPD in Sweden between 1 January 1987 and 31 December 2004 were included in a national prospective study and followed until withdrawal of LTOT, death or 31 December 2004. The primary endpoint was cause of death obtained from the National Causes of Death Register.

Measurements and Main Results: A total of 7,628 patients (53% women) were followed for a median of 1.7 years (range 0-18.0). No patient was lost to follow up and 5,457 patients died during the study. The crude overall mortality increased by 1.6% per year (95% confidence interval (CI), 0.9-2.2; P<0.001). The absolute risk of death increased for circulatory disease by 2.8% (1.3 – 4.3; P<0.001) $year^{-1}$ and for digestive organ disease by 7.8% (1.9 – 14.0; P=0.009) $year^{-1}$. The absolute risk of death decreased for respiratory disease, 2.7% (2.0- 3.3; P<0.001) $year^{-1}$ and for lung cancer, 3.4% (1.1 – 5.7; P=0.004) $year^{-1}$.

Conclusions: In oxygen-dependent COPD, mortality has increased over time both overall and of non-respiratory causes, including cardiovascular disease. This highlights the importance of optimized diagnostics and treatment of co-morbidities in order to decrease morbidity and mortality.

INTRODUCTION

Patients with severe chronic obstructive pulmonary disease (COPD) suffer from high morbidity and mortality (1-2). Long-term oxygen therapy (LTOT) improves the survival time in the most severe COPD with chronic hypoxia ($P_aO_2 < 7.3$ kPa), as was shown in two randomized controlled trials published in the early 1980s (3-4).

A later study of a less selective group of patients showed shorter survival times than in the previous randomized controlled trials, mainly because the less selected patients were older and had more co-morbidities (1). Both age and co-morbidity are important predictors of mortality in COPD (5-6).

In recent decades the demography of patients starting LTOT for COPD has changed markedly. In Sweden, the mean age of patients starting LTOT increased from approximately 66 to 73 years between 1987 and 2000 (7). There has also been a significant increase in the proportion of women; in fact the majority of patients starting LTOT are now women (7). The prevalence of cardiovascular disease, which is increased in severe COPD, has been shown to rise with age (6, 8-9). Thus, the burden of cardiovascular disease and other co-morbidities might have increased, but it is unknown whether mortality and causes of death have changed over time in severe COPD. We hypothesize that the overall mortality has increased, and that over time more patients die from non-respiratory causes, such as cardiovascular disease.

The aim of this national prospective study was to evaluate whether there have been any time trends in overall and cause-specific mortality in patients on LTOT due to COPD, with special attention paid to mortality from cardiovascular disease.

MATERIAL AND METHODS

Patients starting LTOT after 1 January 1987 were prospectively included in a National Oxygen Register administered by the Swedish Society of Respiratory Medicine. Details of the register and the indications for LTOT have been previously published (7).

Patients aged 18 or above who started LTOT between 1 January 1987 and 31 December 2004 were eligible for inclusion in the study. Excluded were patients who started LTOT more than once (n=71) or were incorrectly registered (n=18). All other patients were followed prospectively with cause of death as the primary outcome, as previously reported (2).
Baseline data were collected at the start of LTOT on arterial gas tension of oxygen (P_aO_2) and carbon dioxide (P_aCO_2) when breathing air and during oxygen therapy, forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), smoking history (never, past or current smoking), the prescribed oxygen dose, the prescribed duration of oxygen treatment per day and WHO performance status (10).
The underlying causes of death were obtained from the Swedish Causes of Death Register, coded according to the ninth (before 1997) and tenth revisions of the International Classification of Disease (ICD) (11-12). The definitions and grouping of the diagnosis entities have been described elsewhere (2).

All patients gave their informed consent to participate. The study was approved by all ethics committees in Sweden, the Swedish National Board of Health and Welfare, and the Data Inspection Board.

Statistical methods

Baseline data were summarized using mean ± SD and percentages for continuous and categorical variables respectively. Changes in baseline data with calendar year of starting LTOT (start year) were described using linear regression for continuous and logistic regression for categorical variables.

Time under risk was defined as the time from starting LTOT until death, withdrawal of LTOT or 31 December 2004, whichever came first.

The change in overall mortality rate by starting year was evaluated using Cox regression (13). Changes in absolute risk of death for different causes of death (absolute cause-specific mortality) by starting year were evaluated by the proportional hazards model of Fine and Gray, which addresses the issue of competing risks (14). Overall and absolute cause-specific mortality were presented unadjusted and adjusted for age, sex, P_aO_2 air, smoking history and WHO performance status at baseline. In the adjusted analysis, WHO performance status was included because it predicted missing data in P_aO_2 air, and thereby helped to avoid consequent bias in the regression estimates when analyzing complete cases only (15).

Furthermore, the excess mortality, defined as the cause-specific mortality of the cohort as compared with that of the Swedish general population standardized for age, sex and calendar year, was expressed as standardized mortality rates (SMRs). Trends in SMRs by calendar year, adjusted for age and sex, were estimated using Poisson modelling (16). In all analyses, mortality estimates were tabulated for diagnosis entities accounting for more than 1% of total deaths. All statistical tests were two-sided and P-values below the standard value of 0.05 were considered statistically significant. All confidence intervals were 95%-intervals.

All statistical analyses were performed with Stata version 11.0 (StataCorp LP; College Station, TX).

RESULTS

A total of 7,628 patients, 4,027 women and 3,601 men, were included in the study. No patient was lost to follow up. LTOT was withdrawn prior to death in 522 (6.8%) patients, owing to improvement in oxygenation (n=170), poor compliance (n=31) or for other reasons (n=321).

Baseline data are shown in Table 1. There was a pronounced increase in the proportion of women and in the mean age of patients starting LTOT during the study period. The mean FEV_1, FVC, and the level of P_aO_2 and P_aCO_2 at baseline, both breathing ambient air and on oxygen, remained relatively constant. A total of 73% of the patients had P_aO_2 < 7.3 kPa on air, and this proportion did not change over time (P=0.324).

Overall mortality rate

The median observation time was 1.71 years (range 0-17.97), generating 18,126.6 person-years at risk of death for the cohort as a whole. A total of 5,457 patients, 2,748 women and 2,709 men, died during follow up, resulting in a crude overall mortality rate of 30.1 deaths per 100 person-years (95% CI, 29.3-30.9).

There was a significant increase in the crude overall mortality of 1.6% (95% CI, 0.9-2.2; P<0.001) per year. Between 1987 and 2004, the crude mortality rate increased by a total of 33.1% (95% CI, 17.5-48.0).

However, after adjusting for age, sex, P_aO_2 breathing air, smoking history and WHO performance status, there was no significant time trend in the overall mortality rate, as shown in Table 2.

Absolute cause-specific mortality

The most common causes of death were respiratory (n=3885; 71%), circulatory (n=847; 16%), cancer (n=414; 7.6%) and digestive organ disease (n=62; 1.1%). The autopsy rate for the cohort declined from 16% 1987-1991 to 8% 2000-2004.

Time trends in crude and adjusted absolute cause-specific mortality are listed in Table 3. Crude mortality decreased for respiratory disease and increased for non-respiratory causes, including lung cancer, digestive organ disease and ischemic heart disease. Between 1987 and 2004 the crude mortality decreased for COPD by 29.2% (95% CI, 19.5 – 37.8) and decreased for lung cancer by 46.3% (95% CI, 18.1 – 65.2). During the same period, circulatory disease increased by 61.5% (95% CI, 26.2 – 113.4).

After adjusting, both the decrease in mortality for respiratory disease and the increase in mortality owing to non-respiratory causes became more pronounced. On the other hand, there was no significant trend in adjusted mortality for circulatory disease. The relative change in adjusted mortality between 1987 and 2004 for the main diagnosis groups are visualized in Figure 1.

Excess mortality (SMR)

As shown in Table 4, excess mortality increased over time both overall, as well as for respiratory disease, cancer, digestive and circulatory disease, including ischemic heart disease.

DISCUSSION

The main findings are that the crude overall mortality is increasing over time for patients starting LTOT for COPD, with a shift from respiratory causes and lung cancer to more circulatory causes of death, including ischemic heart disease. Furthermore, the excess mortality is increasing markedly both overall and for cardiovascular disease.

This is, to the authors' knowledge, the first study of changes in cause-specific mortality over time in severe COPD. It is known from previous studies that in oxygen-dependent COPD, a substantial proportion of patients die from non-respiratory causes (17), and that patients starting LTOT today are older, have more co-morbidity and higher overall mortality than the patients in the original randomized trials (1, 3-4, 7). This study extends the previous observations by showing that although most deaths are still attributed to respiratory disease, mortality and causes of death have changed in recent decades in oxygen-dependent COPD, with increasing mortality from non-respiratory causes.

The strength of the present study is the inclusion of a large national cohort of patients starting LTOT for COPD. The coverage of the register has been validated to some 85% of the total number of patients starting LTOT in Sweden (18). The loss of data applies to entire counties owing to temporary shortages of staff, and is not likely to have been selective. Furthermore, no patient was lost to follow up. The findings in the present study are therefore likely to have high validity for clinical practice.

Nevertheless, the mortality estimates should be interpreted with some caution since they are based on data from death certificates. The cause-specific estimates could be affected by changes over time in diagnostics as well as changes in coding and classification of the causes of death by physicians and in the Swedish Causes of Death Register. However, the change from ICD9 to ICD-10 in 1997 is unlikely to have affected the reliability of the results,

according to a analysis performed by the Swedish National Board of Health and Welfare (19). In our opinion, the possible bias does not substantially affect the internal or external validity of the present study.

When considering possible explanations for the observed time trends in mortality, two striking facts are the increase in the proportion of women and the age of the patients starting LTOT. These changes might partly be attributable to changes in the smoking habits of the Swedish population (7). Since the 1970s, the rate of active smokers and the amount of smoking has decreased for both sexes, but less in women than in men (20). Most, but not all (21), studies indicate that women might be more vulnerable to the adverse effects of smoking than men (22-24), and the proportion of ever-smokers has increased more in women than in men (20). As a result, the majority of patient starting LTOT for COPD are now women. Owing to less total tobacco exposure, the decline in lung function is delayed and both men and women are older when they require LTOT (7). Improved survival for other diseases, most notably cardiovascular disease (25), can also have increased the number of elderly patients with COPD eligible for LTOT, as well as the prevalence of co-morbidity. In addition, over time as LTOT has become more established, physicians might have become less reluctant to prescribe LTOT to older patients with more co-morbidity, even if this patient category was not included in the original randomized trials (3-4).

In the multiple regression analysis, the rising age explained most of the increase in crude mortality overall and for circulatory disease. Interestingly, the concomitant increase in overall excess mortality, which is age-standardized, indicates that the association between age and mortality might largely be due to increased morbidity rather than the effect of aging itself.

In our view, the mechanism underpinning the increasing overall and non-respiratory mortality is that the patients have a progressively higher burden of co-morbidity and become more

vulnerable with increasing age. This hypothesis is supported by the previous observations that in severe COPD, co-morbidity is prevalent (5-6, 8), increases further with age (6, 26), and is a strong predictor of mortality (5-6, 27). The remaining time trends in mortality for respiratory and non-respiratory disease after adjusting might be due to residual co-morbidity not accounted for in the multiple regression analysis.

Some additional findings deserve mentioning. The decreasing mortality for COPD and lung cancer might in part be attributed to improved treatment, but may also be a reciprocal effect of the increasing mortality from non-respiratory diseases. The lack of increase in mortality for heart failure might be explained by advances in the treatment of heart failure over the last decades, or by the particular difficulty in differentiating heart failure from the respiratory disease in severe COPD. Thus heart failure might be under-reported as the cause of death, and whether there has been any trend in mortality for heart failure remains uncertain.

Excess mortality consists of a comparison of the mortality trends in the study group with the mortality trends in the general population. The excess mortality decreased for COPD since the mortality from COPD decreased among the study participants, but increased markedly in the general population during the study period (25). For cardiovascular disease, the development was the opposite. The mortality from ischemic heart disease declined by more than 50% between 1986 and 2002 in the general Swedish population (25). According to a recent study, 55% of the decline was attributable to risk factor reductions, such as decreased smoking and total serum cholesterol, and 36% of the decline was attributable to medical and interventional treatments (28). However, it seems as if patients with severe COPD have not benefited from these improvements, since the excess mortality for ischemic heart disease has increased in our patient cohort, and therefore lose progressively more years of life than the general population. This highlights the importance of promoting multidisciplinary risk factor modifications as well as of optimizing the diagnostics and treatment of co-morbidities in COPD.

In conclusion, the present study supports the important prognostic role of co-morbidity in oxygen-dependent COPD and shows that mortality has increased for non-respiratory causes, such as cardiovascular disease.

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FIGURE LABELS

Figure 1. Changes in the adjusted absolute cause-specific mortality for the main diagnosis groups between 1987 and 2004 in patients on long-term oxygen therapy for COPD. Mortality was adjusted for age, sex, P_aO_2 breathing air, smoking history and WHO performance status at baseline. Time trends were significant for respiratory ($P<0.001$) and non-respiratory causes ($P=0.013$), but not for the subgroups cancer ($P=0.101$) or circulatory disease ($P=0.328$).

TABLES

Table 1. Baseline characteristics for 7,628 patients starting long-term oxygen therapy for COPD 1987-2004

Characteristics	**Start year 1987, n=166**	**Start year 2004, n=593**	**Annual change**	**95% CI**
Age, years	65.8 ± 8.2	73.9 ± 8.2	0.41[a]	0.37, 0.46
Female, %	42	56	1.03[b]	1.02, 1.04
P_aO_2 air, kPa	6.7 ± 1.1	6.6 ± 0.9	-0.0060[a]	-0.011, -0.0014
P_aCO_2 air, kPa	6.3 ± 1.2	6.1 ± 1.2	-0.0090[a]	-0.015, -0.0030
P_aO_2 oxygen, kPa	8.9 ± 1.2	8.7 ± 1.0	-0.024[a]	-0.029, -0.018
P_aCO_2 oxygen, kPa	6.5 ± 1.3	6.4 ± 1.2	-0.0089[a]	-0.015, -0.0029
FEV_1, L	0.8 ± 0.4	0.8 ± 0.5	0.0070[a]	0.0045, 0.0093
FVC, L	1.9 ± 0.8	1.8 ± 0.8	-0.0029[a]	-0.0073, -0.0015
Oxygen dose, L/min	1.3 ± 0.7	1.6 ± 0.9	0.0058 [a]	0.0017,

				0.0099
Oxygen duration, h/24h	18.4 ± 3.6	17.5 ± 3.1	-0.055 [a]	-0.070, -0.039
Smoking history, %				
Never	5	5	NS	
Past	89	91	1.02[b]	1.00, 1.04
Current	6	4	0.94[b]	0.92, 0.94
WHO performance status, %				
0-1	53	44	0.95[b]	0.94, 0.96
2-4	45	48	1.01[b]	1.00, 1.02
Missing	2	8	1.26[b]	1.22, 1.30

Data presented as mean ± SD or percentages. WHO performance status is a five point scale (0=fully active; 1=symptomatic but completely ambulatory; 2=cannot work, ambulatory ≥ 50% of the day; 3=capable of only limited self-care, ambulatory < 50% of the day; 4=completely disabled).

[a] Mean increase per year.

[b] Mean increase in odds per year.

Table 2. Cox-regression of the overall mortality rate in patients starting LTOT for COPD 1987-2004

Characteristics	Hazard ratio	95% CI	P-value
Age	1.033	1.029 – 1.037	<0.001
Female	0.797	0.753 – 0.844	<0.001
P_aO_2 air	0.893	0.866 – 0.921	<0.001
WHO status 1	1.374	1.162 – 1.623	<0.001
WHO status 2	1.987	1.677 – 2.354	<0.001
WHO status 3	2.989	2.493 – 3.584	<0.001
WHO status 4	4.470	3.300 – 6.054	<0.001
Past smoking	1.041	0.931 – 1.162	0.481
Current smoking	1.287	1.067 – 1.553	0.008
Start year	0.998	0.991 – 1.005	0.521

Definition of abbreviations: CI = confidence interval; WHO status = WHO performance status (0=fully active; 1=symptomatic but completely ambulatory; 2=cannot work, ambulatory ≥ 50% of the day; 3=capable of only limited self-care, ambulatory < 50% of the day; 4=completely disabled).

Table 3. Changes in crude and adjusted absolute cause-specific mortality in patients starting LTOT for COPD 1987-2004

	Crude annual increase (%)	**95% CI**	**P-value**	**Adjusted annual increase (%)***	**95% CI**	**P-value**
Respiratory	-2.7	-3.3, -2.0	<0.001	-3.8	-4.5, -3.1	<0.001
COPD	-1.9	-2.6, -1.2	<0.001	-3.0	-3.8, -2.2	<0.001
All non-respiratory	5.1	0.4, 9.8	0.031	6.3	1.3, 11.5	0.013
Circulatory	2.8	1.3, 4.3	<0.001	0.8	-0.8, 2.4	0.328
Ischemic heart disease	2.7	0.1, 4.7	0.006	1.3	-0.9, 3.5	0.246
Heart failure	2.3	-1.7, 6.5	0.260	-1.9	-5.9, 2.3	0.373
Cancer	-1.6	-3.5, 0.2	0.094	-1.8	-4.0, 0.4	0.101
Lung cancer	-3.4	-5.7, -1.1	0.004	-3.1	-5.8, -0.3	0.031
Digestive	7.8	1.9,	0.009	7.5	1.4,	0.016

		14.0			14.1	

* Increase in absolute risk of death per year, adjusted for age, sex, P_aO_2 breathing air, smoking history and WHO performance status at baseline.

Table 4. Changes in excess mortality in patients starting LTOT for COPD 1987-2004

	Annual increase in SMR (%)*	**95% CI**	**P-value**
Respiratory	1.6	0.1, 2.3	<0.001
COPD	-2.3	-3.1, -1.5	<0.001
Circulatory	7.3	5.4, 9.2	<0.001
Ischemic heart disease	13.6	10.9, 16.4	<0.001
Heart failure	-0.8	-5.3, 4.0	0.739
Cancer	-0.2	-2.4, 2.2	0.890
Lung cancer	-4.7	-7.5, -1.9	0.001
Digestive	12.4	4.8, 20.5	0.001
All causes	6.1	5.4, 6.8	<0.001

Definition of abbreviations: SMR = standardized mortality ratio

* Increase in SMR per calendar year, adjusted for age and sex.

FIGURES

Figure 1