Amyotrophic lateral sclerosis: gender differences in the use of mechanical ventilation

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\textbf{Background and purpose:} Invasive and non-invasive mechanical ventilation are therapeutic options in patients with amyotrophic lateral sclerosis (ALS). Related to known national ALS incidence figures, the study aims to examine gender aspects versus physiological data in patients with ALS commencing mechanical ventilation.

\textbf{Methods:} Data from two nationwide registers involving all patients with ALS in Norway and Sweden who started invasive and non-invasive mechanical ventilation during 2002-2007.

\textbf{Results:} The total ALS population on invasive and non-invasive mechanical ventilation comprised $n = 308$ subjects [Norway $n = 96$ (72\% men), Sweden $n = 212$ (69\% men)]. Compared to Swedish ALS incidence figures, our finding of a male/female ratio of 2.3/1 in patients with ALS on invasive and non-invasive mechanical ventilation shows a statistically significant male predominance in the use of mechanical ventilation ($P$-value 0.0084 Chi square). Only 6.7\% of men and 3.8\% of women had invasive (via tracheotomy) ventilation ($P = 0.344$). Initiation of mechanical ventilation was acute (not planned) in 18\% of patients (no gender difference). Age distribution (mean age 62), pulmonary function tests (FVC\% pred, FEV\textsubscript{1}\% pred), daytime blood gas analyses (PaO\textsubscript{2}, PaCO\textsubscript{2}) and survival revealed no statistically significant gender differences.

\textbf{Conclusion:} In Norwegian and Swedish patients with ALS on invasive and non-invasive mechanical ventilation, two-thirds were men. Associated with known national ALS male/female incidence figures, our finding shows that statistically significantly more men than women with ALS are using mechanical ventilation. Physiological data and survival were equal in both genders. This may indicate the need for a more aggressive approach to stimulate mechanical ventilation in female patients with ALS.

\textbf{Introduction}

Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disorder of upper and lower motor neurons with a progressive limbic or bulbar muscular weakness and wasting. Respiratory failure is the most common cause of death in patients with ALS; untreated median survival in patients with ALS ranges from 2 to 4 years in both genders [1,2]. Epidemiological studies have reported an incidence of ALS ranging between 0.4 and 2.6/100 000/year [3,4].

The great variability in ALS incidence may be real or merely reflect differences in definition, methods and case ascertainment [4,5]. In Sweden, the ALS age-standardized incidence rates increased from 2.32/100 000 person-years in 1991–1993 to 2.98/100 000 person-years in 2003–2005, with a male/female incidence ratio of 1.5/1 in 2003–2005 [6]. In Norway, during the period 1961 through 1994, 2598 people had a recorded diagnosis of ALS; the male/female ALS incidence ratio decreased from 1.6/1 to 1.3/1 during this period [7].

Invasive and non-invasive mechanical ventilation are therapeutic options in patients with ALS. Invasive, compared to non-invasive, mechanical ventilation may impose a major burden on patients and caregivers and influence on the acceptance rate for this therapeutic option. Beneficial effects on palliation of symptoms,
improvement in quality of life and prolonged life have been reported [8], even though the survival rate is lower than that of other mechanical ventilated patients [9]. Previous studies on ALS and mechanical ventilation have reported populations predominantly of men [10,11]. This is the first prospective study on gender aspects versus physiological data in patients with ALS commencing invasive and non-invasive mechanical ventilation.

Material and methods

The Norwegian mechanical ventilation register was founded to provide reliable national data on mechanical ventilation, frequency, diagnoses, symptoms, physiological findings, treatment modalities, hours of daily ventilator use, supplementary equipment, level of education, family background and the use of health care resources. Inclusion criteria were all Norwegian patients on long-term invasive and non-invasive mechanical ventilation on a daily basis carried out in the user’s home or other long-term care facilities (not hospitals) [8,12,13]. Patients on continuous positive airway pressure or ventilators for physiotherapy only were not included. The first patient was registered on 15 February 2002. The Norwegian variable definitions were based on the previously described Swedish mechanical ventilation register from 1996 [14,15].

Both national registers are based on data from all clinics prescribing mechanical ventilation. Standardized forms were completed by initiating physicians or delegated nurses. Annual follow-up forms (from 2006 in Norway) were requested from the registers with enclosed covering letter of explanation. In Norway, the follow-up forms included data on vital status and dates of death, whilst the Swedish legislation allows these data to be automatically obtained from the Swedish population register. All patients received oral and written information on the registers.

In collaboration between registers, identical variables on patients with ALS who started mechanical ventilation during 2002–2007 were merged. Our finding of a gender difference in the use of mechanical ventilation was compared to the Swedish ALS incidence figures [6].

Both registers have been approved by The Data Inspectorate in respective countries and information was treated according to their guidelines. This study has been approved by the Regional Committee for Medical Research Ethics.

Statistical analyses

spss for windows version 15.0 (SPSS Inc, Chicago, IL, USA) was used for all analyses. Descriptive statistic was derived from $2 \times 2$ contingency tables with use of Pearson Chi-Square tests. All hypothesis testing was conducted using a 5% significance level and a two-sided alternative hypothesis. Calculation of forced vital capacity (FVC) and forced expiratory volume in one-second (FEV$_1$) in per cent of the predicted value (FVC%pred and FEV$_1$%pred) was performed according to Langhammer et al. [16]. Daytime arterial blood gas was taken prior to the initiation of mechanical ventilation and during spontaneous breathing in room air. All values were expressed as mean and standard deviation. Cox proportional hazards regression model was used to assess gender differences in probability to survive after mechanical ventilation initiation. Duration was calculated from mechanical ventilation initiation until the end of the observation period or death. The multivariate survival analysis was stratified by gender and adjusted by age at mechanical ventilation initiation and invasive versus non-invasive mechanical ventilation.

Results

The total ALS population who started invasive and non-invasive mechanical ventilation in Norway and Sweden during 2002–2007 comprised 96 (72% men) and 212 (69% men) subjects, respectively. By 1 January 2008, $n = 115$ (71% men) were still alive and $n = 193$ (70% men) were deceased (Fig. 1). Few patients had invasive mechanical ventilation; 6.7% ($n = 13$) men and 3.8% ($n = 3$) women ($P = 0.344$). The significant gender difference in the use of mechanical ventilation was not altered when invasive ventilated patients were excluded. Age at mechanical ventilation initiation varied between 27 and 89 (mean age 62); 27–89 (mean age 62) in men and 31–85 (mean age 63) in women. There were no significant gender differences in any decades of age nor in age $\leq 40$ ($P = 0.288$) or age $\leq 50$ ($P = 0.148$) (Fig. 2). Mechanical ventilation was initiated acutely (not planned) in 18% of the patients with no gender difference; no statistically significant difference was found between Norway and Sweden.

The pulmonary function tests (FVC%pred and FEV$_1$%pred) and daytime blood gas analyses (arterial $\mathrm{PaO}_2$ and $\mathrm{PaCO}_2$) revealed no statistically significant gender differences, and most patients were moderately hypercapnic prior to mechanical ventilation initiation (Table 1).

Probability to survive in men ($n = 215$) and women ($n = 93$) after mechanical ventilation initiation showed no significant gender difference ($P = 0.401$) (Fig. 3). Invasive (versus non-invasive) mechanical ventilation and age at mechanical ventilation initiation contributed significantly ($P = 0.002$ and $P = 0.015$, respectively).
Discussion

This study was based on two nationwide mechanical ventilation registers, involving essentially all patients with ALS on invasive and non-invasive mechanical ventilation in Norway and Sweden. Two thirds of the mechanical ventilated population were men. During 2002–2007, patients with ALS on mechanical ventilation constituted 9.9% and 13.3% of the total mechanical ventilation register population in Norway and Sweden, respectively. The data from our registers indicated that annually 0.4 patients with ALS per 100,000 inhabitants are commenced on mechanical ventilation. This corresponds to about 15–20% of the ALS incidence and may imply that some patients have no symptoms and decrease in FVC per cent that indicate the need of mechanical ventilation or that only a selected population of patients with ALS choose to receive or are offered mechanical ventilation as a therapeutic option. No gender difference was found in acutely versus planed mechanical ventilation initiation. Age distribution, pulmonary function tests and daytime blood gas analyses revealed no statistically significant gender differences. Mechanical ventilation was mostly non-invasive, and we found equal gender survival.

Many studies have addressed male/female ratio in ALS incidence. In Western countries, several non-population-based studies of ALS published before 1990 consistently reported a male/female ratio of 2/1 [17]. When comparing the oldest to the most recent studies, there is a significant decrease in male/female ratio from 2.6/1 (1965-1974) to 1.1/1 (in the 1990s) [3]. From a methodological perspective, the apparent increase in incidence amongst women may reflect better ascertainment amongst women compared with previous time periods. Alternatively, a genuine alteration in incidence may be a consequence of a change in prevalence of risk factors across genders. The hypothesis of environmental risk factors has been discussed; an increasing exposure of women to the same unknown environmental factors as those postulated for men cannot be excluded. Previous studies have reported evidence in support of

![Graph](https://via.placeholder.com/150)

Figure 1 Annual number of amyotrophic lateral sclerosis patients (n = 308) who started invasive and non-invasive mechanical ventilation during 2002–2007 in Norway and Sweden; new users, total alive and deceased; both gender and stratified by gender.

![Graph](https://via.placeholder.com/150)

Figure 2 Age distribution among amyotrophic lateral sclerosis patients (n = 308) who started invasive and non-invasive mechanical ventilation in Norway and Sweden during 2002–2007, stratified by gender.

![Table](https://via.placeholder.com/150)

Table 1 Lung function and arterial blood gas data (room air, spontaneous breathing) in patients with amyotrophic lateral sclerosis (n = 308) prior to invasive and non-invasive mechanical ventilation initiation in Norway and Sweden during 2002–2007, stratified by gender

<table>
<thead>
<tr>
<th></th>
<th>Females n = 93</th>
<th>Males = 215</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>P</td>
</tr>
<tr>
<td>FVC% predicted*</td>
<td>46.0</td>
<td>19.4</td>
<td>48.2</td>
<td>20.8</td>
<td>0.260</td>
</tr>
<tr>
<td>FEV1% predicted*</td>
<td>50.2</td>
<td>21.0</td>
<td>50.6</td>
<td>21.5</td>
<td>0.457</td>
</tr>
<tr>
<td>Daytime arterial PO2</td>
<td>10.1 kPa (75.75 mmHg)</td>
<td>1.9 kPa (14.3 mmHg)</td>
<td>9.6 kPa (72.0 mmHg)</td>
<td>1.5 kPa (11.3 mmHg)</td>
<td>0.436</td>
</tr>
<tr>
<td>Daytime arterial PCO2</td>
<td>6.3 kPa (47.25 mmHg)</td>
<td>1.6 kPa (12.0 mmHg)</td>
<td>6.8 kPa (51.0 mmHg)</td>
<td>1.5 kPa (11.3 mmHg)</td>
<td>0.452</td>
</tr>
</tbody>
</table>

*Langhammer A. et al. [16]. FVC, forced vital capacity; FEV1, forced expiratory volume in one-second.
smoking being a probable risk factor for ALS [18], but data on tobacco consumption were not included in the Norwegian and Swedish mechanical ventilation registers. An incidence of male/female gender ratio towards 1/1 could be explained by the increased population life expectancy, especially in women; ALS is rare under age 30, is more common in ages 50-60, with a clear increase with age until 70 [3]. However, age should not influence on our result, as no significant gender differences was found in age distribution.

Compared to the previously reported Swedish ALS incidence figures [6], our finding of a male/female gender ratio of 2.3/1 in patients with ALS on invasive and non-invasive mechanical ventilation shows that statistically significantly more men than women are using mechanical ventilation (p-value 0.0084 Chi square). One of several interpretations of the result is an underutilization of mechanical ventilation in women compared to men. We know that there is a strong selection of patients with ALS offered mechanical ventilation. Differences in insurance policies may favour men compared to women; in a study from the U.S.A., patients with ALS on mechanical ventilation were more likely to be men and they had a higher income than those not on mechanical ventilation [10]. Insurance policies, however, should not influence on our result, as both countries have homogeneous public health care systems relating all citizens. The tendency to initiate mechanical ventilation more frequently in men may be related to the preference of both the patient and the physician. The physician having a negative or positive attitude towards mechanical ventilation may influence on patient selection. It has been stated that women may be more accepting of a disease status than men [19]. Also, the decision about mechanical ventilation imposes a major burden on families [11], and genders may express different attitudes towards the impact of mechanical ventilation. These psychological and social factors may be involved even in Norway and Sweden where patients are guaranteed technical and practical support irrespective of their personal financial or familial resources.

An alteration in arterial blood gas levels has been described in more advanced phases of ALS [20]. In our study, men and women had similar measurements in terms of pulmonary function tests and blood gas results prior to mechanical ventilation initiation. Age <40, bulbar onset (versus limb onset) and FVC < 75% have been postulated as negative predictors of ALS disease progression [1], but gender has not been found to be an independent covariate of disease progression [1,2]. The presence or absence of bulbar involvement is probably a strong selection factor for mechanical ventilation. We cannot exclude that the gender difference may partially be explained by different clinical presentation of the disease in men and women, as data on bulbar versus limb onset was not included in our registers. Patients with bulbar onset ALS have been reported to have a shorter survival than those with limb onset ALS [21,22]. Some studies have indicated that there is no gender difference in the bulbar onset group [2,22]. Results from Ireland, United Kingdom and Italy [23] showed that age- and gender-specific incidence rates of bulbar onset ALS were similar amongst men and women whilst the incidence of spinal onset ALS was significantly higher for men compared to women. Based on these studies, we can only presume that the type of onset should not influence on our result from Norway and Sweden. Bulbar onset may also be a negative prognostic factor for survival in patients with ALS on mechanical ventilation [1]. However, studies have indicated that also non-invasive mechanical ventilation improves survival and quality of life in patients with ALS [24–26], although moderate or severe bulbar weakness have been associated with lower compliance and less improvement in quality of life [24]. Most Norwegian and Swedish patients had non-invasive mechanical ventilation, and the result showed equal survival amongst genders after mechanical ventilation was initiated.

The strength of the study was data based on two nationwide registers, involving essentially all invasive
and non-invasive mechanical ventilated patients with ALS. The study was prospective and taking into account the low incidence of the disease, the sample size was large. Occasional physicians may not have reported all users. This potential bias should be reduced to a minimum, as in both countries all clinics were contacted repeatedly by phone and/or mail to ensure optimal patient registration. All Norwegian and Swedish citizens have a unique person identification number, ensuring that no patient still living in respective countries can be lost from follow-up.

Conclusions

Two thirds of Norwegian and Swedish patients with ALS on invasive and non-invasive mechanical ventilation are men. Compared to known national ALS male/female incidence ratio, our finding shows that statistically significantly more men than women with ALS are using mechanical ventilation. We found no gender differences in clinical indications or survival. We therefore suggest a reassessment of mechanical ventilation prescribing strategies to ensure equal access to treatment in men and women.

Disclosure of sources of funding

The Norwegian mechanical ventilation register is owned by the Department of Thoracic Medicine, Haukeland University Hospital, Bergen, in collaboration with the Norwegian Medical Centre for mechanical ventilation, Department of Thoracic Medicine, Haukeland University Hospital, Bergen. The register is funded by the Western Norway Regional Health Authority. The Swedish mechanical ventilation register is owned by the Swedish Society of Chest Medicine and financially supported by the Swedish National Board of Health and Welfare and the Swedish Association of Local Authorities and Regions.

Disclosure of conflict of interest

Elin Tollefsen, Per Bakke and Ove Fonnesen have no conflicts of interest to disclose.

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References


22. Pinto S, Pinto A, De Carvalho M. Do bulbar-onset amyotrophic lateral sclerosis patients have an earlier respiratory involvement than spinal-onset amyotrophic lateral sclerosis patients? *Eura Medicophys* 2007; **43**: 505–509.


