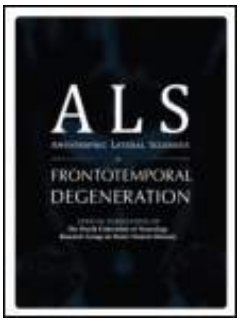

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RESEARCH ARTICLE

Factors predicting survival in amyotrophic lateral sclerosis patients on non-invasive ventilation

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Objective: Non invasive ventilation (NIV) improves quality of life and extends survival in amyotrophic lateral sclerosis (ALS) patients. However, few data exist about the factors related to survival. We intended to assess the predictive factors that influence survival in patients after NIV initiation. ***Methods:*** Patients who started NIV from 2000 to 2014 and were tolerant (compliance ≥ 4 hours) were included; demographic, disease related and respiratory variables at NIV initiation were analysed. Statistical analysis was performed using the Kaplan-Meier test and Cox proportional hazard models. ***Results:*** 213 patients were included with median survival from NIV initiation of 13.5 months. In univariate analysis, the identified risk factors for mortality were severity of bulbar involvement (HR 2), Forced Vital Capacity (FVC) % (HR 0.99) and ALSFRS-R (HR 0.97). Multivariate analysis showed that bulbar involvement (HR 1.92) and ALSFRS-R (HR 0.97) were independent predictive factors of survival in patients on NIV. ***Conclusions:*** In our study, the two prognostic factors in ALS patients following NIV were the severity of bulbar involvement and ALSFRS-R at the time on NIV initiation. A better assessment of bulbar involvement, including evaluation of the upper airway, and a careful titration on NIV are necessary to optimize treatment efficacy.

Key words: *ALS, survival, prognostic*

Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating, progressive neurodegenerative disease of unknown cause, characterized by a loss of motor neurons in the spinal cord, brainstem, and motor cortex. Progressive muscular weakness and atrophy result in disability and ultimately in death, usually within three to five years after symptoms onset. There is currently no curative treatment, and only one drug, riluzole, has been approved for treatment, but has shown to offer only modest benefits, being able to prolong median survival by approximately two to three months (1).

Respiratory failure resulting from progressive respiratory muscle weakness is the main cause of death in more than 80% of patients (2). In recent years, integrated management of the disease, with the development of multidisciplinary units, has contributed to a better implementation of supportive treatments that improve survival (3). Non-invasive ventilation (NIV) has proven to be an efficient treatment for respiratory failure, improving survival and quality of life (4,5) and is currently one of the most important therapeutic interventions used in ALS patients.

The scarce data existing on predictors of survival in patients on non-invasive ventilation have been little studied. Our aim was therefore to assess the predictive factors that influence survival in patients with amyotrophic lateral sclerosis (ALS) following the initiation of non-invasive ventilation (NIV).

Methods

We performed a retrospective analysis of the prospectively collected data of patients diagnosed with definite or probable ALS according to the El Escorial criteria (6) who started NIV from 2000 to 2014 at our centre. Hospital Universitari de Bellvitge is a tertiary hospital providing care for a population of 1.3 million. All patients with suspected or diagnosed ALS by the general neurologists

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in the area are referred to the ALS multidisciplinary unit of our centre. The number of patients followed in the unit has increased progressively and today around 250 patients are followed each year with 70 new cases per year. The Multidisciplinary Unit is composed of neurologists, respiratory physicians, dietitians, rehabilitation physicians and psychosocial support. After diagnosis, patients are assessed every three months by all the specialists during a one-day visit. Respiratory function evaluation includes a symptom questionnaire, spirometry, arterial blood gas analysis, cough efficacy and domiciliary nocturnal pulsoximetry. NIV is proposed on the occurrence of any of the following: the presence of symptoms related to respiratory muscle weakness (especially orthopnoea), Forced Vital Capacity % (FVC%) in sitting position <50% of predicted, hypercapnia (daytime arterial $PaCO_2$ >45 mmHg), or desaturation in nocturnal pulse oximetry (oxygen saturation <90% during 5 consecutive min) (7).

We excluded patients with concomitant respiratory disease or a major comorbidity that can shorten life expectancy. Patients who refused or did not tolerate treatment, or whose compliance was less than 4 h (8,9), were also excluded.

In most cases treatment was initiated during hospital admission as we have observed that a close monitoring and careful titration of ventilator parameters increase tolerance to NIV according to other authors (11). Home ventilators: Vivo 40 or Vivo 50 (BREAS Medical AD, Sweden) and Stellar 150 (RESMED, Sydney, Australia) in pressure assisted control mode or Breas 501 (BREAS Medical AD, Sweden) and Legendair (Airox, Pau, France) in volume-cycled assist control mode were used. Interfaces used included a wide variety of nasal and oronasal masks (Respironics, United States; Fisher-Paykel Healthcare, New Zealand; Res Med Inc., Sydney, Australia/California, United States). Ventilation parameters were adjusted to achieve comfort as well as adequate ventilation depending on daytime arterial blood gas levels and nocturnal oximetry measurements. Changes in ventilator or interface settings were made during disease progression when necessary to optimize the patient's comfort and NIV efficacy. Adherence to NIV was documented, based on device memory data or self-reports by patients and caregivers.

Patients with ineffective cough (peak flow cough <270 l/min) were provided with a mechanical in-exsufflator (cough assist or E-70 cough-assist, Philips Respironics) and the caregivers were trained in the use of assisted cough manoeuvres (10).

Patients with sialorrhoea were treated with anticholinergic drugs or botulinum toxin injection and they were provided with a salivary aspirator when necessary.

Data were collected at initiation of NIV and included anthropometric variables; data of ALS disease: site of disease onset (bulbar/limb); time from first symptoms to diagnosis; time from diagnosis to NIV; Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-R); severity of bulbar involvement and respiratory variables: Forced Vital Capacity (FVC%) in sitting position; arterial blood gases while breathing room air (PaO_2, $PaCO_2$) and nocturnal oxygen desaturation (percentage of time below 90%). Bulbar involvement at initiation of NIV was assessed by a subscale of ALSFRS-R based on components of swallowing, speech and sialorrhoea. We graded the severity of bulbar impairment into two groups: 'absent to mild' (score 8–12) or 'moderate to severe' (score 0–7) (11–12).

Percutaneous gastrostomy (endoscopic or radiologic) was offered to all patients with dysphagia and weight loss. Riluzole was offered to all patients at our centre.

Ethics

Written informed consent was not considered necessary for the study, since it was a retrospective analysis of our usual everyday work. Patient data were anonymized for the purposes of this analysis. Patients' confidential information was protected according to national regulations. This manuscript has been revised for publication by the Clinical Research Ethics Committee of Bellvitge University Hospital.

Statistical analysis

Proportions and means with standard deviations were calculated for demographic variables and baseline patient characteristics.

Survival time was defined as the time from NIV initiation to the time of tracheostomy or death. Survival curves were calculated by the Kaplan-Meier method and compared using the log-rank test (13). When considering covariates, survival was modelled with Cox regression (13). A multivariable model was developed to identify the independent risk factors for survival from NIV. All variables that show a significant association (p-value <0.05) in a univariate Cox proportional hazards modelling were selected.

Hypothesis testing was conducted using a two-sided test, with an alpha-value of 0.05 indicating statistical significance.

Statistical analysis was performed using IBM SPSS Statistics v.19 for Windows.

Results

Non-invasive ventilation was indicated in 251 patients in the period between 2000 and 2014 at our centre. Thirty-eight patients were excluded because of refusal or intolerance to treatment with low compliance (<4 h/day). A total of 213 patients

Table I. Demographic and clinical characteristics of ALS patients ($n = 213$) at non-invasive ventilation initiation.

Demographic and clinical characteristics of ALS patients at NIV initiation		n
Age (years)	65 (10)	213
Gender, male	132 (62%)	213
Disease onset, limb	171 (82%)	208
Bulbar involvement at NIV absent-mild	152 (71.4%)	213
Time from symptoms to diagnosis (months)	10.96 (8)	194
ALSFRS-R	30 (7)	196
Time from diagnosis to NIV (months)	13.64 (13.92)	196
FVC (%)	51 (16)	164
PaO_2 (mmHg)	76 (13)	204
$PaCO_2$ (mmHg)	46.7 (10)	204
TC90 (%)	25 (30)	162
Gastrostomy	14 (7.4%)	188
Compliance hours/day	9.2 (3)	182
Riluzole	190 (98%)	193

Data are expressed by mean (SD) or number (percentage)
ALSFRF-R: ALS rating scale-revised; FVC: Forced Vital Capacity; TC90; oxygen saturation <90% during 5 consecutive min.

were included in our study: 132 (62%) were male with a mean age of 65 ± 10 years. Disease onset was spinal in 171 patients (82%). The mean interval from onset of symptoms to diagnosis was 10.96 ± 8 months and the mean interval from diagnosis to NIV initiation was 13.64 ± 13.92 months.

At the time of NIV initiation, 190 (98%) patients were taking riluzole and 14 (7.4%) were fitted with a gastric feeding tube; 152 patients (71.4%) had absent or mild bulbar involvement, mean FVC% was 51% ± 16 of predicted, mean PaO_2 was 76 mmHg ±13, mean value of $PaCO_2$ was 46.7 mmHg ±10 and the mean percentage of nocturnal time below a saturation of 90% (CT 90) was 25% ± 30. Data are shown in Table I.

Treatment was started during scheduled hospital admission in 76% of cases, in an ambulatory setting in 14% of cases and in an emergency situation in 8.5%, while pressure home ventilators were used by 202 (95%) patients. The most frequent interface was the oronasal mask, used by 59% of patients. Mean ventilator use at the first month of treatment was 9.2 h/day ±3.23.

Survival

Median survival from NIV initiation was 13.5 months (95% CI 11.36–15.64). Kaplan-Meier analysis showed a statistically significant survival difference between the group of patients starting NIV with absent or mild bulbar involvement (median survival 15.67 months), and those with moderate/severe bulbar involvement (median survival 8.77 months), log-rank test 18.52 p-value <0.001 (Figure 1). Moreover, survival was significantly better in the group of patients initiating NIV

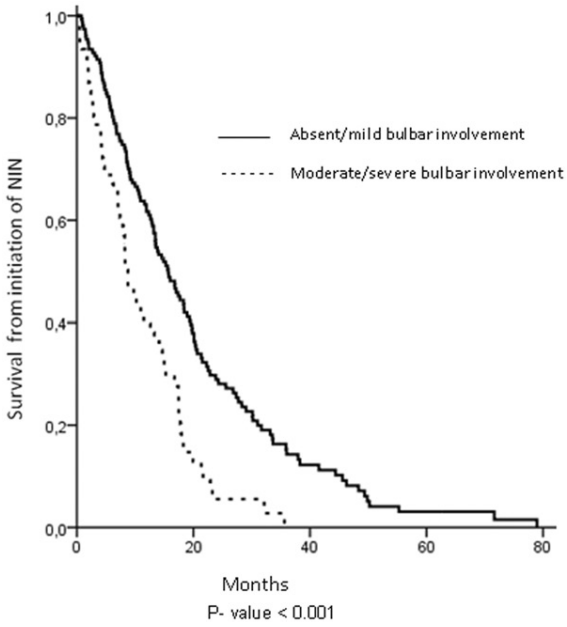

Figure 1. Kaplan Meier curves of survival from NIV initiation. Patients with absent-mild and moderate-severe bulbar involvement.

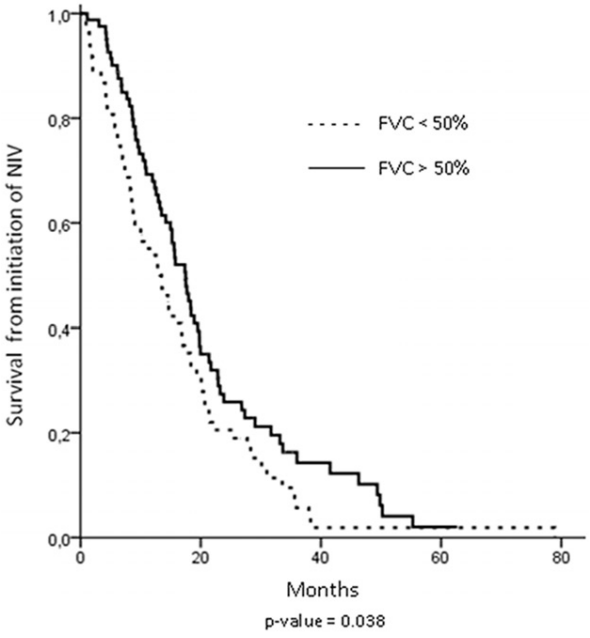

Figure 2. Kaplan Meier curves of survival from NIV initiation. Patients with FVC <50% and FVC >50%.

with a FVC% greater than 50%, log-rank test 4.3, p-value =0.038. Survival curves and curve comparisons are shown in Figure 2.

Prognostic factors, univariate and multivariate analysis

In univariate analysis, the mortality risk factors after the start of NIV were: the severity of bulbar

Table II. Prognostic factors of survival from NIV initiation.

	HR	95%CI	*p*
Univariate analysis			
Gender	1.03	0.77-1.39	0.841
Age	1.01	0.99-1.03	0.112
Site onset (limb/bulbar)	1.33	0.91-1.96	0.143
Bulbar involvement	2.01	1.45-2.77	0.000*
Time symptoms to diagnosis	0.99	0.97-1.01	0.303
Time diagnosis to Start NIV	1.00	0.99-1.01	0.949
ALSFRS-R	0.97	0.95-0.99	0.004
FVC %	0.99	0.98-0.99	0.028*
PaO_2	1.00	0.99-1.01	0.606
$PaCO_2$	0.99	0.98-1.01	0.602
TC90%	0.99	0.99-1.00	0.238
Gastrostomy	0.92	0.67-1.28	0.637
Multivariate analysis			
Bulbar involvement	1.92	1.36-2.72	0.000
ALSFRS-R	0.97	0.95-0.99	0.006

*$p<0.05$ statistically significant.

ALSFRF-R: ALS rating scale-revised; FVC: Forced Vital Capacity; TC90; oxygen saturation <90% during 5 consecutive min.

involvement (HR 2, 95% CI 1.45–2.77, *p*-value <0.001), FVC% (HR 0.99, 95% CI 0.98–0.99, *p*-value =0.028) and ALSFRS-R at NIV initiation (HR 0.97, 95% CI 0.95–0.99, *p*-value =0.004). No other variables, including age, gender, site of onset or diagnosis delay were significantly related to survival (Table II).

FVC was removed from the multivariate analysis because of its close correlation with bulbar involvement. Patients with significant bulbar dysfunction have major constraints with relation to the performance of spirometry and FVC% was therefore available for only 50% of patients with moderate/severe bulbar involvement and for only one-third of patients with severe bulbar involvement.

Finally, multivariate analysis showed that the only covariates that had a significant independent prognostic value were bulbar involvement and ALSFRS-R at NIV initiation (HR 1.92, 95% CI 1.36–2.72, *p*-value <0.001 and HR 0.97, 95% CI 0.95–0.99, *p*-value =0.006) (Table II).

Discussion

The results of our study show that the severity of bulbar involvement at the time of starting NIV treatment is the most important independent prognostic factor of survival in ALS patients on NIV, while the ALSFRS-R score and FVC% are also predictive factors of survival.

The demographic characteristics of our population and mean survival with NIV (13.5 months) are similar to those in a recent study that reported a mean survival of 15 months (14).

The benefits and influence of bulbar involvement on the survival of ALS patients on NIV have been described in other studies but with controversial results: some demonstrated poor tolerance and survival whereas others reported benefits. Different studies have shown a close relationship between bulbar involvement and tolerance and adherence to NIV treatment and also with poor survival in patients with a compliance of less than 4 h (15,16). Lo Coco et al. found that mild to moderate bulbar impairment was strongly associated with NIV tolerance and survival after NIV was independently related to treatment use/tolerance as defined by more than 4 h per day. However, survival after NIV was not related to the severity of bulbar impairment. In our study, patients who did not tolerate treatment (use of NIV <4 h/day) were not included; thus, the purpose of our study was not to assess the factors that influence tolerance but those that influence survival.

Regarding survival, our results are consistent with those of the only randomized controlled trial showing poor survival after NIV initiation in patients with severe bulbar involvement (4). In contrast, Peysson et al. (12) found that advanced age at diagnosis and airway mucus accumulation were poor prognostic factors in patients treated with NIV, but they did not find bulbar involvement at the moment of treatment initiation in itself to be a prognostic factor of survival. Berlowitz et al. (17), in a retrospective analysis of 219 NIV treated patients, observed greater survival benefits of NIV in patients after the onset of bulbar disease. However, it must be borne in mind that survival was considered from the onset of symptoms and not from NIV initiation. On the other hand, bulbar involvement was not assessed at NIV initiation but according to the site of disease onset, while in our study the site of disease onset is not related to survival after NIV initiation. Our results therefore suggest that the key factor is the severity of bulbar involvement at the time of treatment initiation rather than the site of disease onset.

In our cohort, after NIV initiation, patients with moderate to severe bulbar impairment had almost twice the risk of death as those with mild or no bulbar impairment (HR 1.9, *p*-value <0.001). These results are most probably related to poor treatment efficacy in patients with moderate-severe bulbar involvement, even though tolerance and treatment adherence was good in some cases. Possible explanations for this inefficacy could be mucus and saliva accumulation in the upper airway or the 'destabilization' or obstruction of the upper airway (18), which could cause a glottis dysfunction with asynchronisms in cases of severe bulbar impairment. This hypothesis is consistent with the results of a recent study (14) showing that ventilator mode and the severity of bulbar impairment (Norris bulbar scale) at NIV initiation were the variables that most accurately predicted the effectiveness of NIV.

Total ALSFRS-R score was also an independent prognostic factor of survival in our population: patients with worse scores having a higher mortality

risk (HR 0.97, *p*- value =0.006). Our results are in agreement with previous studies that showed a high predictive value of the ALSFRS score in patients' survival after invasive mechanical ventilation (19). The same authors (8) describe the ALSFRS score as one of the factors that influences survival after NIV in univariate analysis, but this has not been confirmed as an independent predictor of survival in multivariate analysis. The ALSFRS-R score is used to assess the course or progression (20) of the disease and to estimate its clinical stage (21). ALSFRS-R score at diagnosis is also an important predictive factor of overall survival in ALS patients (22). Our results therefore probably reflect the poor prognosis of patients with an advanced state of the disease but that does not mean that NIV is not effective in these patients.

Finally, patients who initiated NIV with a FVC above 50% had significantly better survival than those with a FVC below 50% and FVC% value at NIV initiation is a predictive factor of survival in univariate analysis, although this variable was not introduced in the multivariate analysis due to its close relationship with bulbar involvement. These results are consistent with those of recent studies: Lechtzin et al. (23) describe a survival from time of diagnosis of nearly one year longer in the group of patients that started NIV with FVC >65% and Carratú et al. (24) found a significantly better one-year survival rate in patients with FVC <75% treated with NIV compared to those who were not treated.

One limitation of this study is the long period of patient enrolment (2000–2014) and possible changes in clinical practice, although during the whole period the patients were managed by the same ALS multidisciplinary unit using the same respiratory evaluation protocol (7) and the same criteria for NIV treatment introduction. The assessment of bulbar function was by bulbar components of the ALSFRS-R scale and the cut-off points were arbitrary, based on studies that use similar values.

The strengths of our study are the large number of patients included and the data that may contribute to improvement in the clinical practice of the respiratory management of these patients. Consistent with other studies, our results reinforce the relevance of an early and continued respiratory evaluation and the importance that bulbar impairment has in order to offer ventilatory support at the appropriate time. A better assessment of bulbar involvement at the moment of NIV initiation is necessary to optimize the efficacy of treatment.

In conclusion, the two prognostic factors in patients following NIV in our study were severity of bulbar involvement and ALSFRS-R at the time of NIV initiation and these results may be helpful in clinical decision-taking for ALS patients. Patients with a poor bulbar function benefit less from non-invasive ventilation, have shorter survival and this is probably the main prognostic factor after non-invasive ventilation initiation that influences the efficacy of treatment. A careful evaluation of upper airway and an accurate titration of non-invasive ventilation should be considered in these patients.

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Declaration of interest: All the authors declare that no financial or other potential conflicts of interest exist.

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