Letter

Respiratory support in a population-based ALS cohort: demographic, timing and survival determinants

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease leading to a progressive loss of motor function and cognitive impairment of the frontotemporal type (FTD). Respiratory failure is a common symptom and can be treated with non-invasive mechanical ventilation (NIMV) and/or invasive mechanical ventilation (IMV) via tracheostomy.[1] Studies on NIMV report a quite wide range of survival time, due to the heterogeneity of the clinical setting and patients' characteristics, and very few data are available about NIMV and IMV in population-based cohorts.[2 3]

The aim of this study was to assess the outcome and prognostic determinants of ventilatory supports in a large population-based cohort of patients with ALS.

METHODS

The study population includes all patients with ALS diagnosed from 2008 to 2015 in the prospective population-based Piemonte and Valle d'Aosta Register for ALS. Demographic and clinical information, including those related to NIMV/IMV, were collected. The determinants of NIMV, IMV and NIMV to IMV transition were assessed with binary logistic regression analysis (backward). Additional details on methods and statistical analysis are reported in the online supplemental material.

RESULTS

During the study period, 1159 patients were diagnosed with ALS (median age at onset of 68.4 years (IQR 60.3–74.7); 540 females (46.6%); 395 (34.1%) bulbar onset). The characteristics of patients according to the different respiratory supports are reported in the online supplemental table 1. NIMV was performed by 391 (33.7%) patients, NIMV followed by IMV by 88 (7.6%), IMV by 81 (7.0%); 620 patients (53.5%) did not undergo ventilation.

The median survival time after NIMV initiation was 1.00 year (IQR 0.51–2.34). Factors related to the use of NIMV are reported in the online supplemental material. Pre-NIMV spirometry values were available for 308 (64.3%) patients. A dose–response effect of FVC% on the outcome of NIMV was found, with an increased survival at higher FVC% values (p=0.0001) (figure 1A). Therefore, we ran two Cox multivariable models for evaluating factors related to survival after NIMV (online supplemental table 2). In Model A, which excluded Forces Vital Capacity percent of expected (FVC%), a better outcome of NIVM was related to ALSFRS-R decline (ΔALSFRS-R)<0.74 point/month, younger age, higher ALSFRS-R bulbar subscore and absence of chronic obstructive pulmonary disease. In Model B, which included FVC%, FVC% was the strongest determinant of NIMV outcome, followed by age, and higher ALSFRS-R upper limb subscore.

Eighty-eight (18.4%) of the 479 patients who initially performed NIMV subsequently underwent IMV. In 74 cases (84.1%), IMV was performed when the dependence on NIMV exceeded 20 hours/day, and in the remaining 14 for intervening acute events (infective or aspiration pneumonia). Factors related to the transition from NIMV to IMV are reported in the online supplemental material.

A total of 81 patients with ALS (7.0%) underwent directly IMV. In these cases, the events leading to IMV were acute respiratory infections (31, 38.3%), aspiration pneumonia (23, 28.4%) and sudden respiratory failure (27, 33.3%). Factors related to the use of IMV data are reported in the online supplemental material. Factors related to a better survival after IMV were younger age, lower ΔALSFRS-R, previous use of NIMV and to be married (online supplemental table 3).

The median survival time after IMV was 1.97 years (IQR 0.66–5.05); however, it was 3.00 years (IQR 0.70–8.54) for patients undergoing IMV after NIMV, and 1.58 years (IQR 0.59–3.66) (p=0.014) for those who performed directly IMV (figure 1B).

Comparing survival from disease onset in all groups, patients who underwent IMV and/or NIMV had a significantly longer survival compared with non-ventilated patients (figure 1C). NIMV and IMV remained independently significant

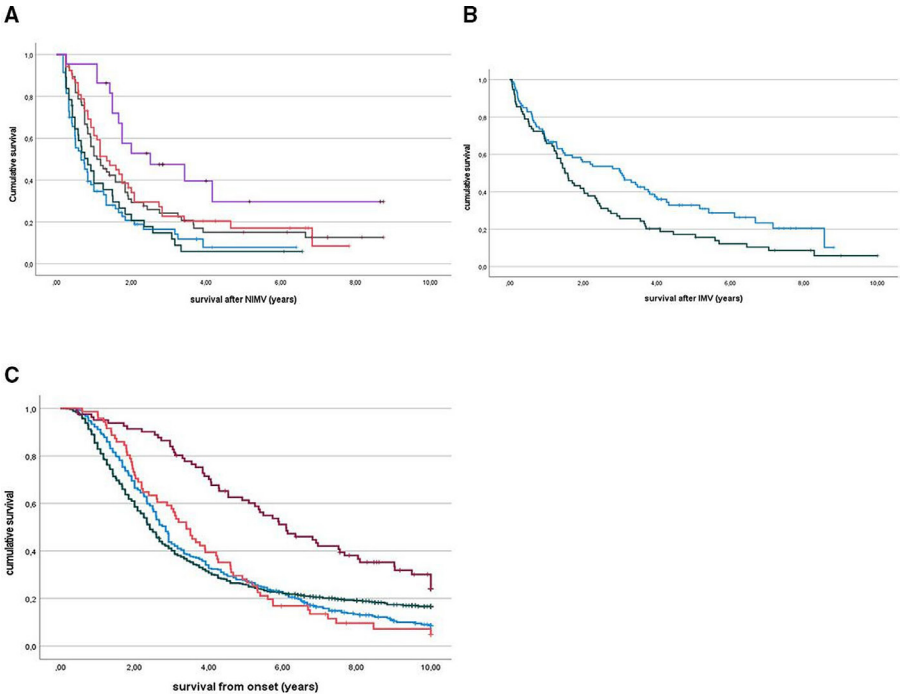

Figure 1 (A) Survival after non-invasive mechanical ventilation (NIMV) according to FVC% performed before NIMV (n=308). FVC% <50% (blue) 85 cases, median survival time 0.66 year (IQR 0.33–1.66); FVC% 50–59 (green) 48 cases, median survival time 0.84 (IQR 0.43–1.84); FVC% 60–69 (black) 85 cases, median survival time 1.08 (IQR 0.74–2.75), FVC% 70–79 (red) 65 cases, median survival time 1.34 (IQR 0.75–2.82), FVC% ≥80 (violet) 25 cases, median survival time 2.51 (1.49–5.00) (p<0.0001). (B) Survival after invasive mechanical ventilation (IMV) in patients who did (blue) and did not (green) undergo NIMV before performing IMV (p<0.014). (C) Survival from amyotrophic lateral sclerosis (ALS) onset. NIMV+IMV (violet), median survival time 6.09 (IQR 3.89->10); IMV alone (red) median survival time 3.40 (IQR 1.95–5.41) (p<0.0001); NIMV (blue) median survival time 2.84 (IQR 1.75–5.25); non-respiratory support (green) median survival time 2.41 (IQR 1.33–5.18).

in Cox multivariable analysis (online supplemental table 4).

DISCUSSION

This is the first study to have systematically assessed in a large ALS population-based series the factors related to the choice to undergo mechanical ventilation and the determinants of survival. About 50% of our cohort underwent NIMV/IMV, confirming an improved adherence to current guidelines. Patients who used mechanical ventilation had an increased overall survival compared with non-ventilated patients. Main factors related to a better survival after NIMV/IMV were a higher FVC% and a lower ΔALSFRS-R at time of ventilation.

In the last two decades, respiratory support via NIMV has become the standard treatment of respiratory failure in ALS. The use of IMV is less explored and neurologists' attitudes are considerably less uniform. In general, when discussing the option of IMV, much emphasis is put on patients' personal motivations and to inform that IMV may prolong survival but does not modify disease progression or quality of life and may increase caregivers' burden.[2 4]

Younger age and attending an ALS multidisciplinary clinic resulted to be independently related to patients' decision to perform NIMV. Younger age was also an independent determinant of the use of IMV, together with male sex, ΔALSFRS-R at diagnosis and bulbar onset. These two latter factors are a novel finding of our study and may be due to the rapid progression of respiratory impairment in fast progressors, and the scarce tolerance of NIMV interface or aspiration pneumonia in patients with bulbar impairment. Another important novel observation of our study is that patients with comorbid FTD had a 50% chance to undergo mechanical ventilation compared with patients with normal cognition. Finally, our data revealed that the sex inequality in the use of mechanical ventilation is declining, although not completely.

In our cohort, ~20% of patients performing NIMV chose to undergo IMV. The transition from NIMV to IMV was significantly more frequent in patients followed by multidisciplinary clinics and it was almost invariably planned in advance by the patients. The main reasons for the transition were the use of NIMV for more than 20 hours/day, acute respiratory infections and increased difficulty in clearing secretions.

Although several studies have reported that NIMV increases survival, the effect on patients' outcome of NIMV and IMV is still controversial.[3–5] In our series, we found that patients who underwent NIVM alone or followed by IMV had a better outcome than non-ventilated ones independently from other prognostic factors. This is true also for patients with bulbar onset, differently from previous reports.[2] Besides, we identified a positive correlation between higher FVC% values and better survival, thus supporting an earlier starting of NIMV, when patients' ventilatory function is still partially preserved. Finally, the prognostic role of lower ΔALSFRS-R before NIMV suggests that respiratory support does not modify the rate of functional decline.

A better survival after IMV was associated with younger age, ΔALSFRS-R before IMV, and to be married. Notably, we also observed a better outcome of IMV in patients who previously underwent NIMV, likely because the intervention is planned in advance and not performed in an emergency setting.

This study is not without limitations. First, we could not include cognitive impairment in the multivariable models since patients with a diagnosis of comorbid FTD were less likely to undergo NIMV, hindering the possibility to unbiasedly assess the effect of cognitive impairment on survival. Second, most patients performing NIMV/IMV attended a multidisciplinary clinic, limiting the possibility to evaluate the effect of multidisciplinary care on mechanical ventilation outcome.

The real-world data of this large population-based study indicate that mechanical ventilation prolongs survival independently from other prognostic factors, including bulbar onset. In addition, our data will be useful for the management of patients and for designing clinical trials, which should keep into account the substantial effect of mechanical ventilation on the course of the disease and its demographic and clinical determinants.

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Supplementary material

Methods

The characteristics of the PARALS have been reported in detail elsewhere.1 A total of 744 ALS patients (64.2%) underwent an extensive cognitive battery at time of diagnosis[2] and classified into five categories according to the consensus criteria for the diagnosis of frontotemporal cognitive and behavioral syndromes in ALS.[3]

Statistical methods

ALSFRS-R mean monthly decline (ΔALSFRS-R) was calculated using the following formula: (48 – ALSFRS-R score at diagnosis)/(months from onset to diagnosis). Survival after NIMV was computed to death/tracheostomy or to the last day of follow-up. Survival after IMV was computed to death or to the last day of follow-up. Overall survival was computed from disease onset to death/tracheostomy or to the last day of follow-up. The last day of follow-up was December 31st, 2019. Survival analyses were performed using the Kaplan-Meier method, and compared with the log-rank test. No patients were lost to follow-up. Multivariable analysis for survival was performed with the Cox proportional hazards model (stepwise backward) with a retention criterion of $p<0.1$. A p level <0.05 was considered significant. Statistical analyses were carried out using the SPSS 26.0 statistical package (SPSS, Chicago, IL, USA). Data will be available upon motivated request by interested researchers.

Ethical considerations. The study was approved by the Ethical Committees of the two regional ALS Expert Centers (Comitato Etico Azienda Ospedaliero-Universitaria Città della Salute e della Scienza, Torino, and Comitato Etico Azienda Ospedaliero-Universitaria Maggiore della Carità, Novara). Patients provided written informed consent before enrollment. The databases were anonymized according to the Italian law for the protection of privacy.

Supplementary results

Factors related to the use of NIMV and IMV

The following factors were independently related to the use of NIMV: younger age at diagnosis (per year, OR 1.02 [95% c.i. 1.01-1.03], p=0.0001), and attending an ALS multidisciplinary clinic (OR 2.19 [1.43-3.35], p=0.006). The factors independently related to the use of IMV were age (per year, OR 1.03 [1.02-1.04]; p=0.0001), sex (male, OR 1.57 [1.11-2.22], p=0.011), ΔALSFRS-R at diagnosis (per unit, OR 1.15 [1.04-1.27], p=0.006), and bulbar onset (OR 1.67 [1.17-2.39, p=0.001]).

Effect of cognitive impairment on the use of NIMV and IMV

Since only 64.2% of cases were tested for cognition, a separate analysis including only these cases showed that patients with co-morbid FTD were less likely to undergo NIMV or IMV than patients with normal cognition (NIMV, OR 0.49 [0.27-0.91] p=0.024; IMV, OR 0.47 [0.35-0.96], p=0.035).

Time to respiratory support use

The median time between ALS onset and the start of NIMV was 1.92 years (IQR 1.08-3.17). The median time from onset and IMV was 1.82 years (IQR 1.08-2.49) for patients undergoing directly IMV, and 2.59 (IQR 2.08-4.08) also including patients who previously underwent NIMV.

Factors related to the transition from NIMV to NIV

The transition from NIMV to IMV occurred after a median of time of 1 year (IQR 0.51-1.75). According to binary logistic regression analysis the following factors were independently related to the transition from NIMV to IMV: age (per year, OR 1.04 [1.02-1.06], p<0.0001; attending a multidisciplinary ALS center (OR 2.82 [1.32-6.00], p<0.008); presence of bulbar symptoms (OR 1.84 [1.17-2.93], p=0.0001) and ΔALSFRS-R at time of IMV (per unit, OR 1.14 [1.02-1.35], p<0.005). Educational level and marital status did not influence patients' choice.

Survival time after NIMV initiation

The median survival time after NIMV initiation to either IMV or death was 1.00 year (IQR 0.51-2.34). The 1-, 3- and 5-year survival were 52.5% (SE 2.6%), 21.3% (SE 2.2%) and 13.7% (SE 2.0%).

Survival time after IMV initiation

The median survival time after IMV initiation to death or the censoring date was 1.97 (IQR 0.66-5.05). The 1-, 3- and 5-year survival were 66.9% (SE 3.7%), 39.2% (SE 3.9%) and 25.4% (SE 3.6%) respectively.

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Table 1. Patients' demographic and clinical characteristics according to mechanical ventilation choice

	Overall (n=1159)	**NIMV (n=391)**	**NIMV+IMV (n=88)**	**IMV (n=81)**	**NO (n=599)**	**p**
Median age at onset, years (IQR)	68.4 (60.3-74.7)	66.8 (59.7-73.6)	62.3 (54.1-67.3)	68.3 (61.5-73.7)	69.9 (63.2-76.3)	<0.0001
Median diagnostic delay, months (IQR)	9.0 (5.1-14.0)	9.0 (5.1-13.9)	8.1 (4.9-14.0)	9.0 (5.1-13.0)	8.9 (5.1-14.0)	0.57
Sex (female, %)	540 (46.6%)	174 (44.5%)	33 (37.5%)	33 (40.7%)	300 (50.1%)	0.054
Site of onset (bulbar, %)	395 (34.1%)	110 (28.1%)	32 (36.4%)	36 (44.4%)	217 (36.2%)	0.009
Education (≥11 years)	240 (20.7%)	80 (20.5%)	22 (25.0%)	16 (19.8%)	122 (20.4%)	0.78
Marital status (Married vs. Single/Widow-widower) §	857 (75.0%)	308 (79.6%)	67 (76.1%)	64 (80.0%)	418 (71.1%)	0.016
Median FVC% at diagnosis (IQR) #	89 (68-103)	87 (66-102)	87 (74-100)	81 (53-99)	90 (70-104)	0.017
Median monthly ALSFRS-R decay at diagnosis (IQR) °	0.66 (0.31-1.35)	0.59 (0.33-1.14)	0.59 (0.25-1.44)	0.79 (0.39-1.56)	0.68 (0.30-1.41)	0.076
ALS multidisciplinary clinic (yes)	1000 (86.3%)	366 (93.3%)	80 (90.9%)	67 (82.7%)	487 (81.3%)	<0.0001
Cognitive status (FTD vs non-FTD) *	144 (19.4%)	37 (13.4%)	4 (6.0%)	13 (24.1%)	90 (26.0%)	<0.0001

§ Available for 1143 patients (98.6%); # available for 1027 patients (88.6%); ° available for 1137 patients (98.1%); * available for 744 patients (64.2%).

Table 2. Factors related to improved survival after non-invasive ventilation (NIMV). Model A excluded FVC% (n=456); model B included FVC (n=296)

Model A				**Model B**			
Factor	**Level**	**HR (95% c.i.)**	**P value**	**Factor**	**Level**	**HR (95% c.i.)**	**P value**
Age at NIV	≥80	1	0.017	Age at NIV	≥80	1	0.002
	70-79	1.27 (0.85-1.90)			70-79	1.76 (1.04-2.86)	
	60-69	1.38 (0.96-2.05)			60-69	1.89 (1.16-3.09)	
	50-59	1.84 (1.23-2.73)			50-59	2.39 (1.44-3.97)	
	20-49	2.49 (1.47-4.22)			20-49	3.67 (1.78-7.59)	
ALSFRS-R decline from onset to NIMV (points/months)	≥0.74	1	0.0001	FVC% before NIMV	≥60	1	0.0001
	<0.74	1.76 (1.33-2.33)			<60	1.92 (1.43-2.66)	
ALSFRS-R bulbar subscore at time of NIMV	0-3	1	0.003	ALSFRS-R upper limbs subscore at time of NIMV	0-3	1	0.026
	4-7	1.56 (1.13-2.15)			4-7	1.28 (0.86-1.77)	
	8-11	1.71 (1.20-2.43)			8	1.83 (1.10-3.02)	
	12	1.89 (1.22-2.91)					

COPD	Yes	1	0.006				
	No	1.99 (1.22-3.24)					

Model A did not include FVC%, model B included FVC%.

ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale, revised. COPD, Chronic obstructive pulmonary disease. NIMV, non-invasive ventilation.

The other variables included in the model were: ALSFRS-R lower limbs score (items 8 + 9); ALSFRS-R respiratory score (items 10 + 11); site of onset (bulbar/spinal); PEG performed before NIMV (yes vs. no); time from diagnosis to NIMV (≥1 year vs. <1 year); BMI mean monthly decline before NIMV; education (≥11 years vs. <11 years); marital status (married vs. single, divorced, widow/widower); family history of ALS and/or FTD (yes/no); King's stage at time of NIMV; MiToS stage at time of NIMV.

Table 3. Factors related to improved survival after tracheostomy

Factor	**Level**	**HR (95% c.i.)**	**P value**
Age at IMV	≥80	1	0.0001
	70-79	1.80 (1.07-3.03)	
	60-69	2.30 (1.39-3.78)	
	50-59	3.98 (2.34-6.78)	
	20-49	4.66 (2.10-10.34)	
Previous NIMV	No	1	0.009
	Yes	1.48 (1.10-1.98)	
ALSFRS-R decline from onset to IMV (points/months)	≥0.91	1	0.015
	<0.91	1.41 (1.07-1.86)	
Marital status	Single, divorced, widow/er	1	0.024
	Married	1.45 (1.05-2.00)	

ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale, revised; NIMV, non-invasive mechanical ventilation; IMV, invasive mechanical ventilation via tracheostomy.

The other variables included in the model were: ALSFRS-R lower limbs score (items 8 + 9); ALSFRS-R respiratory score (items 10 + 11); site of onset (bulbar/spinal); PEG (yes vs. no); PEG performed before IMV (yes vs. no); BMI mean monthly decline before IMV; education (≥11 years vs. <11 years); chronic obstructive pulmonary disease (yes/no); family history of ALS and/or FTD (yes/no); King's stage at time of IMV; MiToS stage at time of IMV.

Table 4. Prognostic factors in ALS. Overall survival from disease onset to death is considered

Factor	**Level**	**HR (95% c.i.)**	**P value**
Age at IMV (years)	≥80	1	0.0001
	70-79	1.16 (0.83-1.63)	
	60-69	1.59 (1.17-2.17)	
	50-59	2.16 (1.59-2.95)	
	20-49	3.51 (2.39-5.18)	
Diagnostic delay (months)	0-6	1	0.0001
	7-12	1.73 (1.16-2.58)	
	13-18	2.31 (1.62-3.30)	
	19-24	3.04 (2.22-4.16)	
	25>	3.40 (2.44-2.74)	
ALSFRS-R decline from onset to diagnosis (points/months)	≥0.91	1	0.0001
	<0.91	1.24 (1.17-1.32)	
Mechanical ventilation	Non-ventilated	1	0.0001
	NIMV-IMV	2.43 (1.81-3.25)	
	IMV	1.34 (1.06-1.79)	
	NIMV	1.23 (1.01-1.55)	

ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale, revised; NIMV, non-invasive mechanical ventilation; IMV, invasive mechanical ventilation via tracheostomy.