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.

Supplementary references

1. Chiò A, Mora G, Moglia C, Manera U, Canosa A, Cammarosano S, Ilardi A, Bertuzzo D, Bersano E, Cugnasco P, Grassano M, Pisano F, Mazzini L, Calvo A; Piemonte and Valle d'Aosta Register for ALS (PARALS). Secular Trends of Amyotrophic Lateral Sclerosis: The Piemonte and Valle d'Aosta Register. JAMA Neurol. 2017 Sep 1;74(9):1097-1104. doi: 10.1001/jamaneurol.2017.1387. PMID: 28692730; PMCID: PMC5710181.

2. Iazzolino B, Pain D, Peotta L, Calvo A, Moglia C, Canosa A, Manera U, Ilardi A, Bombaci A, Zucchetti JP, Mora G, Chio A. Validation of the revised classification of cognitive and behavioural impairment in ALS. J Neurol Neurosurg Psychiatry. 2019 Jul;90(7):734-739. doi: 10.1136/jnnp-2018-319696. Epub 2019 Feb 7. PMID: 30733331.

3. Strong MJ, Abrahams S, Goldstein LH, Woolley S, Mclaughlin P, Snowden J, Mioshi E, Roberts-South A, Benatar M, HortobáGyi T, Rosenfeld J, Silani V, Ince PG, Turner MR. Amyotrophic lateral sclerosis - frontotemporal spectrum disorder (ALS-FTSD): Revised diagnostic

criteria. Amyotroph Lateral Scler Frontotemporal Degener. 2017 May;18(3-4):153-174. doi: 10.1080/21678421.2016.1267768. Epub 2017 Jan 5. PMID: 28054827; PMCID: PMC7409990.

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.