J Neurol
DOI 10.1007/s00415-016-8313-y

ORIGINAL COMMUNICATION

Factors predicting survival in ALS: a multicenter Italian study

Andrea Calvo[1] · Cristina Moglia[1] · Christian Lunetta[2,3] · Kalliopi Marinou[4] · Nicola Ticozzi[5,6] · Gianluca Drago Ferrante[7] · Carlo Scialo[8] · Gianni Sorarù[9] · Francesca Trojsi[10] · Amelia Conte[11] · Yuri M. Falzone[12] · Rosanna Tortelli[13] · Massimo Russo[14] · Adriano Chiò[1] · Valeria Ada Sansone[2,15] · Gabriele Mora[4] · Vincenzo Silani[5,6] · Paolo Volanti[7] · Claudia Caponnetto[8] · Giorgia Querin[9] · Maria Rosaria Monsurrò[10] · Mario Sabatelli[11,16] · Nilo Riva[12] · Giancarlo Logroscino[13] · Sonia Messina[3,14] · Nicola Fini[17] · Jessica Mandrioli[17]

Received: 24 September 2016 / Accepted: 12 October 2016

Abstract The aim of this multicenter, retrospective study is to investigate the role of clinical characteristics and therapeutic intervention on ALS prognosis. The study included patients diagnosed from January 1, 2009 to December 31, 2013 in 13 Italian referral centers for ALS located in 10 Italian regions. Caring neurologists collected a detailed phenotypic profile and follow-up data until death into an electronic database. One center collected also data from a population-based registry for ALS. 2648 incident cases were collected. The median survival time from onset to death/tracheostomy was 44 months (SE 1.18, CI 42–46). According to univariate analysis, factors related to survival from onset to death/tracheostomy were: age at onset, diagnostic delay, site of onset, phenotype, degree of certainty at diagnosis according to revised El Escorial criteria (R-EEC), presence/absence of dementia, BMI at diagnosis, patients' provenance. In the multivariate analysis, age at onset, diagnostic delay, phenotypes but not site of onset, presence/absence of dementia, BMI, riluzole use, R-EEC criteria were independent prognostic factors of survival in ALS. We compared patients from an ALS Registry with patients from tertiary centers; the latter ones were younger,

✉ Jessica Mandrioli
j.mandrioli@ausl.mo.it

[1] "Rita Levi Montalcini" Department of Neuroscience, ALS Center, University of Torino, Turin, Italy

[2] NEuroMuscular Omnicentre (NEMO), Serena Onlus Foundation, Milan, Italy

[3] NEMO Sud Clinical Center for Neuromuscular Diseases, Aurora Onlus Foundation, Messina, Italy

[4] Department of Neurorehabilitation ALS Center Scientific Institute of Milan, Salvatore Maugeri Foundation IRCCS, Milan, Italy

[5] Department of Neurology and Laboratory of Neuroscience, IRCCS Istituto Auxologico Italiano, Milan, Italy

[6] Department of Pathophysiology and Transplantation 'Dino Ferrari' Center, University of Milan, Milan, Italy

[7] Neurorehabilitation Unit/ALS Center, Salvatore Maugeri Foundation, IRCCS, Mistretta, Messina, Italy

[8] Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics Maternal and Child Health (DINOGMI), University of Genova, IRCCS AOU San Martino-IST, Genoa, Italy

[9] Department of Neurosciences Neuromuscular Center, University of Padova, Padua, Italy

[10] Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, MRI Research Center SUN-FISM, Second University of Naples, Naples, Italy

[11] NEuroMuscular Omnicentre (NEMO), Serena Onlus Foundation: Pol. A. Gemelli Foundation, Rome, Italy

[12] Department of Neurology Division of Neuroscience Institute of Experimental Neurology, San Raffaele Scientific Institute, Milan, Italy

[13] Department of Clinical Research in Neurology, University of Bari "A. Moro", at Pia Fondazione "Card. G. Panico" Tricase, Lecce, Italy

[14] Department of Clinical and Experimental Medicine, University of Messina and Nemo Sud Clinical Center for Neuromuscular Diseases, Aurora Foundation, Messina, Italy

[15] Department Biomedical Sciences for Health, University of Milan, Milan, Italy

[16] Institute of Neurology, Catholic University of Sacred Heart, Rome, Italy

[17] Department of Neuroscience, S. Agostino-Estense Hospital and University of Modena and Reggio Emilia, Via Pietro Giardini n. 1355, 41100 Modena, Italy

Published online: 24 October 2016

less frequently bulbar, but more frequently familial and definite at diagnosis. Our large, multicenter study demonstrated the role of some clinical and demographic factors on ALS survival, and showed some interesting differences between referral centers' patients and the general ALS population. These results can be helpful for clinical practice, in clinical trial design and to validate new tools to predict disease progression.

Keywords ALS · Survival · Prognostic factors · Referral centers · Population-based registries

Introduction

Amyotrophic lateral sclerosis (ALS) clinical heterogeneity is generally recognized as one of the most difficult features of ALS to address in relation to patients' prognosis and counselling, and in clinical trials design and conduction. Survival of ALS patients from symptom onset is often reported to be 3-5 years, but published studies report a wide range of outcomes, with considerable inter-individual variability [1].

A number of clinical factors have been reported to predict ALS prognosis: age and site of onset, genotype, clinical phenotype, severity and rate of disease progression, degree of diagnostic certainty, diagnostic delay, and cognitive status [2, 3]. The influence of therapeutic interventions, such as riluzole use [4], enteral nutrition (EN) [5], non-invasive ventilation (NIV) [6–8], and multidisciplinary care [9, 10], on survival is still controversial.

To further evaluate possible prognostic factors in ALS with particular attention to those specific for the Italian population, we performed a large multicenter study involving the main ALS tertiary referral centers in Italy, focusing on clinical features of ALS, with particular attention to clinical prognostic factors and therapeutic interventions. We also aimed to compare these results with those obtained from an ALS regional registry.

Materials and methods

Patient data collection

The study has been performed in 13 ALS Italian referral centers, located in 10 Italian regions covering a population of 45 million inhabitants: ALS centers of Turin, Padua, Genoa, Naples, Modena, Lecce, NEMO clinical centers in Milan, Rome, and Messina, Salvatore Maugeri Foundations in Milan and Mistretta, ALS centers at San Raffaele Institute and Istituto Auxologico Italiano in Milan.

All the involved centers have a wide experience in multidisciplinary management of motor neuron diseases (MND) and identified a supervising neurologist for this project.

The study included patients diagnosed with ALS from January 1, 2009 to December 31, 2013 according to revised El Escorial criteria (R-EEC) for ALS diagnosis [11].

Data have been recorded into an electronic database available to all involved centers. Caring neurologists collected a detailed phenotypic profile for each ALS patient, including the following information: demographic data, age at onset and diagnosis, gender, type of onset, site and time of onset, affected body regions, R-EEC classification at entry, clinical phenotype (classic ALS, bulbar ALS, predominant upper motor neuron ALS (UMNp), flail arm, flail leg, respiratory ALS) [12], presence of concomitant dementia, family history for neurodegenerative disorders, body mass index (BMI), and medication use (including riluzole).

Clinical follow-up has been performed in the 13 ALS centers, collecting and inputting information on ALS clinical course, gastrostomy, respiratory supports, and death.

The center of Modena collected also data from Emilia Romagna Registry for ALS (ERRALS). Detailed description of ERRALS and methodology of cases ascertainment have already been published [13].

Tertiary referral centers care for ALS in Italy

In Italy, patients with ALS receive a certification of rare disease which allows them to have free access to all services, which include outpatients specialists examinations, instrumental testing, aids for motor, communication, nutrition and respiratory impairment, and home care. In tertiary referral centers, after diagnosis, a care manager, case manager and caregiver are identified. Patients are treated according to the American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS) Guidelines on clinical management of ALS [14] [15]. Multidisciplinary care is coordinated by a neurologist (the care manager) with specialist expertise in motor neuron diseases, and includes multiple evaluations, usually organized during the same day. Training for cough machine and non-invasive ventilation can be made with hospital admission or during one-day examinations. Gastrostomy is usually performed during admission to the hospital. Regular team meetings allow cases discussion and shared decision-making process. Home care is coordinated by the general practitioner in collaboration with ALS centers and with community-based palliative care services. Hospice care is available throughout the Italian territory, and on the other side, rapid access to hospital is provided

for patients with increasing symptoms requiring acute intervention or intensive procedures.

Patients can choose to be followed wherever they like, but usually, tertiary centers specialists direct them to the tertiary center which is located nearer to patients' home.

ALS registry and care in Emilia Romagna region

ERRALS has been set up in 2009 and records information on all people diagnosed with ALS in 17 neurological centers of the region [13]. In the region, there are tertiary ALS centers organized as mentioned above, but there are also general neurology units, which follow up patients and refer them to other specialists when they deem it to be necessary. The main differences with tertiary centers are represented by the prompt availability of different specialists and procedures (in particular waiting time for them), the regularity of follow-up, the collaboration and coordination among specialists and with community services, access to research and clinical trials, and, consequently, the level of expertise.

Ethics

The study was approved by the Ethical Committees of the participating ALS centers.

Statistical methods

Chi-squared test was used to explore differences between groups for categorical data; *T* test (or multiple comparison test) for continuous data. Survival was calculated as the time from onset to death/tracheostomy (months) or censoring date (last day of follow-up, December 31, 2014).

Kaplan–Meier survival curves followed by log-rank test were used to evaluate the survival of different groups from

Table 1 Patient's characteristics

Explanatory variables	Males, $N = 1455$ *n* (%) m [SD]	Females $N = 1193$ *n* (%) m [SD]	*p* value
ALS onset			
Bulbar	279 (19.17)	374 (31.35)	**<0.001**
Spinal	1038 (71.34)	718 (60.18)	
Generalized	24 (1.65)	18 (1.51)	
Phenotype			
Bulbar	190 (13.06)	262 (21.96)	**<0.001**
Classic	730 (50.17)	552 (46.27)	
Flail arm	88 (6.05)	36 (3.02)	
Flail leg	105 (7.22)	67 (5.62)	
UMNp	92 (6.32)	94 (7.88)	
Respiratory	30 (2.06)	12 (1.01)	
Age at onset	63.13 [11.20]	64.49 [11.68]	**0.002**
Diagnostic delay	14.21 [15.87]	15.01[15.41]	0.189
R-EEC			
Definite	347 (23.85)	347 (29.09)	**0.013**
Clinically probable	427 (29.35)	322 (26.99)	
Probable lab-supported	176 (12.10)	129 (10.81)	
Possible	265 (18.21)	192 (16.09)	
Dementia (yes)	105 (8.80)	72 (7.31)	0.242
Dead at last observation (yes)	639 (43.92)	539 (45.18)	0.515
Riluzole (yes)	1137 (78.14)	916 (76.78)	0.403
Gastrostomy (yes)	369 (25.36)	366 (30.68)	**0.002**
Non-invasive ventilation (yes)	583 (40.07)	450 (37.72)	0.218
Invasive ventilation (yes)	230 (15.81)	172 (14.42)	0.321
BMI at diagnosis	24.36 [3.75]	23.89 [4.37]	**0.015**
Familiarity (Familial ALS)	81 (5.57)	80 (6.70)	0.222
Total	1455 (100)	1193 (100)	

Significant results in bold

UMNp upper motor neuron-predominant phenotype, *BMI* body mass index, *SD* standard deviation

disease onset. Univariate Cox regression was applied to derive unadjusted HRs for death/tracheostomy and for death. Multivariate Cox regression models were used to estimate covariate-adjusted risk of death/tracheostomy (from onset).

We included in the Cox regression analysis well-known factors as reported previously [2], and based on clinical judgment.

Data were analyzed using Stata 12 (Stata Corp, Texas, USA).

Results

During the 5 years of the study, 2648 incident cases were collected. Clinical features and demographic data are reported in Tables 1 and 2.

Genetic tests were done by 1011 patients (38.18 %); in 835 patients (82.59 %), we did not disclose mutations in ALS-related genes, whereas 94 patients (9.30 %) carried the C9ORF72 repeat expansion, 39 (3.86 %) SOD1 mutation, 27 (2.67 %) TARDBP mutation, 9 (0.89 %) FUS mutation and 7 (0.69 %) were carriers of other rarer mutations.

The median survival time from onset to death or tracheostomy was 44 months (SE 1.18, CI 42–46). The overall 1-year, 2-year, 3-year, 4-year and 5-year survival rates were 93.40 % (SE 0.49 %), 74.80 % (SE 0.87 %), 57.19 % (SE 1.04 %), 45.89 % (SE 1.11 %), and 38.15 % (SE 1.16 %), respectively (Fig. 1a).

According to the univariate analysis, factors related to survival from onset to death/tracheostomy were: age at onset (Fig. 1b), diagnostic delay (Fig. 1c), site of onset, degree of certainty at diagnosis according to R-EEC

Table 2 Patient's characteristics by age classes

Explanatory variables	Patients <55 years, $N = 576$ *n* (%) m [SD]	Patients 55–75 years, $N = 1646$ *n* (%) m [SD]	Patients >75 years, $N = 426$ *n* (%) m [SD[c]]	*p* value
Sex (male)	331 (57.46)	934 (56.74)	190 (44.60)	0.200
ALS onset				
Bulbar	90 (15.62)	393(23.88)	170 (39.91)	**<0.001**
Spinal	427(74.13)	1110 (67.44)	219 (51.41)	
Generalized	6 (1.04)	25 (1.52)	11 (2.58)	
Phenotype				
Bulbar	50 (8.68)	266 (16.16)	136 (31.92)	**<0.001**
Classic	288 (50.00)	807 (49.03)	187 (43.90)	
Flail arm	26 (4.51)	82 (4.98)	16 (3.76)	
Flail Leg	37 (6.42)	110 (6.68)	25 (5.87)	
UMNp	60 (10.42)	110 (6.68)	16 (3.75)	
Respiratory	2 (0.35)	33 (2.00)	7 (1.64)	
Diagnostic delay	16.67 [19.69]	14.34 [15.08]	12.62 [10.71]	**<0.001**
R-EEC				
Definite	129 (22.40)	438 (26.61)	127 (29.81)	0.668
Clinically probable	162 (28.12)	469 (28.49)	118 (27.70)	
Probable lab-supported	68 (11.80)	189 (11.48)	48 (11.27)	
Possible	97 (16.84)	287 (17.44)	73 (17.14)	
Dementia (yes)	21 (4.66)	118 (8.61)	38 (10.67)	**0.009**
Dead at last observation (yes)	154 (26.74)	760 (46.17)	264 (61.97)	**<0.001**
Riluzole (yes)	455 (78.99)	1303 (79.16)	295 (69.25)	**<0.001**
Gastrostomy (yes)	151 (26.21)	482 (29.28)	102 (23.94)	0.057
Non-invasive ventilation (yes)	212 (36.81)	661(40.16)	160 (37.56)	0.160
Invasive ventilation (yes)	94 (16.32)	269 (16.34)	39 (9.15)	**0.001**
BMI at diagnosis	24.20 [4.07]	24.27 [4.05]	23.63 [4.00]	0.052
Familiarity (Familial ALS)	58 (10.07)	91 (5.53)	12 (2.82)	**0.001**
Total	576 (100)	1646 (100)	426 (100)	

Significant results in bold

UMNp upper motor neuron-predominant phenotype, *BMI* body mass index, *SD* standard deviation

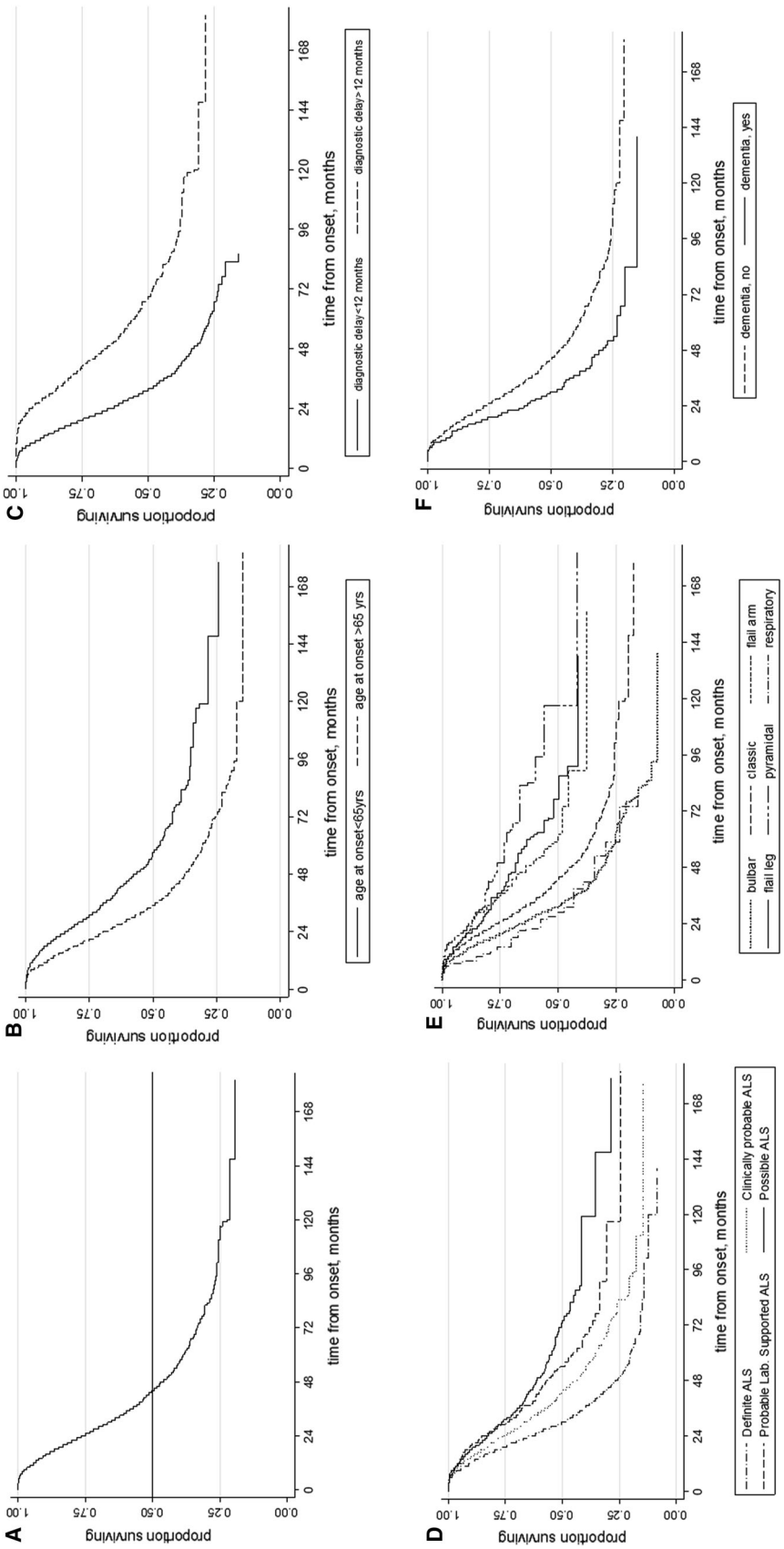

Fig. 1 **a** Overall Kaplan–Meier survival estimates (survival from onset to death or tracheostomy). **b** Kaplan–Meier survival estimates according to age at diagnosis (survival from onset to death or tracheostomy). **c** Kaplan–Meier survival estimates according to diagnostic delay (survival from onset to death or tracheostomy). **d** Kaplan–Meier survival estimates according to degree of diagnostic certainty (survival from onset to death or tracheostomy). **e** Kaplan–Meier survival estimates according to clinical phenotype (survival from onset to death or tracheostomy). **f** Kaplan–Meier survival estimates according to the presence of dementia (survival from onset to death or tracheostomy)

Table 3 Clinical factors and tracheostomy-free survival (univariate analysis)

Variable	Survival from onset to death or tracheostomy			
	Median survival (months)	HR	95 % CI	*p* value
Sex (F/M)	44/44	1.00	0.90–1.11	0.941
Onset (B/S/G)	33/49/24	0.66	0.59–0.74	**<0.001**
Age (< or >64 years)	57/35	1.76	1.58–1.97	**<0.001**
Phenotype (B/CL/FA/FL/UMNp/R)	31/38/62/77/117/29	0.75	0.71–0.80	**<0.001**
Diagnostic delay (< or > 12 months)	32/69	0.36	0.32–0.41	**<0.001**
R-EEC (D/CP/P-LSP/P)	30/43/54/61	0.74	0.70–0.78	**<0.001**
Non-invasive ventilation (yes/no)	36/55	1.59	1.42–1.77	**<0.001**
Gastrostomy (yes/no)	32/58	2.08	1.86–2.32	**<0.001**
BMI at diagnosis (< or >24)	36/48	0.74	0.66–0.85	**<0.001**
ERRALS vs tertiary centers	38/44	0.88	0.77–0.99	**0.043**
Riluzole treatment (yes/no)	43/43	1.04	0.90–1.20	0.552
Dementia (yes/no)	33/44	1.60	1.32–1.94	**<0.001**
Familiarity (yes/no)	38/44	1.21	0.98–1.50	0.074
Genetics (presence/absence of genes mutation)[a]	39/42	1.12	0.90–1.40	0.294

Significant results in bold

F/M female/male, *B/S/G* bulbar/spinal/generalized, *B/CL/FA/FL/UMNp/R* bulbar, classic, flail arm, flail leg, upper motor neuron-predominant, respiratory, *D/CP/P-LSP/P* definite, clinically probable, probable-laboratory supported, possible, *BMI* body mass index

[a] survival of patients carrying C9orf72 repeat expansion, or SOD1, or TARDBP mutations did not differ from other patients

(Fig. 1d), phenotype (Fig. 1e), cognitive impairment (Fig. 1f), BMI at diagnosis (Table 3).

Patients who underwent gastrostomy and NIV were the ones with the shorter survivals (Table 3).

Comparing ALS patients from ERRALS (general ALS population of Emilia Romagna region) with those included by tertiary ALS centers, at univariate analysis, the provenance influenced survival too (Table 3).

We then focused on the characteristics of ALS patients included by tertiary ALS centers and coming from a population-based registry (ERRALS) [13]. Patients from ERRALS showed different characteristics compared to patients referring to ALS tertiary referral centers (Table 4).

Therefore, we performed a multivariate analysis including variables possibly influencing survival that were available at diagnosis, selected on the bases of our data, clinical experience and literature data.

In the initial Cox multivariable model, we included the following variables: sex, age at onset (> or <65 years [median value]), diagnostic delay, site of onset (bulbar/spinal/generalized), phenotypes (bulbar, classic, flail arm, flail leg, UMNp, respiratory), presence/absence of concomitant dementia, riluzole treatment, patients provenance (population-based registry versus tertiary centers), BMI (> or <24 [median value]), degree of diagnostic certainty according to R-EEC criteria (definite, clinically probable, probable-laboratory supported, possible).

After dropping non-significant terms, the final model included age at onset, diagnostic delay, phenotypes, presence/absence of dementia, riluzole use, BMI, R-EEC criteria (Table 5) (LR Chi2 = 294.34, Log likelihood = −4602, Prob > Chi-square = 0.0000). These factors were independent prognostic factors of survival in ALS. Patients' provenance (Registry versus tertiary centers for ALS) did not result to be an independent prognostic factor.

Discussion

We studied a large ALS population coming from the main tertiary referral centers in Italy.

The clinical features of the population are similar to those already reported in previous ALS population studies [16–18]. In particular and according to the literature, female patients presented with a bulbar phenotype more often than males, were generally older, and with a lower BMI at diagnosis [19, 20]. It is not surprising, then, that females underwent gastrostomy more often than males.

Older patients (>75 years old) had a bulbar phenotype and a generalized onset more often than younger ones; diagnostic delay was shorter in these patients despite age, probably because of a faster disease progression. As expected, older patients were less treated with riluzole than the younger ones, rarely underwent invasive ventilation and seldom had a family history of ALS [18, 21].

As regards prognosis, our study confirms the expected role of some well-known factors on ALS survival: age at

Table 4 Patients' characteristics (patients from ERRALS and patients from referral centers)

Explanatory variables	ERRALS patients, $N = 526$ n (%) m [SD[c]]	Tertiary referral centers patients $N = 2122$ n (%) m [SD]	p value
Sex (male)	292 (55.51)	1163 (54.81)	0.771
ALS onset			
Bulbar	149 (28.33)	504 (23.75)	**<0.001**
Spinal	332 (63.12)	1424 (67.10)	
Generalized	38 (7.22)	4 (0.19)	
Phenotype			
Bulbar	179 (34.03)	273 (12.86)	**<0.001**
Classic	225 (42.77)	1057 (49.81)	
Flail arm	33 (6.27)	91 (4.29)	
Flail leg	67 (12.74)	105 (4.95)	
UMNp	24 (4.56)	162 (7.63)	
Respiratory	17 (3.23)	25 (1.78)	
Age at onset	67.04 [11.33]	62.92 [11.32]	**<0.001**
Diagnostic delay	13.14 [12.47]	14.92[16.35]	**0.020**
R-EEC			
Definite	105 (19.96)	589 (27.76)	**0.015**
Clinically probable	151 (28.71)	598 (28.18)	
Probable lab-supported	69 (13.12)	236 (11.12)	
Possible	79 (15.02)	378 (17.81)	
Dementia	46 (9.58)	131 (7.71)	0.225
Dead at last observation (yes)	270 (51.33)	908 (42.79)	**<0.001**
Riluzole (yes)	444 (84.41)	1609 (82.09)	0.213
Gastrostomy (yes)	162 (30.80)	573 (29.20)	0.477
Non-invasive ventilation (yes)	200 (38.02)	833 (42.46)	0.067
Invasive ventilation (yes)	79 (15.02)	323 (15.22)	0.908
BMI at diagnosis	24.29 [3.94]	24.11 [4.09]	0.403
Familiarity (Familial ALS)	17 (3.23)	144 (7.27)	**0.001**
Total	526 (100)	2122 (100)	

Significant results in bold

UMNp upper motor neuron-predominant phenotype, *BMI* body mass index, *SD* standard deviation

diagnosis (with younger patients surviving longer), diagnostic delay (with shorter diagnostic delay indicating a more quick degenerative process and a shorter survival), phenotypes, dementia and degree of certainty at diagnosis according to R-EEC [3, 22–26].

Most of the studies found that age at onset greatly influences a wide range of clinical features, including clinical phenotypes and progression to the end-stage, and the entire clinical phenotypes of ALS, with decreasing survival time correlating with increasing age [2]. The underlying mechanism is still unknown, although one may speculate that subpopulations of the motor neurons may be differentially vulnerable to the aging process, and that the smaller motor neuron "reserve" in elderly patients could contribute to a shorter disease course.

Also, diagnostic delay is a well-known prognostic factor, with shorter diagnostic delay predicting a shorter survival in relation to a more widespread disease expression [2].

Interestingly, in multivariate analysis, only phenotypes resulted to be independent factors for ALS survival, whereas the prognostic role of site of onset was not confirmed. This confirms what has been shown by some recent large studies [27] and could be explained by the better reliability of a classification based on history, clinical examination and patients follow-up, rather than simply the site of onset (usually referred by the patient).

Diagnostic certainty according to R-EEC showed that patients with definite ALS had a shorter survival: this is in accordance with recent reports and could be explained by a more widespread MN involvement as detected at clinical examination, and by the more frequent bulbar involvement in this category with respect to the others [19].

Table 5 Independent prognostic factors (multivariate Cox analysis)

Variables	Categories	Hazard ratio (95 % CI)	$p > z$
Age at onset, years	<65 Years	1 (reference)	**<0.001**
	>65 Years	1.64 (1.41–1.91)	
Diagnostic delay, months	<12 Months	1 (reference)	**<0.001**
	>12 Months	0.38 (0.32–0.45)	
Phenotype	Bulbar	1 (reference)	**0.001**
	Classic	0.90 (0.76–1.06)	
	Flail arm	0.68 (0.47–0.98)	
	Flail leg	0.62 (0.41–0.93)	
	UMNp	0.30 (0.18–0.49)	
	Respiratory	1.30 (0.77–2.17)	
R-EEC criteria	Definite	1 (reference)	**<0.001**
	Clinically probable	0.70 (0.58–0.83)	
	Prob. Lab. Supp.	0.46 (0.35–0.61)	
	POSSIBLE	0.59 (0.47–0.73)	
BMI	<24	1 (reference)	**0.001**
	>24	0.79 (0.68–0.91)	
Dementia	No	1 (reference)	**0.016**
	Yes	1.34 (1.05–1.70)	
Riluzole	No	1 (reference)	**0.030**
	Yes	0.79 (0.64–0.98)	

Significant results in bold

BMI body mass index, *UMNp* upper motor neuron-predominant phenotype

Treatment with riluzole, is the only one recommended by the WHO; its effect on survival was detected only through multivariate analysis, possibly due to an unidentified confounder counterbalancing the drug effects in treated patients. However, these results should be considered with caution due to the observational nature of this study.

Although debated, in our cohort, BMI [28–30] also had an impact on ALS survival; a higher BMI may be associated to a longer survival, because it is associated to higher baseline energy reserves, and to a lower degree of hypermetabolism among ALS subjects [30]. This is of notice in clinical practice as it has important implications for nutritional counselling in ALS.

Neither familiarity nor genetic mutations (together or considering C9orf72 repeat expansion, SOD1 and TARDBP mutations separately) resulted to influence the prognosis significantly, but only 38 % of the patients of our cohort underwent genetic tests.

We also found that median survival of patients who underwent NIV or EN was shorter than survival of patients who did not undergo these procedures. This can be explained by the observational nature of our study, where patients who underwent NIV or gastrostomy were those with a worse respiratory and nutritional status and, thus, with a more rapid progression [8]. Since NIV and EN are procedures performed late in the course of the disease, we did not include these variables in the multivariate analysis, as it was aimed at finding prognostic factors available at diagnosis.

Finally, due to the mixed nature of our population, partly from tertiary centers population and partly coming from ERRALS, we compared patients' characteristics of the two groups.

Considering the general ALS population coming from ERRALS and patients coming from tertiary centers, we confirm that there was a selection of patients with a better prognosis among the ones referring to tertiary centers: these patients were younger, usually had a prolonged diagnostic delay, a longer survival, and a clinical presentation different from the classical phenotype, with less patients presenting bulbar involvement than observed in the general ALS population [16].

The different characteristics between the two populations may reflect the fact that patients with milder phenotypes and less disability can commute more easily to distant tertiary centers. Also, tertiary ALS centers tend to attract a younger population, either because of patients' increased awareness of ALS complications and potential experimental treatments, or due to the fact that patients with atypical, rarer phenotypes are often referred for second opinions.

There were also more definite and familial ALS among tertiary centers than in the general ALS population, but interestingly, there were no differences in the use of procedures (gastrostomy, NIV, IV), in BMI, and in riluzole administration. The same use of procedures and drugs in tertiary centers and in Emilia Romagna can be explained by the organization of Italian National Health Service, which is universal, free and provides high standards of care for the entire population, with little differences, mainly at a management level, among the different Italian regions.

The major strength of this study is the great number of patients involved, coming from different Italian regions and configuring one of the largest observational studies on ALS published so far.

However, our study has also several limitations that should be noticed. First, we have to assume a sample selection bias because of our cases ascertainment, which mainly includes patients coming from tertiary centers. Moreover, we could not include the rate of disease progression assessed by ALSFRS-R, a variable that has been shown to have an important role on ALS survival. Lastly, the current study has all the limitations of observational studies, which are not the gold standard method to evaluate the effect of a treatment (NIV, gastrostomy, riluzole) as a result of the effect of uncontrolled potential confounders on survival. Nevertheless, observational studies have the advantage of longer term follow-up than RCTs and include participants who approximate routine clinical practice much more than RCTs [31].

In conclusion It has been demonstrated that age at diagnosis, diagnostic delay, R-EEC criteria, phenotype, BMI, dementia and riluzole treatment have an important role on ALS survival as independent prognostic factors. With respect to the general ALS population, patients from tertiary centers are younger, less frequently bulbar, but more frequently familial and with definite ALS at diagnosis. There were no differences in the use of procedures (gastrostomy, NIV, IV), in BMI, and in riluzole administration, perhaps because of the organization of Italian National Health Service.

These results can be helpful for daily clinical practice, in clinical trial design and to validate new tools for predicting disease progression.

Acknowledgments The authors thank all the collaborators of the multidisciplinary centers for motor neuron disease involved in the study: Antonio Fasano, Laura Ferri (Modena), Giovanni Novi (Genova), Rosa Capozzo (Tricase), Cinzia Femiano, Mattia Siciliano (Naples), Giulia Bisogni (Rome); Andrea Lizio, Eleonora Maestri, Claudia Tarlarini (Nemo Milano), Claudia Morelli, Federico Verde, Stefano Messina (Istituto Auxologico, Milano), Antonio Onniboni (Fondazione S. Maugeri, Mistretta), Riccardo Sideri (Fondazione S. Maugeri, Milano). Jessica Mandrioli has received research support from Regione EmiIia Romagna (Programma di ricerca Regione-Università 2010–2012, area 2, Ricerca per il Governo Clinico; Emilia Romagna Registry for Amyotrophic Lateral Sclerosis 2009–2015). Outside this work, Francesca Trojsi perceived Grants from Novartis and Maria Rosaria Monsurrò grants from Italfarmaco and Italian Association for Amyotrophic Lateral Sclerosis (AISLA). Amelia Conte and Mario Sabatelli thank I.CO.M.M. onlus, association for Amyotrophic Lateral Sclerosis research. Nicola Ticozzi received research support from the Italian Ministry of Health (Grant GR-2011-02347820—IRisALS) and from the Associazione "Io Corro con Giovanni".

Compliance with ethical standards

Conflicts of interest The authors declare no competing interests.

Ethical standards The study was performed in accordance with the ethical standards statement.

References

1. Beghi E, Chiò A, Couratier P et al (2011) The epidemiology and treatment of ALS: focus on the heterogeneity of the disease and critical appraisal of therapeutic trials. Amyotroph Lateral Scler 12:1–10. doi:10.3109/17482968.2010.502940
2. Chio A, Logroscino G, Hardiman O et al (2009) Prognostic factors in ALS: a critical review. Amyotroph Lateral Scler 10:310–323. doi:10.3109/17482960802566824
3. Creemers H, Grupstra H, Nollet F, van den Berg LHBA (2015) Prognostic factors for the course of functional status of patients with ALS: a systematic review. J Neurol 262:1407–1423. doi:10.1007/s00415-014-7564-8
4. Miller RG, Mitchell JD, Moore DH (2012) Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)(Review). Cochrane Database Syst Rev 3:1–34. doi:10.1002/14651858.CD001447
5. Katzberg H, Benatar M (2011) Enteral tube feeding for amyotrophic lateral sclerosis/motor neuron disease (Review). Cochrane Database Syst Rev 1:CD004030. doi:10.1002/14651858.CD004030.pub3
6. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJGG (2006) Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. Lancet Neurol 5:140–147
7. Radunovic A, Annane D, Jewitt K MN (2009) Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev 4:CD004427. doi:10.1002/14651858.CD004427
8. Fini N, Georgoulopoulou E, Vinceti M, Monelli M, Pinelli G, Vacondio P, Giovannini M, Dallari R, Marudi AMJ (2014) Noninvasive and invasive ventilation and enteral nutrition for ALS in Italy. Muscle Nerve 50:508–516. doi:10.1002/mus.24187
9. Ng L, Khan F MS (2009) Multidisciplinary care for adults with amyotrophic lateral sclerosis or motor neuron disease. Cochrane Database Syst Rev 4:CD007425. doi:10.1002/14651858.CD007425.pub2
10. Rooney J, Byrne S, Heverin M, Tobin K, Dick A, Donaghy CHO (2015) A multidisciplinary clinic approach improves survival in ALS: a comparative study of ALS in Ireland and Northern Ireland. J Neurol Neurosurg Psychiatry 86:406–501. doi:10.1136/jnnp-2014-309601
11. Brooks BR, Miller RG, Swash M, Munsat TL (2000) El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 1:293–299. doi:10.1080/146608200300079536

12. Chiò A, Calvo A, Moglia C, Mazzini L, MGP study group (2011) Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. J Neurol Neurosurg Psychiatry 82:740–746. doi:10.1136/jnnp.2010.235952
13. Mandrioli J, Biguzzi S, Guidi C, et al. (2014) Epidemiology of amyotrophic lateral sclerosis in Emilia Romagna Region (Italy): A population based study. 8421:262–268. doi:10.3109/21678421.2013.865752
14. Andersen PM, Abrahams S, Borasio GD et al (2012) EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS)–revised report of an EFNS task force. Eur J Neurol 19:360–375. doi:10.1111/j.1468-1331.2011.03501.x
15. Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, Kalra S, Katz JS, Mitsumoto H, Rosenfeld J, Shoesmith C, Strong MJ WSQSS of the AA of N (2009) Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American. Neurology 73:1227–1233
16. Logroscino G, Traynor B, Hardiman O et al (2008) Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. J Neurol Neurosurg Psychiatry 79:6–11. doi:10.1136/jnnp.2006.104828
17. Pugliatti M, Parish LD, Cossu P et al (2013) Amyotrophic lateral sclerosis in Sardinia, insular Italy, 1995–2009. J Neurol 260:572–579. doi:10.1007/s00415-012-6681-5
18. Chiò A, Mora G, Calvo A et al (2009) Epidemiology of ALS in Italy: a 10-year prospective population-based study. Neurology 72:725–731. doi:10.1212/01.wnl.0000343008.26874.d1
19. Bandettini di Poggio M, Sormani MP, Truffelli R et al (2012) Clinical epidemiology of ALS in Liguria, Italy. Amyotroph Lateral Scler. doi:10.3109/17482968.2012.729062
20. Georgoulopoulou E, Vinceti M, Bonvicini F et al (2011) Changing incidence and subtypes of ALS in Modena, Italy: a 10-years prospective study. Amyotroph Lateral Scler 12:451–457. doi:10.3109/17482968.2011.593037
21. Chiò A, Calvo A, Ghiglione P et al (2010) Tracheostomy in amyotrophic lateral sclerosis: a 10-year population-based study in Italy. J Neurol Neurosurg Psychiatry 81:1141–1143. doi:10.1136/jnnp.2009.175984
22. Sabatelli M, Madia F, Conte A, Luigetti M, Zollino M, Mancuso I, Lo Monaco M, Lippi GTP (2008) Natural history of young-adult amyotrophic lateral sclerosis. Neurology 71:876–881. doi:10.1212/01.wnl.0000312378.94737.45
23. Chen L, Zhang B, Chen R, Tang L, Liu R, Yang Y, Yang Y, Liu X, Ye S, Zhan SFD (2015) Natural history and clinical features of sporadic amyotrophic lateral sclerosis in China. J Neurol Neurosurg Psychiatry 86:1075–1081. doi:10.1136/jnnp-2015-310471
24. Phukan J, Elamin M, Bede P, Jordan N, Gallagher L, Byrne S, Lynch C, Pender N, Hardiman O (2012) The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. J Neurol Neurosurg Psychiatry 83:102–108. doi:10.1136/jnnp-2011-300188
25. Montuschi A, Iazzolino B, Calvo A, Moglia C, Lopiano L, Restagno G, Brunetti M, Ossola I, Lo Presti A, Cammarosano S, Canosa A, Chiò A (2015) Cognitive correlates in amyotrophic lateral sclerosis: a population-based study in Italy. J Neurol Neurosurg Psychiatry 86:168–173. doi:10.1136/jnnp-2013-307223
26. Sabatelli M, Zollino M, Luigetti M, Grande AD, Lattante S, Marangi G, Monaco ML, Madia F, Meleo E, Bisogni G, Conte A (2011) Uncovering amyotrophic lateral sclerosis phenotypes: clinical features and long-term follow-up of upper motor neuron-dominant ALS. Amyotroph Lateral Scler 12:278–282. doi:10.3109/17482968.2011.580849
27. Wei Q, Chen X, Zheng Z et al (2015) The predictors of survival in Chinese Amyotrophic Lateral Sclerosis patients. Amyotroph Lateral Scler Front Degener 16:237–244. doi:10.3109/21678421.2014.993650
28. Traxinger K, Kelly C, Johnson BA, Lyles RHGJ (2013) Prognosis and epidemiology of amyotrophic lateral sclerosis: analysis of a clinic population, 1997–2011. Neurol Clin Pr 3:313–320
29. Moura MC, Novaes MR, Eduardo EJ, Zago YS, LA Freitas Rdel NC (2015) Prognostic Factors in Amyotrophic Lateral Sclerosis: a Population-Based Study. PLoS One 10:e0141500. doi:10.1371/journal.pone.0141500
30. Paganoni S, Deng J, Jaffa M et al (2011) Body mass index, not dyslipidemia, is an independent predictor of survival in amyotrophic lateral sclerosis. Muscle Nerve 44:20–24. doi:10.1002/mus.22114
31. Chiò A, Canosa A, Gallo S et al (2011) ALS clinical trials: do enrolled patients accurately represent the ALS population? Neurology 77:1432–1437. doi:10.1212/WNL.0b013e318232ab9b