RESEARCH ARTICLE OPEN ACCESS

Changes to Average Survival of Patients With Amyotrophic Lateral Sclerosis (1995–2018)

Results From the Piemonte and Valle d'Aosta Registry

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Neurology® 2025;104:e213467. doi:10.1212/WNL.0000000000213467

Abstract

Background and Objectives

The average survival of patients with amyotrophic lateral sclerosis (ALS) ranges from 2 to 5 years from symptom onset. However, it remains unclear whether this estimate has improved over time. The objective of this study was to analyze the survival trend of a large population-based cohort of patients with ALS over a 24-year period.

Methods

Patients from the Piemonte and Valle d'Aosta registry for ALS (PARALS) were categorized into the first (1995–2002), second (2003–2010), or third (2011–2018) epoch based on their diagnosis date. Survival was defined as the time from diagnosis to death, tracheostomy, or censoring date. A Cox proportional hazard model was developed with diagnosis epoch as the primary variable of interest, adjusted for sex, site of onset, age at onset, diagnostic delay, forced vital capacity at diagnosis, Δbody mass index from onset to diagnosis, noninvasive mechanical ventilation use, gastrostomy use, and site of follow-up. A subset analysis comparing the 2007–2012 and 2013–2018 cohorts was conducted, incorporating riluzole prescription, genetics, and preslope category as additional covariates.

Results

A total of 3,134 patients were included, evenly distributed across the 3 epochs (990, 1,023, and 1,121, respectively). The median survival remained stable during the first and second epoch (18.6 months vs 18.3 months) but improved during the third epoch (20.1 months; $p = 0.0041$), with a hazard ratio (HR) of 0.76 (95% CI 0.67–0.87, $p = 0.00003$). In the subset analysis, the most recent epoch (2013–2018) showed a continued survival advantage (HR 0.77, 95% CI 0.65–0.90). Of interest, the survival benefit was only evident among intermediate progressors (HR 0.60, 95% CI 0.45–0.80).

Discussion

In the PARALS, ALS survival increased over time. In a subset analysis, the beneficial effect of the epoch was only evident among intermediate progressors. The improvement in multidisciplinary care provided by tertiary centers may be one possible explanation for this finding, although further dedicated studies are needed to confirm this hypothesis.

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The Article Processing Charge was funded by the authors.

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Glossary

ALS = amyotrophic lateral sclerosis; **BMI** = body mass index; **FVC** = forced vital capacity; **HR** = hazard ratio; **NIMV** = noninvasive mechanical ventilation; **PARALS** = Piemonte and Valle d'Aosta ALS Register; **PLS** = primary lateral sclerosis.

Introduction

Amyotrophic lateral sclerosis (ALS) is a relentless neurodegenerative disease that causes the progressive degeneration of motor neurons. Ultimately, it leads to death, usually due to respiratory failure, with a median time of 2–3 years from symptom onset.[1]

Numerous demographic, biochemical, environmental, genetic, and clinical characteristics have been found to be associated with the prognosis of ALS.[2,3] While some of these factors are likely consequential to the pathogenetic process and have been used as biomarkers, others have been suggested to modify the disease course. However, most of these latter prognostic factors are nonmodifiable so far and have accordingly been used solely as predictors of disease progression and survival.[3]

In 1994, riluzole has been approved for patients with ALS because it was found to prolong patients' survival by 38% at 12 months, corresponding to approximately 3 months.[4] Nevertheless, we are still striving to find interventions that allow us to further influence the disease course.[5]

Despite the limited availability of effective interventions, some studies suggested that survival of patients with ALS has increased over time.[6-10] However, these findings are inconsistent, with other studies not reporting such improvement in ALS survival over time.[11-14]

Several tertiary centers, along with their respective registries, have been established for a considerable period now, some also spanning almost 30 years of continuous activity.[15] Given their enduring commitment and the consistency of their interventions, these realities serve as ideal settings to evaluate the trend in ALS survival.

In this study, we used data from a long-standing Italian epidemiologic register to assess whether the survival of patients with ALS has increased over a 24-year period.

Methods

Data of patients from the Piemonte and Valle d'Aosta ALS Register (PARALS) who were diagnosed between 1995 and 2018 were used for this study. Since 1995, the PARALS has collected data on patients with ALS residing in these 2 regions of Northern Italy. The register primarily relies on 2 ALS tertiary centers located in the cities of Torino and Novara, with neurology departments from both regions and death certificates serving as secondary sources.[16]

Patients are included in the PARALS if they meet the diagnosis of definite, probable, probable laboratory-supported, or possible ALS according to the revised El Escorial Diagnostic Criteria,[17] at any stage of the disease. Owing to their naturally longer survival, patients with primary lateral sclerosis (PLS) were not included in this study.

In both ALS centers, after diagnosis, patients undergo follow-up at regular intervals as recommended by the European Academy of Neurology guidelines.[18] Consequently, the neurologists in these centers typically collect comprehensive data on patients' demographic and clinical characteristics and on their disease course, resulting in a detailed characterization of each patient's condition. Most of these data are also retrieved for patients followed by general neurologic clinics through medical records. For this study, various demographic and clinical characteristics were considered, including sex, age at onset, diagnostic delay (considered as the time interval from symptom onset to diagnosis, expressed in months), onset site (categorized as bulbar or spinal), riluzole prescription at the time of diagnosis, follow-up site (ALS tertiary centers vs general neurologic clinics), forced vital capacity (FVC) at diagnosis, premorbid body mass index (BMI), BMI at diagnosis, use of noninvasive mechanical ventilation (NIMV) or gastrostomy during the disease course, and utilization of tracheostomy. The date of death is usually communicated by the patients' caregivers or relatives to the referral neurologist, although communities' registries are also periodically consulted. After 2004, patients also undergo genetic analysis, regardless of their familiar history. In particular, pathogenetic variants in the *SOD1*, *TARDBP*, and *FUS* genes and expansions in the *C9orf72* gene were considered for this study.[19]

For the purpose of this study, survival was defined as the time from diagnosis to either death, tracheostomy, or the censoring date, which was set at 6 years after the diagnosis to ensure uniform follow-up across the epochs. To analyze changes in survival over time, patients were classified into 1 of 3 consecutive epochs based on the year of diagnosis: epoch 1 (1995–2002), epoch 2 (2003–2010), or epoch 3 (2011–2018).

Comparisons between medians and proportions across the different epochs were evaluated by the Mann-Whitney test and the χ^2 test, respectively. Survival analyses were performed

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using the Kaplan-Meier method and compared with the log-rank test.

After verifying the hazard proportionality assumption using the Schoenfeld test, a Cox proportional hazard regression model was constructed considering the epoch of diagnosis as the variable of interest. The model was adjusted for sex, age at onset (categorized according to its tertiles), onset site, diagnostic delay, FVC at diagnosis, ΔBMI at diagnosis, use of NIMV and use of gastrostomy (both considered as time-dependent variables), and follow-up site (ALS tertiary centers vs general neurologic clinics). ΔBMI was calculated according to the following formula: (BMI premorbid − BMI at diagnosis)/BMI premorbid × 100.

We then examined a subset of patients with complete data on additional variables, enabling us to include more covariates in the model. These additional covariates included the disease progression rate exhibited at the time of diagnosis, riluzole prescription at the time of diagnosis, smoking information (categorized as never smoker, former smoker, and current smoker), and genetic status (classified as positive if any of the 4 main ALS-related genes were mutated or pathologically expanded). Accordingly, an analysis was performed selecting only patients followed up by 1 of the 2 ALS centers during the 2007–2018 period, divided into 2 consecutive 6-year epochs (2007–2012 and 2013–2018). For this analysis, the so-called preslope was calculated as a measure of disease progression using the following formula: 48 − Revised ALS Functional Rating Scale score collected at diagnosis (considered as the first within 30 days from the date of diagnosis)/time from onset to the visit date in months. Based on tertiles of the preslope distribution during this period, patients were categorized as slow (preslope <0.393 points per month), intermediate (preslope between 0.393 and 0.927), and fast (preslope >0.927) progressors.

In this subset of patients, we also conducted an additional analysis that included cognitive status as an additional covariate for those patients with available data. These patients underwent a comprehensive neuropsychological assessment (described elsewhere[20]) and were classified according to the ALS-FTD Consensus Criteria into the following categories: normal, with isolated behavioral impairment, with isolated cognitive impairment, with both cognitive and behavioral impairment, and with frontotemporal dementia.[21]

To explore whether the effect of the diagnosis epoch on survival was specific to certain patient subgroups and to gain insights into possible explanations, several models were built. Each model included an interaction term between the diagnosis epoch and variables such as sex, onset age, onset site, or the preslope category. The significance of the effect modification was evaluated based on the p value of the interaction terms.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Ethical Committee of the Turin ALS Center (Comitato Etico Azienda Ospedaliero-Universitaria Città della Salute e della Scienza, Torino, #0038876). The Piemonte regional government has recognized the Piemonte ALS Registry as a "Registry of High Sanitary Interest" (Regional Law, April 11, 2012, n. 4). Accordingly, the PARALS has the right to access all the existing databases owned by the regional administration and to obtain clinical information about patients with ALS from public and private hospitals, and general practitioners. The register database is anonymized and treated according to Italian Data Protection Code. Patients signed a written informed consent.

Data Availability

Data and codes for statistical analysis are available on reasonable request by interested researchers.

Results

A total of 3,134 patients were diagnosed in Piemonte and Valle d'Aosta between 1995 and 2018. Of these, 990 (31.6%), 1,023 (32.6%), and 1,121 (35.8%) patients were diagnosed in the 1995–2002, 2003–2010, and 2011–2018 epochs, respectively. Patients exhibited comparable characteristics across the 3 epochs, except for a higher onset age ($p < 0.001$) and a higher frequency of spinal onset ($p = 0.021$) among those diagnosed during the 2011–2018 period. As expected, the percentage of patients followed up by 1 of the 2 ALS centers steadily increased over time, from 45.6% to 93.3% in the most recent period (Table 1).

Although the median survival after diagnosis remained stable between the first and second epoch (18.6 months, 95% CI 17.2–20.5, vs 18.3 months, 95% CI 17.4–20.3), it increased by 9.8% during the third epoch (20.1 months, 95% CI 18.7–22.0; log-rank test p value = 0.0041) (Figure 1). The Cox model indicated that this improvement was independent of the covariates considered, showing an HR of 0.94 (95% CI 0.82–1.07, $p = 0.34$) for patients in the second epoch and 0.76 (95% CI 0.67–0.87, $p = 0.00003$) for those diagnosed in the most recent epoch.

As expected, the survival trend varied significantly based on the follow-up site, with no improvement observed among patients followed by neurologic clinics, likely due to selection bias (eFigures 1, A and B, eTables 1–3).

A total of 1,437 patients were followed up by an ALS tertiary center during the 2007–2018 period. Patients diagnosed during the 2007–2012 and 2013–2018 periods did not exhibit any significant differences in their demographic and clinical characteristics, although gastrostomy and tracheostomy were less frequently performed in the latter period (Table 2). The Cox model showed that patients diagnosed

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Table 1 Demographic and Clinical Characteristics of the Overall ALS Cohort and Divided by Epoch of Diagnosis

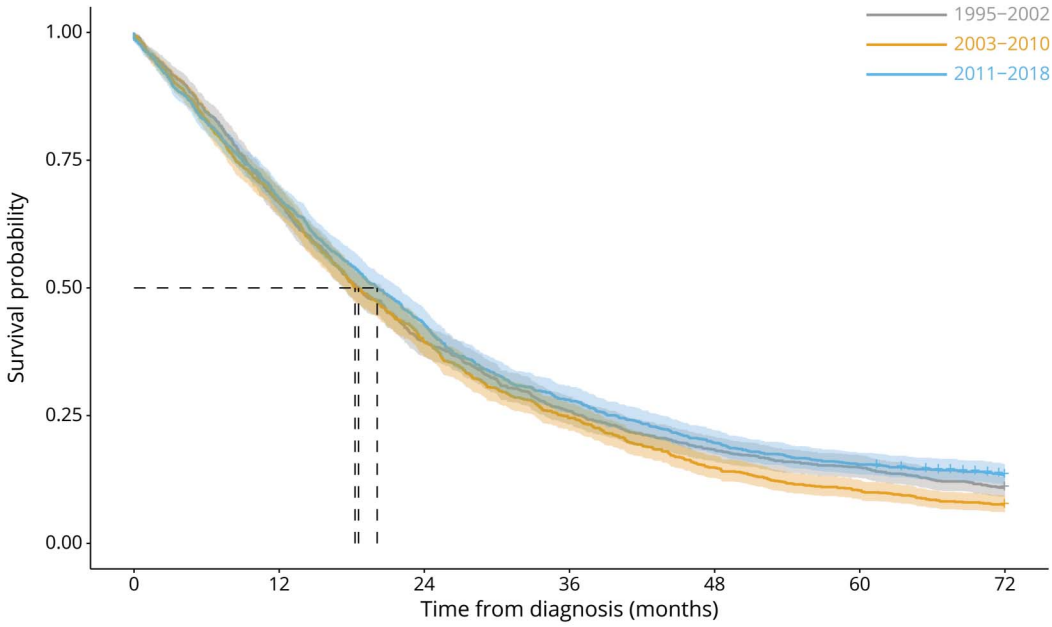
	Overall (n = 3,134)	1995–2002 epoch (n = 990)	2003–2010 epoch (n = 1,023)	2011–2018 epoch (n = 1,121)	*p* Value
Sex, male, n (%)	1,719 (54.9)	547 (55.3)	556 (54.3)	616 (55.0)	0.917
Onset age, y, median (IQR)	67.7 (59.9–73.9)	66.8 (59.1–72.4)	67.4 (60.4–73.9)	69.0 (60.9–75.2)	<0.001
Onset site, spinal, n (%)	2,032 (64.8)	613 (62.2)	662 (64.7)	754 (67.2)	0.021
Diagnostic delay, mo, median (IQR)	9.6 (5.6–13.7)	9.6 (5.6–13.6)	8.6 (5.6–13.6)	9.6 (5.6–14.6)	0.110
ΔBMI at diagnosis, median (IQR)	7.5 (0.0–18.6)	6.8 (0.0–16.2)	6.7 (0.0–17.1)	8.7 (0.0–19.9)	0.057
FVC at diagnosis, median (IQR)	87.0 (68.0–102.0)	85.0 (66.0–100.0)	87.0 (67.0–101.0)	88.0 (69.0–103.3)	0.015
NIMV, yes, n (%)	1,039 (33.2)	205 (20.7)	358 (35.0)	476 (42.5)	<0.001
Gastrostomy, yes, n (%)	985 (31.4)	240 (24.2)	371 (36.3)	374 (33.4)	<0.001
Tracheostomy, yes, n (%)	421 (13.5)	116 (11.7)	152 (14.9)	153 (13.7)	0.112
ALS centers, yes, n (%)	2,188 (69.9)	451 (45.6)	694 (67.8)	1,043 (93.3)	<0.001

Abbreviations: ALS = amyotrophic lateral sclerosis; BMI = body mass index; FVC = forced vital capacity; NIMV = noninvasive mechanical ventilation.
ΔBMI at diagnosis was calculated according to the following formula: (BMI premorbid − BMI at diagnosis)/BMI premorbid × 100.

between 2013 and 2018 exhibited a survival advantage (HR 0.77, 95% CI 0.65–0.90, $p = 0.0016$), with the median survival only slightly further increasing in the latter period (20.4 vs 20.9 months).

Of interest, the effect of the diagnosis epoch on survival did not vary according to any of the variables included as covariates in the model (all p values of the interaction terms were >0.2) with the only exception of the preslope category.

Figure 1 Kaplan-Meier Curves of Survival According to the Epoch of Diagnosis in the Overall Cohort



Number at risk n (%):

990 (100)	661 (67)	391 (39)	256 (26)	182 (18)	147 (15)	108 (11)
1,023 (100)	686 (67)	403 (39)	251 (25)	152 (15)	106 (10)	77 (8)
1,121 (100)	757 (68)	481 (43)	315 (28)	221 (20)	173 (15)	126 (11)

Dotted lines represent the median survival in each epoch.

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Table 2 Demographic and Clinical Characteristics of the Overall ALS Cohort During the 2007–2018 Period and Divided by Epoch of Diagnosis

	Overall cohort (n = 1,437)	2007–2012 epoch (n = 660)	2013–2018 epoch (n = 777)	*p* Value
Sex, male, n (%)	792 (55.1)	353 (33.5)	439 (56.5)	0.275
Onset age, y, median (IQR)	68.2 (60.2–74.4)	67.3 (59.5–73.6)	68.8 (60.9–74.9)	0.029
Onset site, spinal, n (%)	943 (65.7)	425 (64.4)	518 (66.8)	0.457
Diagnostic delay, mo, median (IQR)	9.6 (5.6–13.7)	8.6 (5.6–13.6)	9.6 (6.5–14.7)	0.020
Cognitive status, n (%)				0.001
Normal	505 (35.2)	212 (32.1)	293 (37.7)	
ALSbi	84 (5.8)	46 (7.0)	38 (4.8)	
ALSci	184 (12.8)	59 (8.9)	125 (16.2)	
ALScbi	60 (4.2)	21 (3.2)	39 (5.0)	
FTD	186 (12.9)	91 (13.8)	95 (12.2)	
Missing	418 (29.1)	231 (35.0)	187 (24.1)	
Cigarette smoking status, n (%)				0.110
Never smoker	686 (47.7)	294 (44.5)	392 (50.5)	
Ex-smoker	477 (33.2)	227 (34.4)	250 (32.2)	
Current smoker	246 (17.2)	122 (18.5)	124 (15.9)	
Missing	28 (1.9)	17 (2.6)	11 (1.4)	
Genetics, n (%)				1.000
Positive	148 (9.7)	67 (10.1)	81 (10.4)	
Missing	90 (6.3)	50 (7.6)	40 (5.1)	
***C9orf72*, expanded, n (%)**	93 (6.4)	41 (6.2)	52 (6.7)	0.894
SOD1, mutated, n (%)	27 (1.9)	13 (1.9)	14 (1.8)	0.915
TARDBP, mutated, n (%)	21 (1.5)	9 (1.4)	12 (1.5)	0.996
FUS, mutated, n (%)	7 (0.5)	4 (0.6)	3 (0.4)	0.802
ALSFRS-R preslope, median (IQR)	0.6 (0.3–1.2)	0.6 (0.3–1.1)	0.6 (0.3–1.3)	0.064
ΔBMI, median (IQR)	8.0 (0.0–18.9)	7.06 (0.0–17.6)	8.8 (0.0–19.2)	0.117
FVC at diagnosis, median (IQR)	89.0 (70.0–103.0)	89.0 (69.3–102.0)	89.0 (71.0–104.0)	0.330
NIMV, yes, n (%)	625 (43.5)	292 (44.2)	333 (42.8)	0.635
Gastrostomy, yes, n (%)	516 (35.9)	280 (42.4)	236 (30.4)	<0.001
Tracheostomy, yes, n (%)	205 (14.3)	110 (16.7)	95 (12.3)	0.020
Riluzole, n (%)				0.606
Yes	781 (54.3)	353 (53.5)	428 (55.1)	
Missing	482 (33.5)	224 (33.9)	258 (33.2)	

Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = Revised ALS Functional Rating Scale; BMI = body mass index; FVC = forced vital capacity; NIMV = noninvasive mechanical ventilation.
Cognitive status was classified according to the revised Strong criteria: ALSbi = behavioral impairment; ALSci = cognitive impairment; ALScbi = cognitive and behavioral impairment; FTD = frontotemporal dementia.
Genetics was considered as positive if a pathogenetic variant was detected in any of the 4 main genes.
ALSFRS-R preslope was calculated according to the following formula: 48 − ALSFRS-R score at diagnosis (considered as the first within 30 days from the date of diagnosis)/time from onset to the visit date in months.
ΔBMI was calculated according to the following formula: (BMI premorbid − BMI at diagnosis)/BMI premorbid × 100.

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Specifically, the beneficial effect of being diagnosed during the 2013–2018 epoch was detectable only among intermediate progressors, showing an HR of 0.60 (95% CI 0.45–0.80), compared with slow progressors (HR 0.80, 95% CI 0.61–1.07) and fast progressors (HR 0.87, 95% CI 0.67–1.16), with these differences being statistically significant (p = 0.05 and 0.025, respectively) (Figure 2). A sensitivity analysis including only patients for whom cognitive status was available did not modify the results (data not shown).

Discussion

Using 24 years of data from a single long-standing register, we demonstrated that survival of patients with ALS has increased by approximately 10% in the last 8 years of this period, reaching 20 months from diagnosis (which corresponds to a median survival of approximately 2.5 years from symptom onset, after accounting for diagnostic delay) in line with other studies.[22,23] This improvement was independent of the varying distributions of confounding factors across the 3 epochs. Notably, in a subset of patients, the survival advantage was specific to those with an intermediate rate of progression at diagnosis.

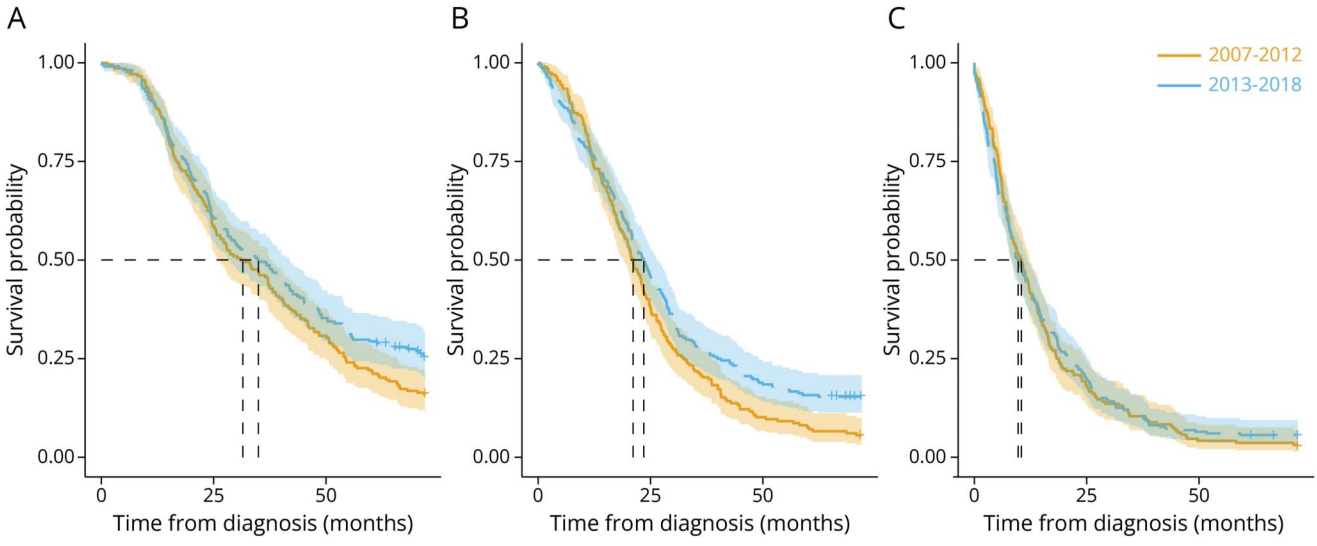
Because the analysis took into account most of the known prognostic factors for ALS, as well as the site of follow-up and, therefore, the increasing percentage of patients being followed up in tertiary centers, we believe that the observed improvement in survival may be driven by enhancements in the comprehensive care provided to these patients. It could be also argued that the beneficial effect of the multidisciplinary care for patients with ALS is less pronounced in patients with slow progression and in those with such rapid progression that complications cannot be effectively managed, thus being evident only among intermediate progressors.

Even in the absence of randomized clinical trials,[24] it is broadly accepted that attending a tertiary center gives a survival advantage, because of the multidisciplinary care offered.[8,25-29] Thus, it is reasonable to hypothesize that the quality of multidisciplinary care provided in these centers has improved over time, potentially explaining the observed increase in survival. However, this study did not include any formal measure of the quality of multidisciplinary care, leaving this as a speculative point.

In addition, we may have misestimated the impact of NIMV or gastrostomy, although they were considered as time-dependent variables. In fact, factors such as patient compliance, the timing of its initiation, and cases where these interventions were indicated but not initiated should also be examined to comprehensively assess their efficacy. Notably, even if we assume a survival advantage associated with gastrostomy placement, this procedure was performed less frequently in the most recent years, as provided in Table 2. We do not have a definitive explanation for this finding. However, alongside the reduced percentage of tracheostomies performed, this trend could reflect a cultural shift in end-of-life decision making. Alternatively, it might result from improved selection criteria for identifying patients suited for these procedures.

Of interest, while some studies confirmed an increase in ALS survival trends,[6-10] others have not.[11-14] It is important to note

Figure 2 Kaplan-Meier Curves of Survival According to the Preslope Category and the Epoch of Diagnosis



Preslope categories: (A) slow progressors, (B) intermediate progressors, and (C) fast progressors. Epochs of diagnosis: yellow is 2007–2012; blue is 2013–2018. Dotted lines represent the median survival in each epoch.

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that some of the latter studies were conducted many years ago, shortly after the 1999 guidelines,[22,30] while others compared short periods. However, a recent article using 25 years of data from the Irish ALS register also did not reveal an increase in the ALS survival, but rather suggested a trend toward a decrease.[11] While the higher onset age (and thus worse prognosis) of patients during the last period could explain the decreased survival, the reason for the discrepancy with our results is less clear, especially considering that an increase in the age at onset was also observed in our registry. One possible explanation, in line with the hypothesis that multidisciplinary care contributed to improved survival, is that the much smaller area of Piemonte and Valle d'Aosta compared with Ireland (28,587 vs 70,273 km^2) could make it easier to provide multidisciplinary care throughout the disease course because no location in Piemonte and Valle d'Aosta is more than 120 km away from one of the 2 ALS Centers. However, we do not have a definitive explanation for this discrepancy.

The main limitation of this study is that it was not designed to establish causal inference; thus, we cannot provide a definite explanation for the survival increase we observed. While we addressed numerous variables, thanks to the deeply characterized cohort of the register, we could not account for any known and unknown prognostic factors that, if differently distributed across epochs, could explain the observed increase in survival. In addition, factors such as riluzole prescription and genetic status were analyzed only in a subset of patients. Although we hypothesize no significant variation in their distribution across epochs, we cannot completely rule out their potential impact on the observed survival increase over time.

In addition, it should be considered that we did not include patients affected by progressive muscular atrophy or PLS and, therefore, these results do not necessarily apply to those subpopulations.

On the contrary, although the use of preslope to summarize the disease progression has its limitations,[31] it allowed us to identify a survival advantage of multidisciplinary care among intermediate progressors, a finding not previously reported to our knowledge. In addition, using epidemiologic register data, collected prospectively during the 24 years of the study, overcomes the risk of referral bias, which is particularly important when studying survival, because younger and slower progressing patients may be overrepresented in center-based cohorts.[15]

In conclusion, our study demonstrated that ALS survival has increased over time. We hypothesize that this improvement may be attributable to a combination of a higher number of patients being followed by ALS tertiary centers and advancements in multidisciplinary care. However, dedicated studies are needed to support this hypothesis. Notably, in the most recent years of our study period, the observed survival benefit seemed to be specific to patients with an intermediate rate of progression.

Author Contributions

R. Vasta: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. F. De Mattei: major role in the acquisition of data; analysis or interpretation of data. S. Tafaro: major role in the acquisition of data; analysis or interpretation of data. A. Canosa: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. U. Manera: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Grassano: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F.F. Palumbo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Cabras: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E. Matteoni: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F. Di Pede: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. G. Zocco: drafting/revision of the manuscript for content, including medical writing for content. G. Pellegrino: drafting/revision of the manuscript for content, including medical writing for content. E. Minerva: drafting/revision of the manuscript for content, including medical writing for content. D. Pascariu: drafting/revision of the manuscript for content, including medical writing for content. B. Iazzolino: drafting/revision of the manuscript for content, including medical writing for content. S. Callegaro: drafting/revision of the manuscript for content, including medical writing for content. G. Fuda: drafting/revision of the manuscript for content, including medical writing for content. P. Salamone: drafting/revision of the manuscript for content, including medical writing for content. F. De Marchi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Mazzini: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Moglia: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Calvo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Chiò: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design.

Study Funding

This work was in part supported by the Horizon 2020 Programme (project Brainteaser under grant agreement

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101017598; project Hereditary under grant agreement 101137074), the Italian Ministry of Education, University and Research (Progetti di Ricerca di Rilevante Interesse Nazionale, PRIN 20228N7573) and ALS Association (grant number 24-SI-684).

Disclosure

All authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* August 27, 2024. Accepted in final form January 30, 2025. Submitted and externally peer reviewed. The handling editor was Associate Editor Brian C. Callaghan, MD, MS, FAAN.

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