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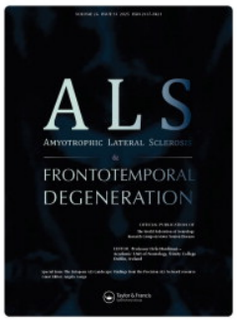

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RESEARCH ARTICLE

Mapping the natural history of amyotrophic lateral sclerosis: time-to-event analysis of clinical milestones in the pan-European, population-based PRECISION-ALS cohort

ALEJANDRO CARAVACA PUCHADES[1], HARRY E. MCDONOUGH[2,3], AMMAR AL-CHALABI[4,5], ADRIANO CHIÒ[6], PHILIPPE CORCIA[7,8], MIRIAM GALVIN[9], ORLA HARDIMAN[9,10], MARK HEVERIN[9], FREDERIK HOBIN[11,12], OSKAR HOLMDAHL[13], CAROLINE INGRE[13,14], NIKITA LAMAIRE[11,12], ÉANNA MAC DOMHNAILL[9], UMBERTO MANERA[6], ROBERT MCFARLANE[9,10], MOHAMMED MOUZOURI[7], FOUKE OMBELET[11,12], SARAH OPIE-MARTIN[4], STEFAN SENNFÄLT[13,14], CRISTINA TERRAFETA PASTOR[1], JAN H. VELDINK[15], PHILIP VAN DAMME[11,12], LEONARD VAN DEN BERG[15], RUBEN P.A. VAN EIJK[15,16], ROSARIO VASTA[6], DAPHNE N. WEEMERING[15], PAMELA SHAW[2,3], CHRISTOPHER J. MCDERMOTT[2,3] & MÓNICA POVEDANO PANADÉS[1]

[1]Hospital Universitari de Bellvitge–IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain, [2]Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, UK, [3]NIHR Sheffield Biomedical Research Centre, Sheffield Teaching Hospitals, Sheffield, UK, [4]Department of Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, King's College London, London, UK, [5]Department of Neurosciences, King's College Hospital, London, UK, [6]Rita Levi Montalcinì Department of Neuroscience, University of Turin, Turin, Italy, [7]Centre de Référence Maladies Rares SLA, CHU Tours, Tours, France, [8]UMR 1253 iBrain, Université de Tours, Inserm, Tours, France, [9]Academic Unit of Neurology, Trinity Biomedical Sciences Institute, School of Medicine, Trinity College Dublin, The University of Dublin, Dublin, Ireland, [10]Department of Neurology, Beaumont Hospital, Dublin, Ireland, [11]Neurology Department, University Hospitals Leuven, Leuven, Belgium, [12]Neuroscience Department, Leuven Brain Institute, University of Leuven (KU Leuven), Leuven, Belgium, [13]Department of Neurology, Karolinska University Hospital, Stockholm, Sweden, [14]Department of Clinical Neurosciences, Karolinska Institutet, Stockholm, Sweden, [15]Department of Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, the Netherlands, and [16]Biostatistics & Research Support, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

Abstract

Objective: Map time to key clinical milestones in amyotrophic lateral sclerosis (ALS), highlighting underlying genotypic and phenotypic prognostic factors. *Background*: Understanding the ALS disease trajectory and factors influencing the heterogeneous disease course is important to guide clinical care and stratify individuals to effectively assess therapeutics in clinical trials. *Methods*: Population-based datasets from nine European ALS care centers were collated. Time-to-event analysis was conducted for key clinical milestones: symptom onset, diagnosis, gastrostomy insertion, noninvasive ventilation (NIV) initiation, and survival. Independent prognostic factors were determined. *Results:* 21,820 people with ALS from nine ALS centers were included. Median age of symptom onset was 63.9 years. Median diagnostic delay was 1.0 years, with median survival of 33.7 months from onset. Prognostic factors for survival included age at onset, baseline vital capacity, progression rate, diagnostic delay, site of onset, and C9orf72-positive status. SOD1 variants D91A and G94C had protective prognostic effects in the whole cohort. Median time from diagnosis to gastrostomy insertion in

Correspondence: Harry E. McDonough, Sheffield Institute for Translational Neuroscience, The University of Sheffield, Sheffield S10 2TN, UK. E-mail: h.mcdonough@sheffield.ac.uk

Alejandro Caravaca Puchades and Harry E. McDonough are joint first authors.

Pamela Shaw, Christopher J. McDermott and Mónica Povedano Panadés are joint last authors.

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bulbar-onset disease was 2.34 years. Median time from diagnosis to NIV initiation in those diagnosed between 2010 and 2019 was 3.61 years. Significant differences between ALS clinical center cohorts were seen in time to gastrostomy insertion, time to NIV initiation, and in overall survival time. *Conclusion*: Our analysis of a large, well-defined, population-based European cohort provides detailed insight into the natural history of ALS, highlighting phenotypic and genetic factors affecting time to key clinical milestones. Further study is needed to determine the drivers in observed differences between ALS clinical center cohorts in time to clinical interventions and overall survival.

Keywords: *Time-to-event, survival analysis, clinical milestones, disease trajectory, disease progression*

Introduction

Heterogeneity is seen throughout the amyotrophic lateral sclerosis (ALS) disease process, from genotype through to translated phenotype. An increasing number of disease-associated genetic variants interact across neuronal and non-neural cell types, contributing to complex biological heterogeneity (1,2). Genetic background is a key determinant of the clinical phenotype, however observed differences in disease course between individuals seemingly harboring similar genetic variants suggest other factors, such as gene-gene interaction or epigenetic control, are implicated (3,4). Clinical variation in people with ALS (pwALS) occurs with respect to age at diagnosis and site of onset, relative involvement of upper and lower motor neurons, rate of disease progression, and presence of cognitive and behavioral change.

This heterogeneity leads to difficulties in providing accurate estimates of progression to specific ALS milestones, for example the need for gastrostomy insertion, or noninvasive ventilation (NIV) initiation (4–6). Accordingly, clinical services are reactive to the needs of pwALS rather than proactive, leading to delays in procedure scheduling and equipment delivery (7,8). From a clinical trial perspective, heterogeneity ultimately complicates trial design. If recruited pwALS follow a variable disease trajectory, inflated variability in measured endpoints requires a larger sample size to mitigate this measurement noise and effectively assess therapeutic efficacy (9–12).

Studying the natural history of ALS can help to provide insight into the factors that influence clinical variation. Analysis of population-based data is well placed to address this, collecting real-world data from a large, diverse, and representative population of pwALS. Such data have played a crucial role in defining the breadth of disease phenotypes, with ALS registers providing new insights to help accurately classify pwALS into different clinical and prognostic subgroups which, in turn, helps to stratify pwALS in clinical trial recruitment (13,14). This study aims to bring together population-based registries from across Europe, carrying out time-to-event analysis to better understand the trajectories pwALS follow between ALS care centers and the factors that influence the disease course, ultimately informing clinical practice and trials with the aim to improve outcomes for pwALS.

Methods

Data sources and pre-processing

Data for this study originated from the PRECISION-ALS Extant Study. In brief, nine European specialized ALS centers comprising the PRECISION Consortium provided data from prospective population-based, or extensive clinic-based registers. On completion of GDPR compliant data sharing agreements, each center provided patient-level, de-identified data on demographic and disease characteristics obtained at diagnosis. All patients presenting with possible, probable (laboratory supported) or definite ALS, according to the revised El Escorial criteria, were eligible. Patients fulfilling the criteria for Primary Lateral Sclerosis, Progressive Muscular Atrophy or atypical ALS were excluded. Centers provided all consecutively diagnosed patients from the beginning of their registry until December 2022. Complete survival data (date of death or last follow-up) were obtained by checking the municipal population register at three-monthly intervals. Datasets were harmonized and combined into a single database, together with an indicator variable for each cohort.

Data regarding the genotype of SOD1, TARDBP, FUS and C9orf72 genes were collected. A pathological cutoff of 25 repeats was applied for hexanucleotide C9orf72 expansions. SOD1-positive patients were further categorized according to the predicted change at the protein level using the new numbering nomenclature, that is counting the first (ATG) codon of the sequence NP_000445. Longitudinal follow-up of the ALS Functional Rating Scale revised (ALSFRS-R) collected during the disease course was collated. Delta-FS scores at baseline were calculated as previously published (15) utilizing ALSFRS-R scores at least six months after disease onset.

Using the delta-FS at baseline from the entire PRECISION ALS cohort, pwALS were stratified in three progression categories; those with a delta-FS below the 25th percentile ($p25 = 0.28$) were defined as "slow" progressors, pwALS with a delta-FS between the 25th and 75th percentile were considered "intermediate" progressors, and

those with a delta-FS over the 75th percentile ($p75 = 0.91$) were deemed "fast" progressors.

Outcome data were available for the following clinical milestones: onset of symptoms, diagnosis, NIV initiation, gastrostomy insertion, and death. Time to initiation of NIV was also derived from ALSFRS-R scores and used as a proxy for missing data where appropriate. Vital capacity at baseline was defined as either a forced vital capacity or a slow vital capacity assessment available from the first six months following diagnosis (16,17).

Clinical phenotypes as reported by cohorts were harmonized into the following categories: ALS, ALS/FTD, FTD, PLS, PMA, PBP, UMN- or LMN- predominant, flail-arm and flail-leg disease. Data on site of onset were harmonized into the following categories: bulbar, spinal, cognitive, respiratory, or generalized. pwALS diagnosed with FTD were classified as having cognitive onset. Generalized disease was defined as the presence of symptoms in two or more domains at onset.

Data were aggregated for pwALS regarding sex, age at onset, elapsed time between symptom onset and time of diagnosis (diagnostic delay), delta-FS at diagnosis, clinical phenotype, genetic status for C9orf72, SOD1, TARDBP or FUS, and percentage predicted vital capacity at baseline. Data on time of diagnosis was not available for pwALS from three clinical cohorts.

Statistical analysis

All analyses, including imputation, were performed using R (version 4.3.2) (18).

Survival analysis. Kaplan-Meier analysis on time from birth to onset of clinical symptoms, from symptom onset to diagnosis, and from diagnosis to clinical milestones, were produced using the survival package (version 3.5-8) (19). pwALS were censored when lost to follow-up, or after a prespecified maximum observation time of 100 years for symptom onset, 10 years from onset to time of diagnosis, and 10 years from time of diagnosis to other clinical milestones.

SOD1-positive patients were grouped by their specific mutation. Their survival was compared against that of patients with no known mutation. Only SOD1 variants with at least 3 observed cases are reported.

Imputation. To prepare the dataset for Cox survival analysis, multiple imputation by chained equations was performed on the dataset using the mice package (version 3.16.0) (20). Imputation quality was assessed visually; density plots compared the distribution of observed and imputed values for continuous variables, and the distribution of continuous variables across categorical variables. The frequency of missing data, along with the variables imputed and distributions of observed and imputed values are available in e-Methods.

Cox survival analysis. To determine independent prognostic factors for time to clinical milestones from diagnosis, mixed-effects Cox proportional hazards regression analysis (21) was performed using the coxme package (version 2.2-18.1) (22). Effect estimates were pooled among the imputed datasets using Rubin's rules (23). The proportional hazards assumption was assessed by visual inspection of the Schoenfeld residuals of pooled analyses. Description of how variables were handled in the analysis is available in e-Methods. To limit the effect of data/concept drift (24), likely in part due to the advent of widespread NIV use during our dataset lifespan (1990–2022), only pwALS diagnosed from 2010 onwards were included in the analysis. Consequently, pwALS from the three clinical cohorts not reporting date of diagnosis could not be included. Analysis comparing the "whole" cohort and post-2010 cohort is available in e-Table 1 in Supplementary Material.

To investigate differences in time to clinical milestones between cohorts from each ALS clinical center, stratified Cox proportional hazards regression analysis was performed using the survival package (version 3.5-7) (19). As in the mixed-effects analysis above, only pwALS diagnosed from 2010 onwards were included, effect estimates were pooled, and the proportional hazards assumption was assessed by means of visual inspection of Schoenfeld residuals. Detail of stratification and included covariates is available in e-Methods.

Given the relatively small number of SOD1-positive patients available in each cohort using the aforementioned criteria, data on survival by SOD1 mutation was analyzed by means of non-stratified Cox proportional hazards regression with only sex, age at onset and site of onset as covariates, in concordance with most published literature.

In our analysis of NIV use, we assessed the vital capacity at which pwALS started NIV. In this analysis, we used the % predicted values for forced vital capacity and slow vital capacity interchangeably (16,17), taking the vital capacity measurement closest to the time of NIV initiation, with a time window of up to six months.

Results

Cohort

Time-to-event data were available in 21,820 pwALS from nine European care centers (Table 1). The cohort total aggregated follow-up time was 61,884 person-years from symptom onset, with a median follow-up time per pwALS of 2.68 years (IQR = 2.64 years). There was a male cohort predominance, with a 1.35: 1 ratio of males-to-females.

Spinal-onset disease was seen in 62.3% of individuals, with bulbar-onset in 27.8%. C9orf72 was the most common gene mutation seen; of those tested, 8.9% were C9orf72-positive, 2.9% SOD1-positive, 1.6% TARDBP-positive, and 0.8% FUS-positive.

Time to clinical milestones

Symptom onset. The median age at symptom onset was 63.9 years (95% CI: 63.7–64.0). Age at onset was earlier in males and in those with spinal-onset disease, a known gene mutation, and slow progressors, as defined by the delta-FS (Table 2).

Diagnostic delay. Median diagnostic delay across the cohort was 1.00 years (95% CI: 1.00–1.00). Diagnostic delay was longer in spinal- and cognitive-onset disease, and in those with slow and intermediate disease progression (Table 2).

Table 1. Demographic and clinical characteristics of cohort, with frequency of missing data.

Characteristic		n (%)	Missing (%)
Sex	Male	12,455 (57.1)	163 (0.7)
	Female	9202 (42.2)	
Site of onset	Spinal	13,583 (62.3)	1401 (6.4)
	Bulbar	6061 (27.8)	
	Respiratory	441 (2.0)	
	Cognitive	23 (0.1)	
	Generalized	311 (1.4)	
Genetics	*C9orf72* +ve	866 (8.9)[a]	12,138 (55.6)
	SOD1 +ve	149 (2.9)[a]	16,610 (76.1)
	TARDBP +ve	71 (1.6)[a]	17,288 (79.2)
	FUS +ve	36 (0.8)[a]	17,460 (80.0)

[a]Represents pwALS with the specified genetic change as a proportion of those tested, not taking variant information into account.

Overall survival. Median time from onset to death was 2.81 years (95% CI: 2.77–2.85). Survival time was shorter in pwALS who were female, had bulbar-, respiratory-, or generalized-onset disease, a fast progression rate, or C9orf72-positive status (Table 2).

To explore factors influencing survival time from diagnosis, we carried out a mixed-effects Cox proportional hazards regression analysis. Independent negative prognostic effects were seen for increasing age at onset, lower baseline vital capacity, faster disease progression, shorter diagnostic delay, bulbar- and generalized-onset disease, and C9orf72-positive status (Tables 3, 4 and 5).

At a group-level, we did not observe a significant prognostic effect for SOD1-positive status (Table 3). We hypothesized this finding may, in part, be due to our cohort reflecting the known heterogeneity within Europe in SOD1 variants and resulting phenotypes (25–29), with relatively aggressive and benign variants potentially canceling respective effects on survival. To investigate this, we carried out exploratory Cox proportional hazards analyses. In the cohort used for the above group-level Cox proportional hazards analysis (i.e. those diagnosed since 2010), SOD1 variant data was available for 19 pwALS, with 11 individual variants identified (e-Table 2in Supplementary Material). Neither of the two variants observed in at least three cases were found to have a significant effect on overall survival (Table 4).

Broadening the SOD1 cohort to include those diagnosed prior to 2010, SOD1 variant data was available for 73 pwALS, with 28 individual variants identified (e-Table 3). Applying the same sample size threshold, D91A (HR 0.381; 95% CI: 0.190–0.762) and G94C (HR 0.374; 95% CI: 0.178–0.785)

Table 2. Median time to clinical milestones by patient characteristics.

		Symptom onset		Diagnosis		Survival		
Characteristic		n (%)	Median (95% CI)	n (%)	Median (95% CI)	n	events	Median (95% CI)
Sex	Male	11,453 (52.5)	63.0 (62.7–63.2)	10,474 (48.0)	1.00 (1.00–1.00)	9565	8042	2.89 (2.84–2.94)
	Female	8480 (38.9)	65.2 (65.0–65.6)	7722 (35.4)	1.00 (1.00–1.00)	7150	6187	2.72 (2.67–2.77)
	Missing	1887 (8.6)		3624 (16.6)				
Site of onset	Spinal	13,079 (59.9)	62.4 (62.1–62.7)	11,969 (54.9)	1.02 (1.00–1.04)	10,705	8892	3.17 (3.11–3.23)
	Bulbar	5742 (26.3)	66.7 (66.4–67.0)	5268 (24.1)	0.89 (0.86–0.91)	5070	4590	2.31 (2.26–2.35)
	Respiratory	421 (1.9)	68.6 (67.5–70.0)	393 (1.8)	1.00 (0.97–1.05)	364	308	2.47 (2.12–2.66)
	Cognitive	21 (0.1)	63.0 (61.0–73.8)	14 (0.1)	1.86 (1.36–4.00)	19	16	2.86 (2.25–5.98)
	Generalized	285 (1.3)	65.5 (63.7–66.8)	269 (1.2)	1.00 (0.93–1.06)	215	195	2.32 (2.14–2.67)
	Missing	2272 (10.4)		3907 (17.9)				
Genetics	No known mutation	18,970 (86.9)	64.2 (64.0–64.4)	17,287 (79.2)	1.00 (1.00–1.00)	15,721	13,404	2.82 (2.77–2.85)
	C9orf72 +ve	835 (3.8)	59.4 (58.4–60.3)	778 (3.6)	0.85 (0.80–0.94)	798	708	2.64 (2.53–2.77)
	SOD1 +ve	145 (0.7)	54.4 (52.2–57.9)	133 (0.6)	0.91 (0.73–1.00)	136	81	6.28 (4.19–8.51)
	TARDBP	62 (0.3)	59.1 (56.0–65.1)	62 (0.3)	1.00 (0.79–1.17)	57	39	5.91 (4.54–7.50)
	FUS	34 (0.2)	51.2 (44.0–63.0)	33 (0.2)	0.95 (0.59–1.22)	32	27	2.62 (2.39–4.71)
	Missing	1774 (8.1)		3527 (16.2)				
Progression rate (Delta-FS)	Slow[a]	2212 (10.1)	60.4 (59.9–61.2)	1997 (9.2)	1.74 (1.67–1.82)	1844	1064	6.58 (6.24–6.87)
	Intermediate[a]	4421 (20.3)	64.3 (64.0–64.8)	4099 (18.8)	1.12 (1.09–1.14)	3904	3224	3.30 (3.23–3.37)
	Fast[a]	2210 (10.1)	67.2 (66.7–67.9)	2054 (9.4)	0.75 (0.73–0.76)	2077	1825	1.94 (1.89–1.99)
	Missing	12,977 (59.5)		13,670 (62.6)				

[a]Slow progressors (Delta-FS <0.28), intermediate progressors (Delta-FS 0.28—–0.91), fast progressors (Delta-FS >0.91); Clinical milestones defined as: symptom onset (birth to onset of symptoms), diagnosis (onset of symptoms to diagnosis), survival (onset of symptoms to death).

Table 3. Mixed-effects Cox proportional hazards analysis of prognostic factors for clinical milestones (gastrostomy insertion, NIV initiation, and survival) from diagnosis.

		Gastrostomy		NIV		Survival	
Factor		HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Age at onset		1.000 (0.995–1.004)	0.941	1.000 (0.996–1.004)	0.893	1.025 (1.022–1.028)	<0.001
Baseline VC (% predicted)		0.995 (0.992–0.997)	<0.001	0.988 (0.985–0.991)	<0.001	0.992 (0.990–0.994)	<0.001
Progression rate (Delta-FS)[a]		3.159 (2.403–4.153)	<0.001	3.276 (2.556–4.199)	<0.001	3.273 (2.735–3.918)	<0.001
Diagnostic delay[a]		0.864 (0.793–0.941)	<0.001	0.979 (0.916–1.046)	0.534	0.845 (0.806–0.887)	<0.001
Site of onset	Spinal	Reference		Reference		Reference	
	Bulbar	3.594 (3.244–3.981)	<0.001	1.089 (0.989–1.200)	0.083	1.172 (1.105–1.245)	<0.001
	Respiratory	1.139 (0.805–1.613)	0.462	1.647 (1.258–2.157)	<0.001	0.951 (0.811–1.115)	0.537
	Cognitive	4.519 (0.000–Inf)	0.994	0.712 (0.172–2.943)	0.639	1.820 (0.826–4.011)	0.137
	Generalized	1.402 (0.720–2.727)	0.320	0.685 (0.387–1.214)	0.195	1.519 (1.186–1.944)	0.001
Sex	Male	Reference		Reference		Reference	
	Female	1.128 (1.023–1.245)	<0.001	0.862 (0.789–0.940)	<0.001	1.049 (0.994–1.107)	0.080
Genetics	C9orf72 +ve	1.293 (1.099–1.521)	0.002	1.005 (0.847–1.193)	0.951	1.166 (1.052–1.292)	0.003
	SOD1 +ve	0.725 (0.469–1.123)	0.148	0.799 (0.509–1.255)	0.324	0.847 (0.614–1.167)	0.302
	TARDBP + ve	0.695 (0.366–1.321)	0.267	1.084 (0.655–1.795)	0.752	0.810 (0.645–1.221)	0.313
	FUS + ve	0.743 (0.366–2.828)	0.662	0.809 (0.280–2.339)	0.695	1.187 (0.645–2.185)	0.580

Note: Baseline VC = either a forced vital capacity or a slow vital capacity assessment within six months of diagnosis.
[a]Normalised by means of cubic root.

Table 4. Cox proportional hazards analysis of prognostic factors for overall survival from time of onset, in those diagnosed since 2010.

		Survival	
Factor		HR (95% CI)	*p* Value
Age at onset		1.029 (1.027–1.032)	<0.001
Site of onset	Spinal	Reference	
	Bulbar	1.497 (1.409 0–1.590)	<0.001
	Respiratory	1.283 (1.101–1.496)	0.001
	Cognitive	1.581 (0.753–3.321)	0.226
	Generalized	1.778 (1.390–2.273)	<0.001
Sex	Male	Reference	
	Female	1.011 (0.955–1.069)	0.712
SOD1 variant[a]	D77Y	0.546 (0.136–2.184)	0.392
	I114T	1.143 (0.428–3.050)	0.789

[a]Cox proportional hazards analysis including SOD1 variants in which at least three cases were present in the population studied.

Table 5. Cox proportional hazards analysis of prognostic factors for overall survival from time of onset, including those diagnosed pre-2010.

		Survival	
Factor		HR (95% CI)	*p* Value
Age at onset		1.027 (1.025–1.028)	<0.001
Site of onset	Spinal	Reference	
	Bulbar	1.524 (1.467–1.584)	<0.001
	Respiratory	1.344 (1.196–1.510)	<0.001
	Cognitive	1.144 (0.700–1.868)	0.591
	Generalized	1.289 (1.116–1.490)	<0.001
Sex	Male	Reference	
	Female	1.001 (0.966–1.037)	0.956
SOD1 variant[a]	A90V	0.848 (0.212–3.393)	0.816
	D77Y	0.516 (0.129–2.062)	0.349
	D91A	0.381 (0.190–0.762)	0.006
	G94C	0.374 (0.178–0.785)	0.009
	I114T	1.139 (0.512–2.537)	0.750

[a]Cox proportional hazards analysis including SOD1 variants in which at least three cases were present in the population studied.

variants were observed to have a statistically significant protective effect on overall survival (Table 5).

Time to clinical interventions

Gastrostomy. At a whole-cohort level, there were insufficient events to calculate median time to gastrostomy (e-Figure 4(a) in Supplementary Material). Subgroup analysis demonstrated that time from diagnosis to gastrostomy insertion in bulbar-onset disease was 2.34 years (95% CI: 2.06–2.58). Visual inspection of Kaplan-Meier plots (e-Figure 5(a–d) in Supplementary Material) suggested that pwALS underwent gastrostomy insertion earlier if they were female, had bulbar-onset disease, were C9orf72- or FUS-positive, or were fast progressors.

To determine independent factors influencing time to gastrostomy insertion, we carried out a mixed-effects Cox proportional hazards analysis. Lower baseline vital capacity, faster disease progression, shorter diagnostic delay, bulbar-onset disease, female sex, and C9orf72-positive status were independent negative prognostic factors (Table 3).

Noninvasive ventilation. At a whole-cohort level, there were insufficient events to calculate median time to NIV initiation (e-Figure 4(b) in Supplementary Material). Subgroup analysis showed median time to NIV initiation of 3.61 years (95% CI: 3.34–3.96) in those diagnosed between 2010 and 2019, the largest subgroup when stratifying our cohort by period of diagnosis ($n = 6034$). Kaplan–Meier survival plots (e-Figure

6(a–c) in Supplementary Material) showed NIV was initiated at an earlier stage in those with respiratory- or bulbar-onset, fast progressing disease, or FUS-/C9-positive status.

Mixed-effects Cox proportional hazards analysis was used to investigate independent prognostic factors. We observed independent, negative prognostic effects for reduced baseline vital capacity, faster disease progression, respiratory-onset disease, and female sex (Table 3).

Time-to-event analysis comparing clinical cohorts

To determine if there were significant differences in time to clinical milestones between the cohorts of the nine ALS clinical centers, we carried out stratified Cox proportional hazards analysis, accounting for differences between the different clinical cohorts in terms of sex, age of onset, site of onset, progression rate (delta-FS) at baseline, vital capacity at baseline, and genetic status.

Diagnostic delay. We observed significant differences in time from symptom onset to diagnosis between cohorts (Table 6). With cohort 1 as a reference, those in cohort 6 had a shorter diagnostic delay (HR 0.700, 95% CI: 0.632–0.775), with those in cohort 8 a longer delay (HR 1.391, 95% CI: 1.269–1.526).

Gastrostomy. We observed significant differences in time to gastrostomy insertion between clinical cohorts (Table 6). pwALS from cohorts 8 (HR 1.905, 95% CI: 1.591–2.281) and 9 (HR 1.370, 95% CI: 1.150–2.632) underwent gastrostomy insertion more readily, when using cohort 1 as a comparator.

NIV. With time to NIV initiation, we again observed differences between clinical cohorts (Table 6). When compared to cohort 1, NIV was started more readily in cohorts 6 (HR 2.092, 95% CI: 1.719), 7 (HR 2.186, 95% CI: 1.860–2.570), and 8 (HR 2.107, 95% CI: 1.786–2.485), and less readily in cohort 9 (HR 0.744, 95% CI: 0.625–0.886).

In interpreting the observed differences in time to NIV between cohorts, we examined the percentage of each cohort initiated on NIV and the vital capacity at which this was done. We observed substantial differences between clinical centers in the proportion started on NIV (Table 7), however there was no statistically significant difference in the vital capacity at which NIV was initiated between clinical centers (Figure 1, Table 7).

Survival. Having observed differences in time to clinical interventions between the cohorts of ALS clinical centers, coupled with the known survival benefit of NIV use (30), we carried out preliminary analysis to determine if differences in overall survival were seen. We did ultimately observe differences in overall survival between cohorts (Table 6), though this did not cleanly map to the differences in time to NIV observed.

Discussion

This study presents time-to-event analysis for the largest, multi-center European cohort to date, compiled via the PRECISION-ALS collaboration. Access to this population-based cohort has provided detailed insight into the natural history of ALS in Europe, highlighting phenotypic and genetic factors impacting upon time to key clinical milestones.

In our cohort, we observed a male-to-female ratio of 1.35 and peak onset of symptoms in the 7th decade of life. This aligns with previously published data describing the timing of symptoms (6) and male predominance of the disease (31), though it is worth noting that the extent of this predominance has been shown to vary with the age of the population under study (31).

Of those tested in our cohort, 8.9% were C9orf72-positive, 2.9% SOD1-positive, 1.6% TARDBP-positive, and 0.8% FUS-positive. Epidemiological studies carried out in Asia typically show C9orf72 repeat expansions to be relatively rare compared to Caucasian populations, with SOD1 mutations more frequent (32). Since the proportion of those with a family history of ALS was not captured in our study, it is not possible to draw comparisons on the frequency of these mutations in familial or sporadic populations (1,33,34). What is clearer, however, is that genetic testing information was available for only a minority of our multi-center European cohort. Large-scale study of genetic testing in ALS has shown the importance of broadening its availability, ensuring that age of onset and the presence of family history are not barriers to access, especially in the age of targeted genetic therapies (33,35).

The median diagnostic delay of 12 months observed in our cohort also aligns with previous pooled data (36,37). Diagnostic delay in other populations, such as in the US, has both been reported to be substantially shorter (38) and longer (39) than in our European cohort. However, this may in part reflect studies sampling differing US populations in the context of the broad inequity in access to healthcare (40). Spinal-onset ALS has been noted to experience longer diagnostic delay than bulbar-onset disease, likely owing to the increased likelihood of referral to a non-neurologist and undergoing additional diagnostic testing (39). Whilst we did observe this trend in our data, the difference was substantially less pronounced than reported previously (39).

We verified several reported prognostic factors for overall survival, namely age at symptom onset, bulbar-onset disease, shorter diagnostic delay, faster disease progression (as measured by the delta-FS),

C9orf72-positive status, and lower baseline vital capacity (6,41,42). Our cohort median survival time of 33.7 months aligns with the range previously published, further highlighting the representation of our multi-center European cohort (43).

At a group level, we did not identify an independent prognostic effect for SOD1-positive status. In pwALS diagnosed after 2010, we did not observe any SOD1 variants with significant impact on prognosis. When including a broader cohort, however, D91A and G94C variants were observed to have a significantly protective prognostic effect, as has been described previously (44). This was likely not borne through in our post-2010 cohort given a reduction in sample size and resulting statistical power.

Significant differences between ALS clinical center cohorts were observed in our data in time to gastrostomy insertion, NIV initiation, and overall survival. To determine whether these differences were driven by phenotypic variance between geographies, our analysis accounted for phenotypic prognostic factors. Time-to-event differences between cohorts continued to be observed, however further study is needed to investigate if yet unidentified divergence between cohorts in factors such as the ALS exposome or underlying genetic variants may be responsible (45). It is also important to consider that variance in clinical practice may be involved. Potential factors may include differing thresholds for initiating clinical interventions, differing waiting times for clinical procedures and services, differing access to specialized care between healthcare systems, or differing cultural and societal views and preferences toward specific clinical interventions, for example. Future work investigating the drivers behind these differences between cohorts will likely inform consensus guidelines ensuring parity in ALS care across Europe (46). Such work will also inform future clinical trial protocols, where variation in the use of clinical interventions known to have an effect on survival, such as NIV, may affect trial results if not used homogeneously within a trial population. Defining an expected standard of care with criteria for NIV initiation and, perhaps, nutritional targets, would mitigate this potential bias.

Our study has several limitations, many of which are inherent to secondary data analysis. Firstly, despite extensive effort to harmonize the multi-center cohort, there is inevitably variance in data acquisition between ALS centers, including for example the method of case identification, data completeness, or definition of disease states/phenotypes. In data cleaning, these differences necessitate the identification of a common denominator across cohorts to enable comparison, likely causing a dilution in data granularity and utility.

Secondly, several known prognostic factors were not systematically collected or available in these

Table 6. Stratified Cox proportional hazards analysis of time from symptom onset to diagnosis, and time from diagnosis to gastrostomy insertion, NIV initiation, and death.

		Diagnosis		Gastrostomy		NIV		Survival	
Factor		HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Age at onset		0.999 (0.997–1.001)	0.322	1.000 (0.995–1.004)	0.881	1.000 (0.996–1.004)	0.937	1.025 (1.022–1.028)	<0.001
Baseline VC (% predicted)		1.004 (1.002–1.005)	<0.001	0.995 (0.992–0.998)	<0.001	0.988 (0.985–0.991)	<0.001	0.992 (0.990–0.994)	<0.001
Progression rate (Delta-FS)[a]		8.198 (6.672–10.073)	<0.001	3.212 (2.451–4.208)	<0.001	3.321 (2.593–4.253)	<0.001	3.298 (2.772–3.925)	<0.001
Diagnostic delay				0.876 (0.804–0.954)	0.002	0.985 (0.921–1.052)	0.647	0.846 (0.806–0.887)	<0.001
Cohort from ALS clinical center	Cohort 1	Reference		Reference		Reference		Reference	
	Cohort 5	0.871 (0.787–0.965)	0.008	1.056 (0.864–1.290)	0.596	0.982 (0.818–1.178)	0.843	1.091 (0.977–1.219)	0.122
	Cohort 6	0.700 (0.632–0.775)	<0.001	1.152 (0.896–1.481)	0.268	2.092 (1.719–2.545)	<0.001	1.770 (1.539–2.035)	<0.001
	Cohort 7	0.983 (0.900–1.074)	0.703	0.852 (0.700–1.037)	0.110	2.186 (1.860–2.570)	<0.001	1.322 (1.191–1.469)	<0.001
	Cohort 8	1.391 (1.269–1.526)	<0.001	1.905 (1.591–2.281)	<0.001	2.107 (1.786–2.485)	<0.001	0.968 (0.869–1.078)	0.549
	Cohort 9	0.926 (0.849–1.009)	0.077	1.370 (1.150–2.632)	<0.001	0.744 (0.625–0.886)	0.001	1.656 (1.508–1.819)	<0.001

Note: Baseline VC = either a forced vital capacity or a slow vital capacity assessment within six months of diagnosis.
[a]Normalised by means of cubic root.

Table 7. Proportion of each ALS clinical center cohort initiated on NIV and vital capacity threshold at which NIV was initiated.

Cohort from ALS clinical center (n)	NIV initiated n (%)	Vital capacity threshold at NIV initiation, n (% of those initiated on NIV)					
		<50%	50–60%	60–70%	>70%	N/A	
Cohort 1 (865)	259 (29.9)	28 (10.8)	24 (9.3)	24 (9.3)	32 (12.4)	151 (58.3)	ANOVA
Cohort 5 (978)	272 (27.8)	41 (15.1)	28 (10.3)	26 (9.6)	56 (20.6)	121 (44.5)	$F = 1.093$
Cohort 6 (724)	226 (31.2)	0	0	0	0	226 (100)	$p = 0.359$
Cohort 7 (1678)	832 (49.6)	30 (3.6)	22 (2.6)	28 (3.4)	57 (6.9)	695 (83.5)	
Cohort 8 (1264)	626 (49.5)	35 (5.6)	18 (2.9)	26 (4.2)	56 (9.0)	491 (78.4)	
Cohort 9 (2701)	229 (8.5)	8 (3.5)	9 (3.9)	6 (2.6)	13 (5.7)	193 (84.3)	

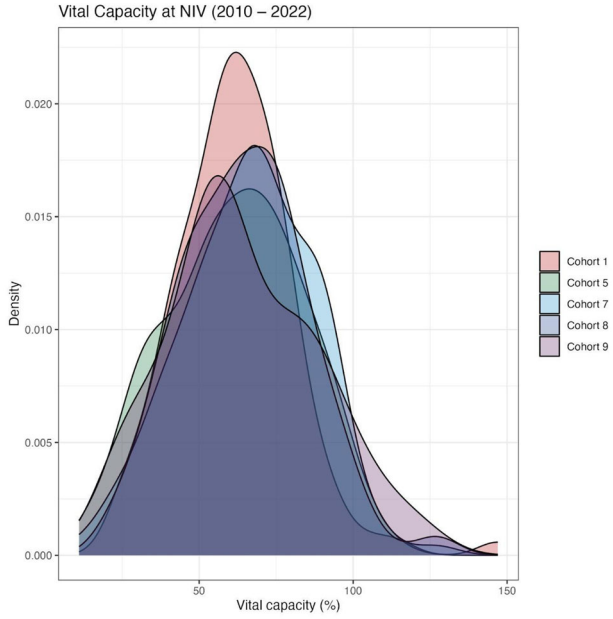

Figure 1. Density plot demonstrating vital capacity (% predicted) at which NIV was initiated by ALS clinical center cohort.

extant datasets, which date back as far as the early 1990s. Examples of this are the lack of cognitive assessment and height/weight/BMI data, despite these factors being recognized as prognostic factors in time to key clinical milestones, such as gastrostomy insertion and overall survival (6,47,48).

Thirdly, our multi-center, population-based dataset had significant data missingness. To mitigate this, we used multiple imputation prior to our Cox survival analysis. We also restricted the dataset for this analysis to those diagnosed after 2010, given the reduced degree of missingness and changes in ALS management (30). As a result, our cohort was both smaller in size ($n = 8210$ vs 21,820) and imputed, however we argue a cohort diagnosed after 2010 is likely more representative of those seen and treated in ALS care centers today. Future work will benefit from the availability and completeness of multi-modal, prospectively collected data that are harmonized and coordinated in their collection across geographies. The integrated data platform disseminated across Europe by the PRECISION-ALS consortium is an example of this, demonstrating the power that uniformly collected, granular clinical data has in unraveling the unknowns in the natural history of ALS (49).

It has previously been identified that there is significant variation in the ALS phenotype between geographical areas and admixed populations (50–55). Whilst this study has comprehensively examined the European ALS population, future work bringing together population-based data across geographic regions will help in understanding the differences and factors driving difference between populations, in turn facilitating a deeper understanding of and prognostication within diverse clinic populations.

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Ethical approval

All procedures and methodologies were in accordance with the ethical guidelines and standards of the institutional and national ethics

committees of each of the sites involved. Informed consent was obtained from all participants, ensuring their autonomy and understanding of the study's objectives. Ethical approvals were obtained from the local Institutional Review Board (IRB) at each participating site for use of the data in this study and for the central storage required to facilitate the cleaning and harmonization of the data. Personal data were transferred and stored securely to ensure that the privacy of these data was maintained, and relevant steps were taken to minimize any potential harm to participants.

Declaration of interest

Alejandro Caravaca Puchades, Cristina Terrafeta Pastor, Stefan Sennfält, Oskar Holmdahl, Nikita Lamaire, Sarah Opie-Martin, Frederik Hobin, Fouke Ombelet, Harry E. McDonough, Mohammed Mouzouri, Robert McFarlane, Miriam Galvin, Mark Heverin, Éanna Mac Domhnaill, Rosario Vasta, Umberto Manera, Ruben van Eijk, Daphne Weemering, Jan Veldink, and Leonard van den Berg report no competing interests to declare. Mònica Povedano Panadés reports consultancies/advisory boards for Amylyx Pharmaceuticals, Biogen, Ferrer, Grifols, Italfarmaco, Mitsubishi Tanabe Pharma and Roche. Caroline Ingre has consulted for Cytokinetics, Pfizer, BioArctic, Novartis, Tikomed, Ferrer, Amylyx, Prilenia and Mitsubishi. She is also a board member of Tobii Dynavox; all outside the submitted work. Ammar Al-Chalabi reports consultancies or advisory boards for Amylyx, Apellis, Biogen, Brainstorm, Clene Therapeutics, Cytokinetics, GenieUs, GSK, Lilly, Mitsubishi Tanabe Pharma, Novartis, OrionPharma, Quralis, Sano, Sanofi, and Wave Pharmaceuticals. Philip Van Damme reports advisory boards for Biogen, CSL Behring, Alexion Pharmaceuticals, Ferrer, QurAlis, Cytokinetics, Argenx, UCB, Muna Therapeutics, Alector, Augustine Therapeutics, VectorY, Zambon, Amylyx (paid to institution). He has received speaker fees from Biogen, Zambon and Amylyx (paid to institution). He is supported by the E. von Behring Chair for Neuromuscular and Neurodegenerative Disorders (from CSL Behring, paid to institution). Cristopher J. McDermott reports consultancies or advisory boards for Amylyx, Ferrer, Novartis, PTC therapeutics, Verge Therapeutics. Pamela J. Shaw reports consultancies or advisory boards for Biogen, Aclipse Therapeutics, Quell Therapeutics, BenevolentAI, QurAlis, Astex, GeniUS, Lilly, Novartis, Samsara, Eikinoklastes, Maat Pharma and AL-S Pharma and collaborates with and has received research funding from Quell Therapeutics, Aclipse Therapeutics, Pfizer SwanBio, and Takeda. Philippe Corcia reports consultancies or advisory boards for Amylyx, Biogen, Coave Therapeutics, Cytokinetics, Ferrer, Mitsubishi Tanabe,QurAlis, Vectory, Zambon. He is member of the Board of the Journal Amytrophic Lateral Sclerosis and the Frontotemporal Dementias and of the Revue Neurologique. Orla Hardiman reports consultancies/ advisory boards for Biogen, Takeda, Ferrer, Novartis, Alchemab and Medici Nova. She is Editor in Chief of the Journal Amyotrophic Lateral Sclerosis and the Frontotemporal Dementias. Adriano Chiò serves on the editorial advisory board of Amyotrophic Lateral Sclerosis and Neurological Sciences. Adriano Chiò serves on scientific advisory boards for Mitsubishi Tanabe, Biogen, Roche, Denali Pharma, Cytokinetics, Lilly, Ferrer, Zambon Biotech, and Amylyx Pharmaceuticals, has received a research grant from Biogen and serve on Drug Safety Monitoring Board for AB Science, Corcept, and Eli Lilly. He has received research support from the Italian Ministry of Health (Ricerca Finalizzata), Regione Piemonte (Ricerca Finalizzata), Italian Ministry of University and Research (PRIN projects), University of Turin, and the European Commission (Health Seventh Framework Programme, Horizon 2020 and Horizon Europe).

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ORCID

Ammar Al-Chalabi http://orcid.org/0000-0002-4924-7712
Adriano Chiò http://orcid.org/0000-0001-9579-5341
Miriam Galvin http://orcid.org/0000-0002-8232-8020
Orla Hardiman http://orcid.org/0000-0003-2610-1291
Caroline Ingre http://orcid.org/0000-0001-5327-7204
Umberto Manera http://orcid.org/0000-0002-9995-8133
Robert McFarlane http://orcid.org/0000-0001-7380-4219
Sarah Opie-Martin http://orcid.org/0000-0003-0951-8589
Philip Van Damme http://orcid.org/0000-0002-4010-2357
Ruben P.A. van Eijk http://orcid.org/0000-0002-7132-5967
Christopher J. McDermott http://orcid.org/0000-0002-1269-9053

Data availability statement

The data set used for the analysis in this paper was provided by PRECISION ALS. These data are stored, and access governed by the PRECISION ALS Consortium. Requests to access this data can be made through the Scientific Board of the PRECISION ALS Consortium.

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