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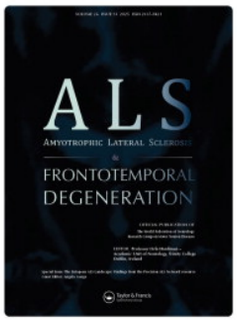

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RESEARCH ARTICLE

Respiratory function, survival, and NIV prevalence over time in ALS - a PRECISION ALS study

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Abstract

Introduction: Respiratory function typically deteriorates as ALS progresses and is associated with shorter survival. This study aims to describe respiratory function and the prevalence of noninvasive ventilation (NIV) along the disease trajectory using prospective data from the PRECISION ALS project. *Methods*: We included 3449 ALS patients from six European population-based cohorts. All had comparable assessments of vital capacity, percent predicted (VC%) (58.1% had multiple assessments) and 56% had assessments of the revised ALS Functional Rating Scale (ALSFRS-R). The data were analyzed in relation to survival, NIV, and genetic status (*C9orf72*, *SOD1*, *FUS*, and *TARDBP)*. *Results*: In those with a survival time of 1–4 years from diagnosis, the median VC% declined from 91 to 97% at the first assessment to 47–50% at the last assessment 6 months before death. In those with longitudinal assessments, the median VC% declined an average of 24 percentage points per year. Over time, there was an increase in respiratory symptoms relative to general functional impairment, as measured by the ALSFRS-R, and VC% was strongly associated with shorter survival. The confirmed prevalence of NIV was approximately 3%, 15%, and 25% in patients with a VC% of >80, 50-80, and <50, respectively. *Conclusion*: There was a trend of worsening respiratory function over time and an increase in

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respiratory symptoms relative to general functional impairment. Survival was strongly associated with respiratory function. In those with impaired respiratory function, there was significant variation in the introduction of NIV.

Keywords: *ALS, respiratory, noninvasive ventilation, precision*

Introduction

Amyotrophic Lateral Sclerosis (ALS) typically presents with extremity motor weakness and impaired speech and swallowing (1). Although respiratory muscle weakness can be detected by objective measures (e.g., decrease in vital capacity [VC]) in many patients at diagnosis, the prevalence of respiratory symptoms at disease onset is low (2). In a small percentage of patients this is the first manifestation of disease, termed respiratory onset ALS, which is associated with a less favorable prognosis (3). As the disease progresses, motor weakness starting elsewhere generalizes to involve respiratory musculature; there is commonly a steady decline in respiratory function and a range of respiratory measures, such as VC, are strongly associated with shorter survival (4–6). Indeed, the most frequently reported mode of death is respiratory failure, often exacerbated by a provoking factor such as pneumonia (7–9).

In patients with prominent respiratory symptoms, noninvasive ventilation (NIV) is recommended as it improves survival and quality of life (10–12). NIV is commonly offered to patients with signs or symptoms of daytime or nocturnal respiratory insufficiency. This can be assessed using several methods, such as VC where a recommended threshold is <80% of the predicted value when there are symptoms of respiratory impairment and <50% otherwise, which may indicate significant respiratory impairment (13).

Although most ALS patients have no relevant family history, there is a strong genetic component in ALS (14). The most common high penetrance pathologic gene variants reported in European populations are in *C9orf72* (33.7% familial, 8-10% non-familial), *SOD1* (14.8% familial, 2% non-familial), *TARDBP* (4.2% familial, 1% non-familial) and *FUS* (2.8% familial, 1% non-familial) (15). These variants are associated with different but overlapping phenotypic presentations. However, the differences in respiratory involvement have not been extensively studied.

This study aims to describe respiratory function in relation to survival, prevalence of NIV use, and genetic status, using a large multinational dataset including 3449 ALS patients.

Methods

This manuscript is part of a series of papers describing a large multinational dataset from the PRECISION ALS project including in total 21830 ALS patients. 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 in order to limit the number of confounders.

Centers provided all consecutively diagnosed patients from the beginning of their registry (earliest registration in 1993) until December 2022. Complete survival data (date of death or last follow-up) were obtained by checking the municipal population register at 3-monthly intervals. Datasets were harmonized and combined into a single database, together with an indicator variable for each cohort.

For the present study, data were included from six of the European centers: King's College London, Leuven University Hospitals, Sheffield Teaching Hospitals, Trinity college Dublin, University of Turin, and University Medical Center Utrecht (UMCU).

The manuscript was prepared in collaboration with Biogen. During the peer review process, Biogen had the opportunity to review the manuscript. The authors had full editorial control of the manuscript and provided their final approval on all content

Patients

We included ALS patients with at least one comparable respiratory assessment (see below for definition) within four years from diagnosis. We excluded those with unknown date of diagnosis/respiratory assessment, unknown vital status (dead or alive), missing/negative follow-up time or a follow-up time less than four years/more than 20 years (Supplementary Figure 1). This resulted in a cohort of 3449 patients, 15.8% of the original PRECISION ALS data set cohort of 21820 patients. Exclusion was mainly due to a lack of a comparable respiratory assessment. Patient characteristics were compared between the study cohort and original PRECISION ALS data set cohort (minus study cohort) to assess selection bias (Supplementary Table 1). There was a small but statistically significant difference in most variables, notably a substantial difference in NIV status (32.5% with NIV in included patients versus

17.3% in those excluded). Also, patient characteristics were compared between sites showing significant differences in most variables (Supplementary Table 2).

Data and measurements

Respiratory function

In the original PRECISION ALS cohort, data on various methods of assessing respiratory function were available from the different centers, including forced vital capacity (FVC) (by some centers defined as supine or sitting), slow VC, and sniff nasal inspiratory pressure. Measures that were considered comparable were included in the present study: FVC (not specified position), slow VC, and FVC sitting up, all reported as percent of predicted (1-200%). The results were merged and collectively referred to as vital capacity, percent of predicted (VC%).

One VC% assessment per individual was included for each six-month period after diagnosis. The assessment closest to the end of the period was chosen. Longitudinal decline in VC% was calculated in patients with more than one assessment by subtracting the last from the first assessment available and divided by the time difference in years, yielding the average decline in percentage points per year.

Functional impairment

This was assessed using the revised ALS Functional Rating Scale (ALSFRS-R). One assessment per individual was included for the analysis of each six-month period after diagnosis. The assessment closest to the end of the period was chosen. The scale is composed of 12 items indicating impairment in different domains and has a maximum score of 48 (16). The rate of change in the ALSFRS-R per month was calculated by subtracting the last from the first available ALSFRS-R score and then dividing this number with the time difference in months. A respiratory sub-score was calculated by adding items 10-12, yielding a total score of 12. A ratio representing the decline in the respiratory sub-score relative to the total ALSFRS-R score was computed by dividing the decline in the respiratory sub-score by the decline in the total score. A ratio of 0.25 was anticipated if both the total and respiratory scores were equally impacted. For better comprehension, the ratio was normalized by dividing it by 0.25, resulting in an expected value of one under equal impact on both total and respiratory scores.

NIV

The use of NIV was defined as having been prescribed NIV for home use for any amount of time per day. All centers except University Medical Center Utrecht provided NIV data ($n = 3223$). Two centers consistently coded NIV status as 'yes' or 'no' (University of Turin and King's College London) whereas the others included a large proportion of 'missing' data ($n = 1730$). After consulting the individual centers, these values were interpreted as 'no'. The characteristics in patients with NIV status reported as 'missing' versus 'no' were compared. Sex, age at diagnosis, and ALSFRS-R at six months differed (Supplementary Table 3). In addition to patients reported as 'yes' we classified patients reported as 'missing' but with a score of 0 on ALSFRS-R question 11 or <4 on question 12, as 'yes' (an additional 69 patients).

Genetic testing

Testing for the most common high-penetrance genetic variants associated with ALS was undertaken as follows (14): 2232 (64.7%) were tested for variants in *C9orf72*, 1488 (43.1%) for variants in *SOD1*, 1563 (45.3%) for variants in *FUS*, and 1616 (46.9%) for variants in *TARDBP*.

Statistics

Categorical variables were summarized as proportions (percent) and bivariate analyses were performed using the χ^2 test to assess for group differences. Continuous variables were reported as medians with interquartile range (IQR), except for the ALSFRS-R respiratory/total score decline ratio which was presented as mean. If normally distributed (age), Student's *t*-test (for two groups) or the ANOVA test (for >2 groups) was performed to assess for group differences. If non-normally distributed, the Mann-Whitney-U (for two groups) and the Kruskal-Wallis (for > 2 groups) tests was used instead.

To model repeated measures and factors predictive of VC% over time, a multivariable mixed regression model was constructed. We included all VC% assessments (11554 in total) from all patients and entered the VC% as a dependent variable, subject as a random factor and age at diagnosis (categorical), sex, site of onset, genetic status, ALSFRS-R progression rate, and years from diagnosis to assessment (categorical) as fixed factors. Estimates for each variable within the multivariable model were reported with 95% Confidence Interval (CI).

Survival as a function of respiratory status was analyzed by Kaplan-Meier product limit distribution, grouping patients by VC% at their first respiratory assessment within two years from diagnosis ($n = 3040$). Survival times were calculated from the first assessment and patients were followed for up to four years and then censored. The significance of group differences was tested using

Table 1. Patient characteristics, grouped by genetic subtype.

		Genetic mutation					
	Total *N = 3449*	*C9orf72* *n = 210*	*SOD1* n = 56	*FUS* n = 17	*TARDBP* n = 25	Tested, negative # n = 1226	Not tested n = 1915
Age at diagnosis, median (IQR)**	64 (15)	60 (12)	54 (16)	64 (28)	58 (24)	66 (14)	64 (15)
Sex (male), n (%)*	2046 (59.5)	115 (54.8)	24 (42.9)	8 (47.1)	18 (72.0)	725 (59.2)	1159 (60.6)
Site of onset, n (%)**							
Spinal	2399 (70.5)	135 (64.6)	49 (87.5)	12 (70.6)	18 (72.0)	865 (70.9)	1320 (70.3)
Bulbar	945 (27.8)	73 (34.9)	3 (5.4)	5 (29.4)	7 (28.0)	339 (27.8)	518 (27.6)
Cognitive	2 (0.1)	1 (0.5)	0	0	0	0	1 (0.1)
Respiratory	58 (1.7)	0	4 (7.1)	0	0	16 (1.3)	38 (2.0)
ALSFRS-R in the first 6 months, median (IQR)	38 (9)	38 (10)	38 (11)	38 (8)	42 (5)	39 (10)	38 (10)
ALSFRS-R respiratory sub-score within the first 6 months, median (IQR)	12 (1)	12 (0)	12 (2)	12 (1)	12 (0)	12 (1)	12 (2)

*Significant difference between groups at $p < 0.05$.
**Significant difference between groups at $p < 0.01$.
#Tested negative for all four variants.
ALSFRS-R = revised ALS functional rating scale; IQR = Interquartile range, NIV = noninvasive ventilation.

the pooled Log Rank test and a multivariable Cox regression was performed to assess factors predictive of death.(hazard ratio [HR] with 95% CI). The model included sex, age, site of onset, progression rate, and genetic status as covariates. For the survival analyses, patients were censored upon end of follow-up for any reason.

The Pearson's correlation coefficient was used to assess correlation between the ALSFRS-R respiratory sub-score and the VC% and was calculated separately for each six-month period.

For all tests the significance level was set to 95%. All statistical analyses were conducted in IBM SPSS Statistics version 28.

Results

Patient characteristics

Data were almost complete for age at diagnosis (100%), sex (99.9%), and site of onset (98.7%). Among all patients ($N = 3449$), the median age of onset was 64 years and there was a slight preponderance of males (59.5%) (Table 1). The majority (70.5%) had spinal onset disease, 27.8% had bulbar onset, and there was a small proportion (1.7%) with respiratory onset. The patients were grouped by genetic subtype. Of those who were tested, 9.6%, 3.7%, 1.1%, and 1.5%, were positive for pathogenic variants in *C9orf72, SOD1, FUS,* and *TARDBP*, respectively. Notably, in those positive for *SOD1*, the proportion with bulbar onset was only 5.4% whereas the proportion with respiratory onset was (7.1%). ALSFRS-R and its respiratory sub-score were similar across groups.

Respiratory function

The total number of VC% assessments from diagnosis and up to four years was 11554. All patients had at least one assessment, 2004 (58.1%) had more than one assessment, and 1012 (29.3%) had more than three. At 0-6 months after diagnosis, 67.0% of living patients had a respiratory assessment and at subsequent time periods this proportion decreased (Figure 1a).

Respiratory function was described in relation to time from diagnosis in addition to time to death. There was a clear trend of lower median VC% the longer from diagnosis and the closer to death (Figure 2). In patients alive at 1, 2, 3 and 4, years after diagnosis the median VC% was 74-80% at that time as compared to 90-96% within six months from diagnosis (Figure 2a). Similarly, in deceased patients with a survival time from diagnosis of 1–2, 2–3, and 3–4 years, there was a median VC% of 91–97% within 6 months from diagnosis, and 47–50% at the last assessment, within six months before death (Figure 2b). However, in the group with the shortest survival, 0–1 year, there was a substantially lower VC% of 71% at the first assessment. In patients with longitudinal assessments ($n = 2004$), the median decline in VC% per year was 24.0 percentage points (IQR 43.9), larger in those with shorter survival: 68.0 (IQR 96.0), 43.0 (IQR 66.5), 27.2 (IQR 32.9), and 21.2 (IQR 21.3), respectively, in patients with a survival time of 0-1, 1-2, 2-3, and 3-4 years from diagnosis.

A multivariable mixed regression model provided estimations of the effects of various variables, including time from diagnosis, on VC% (Table 2).

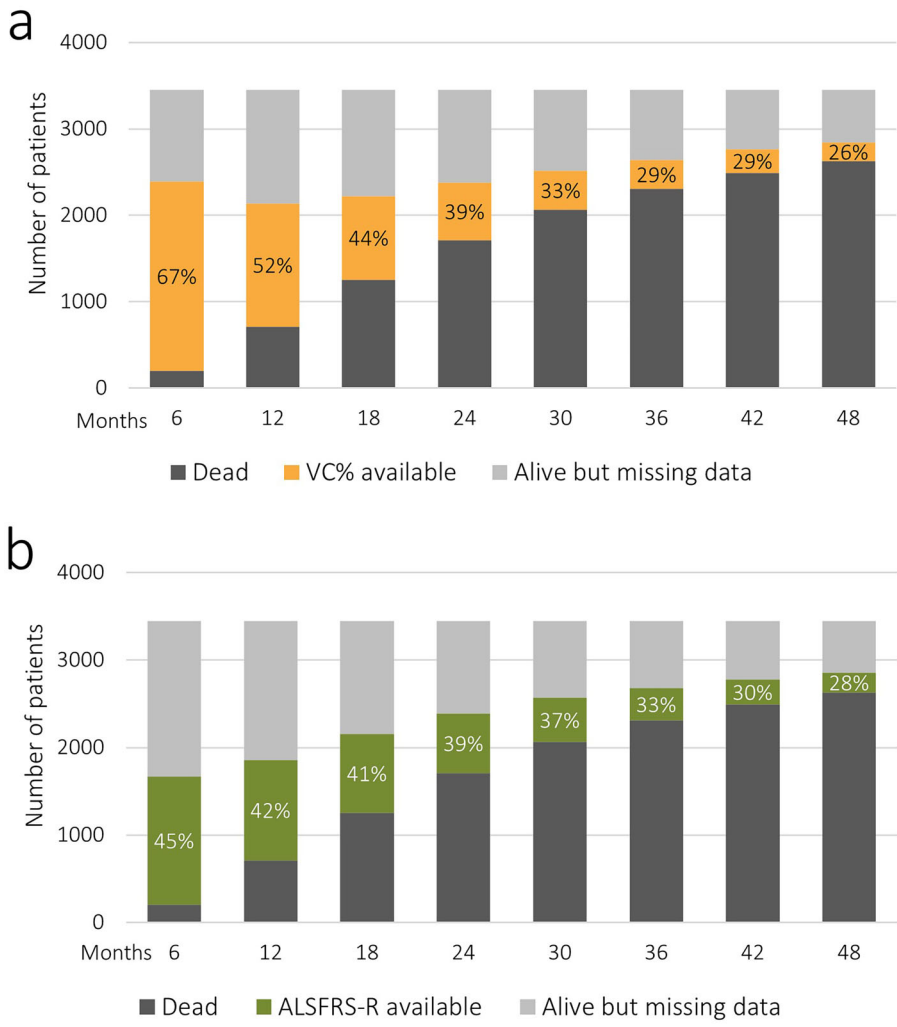

Figure 1. Proportion of patients with available measurement of VC% (a) and ALSFRS-R (b) at different time points after diagnosis. The percentages refer only to the proportion of living patients. The time periods in months refer to the preceding 6-month period, e.g., month 6 refers to months 0-6.
ALSFRS-R = revised ALS functional rating scale, VC% = vital capacity, percent of predicted.

From an intercept of 102 (95% CI 99.1-105.7), the estimated VC% decreased with 11.7 (10.6-12.9), 26.0 (24.3-27.6), 32.6 (30.4-34.8), and 40.1 (37.3-42.9) percentage points, respectively at 1, 2, 3, and 4 years after diagnosis (more specifically at assessment at some point in the preceding 6 months). The model showed a significant negative effect of bulbar and respiratory onset compared to spinal onset as well as for ALSFRS-R progression rate. However, genetic status was not predictive of respiratory function in our model.

Respiratory function relative to general functional decline

ALSFRS-R measurement was available for 1935 (56.0%) patients at some point within four years after diagnosis (Figure 1b). Parallel to the decline in VC%, there was an increase in respiratory impairment relative to general functional impairment as evidenced by an increase in the ALSFRS-R respiratory/total score decline ratio (Figure 3).

At all time-points, there was a moderate correlation between VC% and the ALSFRS-R respiratory sub-score: a Pearson's correlation coefficient of 0.38-0.56 ($p < 0.001$).

Survival in relation to respiratory function

Patients with respiratory assessment within two years from diagnosis ($n = 3040$) were grouped according to the VC% at the first available respiratory assessment within two years from diagnosis (median 0.07 years [IQR 0.29]): ≥100% $n = 971$, 90-99% $n = 531$, 75-89% $n = 606$, 60-74% $n = 472$, and <60% $n = 461$. The survival from the time of the assessment was estimated, showing significant differences between groups ($p < 0.001$). The two-year survival was 62.3%, 50.3%, 43.4%, 31.6%, and 20.4%, respectively (Figure 4). A Cox regression model revealed a significant increase in HR for death with lower respiratory function: 1.23 (CI 95% 1.02-1.47), 1.37 (1.15-1.64), 1.54 (1.26-1.88), and 1.75 (1.39-2.20) for a VC% of 90-

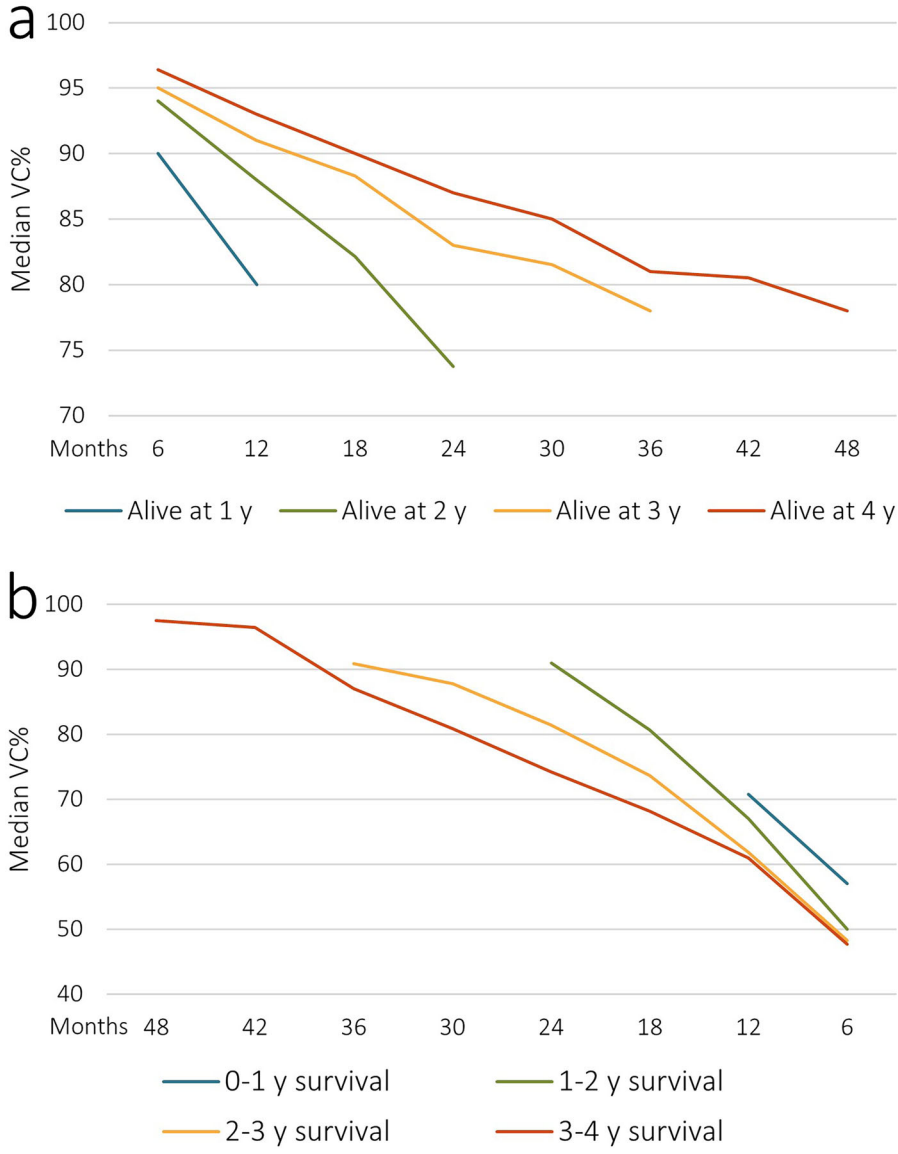

Figure 2. Median VC% x months after diagnosis (a) and before death (b). For a, patients were stratified according to vital status: those alive at 1 ($n = 2749$, 2 ($n = 1764$), 3 ($n = 1171$), and 4 years ($n = 853$) after diagnosis. For b, deceased patients were stratified according to survival time from diagnosis: 0-1 ($n = 710$), 1-2 ($n = 981$), 2-3 ($n = 589$), and 3-4 years ($n = 316$), respectively. The time periods in months refer to the last assessment during the preceding (a) or the subsequent (b) 6-month period.
VC% = vital capacity percent of predicted, y = years

99%, 75-89%, 60-74%, and <60%, respectively, as compared to ≥100% (Supplementary Table 4).

NIV

We included 3223 patients for NIV analyses. The proportion of living patients with NIV (not including those with unknown NIV initiation date) was 16.1%, 19.1%, 22.8%, and 23.6% at 12, 24, 36, and 48 months, respectively. The prevalence of NIV was substantially higher in those with evidence of impaired respiratory function based on VC%. Throughout the study period there was a confirmed proportion equipped with NIV of approximately 3%, 15%, and 25% in those with a VC% of >80, 50-80, and <50, respectively (Figure 5). In addition, there was a large proportion of patients known to be equipped with NIV at some point but with unknown initiation date. When including these individuals, the prevalence reached a maximum of 44%, for the VC% <50 group at 36 months.

Discussion

Respiratory function and survival

There was a trend of worsening respiratory function with disease progression (median decline in VC% per year was 24 percentage points), and a lower VC% was associated with shorter survival, consistent with previous findings (2, 4–6, 17, 18).

Specifically, our findings are in line with those from an earlier large study that utilized trial data

Table 2. Multivariable mixed regression model showing estimations of VC% dependent on various factors. n = 11554 assessments, 3449 patients

	Estimate (95% CI)	P-value
Intercept	102.4 (99.1–105.7)	
Age at diagnosis		
<55	0	–
55–64	−0.1 (−3.2–3.1)	0.144
65–74	−1.0 (−4.1–2.1)	0.535
>75	−3.0 (−7.0–1.0)	0.973
Sex (male)**	−3.8 (−6.1 to −1.5)	<0.001
Site of onset $		
Spinal	0	–
Bulbar**	−8.2 (−108 to −5.6)	<0.001
Respiratory**	−26.8 (−36.1 to −17.5)	<0.001
Genetic status		
Negative or not tested	0	–
C9orf72	−3.6 (−7.8–0.7)	0.103
SOD	5.3 (−2.8–13.4)	0.203
FUS	−12.2 (−25.6–1.1)	0.072
TARDBP	3.0 (−7.6–13.5)	0.58
ALSFRS-R progression rate		
<0.5	0	–
0.5–1.49*	−3.1 (−5.8 to −0.3)	0,028
>1.5**	−16.8 (−19.6 to −14.0)	<0.001
Months after diagnosis		
<6	0	
12**	−11.7 (−12.9 to −10.6)	<0.001
18**	−21.0 (−22.4 to −19.6)	<0.001
24**	−26.0 (−27.6 to −24.3)	<0.001
30**	−30.2 (−32.1 to −28.4)	<0.001
36**	−32.6 (−34.8 to −30.4)	<0.001
42**	−36.3 (−38.7 to −33.8)	<0.001
48**	−40.1 (−42.9 to −37.3)	<0.001

*$p < 0.05$.
**$p < 0.001$.
$Cognitive onset not included due to too few patients ($n = 2$).
ALSFRS-R = revised ALS functional rating scale, CI = confidence interval, VC% = vital capacity percent of predicted.

from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) dataset (19). In that study, the authors employed a similar approach to ours, plotting respiratory function over time in patients grouped by survival duration. Like us, they demonstrated that longitudinal respiratory function declined in a linear fashion, with a faster and more compressed decline in individuals with shorter survival times. The PRO-ACT and clinic datasets have also been used by other researchers to identify patient clusters based on respiratory decline (20–23).

Additionally, we show that respiratory impairment becomes a more prominent feature as the disease progresses, as indicated by the increasing ratio of the ALSFRS-R respiratory/total score decline ratio. We also present a multivariable analysis identifying factors associated with impaired respiratory function. In this way, our study builds upon and extends important previous findings. The results may be valuable in developing useful clinical markers for estimating disease trajectories, such as for stratification in clinical trials. This is important topic for further research.

Of note, whereas some authors have observed decreasing respiratory function of a sigmoid curve appearance (17, 22), we observed a linear decline. This could be accounted for by inclusion of different patients at different time points. Also, bulbar onset was predictive of lower VC%, which has previously been reported (18, 21, 24, 25). However, respiratory testing in a patient with bulbar symptoms might be compromised by poor lip seal, apraxia, sialorrhea etc. and might not necessarily reflect poor respiratory function.

Also, although respiratory onset was more common in patients with a *SOD1* mutation, genetic status for the major genes tested did not affect respiratory function when adjusting for potential confounders. This might suggest that while many genetic variants display different clinical profiles (14), the presence of respiratory impairment might not be a distinguishing feature. It is worth noting however that other studies have identified associations between genetic variants, such as the *C9orf72* expansion, and faster respiratory decline in ALS (26, 27). The absence of such findings in our study may reflect a selection bias, as genetic testing may have been more accessible to patients with relatively stable respiratory function. Additionally, combining *C9orf72*-negative patients with untested individuals, some of whom may carry undiagnosed positive cases, could explain our results.

NIV

There is no commonly accepted threshold for initiation of NIV, although recommendations have been made to offer NIV for those with mild to severe respiratory failure (<80% and <50%, respectively) (13). Although the prevalence of NIV was higher in patients with worse respiratory function, the proportions were relatively low at approximately 3%, 15%, and 25% in those with a VC% of >80, 50-80, and <50, respectively. Even when including the proportion of patients with NIV but unknown initiation date, the prevalence remained lower than expected, with a maximum of 44% for the VC%<50 group. Given that NIV is associated with improved quality of life and survival (10, 11) there might be under-prescription. However, the reasons could not be assessed with the available dataset, and data from the different centers were very heterogenous.

Methodological considerations

The present study is relatively large, including over 3000 patients. The multinational nature of the (secondary use) dataset, brings a potential for data heterogeneity and bias. The original data set cohort included over 20 000 patients of which the

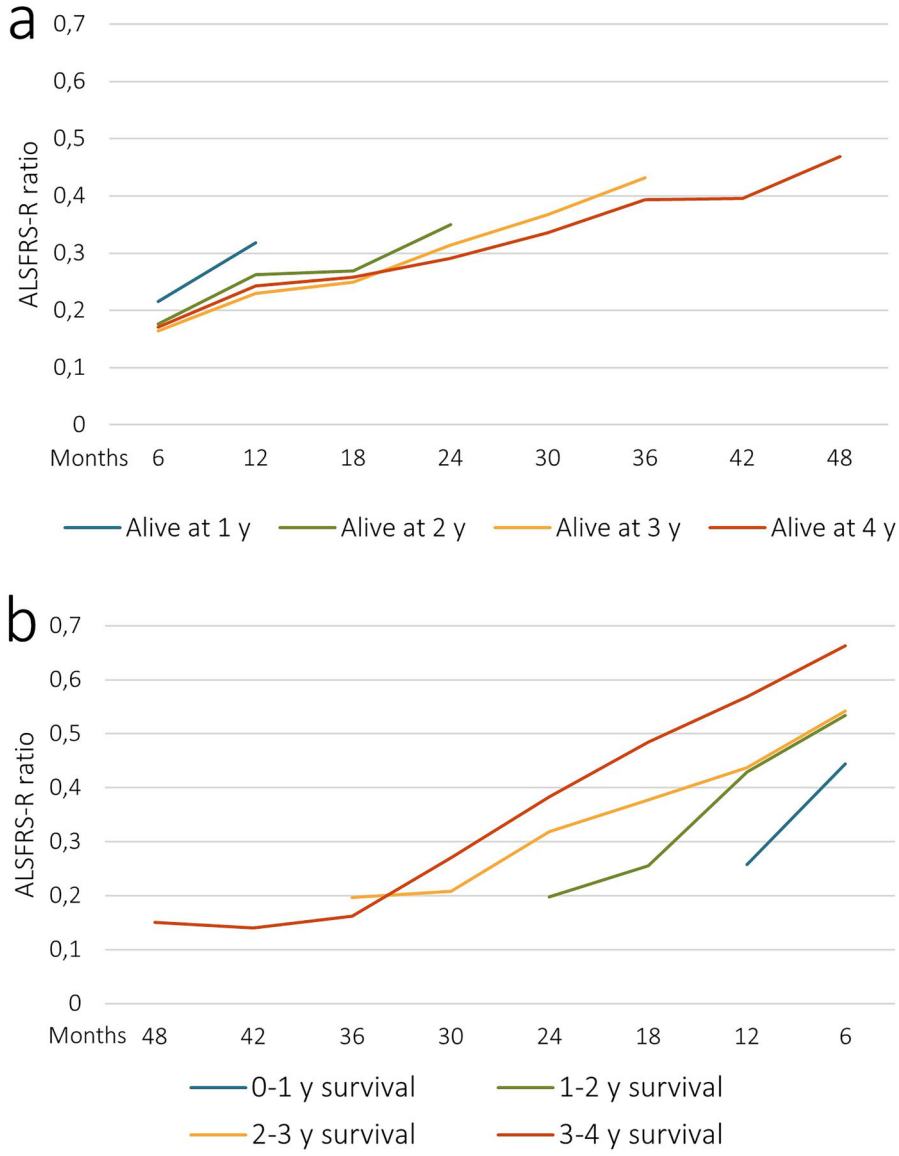

Figure 3. Mean ALSFRS-R respiratory/total decline ratio x months after diagnosis (a) and before death (b). The ratio was normalised such that an equal effect on respiratory and general decline would yield a value one. For a, patients were stratified according to vital status: those alive at 1 ($n = 2749$, 2 ($n = 1764$), 3 ($n = 1171$), and 4 years ($n = 853$) after diagnosis. For b, deceased patients were stratified according to survival time from diagnosis: 0-1 ($n = 710$), 1-2 ($n = 981$), 2-3 ($n = 589$), and 3-4 years ($n = 316$), respectively. The time periods in months refer to the last assessment during the preceding (a) or the subsequent (b) 6-month period.
ALSFRS-R = revised ALS functional rating scale, ALSFRS-R ratio = ALSFRS-R respiratory/total decline ratio, y = years

majority were excluded, predominantly because of a lack of a comparable respiratory measurement.

Although statistically significant, the differences in characteristics between those included and excluded were small, indicating limited selection bias. Nevertheless, the comparison indicated that patient selection seems to have favored patients equipped with NIV: 32.5% in included patients versus 17.3% in those excluded. This might be partly explained by a higher likelihood of recognizing the need for NIV in patients with respiratory assessment (i.e., those included in the study).

Patient characteristics were compared between centers showing differences in most variables, indicating differences in patient composition, standard of care, and reporting practices. Most importantly, the centers used a range of different respiratory measurements. We included patients with comparable methods of assessment, namely FVC% (not specified position), slow VC%, and FVC% sitting up. This merging was motivated by previous research showing FVC and slow VC to be strongly correlated, and interchangeable in predicting survival (4). We also included the ALSFRS-R respiratory sub-score which correlates to VC% (28). Another notable difference was seen in NIV registration from the participating sites, the lowest proportion of 12% compared to the highest of 74%, which is likely to be explained in part by reporting practices.

Also, given that respiratory function is sometimes not reassessed following the initiation of NIV, there is a risk of underestimating the number of individuals with low VC%. Although the reported

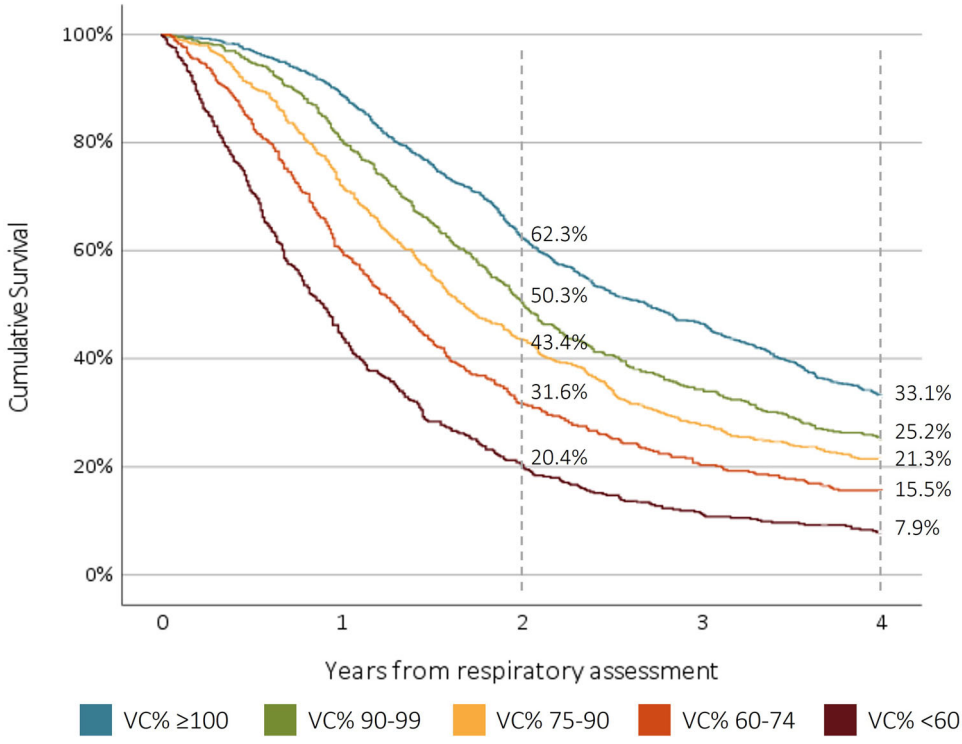

Figure 4. Kaplan-Meier diagram illustrating survival after the first respiratory assessment within two years of diagnosis ($n = 3040$). Pooled Log Rank test $p < 0.001$.
VC% = vital capacity percent of predicted

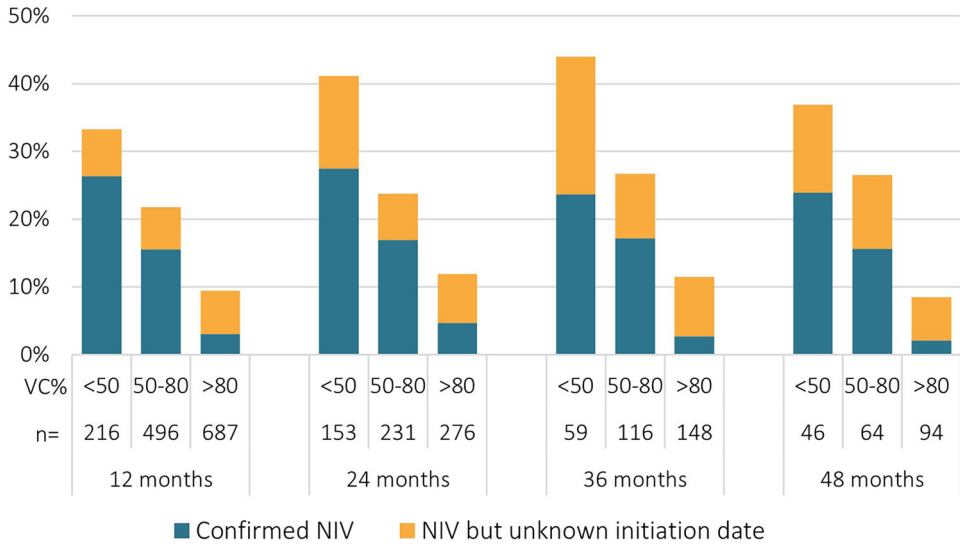

Figure 5. Prevalence of NIV over time in living patients at each time point grouped by VC%. $n = 3223$.
NIV = noninvasive ventilation, VC% = vital capacity percent of predicted

number receiving NIV was relatively low, 25% in the most affected group, the data was incomplete and the proportion on NIV (at higher risk of not being assessed) might have been higher in reality.

Notwithstanding these limitations, we have demonstrated the power of multicenter data to enable large-scale analyses, which is otherwise difficult for rare diseases such as ALS. In summary, we show a trend of worsening respiratory function over time and an increase in respiratory symptoms relative to general functional impairment, associated with shorter survival. We have identified variability in the initiation of NIV which merits further exploration. These data support the need for harmonized prospective natural history data collection (including more stringent reporting practices regarding NIV), as is currently underway as part of the PRECISION ALS initiative.

Statements

Ethics

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.

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Declaration of interest

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.

Mònica Povedano Panadés reports consultancies/advisory boards for Amylyx Pharmaceuticals, Biogen, Ferrer, Grifols, Italfarmaco, Mitsubishi Tanabe Pharma and Roche.

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.

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The other authors (Stefan Sennfält, Oskar Holmdahl, Nikita Lamaire, Alejandro Caravaca Puchades, Cristina Terrafeta Pastor, Sarah Opie-Martin, Frederik Hobin, Fouke Ombelet, Harry E. McDonough, Mouzouri, Robert McFarlane, Miriam Galvin, Mark Heverin, Éanna Mac Domhnaill, Rosario Vasta, Umberto Manera, Ruben van Eijk, Daphne Weemering, Jan Veldink, Leonard van den Berg) reports no competing interests to declare.

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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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