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Long-term non-invasive ventilation adherence in amyotrophic lateral sclerosis patients

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Research Article

Keywords: amyotrophic lateral sclerosis, non-invasive ventilation, adherence, diagnostic delay, disease progression

Posted Date: November 12th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11513374/v1

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Additional Declarations: No competing interests reported.

Long-term non-invasive ventilation adherence in amyotrophic lateral sclerosis patients

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Abstract

Purpose**:** The aim of the present study was to identify clinical predictors associated with longitudinal increases in daily non-invasive ventilation (NIV) use during the first year following its initiation, in patients with amyotrophic lateral sclerosis (ALS).

Methods**:** This retrospective cohort study included adults with ALS who initiated NIV 2010 and 2020 at the Leuven University Center for Sleep and Wake Disorders and had available NIV usage data throughout the first year. Monthly adherence data were analyzed using linear mixed-effects models. Clinical predictors included age at symptom onset, delay in diagnosis, forced vital capacity at diagnosis, and ALS Functional Rating Scale-Revised (ALSFRS-R) score and slope at diagnosis, with bulbar phenotype and frontotemporal dementia presence evaluated as potential effect modifiers.

Results**:** Sixty-one patients were included. Shorter diagnostic delay and a more negative ALSFRS-R slope predicted a greater increase in daily NIV usage over the 12-month follow-up. Patients diagnosed earlier than the cohort average and those with more rapid functional decline showed sustained increases in NIV usage. No significant effect modification by bulbar status or frontotemporal dementia was observed.

Conclusion**:** Shorter diagnostic delay and a more negative ALSFRS-R slope were associated with a greater increase in daily NIV use during the first year after NIV initiation. Patients with more aggressive disease trajectories may develop increasing ventilatory dependence more rapidly after respiratory support is initiated. These results underscore the importance of timely diagnosis and monitoring of functional decline to optimize respiratory support strategies in ALS care.

Keywords: amyotrophic lateral sclerosis; non-invasive ventilation; adherence; diagnostic delay; disease progression

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by degeneration of upper and lower motor neurons, leading to progressive weakness, paralysis and ultimately respiratory failure [1]. Respiratory failure remains the leading cause of death in ALS and represents a major determinant of quality of life and survival [2]. Despite recent advances in therapies targeting specific genetic subgroups, ALS remains an incurable disease for the vast majority of patients. Consequently, multidisciplinary supportive care, including respiratory management, nutritional support, communication assistance, and symptom control, remains central to patient care [3-7].

Respiratory muscle weakness develops in most patients during the course of the disease and can result in sleep-related hypoventilation, fragmented sleep architecture, impaired gas exchange, and ultimately diurnal respiratory failure [8]. Weakness of the diaphragm, accessory respiratory muscles, and bulbar musculature, contributes to progressive respiratory insufficiency and compromised airway protection. Non-invasive ventilation (NIV) is considered a cornerstone of respiratory management and has been consistently shown to improve survival, quality of life, sleep quality, and symptom burden in patients with ALS [9-11]. In a pivotal study by Bourke et al. [10], NIV improved survival and quality of life in patients without severe bulbar involvement and improved sleep-related symptoms even in patients with advanced bulbar dysfunction [10].

Current European Academy of Neurology (EAN) guidelines recommend offering NIV to patients with ALS who exhibit clinical symptoms, signs, or objective evidence of respiratory insufficiency [12]. Accordingly, NIV initiation does not necessarily require established daytime hypercapnia, as respiratory muscle weakness and nocturnal ventilatory abnormalities may precede overt daytime respiratory failure. Observational studies have associated NIV use with improved survival, with some reporting better outcomes among patients achieving longer daily ventilation times [11]. Furthermore, earlier initiation of NIV may provide additional respiratory benefits, with a multicentre randomized controlled trial suggesting that NIV initiated at less advanced stages of respiratory impairment may attenuate the decline in respiratory muscle function [13].

As respiratory muscle weakness progresses, patients with ALS will eventually be continuously NIV dependent. This progressive increase in NIV dependence represents an important clinical milestone reflecting respiratory failure, increasing care requirements, and reduced functional autonomy [14]. Therefore, identifying patients at risk of rapidly increasing ventilatory dependence can lead to earlier patient management and improved survival.

While predictors of survival, decline of respiratory function, and NIV initiation have been extensively investigated, factors associated with subsequent trajectories of NIV use following treatment initiation remain poorly characterized [13,15]. Modern ventilatory platforms allow continuous remote monitoring of NIV use through cloud-based systems, providing a unique opportunity to characterize longitudinal patterns of ventilatory dependence. Therefore, the aim of the present study was to identify clinical predictors associated with longitudinal increases in daily NIV use during the first year following NIV initiation in a retrospective cohort of patients with ALS.

Methods

Study design and setting

This retrospective cohort study was conducted at the Leuven University Center for Sleep and Wake Disorders (LUCS), University Hospitals Leuven, Belgium. We included patients with ALS who initiated NIV at our centre between December 2010 and December 2020. Longitudinal NIV usage data were collected for all included patients during the first year following treatment initiation.

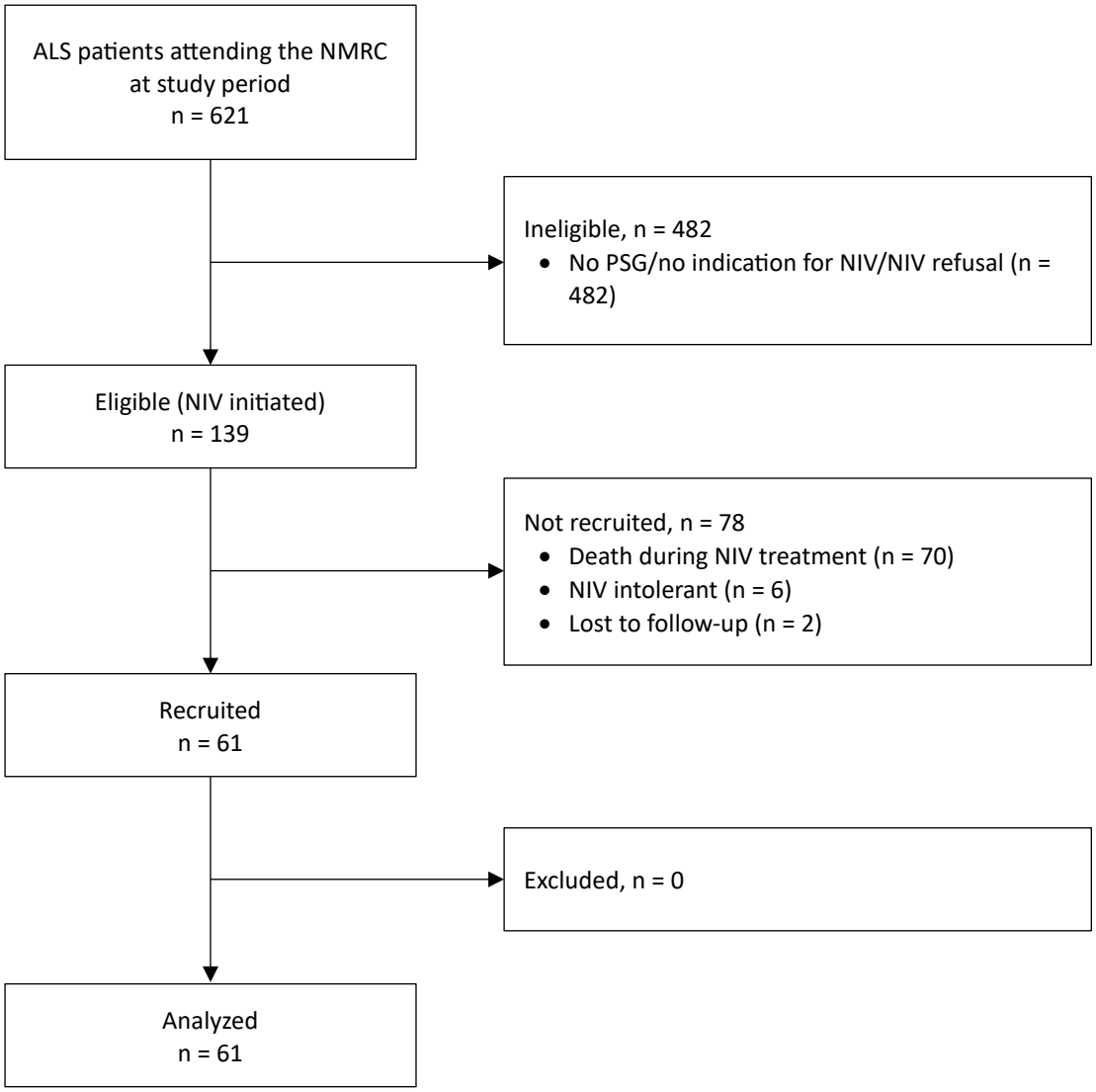
Participants

In our institution, ALS patients treated at the Neuromuscular Reference Center of the Department of Neurology are evaluated every 3 months and undergo an attended overnight polysomnography (PSG) with percutaneous capnography in case of suspicion of sleep-disordered breathing. If (nocturnal) hypoventilation is diagnosed, NIV is being offered and subsequently titrated over 2-3 consecutive nights in the sleep laboratory. We identified

patients with ALS accepting and initiating long-term home NIV during the aforementioned periods from our database. All patients had cloud storing of the device data during treatment.

To be enrolled, patients should be at least 18 years old, have been diagnosed with ALS according to the El Escorial criteria [16], and have evidence of nocturnal hypoventilation according to the American Academy of Sleep Medicine criteria [17] on PSG necessitating NIV treatment. Patients that died or stopped treatment before the end of the first year were excluded (Figure 1). Consequently, the study population comprised patients who remained on NIV and had available usage data throughout the first year following treatment initiation.

Fig.1 Study flow diagram



ALS: amyotrophic lateral sclerosis, NMRC: Neuromuscular Reference Center, PSG: polysomnography, NIV: non-invasive ventilation

The study was approved by the local Ethics Committee (ML7962) and written informed consent had been obtained from all participants at the time of PSG to allow the use of their data for research purposes.

Variables and data sources

Monthly NIV usage, defined as the mean daily NIV usage in hours for each month over the first year, was the primary outcome. Predictors were age at symptom onset in years, onset type (spinal/limb versus bulbar or respiratory), delay from symptom onset to diagnosis in months, time from diagnosis to NIV initiation in months,

forced vital capacity (FVC) percentage of predictive (FVC%) at diagnosis, the Revised ALS Functional Rating Scale (ALSFRS-R) score at diagnosis and at NIV initiation, and the ALSFRS-R slope at diagnosis and between diagnosis and NIV initiation. FVC at NIV initiation was not considered, as many participants were unable to perform acceptable lung function testing (spirometry) due to respiratory failure by that time. Age at NIV initiation in years and sex were treated as confounders.

The ALSFRS-R is a scale rating the functional status of the patient in 12 domains, representing 3 common areas of loss of function in ALS patients (bulbar, limb, and respiratory) [18]. The score in each domain varies from 0 to 4, where a lower score indicates less functionality. The ALSFRS-R slope is the rate of change in ALSFRS-R score over a specific time period, and it has been proven to be a valid prognostic measure, accurately depicting disease progression through time [19]. It is calculated by dividing the difference in the ALSFRS-R score between 2 time points to the respective time period in months:

$$\frac{ALSFRS\text{-}R\ score\ at\ time\ (2) - ALSFRS\text{-}R\ score\ at\ time\ (1)}{time\ period\ (in\ months)}.$$

We calculated the ALSFRS-R slope at diagnosis by assuming full functionality at symptom onset (score = 48) and subtracting it from the measured ALSFRS-R score at diagnosis. This difference was then divided by the number of months between symptom onset and diagnosis. For the ALSFRS-R slope at NIV initiation, the time between diagnosis and start of NIV was accounted for. A lower (more negative) value corresponds to greater decline in functional status for the respective period.

The bulbar sub-score of the ALSFRS-R assesses functions related to the bulbar region and is composed of 3 items: speech, swallowing, and salivation. Since bulbar symptoms may impair the application of the face mask for NIV delivery and thereby influence treatment adherence, the bulbar sub-score of the ALSFRS-R at NIV initiation was evaluated as an effect modifier in the analyses. We classified patients into the bulbar phenotype if their ALSRFS-R score at NIV initiation was below 10, according to previous research [20]. The concurrent presence of frontotemporal dementia (FTD) was also explored as a potential effect modifier.

NIV usage was ascertained by the device data, which were retrieved from cloud storage and averaged over each month. The other variables were collected from the electronic patient records.

Study size

The study size was determined by all the available cases in our institution during the predefined time period. This period was selected to reflect in the greatest possible extent, identical diagnostic, therapeutic, and follow-up procedures.

Statistical methods

For descriptive statistics, categorical variables were expressed in the form of count and percentage and continuous variables as mean ± standard deviation. The Spearman's rank order correlation coefficient was used to evaluate correlations between continuous variables, while independent-samples t-tests were applied to test associations between categorical and continuous variables. We employed linear mixed effects models with the restricted maximum likelihood method to test the effect of the predictors on the variation of NIV usage over a 12-month follow-up. Age and sex were included as covariates in all models. Fit of the models was evaluated with the Bayesian Information Criterion, where lowest value indicated better fit. We used a first-order autoregressive covariance structure to model the repeated effects of time (12 time points). Time was modelled either as a linear or a quadratic or a cubic term. The estimate of interest was the interaction between time and each predictor on the outcomes (9 models). The fixed effect estimates of the interactions are presented as unstandardized regression coefficients (95% confidence intervals [CIs]). For each interaction between a predictor and time that reached statistical significance, we divided the sample in 2 groups using the mean value of that predictor as the cut point. To visualize the interactions, we plotted the estimated marginal means (EMMs) of the outcomes across follow-up time points stratified by the predictor group. Moderation analyses according to bulbar status and FTD co-occurrence were performed by entering 3-way interactions between the predictors, time, and presence or absence of the modifier. All significance tests were two-sided, with a p-value <0.05 being considered statistically

significant. Given the exploratory nature of this study, no adjustment for multiple comparisons was performed. The analyses were conducted with the statistical software package IBM® SPSS® Statistics Version 25.

Results

Sixty-one patients had available usage data for the first year after initiating NIV and were included in the present analysis (Figure 1). Demographic and clinical information of the cohort is presented in Table 1.

Table 1. Baseline demographic and clinical information of the cohort

Variables	Summary data
Male sex, n (%)	48 (78.7)
Age at NIV initiation, mean ± SD	60.1 ± 9.4
Age at symptom onset, mean ± SD	57.1 ± 10.0
Onset type, n (%)	
Spinal/limb	47 (77.0)
Bulbar	10 (16.4)
Respiratory	4 (6.6)
Months from symptom onset to diagnosis, mean ± SD	15.1 ± 14.9
Months from diagnosis to NIV initiation, mean ± SD	22.5 ± 35.5
FVC% at diagnosis, mean ± SD	89.2 ± 22.5
ALSFRS-R score at diagnosis, mean ± SD	37.5 ± 7.0
ALSFRS-R score at NIV initiation, mean ± SD	30.5 ± 7.8
ALSFRS-R bulbar sub-score at NIV initiation, mean ± SD	9.6 ± 2.5
ALSFRS-R slope from symptom onset to diagnosis, mean ± SD	–0.96 ± 0.81
ALSFRS-R slope from diagnosis to NIV initiation, mean ± SD	−0.76 ± 0.56
FTD co-occurrence, n (%)	4 (6.6)

NIV: non-invasive ventilation, SD: standard deviation, FVC%: forced vital capacity percentage of predicted, ALSFRS-R: Revised ALS Functional Rating Scale, FTD: frontotemporal dementia

Pairwise Spearman correlations (Table 2) showed that higher FVC% at diagnosis was associated with younger age at symptom onset, higher ALSFRS-R scores at diagnosis, and a longer interval from diagnosis to NIV initiation. Higher FVC% at diagnosis and a longer diagnosis-to-NIV interval were each associated with lower ALSFRS-R scores at NIV initiation. Higher ALSFRS-R scores at diagnosis were associated with shorter diagnostic delay and higher scores at NIV initiation. A longer diagnosis-to-NIV interval was also associated with younger age at symptom onset. Comparison between onset types (Table 3) revealed that patients with bulbar or respiratory onset had significantly lower FVC% and ALSFRS-R scores at diagnosis than those with spinal/limb onset.

Table 2. Spearman's correlation coefficients between predictors

	Age at symptom onset	Delay in diagnosis	Time to NIV initiation	FVC% at diagnosis	ALSFRS-R at diagnosis	ALSFRS-R at NIV initiation
Age at symptom onset	-	0.241	−0.289*	−0.276*	−0.142	0.197
Delay in diagnosis	0.241	-	0.009	−0.041	−0.452**	−0.208
Time to NIV initiation	−0.289*	0.009	-	0.691**	0.226	−0.401**
FVC% at diagnosis	−0.276*	−0.041	0.691**	-	0.342**	−0.265*
ALSFRS-R at diagnosis	−0.142	−0.452**	0.226	0.342**	-	0.286*
ALSFRS-R at NIV initiation	0.197	−0.208	−0.401**	−0.265*	0.286*	-

**p-value<0.05, **p-value <0.01. NIV: non-invasive ventilation, FVC%: forced vital capacity percentage of predicted, ALSFRS-R: Revised ALS Functional Rating Scale*

Table 3. Differences in clinical variables between onset types

Variables	Spinal/limb onset (n = 47)	Bulbar/respiratory onset (n = 14)	p-value
Age at symptom onset	57.0 ± 10.5	57.3 ± 8.2	0.929
Delay in diagnosis	16.9 ± 16.3	9.4 ± 5.9	0.100
Time to NIV initiation	26.4 ± 39.1	9.3 ± 12.3	0.114
FVC% at diagnosis	92.8 ± 21.9	76.9 ± 20.7	0.019
ALSFRS-R at diagnosis	37.8 ± 6.4	36.4 ± 8.9	0.522
ALSFRS-R at NIV initiation	29.7 ± 7.4	33.3 ± 8.9	0.136
ALSFRS-R slope at diagnosis	−0.79 ± 0.57	−1.56 ± 1.18	0.001
ALSFRS-R slope at NIV initiation	−0.70 ± 0.55	−0.98 ± 0.54	0.107

NIV: non-invasive ventilation, FVC%: forced vital capacity percentage of predicted, ALSFRS-R: Revised ALS Functional Rating Scale

Mean NIV usage across the 12 time points is presented in Figure 2. Linear mixed effects models were best fitted with time as a linear term. The effect estimates for the interactions between time and each predictor on NIV usage from the 9 models are shown in Table 4. Shorter time from symptom onset to diagnosis and more negative ALSFRS-R slope predicted higher rate of increase in NIV usage over time. The EMM plots (Figure 3) reveal that patients whose diagnoses were delayed less than the average (i.e., faster diagnosis) and whose ALSFRS-R slope was lower than the mean (i.e., higher rate of functional loss) had consistent increase in the use of NIV throughout the 12 months, as opposed to the rest whose adherence remained stable after a short increase in the first 3 months. There was no evidence for effect modification by bulbar status or FTD presence in all models.

Fig. 2 Mean NIV usage in hours across 12 months for the whole sample (n = 61).
NIV: non-invasive ventilation, SD: standard deviation

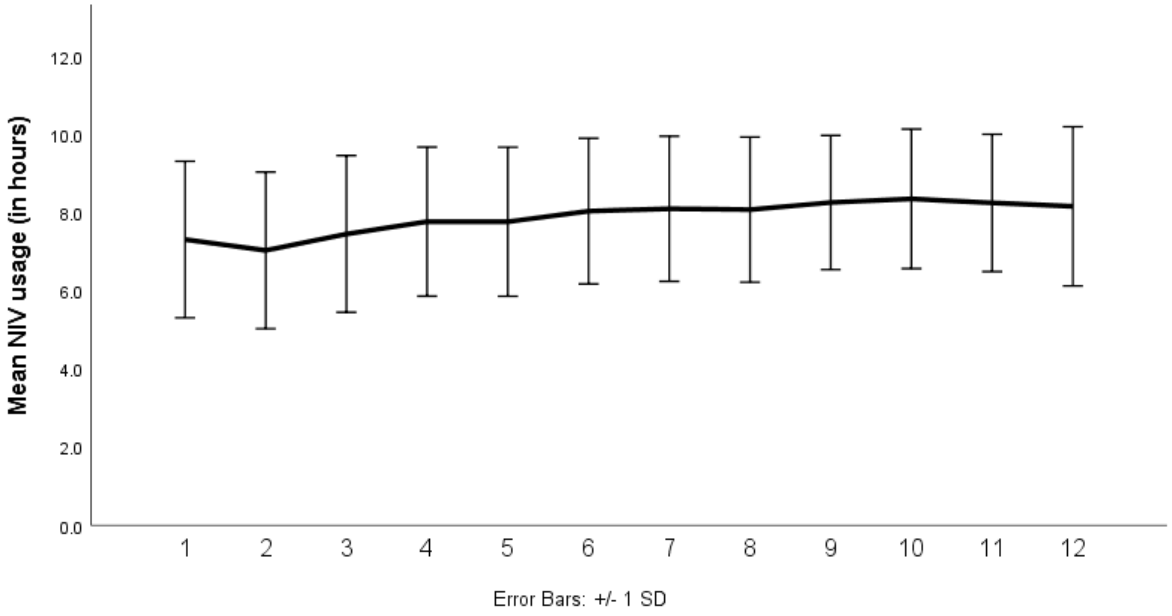


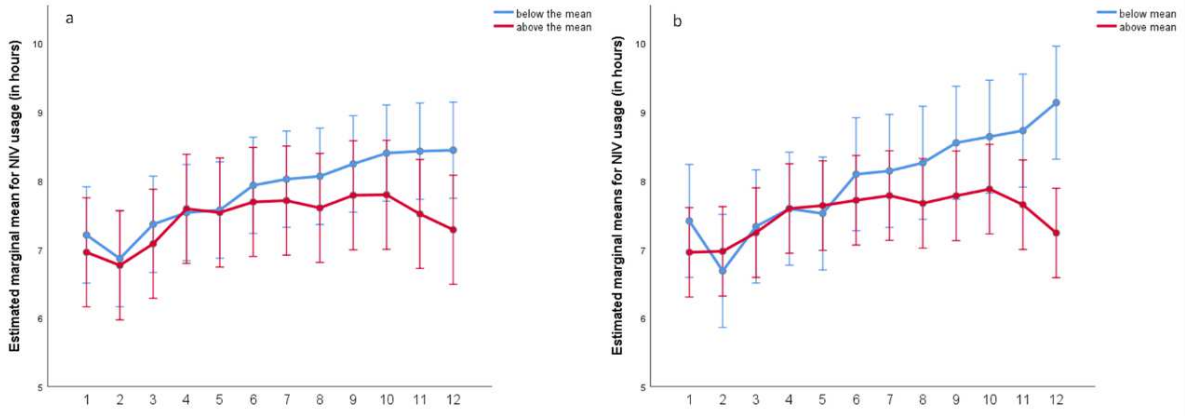
Table 4. Fixed effect estimates for the interaction between each predictor and time on NIV usage from the 9 mixed effects models with age and sex as covariates

Predictor	Unstandardized regression coefficient (95% CI)	p-value

Age at symptom onset	−0.004 (−0.010, 0.001)	0.125
Bulbar/respiratory onset	−0.012 (−0.144, 0.120)	0.862
Delay in diagnosis	**−0.004 (−0.007, −0.00002)**	**0.049**
Time to NIV initiation	0.000 (−0.001, 0.002)	0.611
FVC% at diagnosis	0.000 (−0.003, 0.002)	0.956
ALSFRS-R at diagnosis	−0.002 (−0.010, 0.006)	0.672
ALSFRS-R at NIV initiation	−0.001 (−0.008, 0.006)	0.758
ALSFRS-R slope at diagnosis	**−0.069 (−0.138, −0.0007)**	**0.048**
ALSFRS-R slope at NIV initiation	−0.043 (−0.143, 0.057)	0.397

Values in bold are statistically significant. CI: confidence interval, NIV: non-invasive ventilation, FVC%: forced vital capacity percentage of predicted, ALSFRS-R: Revised ALS Functional Rating Scale

Fig. 3 Estimated marginal means plots for NIV usage over the 12 time points stratified by delay in diagnosis (a) and ALSFRS-R slope (b), grouped above and below their mean value



NIV, non-invasive ventilation

Discussion

The present study demonstrates that a shorter diagnostic delay and a faster rate of functional decline are associated with a steeper increase in daily NIV use during the first year after NIV initiation. These findings suggest that patients with more aggressive disease trajectories develop increasing ventilatory dependence more rapidly following the initiation of respiratory support with NIV.

Nighttime NIV is usually initiated in ALS patients as soon as signs of ventilatory impairment emerge [21]. Several retrospective cohort studies, including Ackrivo et al. [11], have shown that NIV usage of at least 4 hours daily is associated with improved survival in ALS patients. In a 2006 cohort, survival after NIV was independently related to ventilatory use (≥ 4 h/day) and to the slope of FVC decline after treatment initiation [22]. The authors concluded that the severity of bulbar impairment and the nutritional status of the ALS patients at the introduction of ventilation may predict treatment tolerance and survival. The retrospective analysis of a larger ALS cohort showed that increased NIV usage >8 h/day, as part of an "optimized" therapeutic protocol was linked to an improved survival [23]. This study highlighted the role of early access to NIV and the synergistic effect of cough assist implementation. Additional evidence suggests that the early introduction of NIV prior to the onset of hypoventilation, known as "early NIV", may confer a survival advantage by supporting respiratory muscle function [14]. Vitacca et al. found that very early introduction of NIV in ALS, when FVC ≥ 80% of predicted, prolonged the time from diagnosis to death compared to the group of patients who received NIV when FVC was < 80% of predicted [24].

The interpretation of diagnostic delay in ALS is complex. A systematic review by Richards et al. reported a median diagnostic delay of 10-16 months from symptom onset, with delays influenced not only by disease progression but also by referral pathways, specialist access, and diagnostic uncertainty [25]. The prognostic significance of diagnostic delay has been extensively investigated, and a large meta-analysis demonstrated that shorter

diagnostic delay (≤1 year) is associated with more rapid disease progression and reduced survival [26]. In our cohort, shorter diagnostic delay was associated with a steeper increase in NIV use over time, suggesting that patients reaching diagnosis more rapidly, subsequently develop increasing ventilatory dependence at a faster rate. One possible explanation could be that shorter diagnostic delay reflects a more aggressive disease phenotype that becomes clinically apparent earlier in the disease course. However, given the retrospective nature of the study, the relative contributions of disease aggressiveness and healthcare-related factors cannot be determined.

In our cohort, longer diagnostic delay was associated with lower ALSFRS-R scores at diagnosis. The other pairwise correlations should be interpreted in the context of the variable interval between diagnosis and NIV initiation. Higher FVC% at diagnosis was associated with a longer interval before NIV initiation, potentially allowing more time for functional decline before the second assessment. This may help explain its inverse association with ALSFRS-R scores at NIV initiation, despite its positive association with scores at diagnosis. The positive correlation between ALSFRS-R scores at the two assessments does not establish preservation of function and may partly reflect patients who initiated NIV shortly after diagnosis and had identical scores at both assessments.

The association between a more negative ALSFRS-R slope and increasing NIV use is biologically plausible. ALSFRS-R slope is widely recognized as a marker of disease aggressiveness and has consistently been associated with shorter survival and faster functional deterioration [27,28]. Patients with more rapidly progressive disease are likely to develop respiratory muscle weakness earlier and therefore require progressive expansion of ventilatory support. Our findings extend previous observations on survival and disability outcomes by demonstrating that ALSFRS-R slope is associated not only with survival and disability outcomes but also with subsequent trajectories of NIV use following treatment initiation.

Our study provides important data from a well-characterized Belgian cohort of ALS patients, which enhances the generalizability of our findings to the national patient population and supports the external validity of the results. To our knowledge this is the first study demonstrating that shorter time to diagnosis and more negative ALSFRS-R slope (i.e., higher rate of functional loss) correlated with a consistent increase in the use of NIV throughout the first 12 months of the treatment.

Despite the strengths of this study, several limitations should be acknowledged. The first limitation of the current research is that patients were excluded if NIV discontinuation, death, or change in healthcare facility occurred prior to a one-year follow-up period. It might have helped eliminate heterogeneity of an observation period; however, selection bias occurred. This is particularly relevant in ALS as patients with more aggressive disease progression and severe respiratory involvement may have died before completing the observation period. Consequently, the identified predictors should be interpreted as predictors of increasing NIV use among patients who successfully maintained long-term NIV rather than predictors of NIV-use trajectories in the overall ALS population.

Second, longitudinal respiratory factors were not taken into consideration during the analysis process. According to Belgian guidelines for the start and adaptation of NIV in neuromuscular diseases, FVC is one of several important parameters that determine whether it is necessary to use NIV in such patients. Other factors include clinical symptoms, nocturnal hypoventilation, and daytime and/or nocturnal hypercapnia. As a result, serial FVC measurements were not considered sufficiently representative of respiratory decision-making in our cohort.

Third, ventilator settings were not included in the analytical models. These settings are generally optimized during NIV initiation and subsequently modified only when clinically indicated. Given the retrospective design, the absence of standardized adjustment intervals, and the relatively limited variability in settings over time, they were not considered reliable covariates for longitudinal modelling. The study was also underpowered to evaluate the potential influence of FTD on NIV-use trajectories. Only four patients had documented FTD, precluding meaningful conclusions regarding the impact of cognitive and behavioural impairment on ventilatory support utilization. Therefore, the absence of a significant association between FTD and longitudinal NIV use should be interpreted with caution.

Finally, the relationship between disease progression, respiratory decline, and the longitudinal evolution of NIV use remains incompletely understood. Future prospective studies incorporating detailed respiratory parameters, cognitive assessments, ventilator settings, and real-time remote monitoring data will be important to validate our findings and further refine individualized respiratory management strategies in ALS.

To conclude, in out study shorter diagnostic delay and a more negative ALSFRS-R slope were associated with a greater increase in daily NIV use during the first year after NIV initiation. These findings suggest that patients with more aggressive disease trajectories develop increasing ventilatory dependence more rapidly after respiratory support is initiated. Therefore, early identification of such patients may facilitate anticipatory respiratory management and optimization of supportive care. Additional prospective studies will be needed for confirmation of this hypothesis and further analysis of NIV use trajectory as a marker of respiratory worsening in ALS.

Statements and declarations

Acknowledgements

The authors would like to thank all the personnel of the NMRC and the sleep clinic in UZ Leuven for their assistance.

Declarations of interest

The authors declare that they have no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at UZ Leuven/KU Leuven, Leuven, Belgium.

Ethical statement

The study was approved by the local Ethics Committee (ML7962) and written informed consent had been obtained from all participants at the time of PSG to allow the use of their data for research purposes. It has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

References

1. Ravits J, Ferrey D, Gundogdu B, Qayoumi W, Zale C (2026) Amyotrophic lateral sclerosis: a review. JAMA 335:1970–1982.

2. Ackrivo J, Hansen-Flaschen J, Wileyto EP, Schwab RJ, Elman L, Kawut SM (2019) Development of a prognostic model of respiratory insufficiency or death in amyotrophic lateral sclerosis. Eur Respir J 53(4):1802237.

3. Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, Shaw PJ, Simmons Z, van den Berg LH (2017) Amyotrophic lateral sclerosis. Nat Rev Dis Primers 3:17071.

4. Niedermeyer S, Murn M, Choi PJ (2019) Respiratory failure in amyotrophic lateral sclerosis. Chest 155:401–408.

5. Boentert M, Glatz C, Helmle C, Okegwo A, Young P (2018) Prevalence of sleep apnoea and capnographic detection of nocturnal hypoventilation in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 89:418–424.

6. Zhang Y, Ren R, Yang L, Nie Y, Zhang H, Shi Y, Sanford LD, Vitiello MV, Tang X (2023) Sleep in amyotrophic lateral sclerosis: a systematic review and meta-analysis of polysomnographic findings. Sleep Med 107:116–125.

7. Masrori P, Van Damme P (2020) Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol 27:1918–1929.

8. Boentert M (2020) Sleep and sleep disruption in amyotrophic lateral sclerosis. Curr Neurol Neurosci Rep 20(7):25.

9. Radunovic A, Annane D, Rafiq MK, Mustfa N (2013) Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev:CD004427.

10. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ (2006) Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. Lancet Neurol 5:140–147.

11. Ackrivo J, Hsu JY, Hansen-Flaschen J, Elman L, Kawut SM (2021) Noninvasive ventilation use is associated with better survival in amyotrophic lateral sclerosis. Ann Am Thorac Soc 18:486–494.

12. Van Damme P, Al-Chalabi A, Andersen PM, Chiò A, Couratier P, De Carvalho M, Hardiman O, Kuźma-Kozakiewicz M, Ludolph A, McDermott CJ, Mora JS, Petri S, Probyn K, Reviers E, Salachas F, Silani V, Tysnes OB, van den Berg LH, Villanueva G, Weber M (2024) European Academy of Neurology (EAN) guideline on the management of amyotrophic lateral sclerosis in collaboration with European Reference Network for Neuromuscular Diseases (ERN EURO-NMD). Eur J Neurol 31:e16264.

13. Sarasate M, González N, Córdoba-Izquierdo A, Prats E, Gonzalez JMR, Martí S, Lujan M, Calle M, Antón A, Povedano M, Farrero E (2023) Impact of early non-invasive ventilation in amyotrophic lateral sclerosis: a multicenter randomized controlled trial. J Neuromuscul Dis 10:627–637.

14. O'Brien D, Stavroulakis T, Baxter S, Norman P, Bianchi S, Elliott M, Johnson M, Clowes M, Garcia-Sánchez A, Hobson E, McDermott C (2019) The optimization of noninvasive ventilation in amyotrophic lateral sclerosis: a systematic review. Eur Respir J 54:1900261.

15. Sancho J, Ferrer S (2023) How to increase noninvasive ventilation effectiveness in bulbar amyotrophic lateral sclerosis patients. Breathe 19:220266.

16. Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron Diseases (2000) El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 1:293–299.

17. Troester MM, Quan SF, Berry RB, Plante DT, Abreu AR, Alzoubaidi M, Bandyopadhyay A, DelRosso L, Ebben M, Kwon Y, Mao MM, Munir SS, Pressman MR, Rodriguez AJ, Ryals S, So JY, Vaughn BV, Thomas SM, American Academy of Sleep Medicine (2023) The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications, version 3. American Academy of Sleep Medicine, Darien, IL.

18. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, Nakanishi A (1999) The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. J Neurol Sci 169:13–21.

19. Kjældgaard AL, Pilely K, Olsen KS, Jessen AH, Lauritsen AØ, Pedersen SW, Svenstrup K, Karlsborg M, Thagesen H, Blaabjerg M, Theódórsdóttir Á, Elmo EG, Møller AT, Bonefeld L, Berg M, Garred P, Møller K (2021) Prediction of survival in amyotrophic lateral sclerosis: a nationwide, Danish cohort study. BMC Neurol 21:164.

20. Chapin JL, Gray LT, Vasilopoulos T, Anderson A, DiBiase L, York JD, Robison R, Wymer J, Plowman EK (2020) Diagnostic utility of the amyotrophic lateral sclerosis Functional Rating Scale-Revised to detect pharyngeal dysphagia in individuals with amyotrophic lateral sclerosis. PLoS One 15:e0236804.

21. Morelot-Panzini C, Bruneteau G, Gonzalez-Bermejo J (2019) NIV in amyotrophic lateral sclerosis: the “when” and “how” of the matter. Respirology 24:521–530.

22. Lo Coco D, Marchese S, Pesco MC, La Bella V, Piccoli F, Lo Coco A (2006) Noninvasive positive-pressure ventilation in ALS: predictors of tolerance and survival. Neurology 67:761–765.

23. Khamankar N, Coan G, Weaver B, Mitchell CS (2018) Associative increases in amyotrophic lateral sclerosis survival duration with non-invasive ventilation initiation and usage protocols. Front Neurol 9:578.

24. Vitacca M, Montini A, Lunetta C, Banfi P, Bertella E, De Mattia E, Lizio A, Volpato E, Lax A, Morini R, Paneroni M, ALS RESPILOM Study Group (2018) Impact of an early respiratory care programme with non-invasive ventilation adaptation in patients with amyotrophic lateral sclerosis. Eur J Neurol 25:556–e33.

25. Richards D, Morren JA, Pioro EP (2020) Time to diagnosis and factors affecting diagnostic delay in amyotrophic lateral sclerosis. J Neurol Sci 417:117054.

26. Su WM, Cheng YF, Jiang Z, Duan QQ, Yang TM, Shang HF, Chen YP (2021) Predictors of survival in patients with amyotrophic lateral sclerosis: a large meta-analysis. EBioMedicine 74:103732.

27. Requardt MV, Görlich D, Grehl T, Boentert M (2021) Clinical determinants of disease progression in amyotrophic lateral sclerosis—a retrospective cohort study. J Clin Med 10:1623.

28. Chiò A, Hammond ER, Mora G, Bonito V, Filippini G (2015) Development and evaluation of a clinical staging system for amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 86:38–44.