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The decline of respiratory function in amyotrophic lateral sclerosis patients and the role of non-invasive ventilation

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Abstract

Amyotrophic lateral sclerosis (ALS) is a chronic neurodegenerative disease characterized by a poor prognosis, with an average survival of 3 to 5 years from symptom onset. Respiratory failure is the main cause of death, and non-invasive ventilation (NIV) is a cornerstone in the management of ALS patients. This single-center retrospective study was conducted at Siena University Hospital between 2010 and 2024 to analyze respiratory function parameters in ALS patients undergoing NIV, stratified by disease severity and followed over one year, to assess the relationship between lung function decline and the timing of NIV initiation. A total of 49 patients (29 males, 20 females; mean age 67±12 years) were enrolled, and 31 (63%) received NIV. Clinical and functional parameters, including forced vital capacity (FVC), pCO_2, respiratory symptoms at baseline, and longitudinal measurements of sitting FVC (FVCsit%), supine FVC (FVCsup%), and pCO_2, were collected and analyzed over time. Differences in FVC decline were observed according to the timing of NIV initiation. Among non-severe patients, those starting NIV at T0 showed a 22.5% reduction in FVC over a mean follow-up of 12.8±4.8 months. Patients initiating NIV at T2 exhibited a reported FVCsit decline of 26% (p=0.0488) and a survival of 51.3±50 months from NIV initiation, whereas those starting later (T3–T6) showed a greater decline (FVCsit decline 34%, p=0.0002) and shorter survival duration (15.7±28.6 months). These findings describe differences in respiratory function trajectories and observed survival among patients initiating NIV at different follow-up time points. However, the retrospective design, small sample size, baseline differences between groups, and potential confounding and survival-related selection bias limit causal interpretation. Further studies are needed to clarify the relationship between NIV initiation timing and clinical outcomes in ALS.

Key words: amyotrophic lateral sclerosis, non-invasive ventilation, respiratory function.

Introduction

Amyotrophic lateral sclerosis (ALS) is a chronic neurodegenerative disease with a poor prognosis and an average survival of 3 to 5 years from the onset of symptoms. ALS is predominantly sporadic, although approximately 5% of patients have a positive family history [1,2]. The incidence of ALS is higher in men than in women, with a ratio of 1.3:1 [3,4]. The average age of onset is between 51 and 66 years [5-12]. Depending on the site of symptom onset, two main clinical presentations are distinguished: spinal-onset ALS, characterized by limb weakness, and bulbar-onset ALS, characterized by dysphagia and speech disturbances. Spinal-onset ALS accounts for 58–82% of cases [5,8,10-17], bulbar-onset disease is more frequent among female patients [10,13,18], patients with cognitive impairment [19] and older individuals [10]. Although little is known about the etiology of the disease, possible risk factors such as cigarette smoking, agricultural activities, and head trauma have been suggested [20]. The main pathological features are the degeneration and loss of motor neurons (up to 70%), with astrocytic gliosis and the presence of intraneuronal inclusions affected neurons and glial cells. The involved neurons are the upper motor neurons in the motor cortex, whose axons form the corticospinal and corticobulbar tracts [21], and the lower motor neurons in the anterior horn of the spinal cord and the motor nuclei of the brainstem [22]. Bulbar-onset ALS is characterized by dysarthria or dysphagia and tongue wasting, while spinal-onset ALS typically presents with weakness and wasting—often asymmetrical—in the upper or lower limbs [23].

Traditionally, the diagnosis of ALS has been based primarily on clinical findings, with electrophysiological data used to support the diagnosis [23]. Due to progressive respiratory muscle involvement and the risk of respiratory failure, patients with ALS require regular respiratory monitoring, with follow-up assessments generally performed every 1–3 months. Patient management also includes symptomatic and supportive care, including nutritional support, aspiration prevention and respiratory support, as well as the use of various devices and multidisciplinary team approaches [24-26]. Non-invasive ventilation (NIV) represents an important component of respiratory management in ALS patients with respiratory impairment [27-29]. Current recommendations consider both respiratory symptoms and objective evidence of respiratory impairment when evaluating patients for NIV, including forced vital capacity (FVC) <50% predicted, FVC <80% predicted in the presence of respiratory symptoms, reduced inspiratory muscle strength, and hypercapnia [26,27]. However, some studies suggest

that starting NIV with higher FVC values may be associated with more favorable clinical outcomes [27,28].

Nevertheless, the relationship between NIV initiation timing and subsequent clinical outcomes remains an important area of investigation. Therefore, this retrospective study aimed to describe longitudinal changes in respiratory function among patients with ALS, stratified by baseline respiratory impairment and timing of NIV initiation, and to explore their associations with observed survival outcomes.

Materials and Methods

The retrospective study was performed at the Siena Referral Center for Rare Lung Diseases from 2010 to 2024. Diagnosis of ALS was performed according to international guidelines and all patients underwent specialist evaluation and multidisciplinary discussion involving pulmonologists, neurologists, physiotherapists, psychologists and otolaryngologists, experienced in the management of disease [30]. Diagnostic, demographic, clinical, and respiratory functional data were retrospectively collected from medical records and entered into a database for statistical analysis. All available pulmonary function tests (PFTs), performed throughout the follow-up were collected. To minimize inter- and intra-observer variability, only PFTs performed at the Respiratory Diseases Unit of Siena were considered. Data on heart rate, oxygen saturation, Forced vital capacity (FVC) in the sitting position (FVCsit%) and supine position (FVCsup%), Forced expiratory volume in 1 second (FEV1), Tidal volume (VC), Maximum Inspiratory Pressure (MIP), Maximum Expiratory Pressure (MEP), maximal voluntary ventilation (MVV) and blood gas analysis (pCO2, pO2, bicarbonates and pH) were collected as well as symptoms at the time of diagnosis, comorbidities, age, sex, smoking habits, work history and BMI (body mass index).

The terms FVCsit% and FVCsup% were used throughout the manuscript to distinguish FVC measurements obtained in the sitting and supine positions, respectively, both expressed as percentages of predicted values.

Patient selection and stratification

Patients were stratified into two groups, severe (baseline FVCsit <50% predicted) and non-severe (baseline FVCsit >50% predicted).

A total of 49 patients with ALS were assessed for eligibility during the study period. All 49 patients were included, and no patients were excluded. Written informed consent was

obtained from all patients or their legal representatives. No patients were lost to follow-up. Deaths occurring during the observation period were considered outcome events rather than losses to follow-up.

Among the 49 included patients, 31 received NIV and 18 did not. Patients receiving NIV were further classified as severe patients initiating NIV at T0 (n=8), non-severe patients initiating NIV at T0 (n=2), non-severe patients initiating NIV at T2 (n=5), and non-severe patients initiating NIV between T3 and T6 (n=16). The patient-selection process and distribution according to NIV initiation timing are illustrated in Figure 1.

Follow-up assessments and definition of time points

The first available respiratory assessment was defined as T0 (baseline). Subsequent follow-up assessments were identified as T1–T6, corresponding to consecutive clinical evaluations performed at variable intervals. The mean time elapsed from baseline was 2.92 ± 1.68 months at T1, 4.83 ± 2.29 months at T2, 6.67 ± 2.61 months at T3, 8.73 ± 3.23 months at T4, 10.40 ± 4.01 months at T5, and 12.80 ± 4.83 months at T6.

Therefore, T1–T6 represented successive follow-up visits rather than fixed monthly time points.

Criteria for NIV initiation

The primary indications for NIV initiation were retrospectively categorized according to clinical and respiratory functional findings. These included FVC <50% predicted, FVC <80% predicted in the presence of respiratory symptoms, daytime hypercapnia ($PaCO_2$ >45 mmHg), and reduced inspiratory muscle strength (MIP ≤40 cmH_2O). Each patient was classified according to the primary recorded indication for NIV initiation.

The outcomes of interest were longitudinal changes in respiratory function, assessed primarily through FVC measurements, and observed survival following NIV initiation. Survival duration was calculated from the time of NIV initiation. Comparisons of survival between NIV initiation groups were considered descriptive and exploratory because treatment timing was not randomly assigned.

Lung function tests (PFTs)

The following lung function measurements were recorded according to ATS/ERS standards using a Jaeger Body Plethysmograph with corrections for temperature and barometric pressure: forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, total

lung capacity (TLC), diffusing capacity of the lung for carbon monoxide (DLCO) and DLCO adjusted for alveolar volume (DLCO/VA). All parameters were expressed as percentages of predicted reference values. The DLCO was not assessed in patients who were on oxygen therapy.

The follow-up of ALS patients was carried out every 1-3 months (*Supplementary Table 1*) with respiratory evaluations, including FVCsit%, FVCsup%, FEV1, MIP, MEP, and blood gas measurements.

Statistical analysis

Results were expressed as means and standard deviations (SD) or medians and quartiles (25th and 75th percentiles) for continuous variables, as appropriate.

Non-parametric Mann-Whitney tests were performed for comparisons between two groups, particularly severe vs. non-severe patients. Non-severe patients receiving NIV were stratified into three groups according to the timing of treatment initiation: group 1 (NIV initiated at T0), group 2 (NIV initiated at T2), and group 3 (NIV initiated between T3 and T6). The non-parametric Kruskal-Wallis test was used for analyses between more than two groups. The Friedman test was used for the analysis of FVCsit%, FVCsup% and pCO2 data over time (T0, T1, T2, T3, T4, T5, T6). Spearman's test was used to test the statistical significance of correlations between data and probability values less than 0.05 were considered significant. Statistical analysis was performed using GraphPad Prism 10 software.

Given the retrospective nature of the study, the limited subgroup sample sizes, and the absence of random assignment to NIV initiation timing, the analyses were considered exploratory. No time-dependent survival adjustment was performed.

Results

The study population comprised 49 patients with ALS, including 29 males and 20 females, with a mean age of 67 ± 12 years. Demographic and clinical characteristics of the overall population are summarized in Table 1.

All 49 patients assessed for eligibility were included in the study, with no exclusions or losses to follow-up. Of these, 31 patients (63.3%) received NIV, whereas 18 (36.7%) did not. The study population and NIV initiation groups are illustrated in Figure 1.

The primary indications for NIV initiation varied across the groups. All eight patients with severe respiratory impairment at T0 initiated NIV due to FVC <50% predicted. Among non-

severe patients initiating NIV at T0 (n=2), one patient started treatment due to daytime hypercapnia ($PaCO_2$ >45 mmHg) and one due to reduced inspiratory muscle strength (MIP ≤40 cmH_2O). In the T2 group (n=5), NIV was initiated due to FVC <80% predicted with respiratory symptoms (n=3), daytime hypercapnia (n=1), or reduced inspiratory muscle strength (n=1). Among patients initiating NIV at T3–T6 (n=16), the primary indications were FVC <50% predicted (n=4), FVC <80% predicted with respiratory symptoms (n=8), daytime hypercapnia (n=2), and reduced inspiratory muscle strength (n=2).

No patients permanently discontinued NIV during follow-up. Quantitative information on daily or nightly NIV usage and standardized tolerability assessments was not systematically available.

Analysis of clinical data

Among patients receiving NIV, eight had severe respiratory impairment at baseline (FVCsit <50% predicted) and initiated NIV at T0. These patients showed a progressive reduction in FVCsit% and FVCsup% during follow-up, with a reported survival duration of 5.71 ± 3.73 months from NIV initiation (Figure 2). The remaining 23 patients receiving NIV had non-severe respiratory impairment at baseline and were stratified according to treatment initiation timing: group 1 (T0, n=2), group 2 (T2, n=5), and group 3 (T3–T6, n=16).

The main baseline demographic, anthropometric and clinical characteristics of the three NIV initiation groups are summarized in Table 2. Among the variables examined, baseline FVCsit% was the only parameter showing a statistically significant difference across groups, with values of 79.0 ± 2.8%, 73.0 ± 9.0%, and 85.0 ± 6.6% in the T0, T2, and T3–T6 groups, respectively (p=0.026). No statistically significant differences were observed in the other assessed demographic and clinical characteristics or in the remaining functional and laboratory parameters.

Comparisons of FVCsit%, FVCsup%, and pCO_2 values were performed between patients with severe baseline respiratory impairment and each of the three non-severe NIV initiation groups. FVCsit% was significantly lower in severe patients than in group 2 at T0 (42.5% vs. 73.0%, p=0.0188), T1 (29.5% vs. 57.0%, p=0.0203), and T2 (25.0% vs. 51.0%, p=0.024). Similarly, FVCsit% was lower in severe patients than in group 3 at T0 (42.5% vs. 85.0%), T1 (29.5% vs. 80.0%), and T2 (25.0% vs. 70.5%) (reported p<0.0001). FVCsup% was also significantly lower at T0 in severe patients compared with group 3 (reported p<0.0001).

Longitudinal changes in FVCsit%, FVCsup%, and pCO_2 were subsequently assessed within each NIV initiation group.

Group 1 (n=2) showed a reduction in FVCsit% and FVCsup% over time, with a reported FVCsit decline of 22.5% over the follow-up period. The mean survival duration following NIV initiation was 17.5 ± 16.3 months (Figure 3).

Group 2 (n=5) showed a reported FVCsit decline of 26%, with a statistically significant longitudinal reduction in FVCsit% at T6 ($p=0.0488$). Among the three patients who died during follow-up, the mean survival duration following NIV initiation was 51.3 ± 50 months (Figure 4).

Group 3 (n=16) showed a reported FVCsit decline of 34%, with statistically significant longitudinal reductions in FVCsit% ($p=0.0002$) and FVCsup% ($p<0.05$), Among the 12 patients who died during follow-up, the mean survival duration following NIV initiation was 15.7 ± 28.6 months (Figure 5).

Discussion and Conclusions

Non-invasive ventilation (NIV) is a cornerstone in the management of respiratory impairment associated with amyotrophic lateral sclerosis (ALS). Although FVC <50% predicted represents an established criterion for considering respiratory support, current recommendations also incorporate respiratory symptoms, earlier FVC impairment, inspiratory muscle weakness, and hypercapnia [26,27]. Emerging evidence suggests that earlier initiation—at higher FVC values—may provide greater clinical benefits. For instance, Lechtzin et al. [28] reported a nearly one-year longer survival from diagnosis in patients initiating NIV at a mean FVC of 74%, compared to those starting at 48%. Similarly, Carratù et al. [29] observed significantly improved one-year survival in patients treated early (mean FVC 65%) versus those who refused or could not tolerate NIV. Additionally, these patients exhibited a slower rate of FVC decline. Further support comes from two large retrospective studies [30-32]. Vitacca et al. [31], comparing NIV initiation above and below 80% FVC in 194 patients, found a 36-month mortality rate of 35% in the early group versus 52% in the standard group. Khamankar et al. [30] observed increased survival across FVC initiation thresholds (<50%: 20.3 months; ≥50%: 23.6 months; ≥80%: 25.4 months), emphasizing the benefits of earlier intervention. Other studies have also highlighted increased survival when NIV is used for at least 4 consecutive hours overnight [33,34].

In this context, our study provides additional descriptive data on respiratory function trajectories and observed survival among patients initiating NIV at different follow-up time points. Across the follow-up period, we observed a general decline in FVCsit%. In non-severe patients who began NIV at baseline (T0), the FVCsit% decline from T0 to T6 was 22.5%, though this reduction did not reach statistical significance, likely due to the limited sample size. Patients initiating NIV at T2 showed a reported FVCsit decline of 26%, compared with 34% among those initiating NIV between T3 and T6. Both reductions were statistically significant in the respective longitudinal analyses, with a numerically greater decline observed in patients initiating NIV later. However, these findings should be interpreted cautiously, considering the observational study design and baseline differences between groups. Alongside these differences in respiratory function trajectories, differences in observed survival duration were also identified. Patients initiating NIV at T2, after a reported 17% decline in FVCsit% before treatment initiation, had an observed survival duration of 51.3 ± 50 months from NIV initiation. Conversely, patients initiating NIV later (T3–T6), after a greater reported decline in FVCsit% before treatment initiation (29%), showed a shorter observed survival duration of 15.7 ± 28.6 months. Notably, this pattern was observed despite the T3–T6 group having higher baseline FVCsit% values than the T2 group (85.0 ± 6.6% vs. 73.0 ± 9.0%). Thus, the groups showing different magnitudes of respiratory function decline also exhibited different observed survival durations, although these findings do not establish a causal relationship between the timing of NIV initiation, respiratory function deterioration, and survival.

An important finding is that baseline respiratory function differed across NIV initiation groups (p=0.026). Patients initiating NIV at T2 had lower baseline FVCsit% than those initiating NIV between T3 and T6, suggesting that the groups were not entirely comparable at study entry. This difference must be considered when interpreting subsequent respiratory function trajectories and survival outcomes. Although patients initiating NIV at T2 showed a smaller reported FVC decline and longer observed survival than those initiating NIV at T3–T6, these findings cannot establish a direct beneficial effect of earlier NIV initiation. Differences in baseline disease severity, respiratory impairment, disease progression, and other prognostic factors may have influenced both the timing of NIV initiation and subsequent outcomes. Moreover, because treatment initiation was determined by clinical circumstances rather than random assignment, confounding by indication cannot be excluded.

This study has several important limitations. First, its retrospective, single-center design and relatively small sample size limit the generalizability and statistical reliability of the findings.

In particular, the limited number of patients in some NIV initiation subgroups, especially the two non-severe patients initiating NIV at T0, restricts the interpretation of subgroup comparisons.

Second, NIV initiation was not randomly assigned. Patients receiving NIV at different follow-up time points may have differed in baseline respiratory function, disease severity, rate of progression, bulbar involvement, and other prognostic characteristics. Indeed, significant differences in baseline FVCsit% were observed among the non-severe NIV initiation groups. Therefore, the possibility of confounding by indication must be acknowledged.

Third, the retrospective classification of patients according to NIV initiation timing introduces potential survival-related selection bias. Patients initiating NIV at later follow-up visits necessarily survived and remained under observation until treatment initiation. Although survival duration was calculated from NIV initiation rather than from the baseline assessment, this approach does not eliminate selection bias or differences in disease progression between groups. Consequently, the observed differences in survival should be considered descriptive and exploratory rather than evidence of a causal effect of NIV initiation timing. No time-dependent survival analysis was performed to address this potential bias.

Fourth, detailed information regarding NIV adherence, including average daily or nightly usage hours and standardized measures of treatment tolerability, was not systematically available in the retrospective dataset. Although no patients permanently discontinued NIV during follow-up, the potential influence of treatment adherence on respiratory function and survival could not be evaluated.

Finally, the timing of respiratory follow-up assessments was not fixed, with variable intervals between consecutive evaluations. This variability should be considered when interpreting longitudinal changes in respiratory function.

Taken together, these limitations indicate that the present findings should be interpreted as exploratory associations and should not be used to infer that NIV initiation at a specific follow-up time directly modifies disease progression or survival.

In conclusion, this retrospective study identified differences in respiratory function trajectories and observed survival among patients with ALS initiating NIV at different follow-up time points. Patients initiating NIV earlier in the observation period showed smaller reported declines in FVC, while differences in observed survival were also identified between treatment groups. However, baseline differences, potential confounding, and survival-related selection bias preclude causal conclusions regarding the effects of NIV initiation timing. Larger studies

incorporating standardized treatment criteria, detailed adherence data, and appropriate time-dependent analyses are warranted to further investigate these associations.

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Table 1. Characteristics of the analyzed population in terms of gender, inclusion or non-inclusion of NIV, smoking habit, BMI, work history, onset symptoms, age at the moment of diagnosis and comorbidities.

Parameters	Patients (n)
Sex	
Male	29
Female	20
NIV	
Yes	31
No	18
Smoking habit	
Smoker/Former	26
Never	23
BMI	
Underweight (<18.5)	2
Normal weight (18.6-24.9)	27
Overweight (25-29.9)	15
Obese (>30)	5
Employment	
Hairdresser	2
Waiter	2
Housewife	5
Employee	3
Nurse	2
Teacher	3
Leatherworker	2
Mechanic	4
Other	26
Symptoms	
Dysarthria	15
Difficulty walking	8
Asthenia	10
Dysphagia	16
Dyspnea	12
Strength deficiency	15
Age at the moment of diagnosis (years)	
<40	1
40-50	3
50-60	7
60-70	17
70-80	14
>80	7
Anamnesis	
Hypertension	14
Hypercholesterolaemia	5
Sars-Cov2 infections	9

Table 2. Main baseline demographic, anthropometric and clinical characteristics of non-severe ALS patients according to the timing of NIV initiation.

Characteristics	NIV at T0 (n=2)	NIV at T2 (n=5)	NIV at T3-T6 (n=16)	p
Demographic and anthropometric characteristics				
Age, years	71.5±4.9	74.8±7.9	63.4±13.3	0.116
Male sex, n (%)	2 (100)	2 (40.0)	9 (56.3)	0.351
BMI, kg/m²	19.7±0.8	22.1±3.9	24.4±4.7	0.207
Smoking status, n (%)				0.330
Current/former smokers	2 (100)	2 (40.0)	10 (62.5)	
Never smokers	0 (0)	3 (60.0)	6 (37.5)	
Clinical and respiratory characteristics				
Dysarthria,n (%)	1 (50.0)	0 (0)	6 (37.5)	0.232
Difficulty walking, n (%)	0 (0)	2 (40.0)	4 (25.0)	0.544
Asthenia, n (%)	1 (50.0)	1 (20.0)	4 (25.0)	0.705
Dysphagia, n (%)	1 (50.0)	4 (80.0)	4 (25.0)	0.084
Dyspnea, n (%)	0 (0)	2 (40.0)	5 (31.3)	0.578
Strength deficiency, n (%)	0 (0)	1 (20.0)	5 (31.3)	0.600
FVCsit at baseline, % predicted	79.0±2.8	73.0±9.0	85.0±6.6	**0.026**

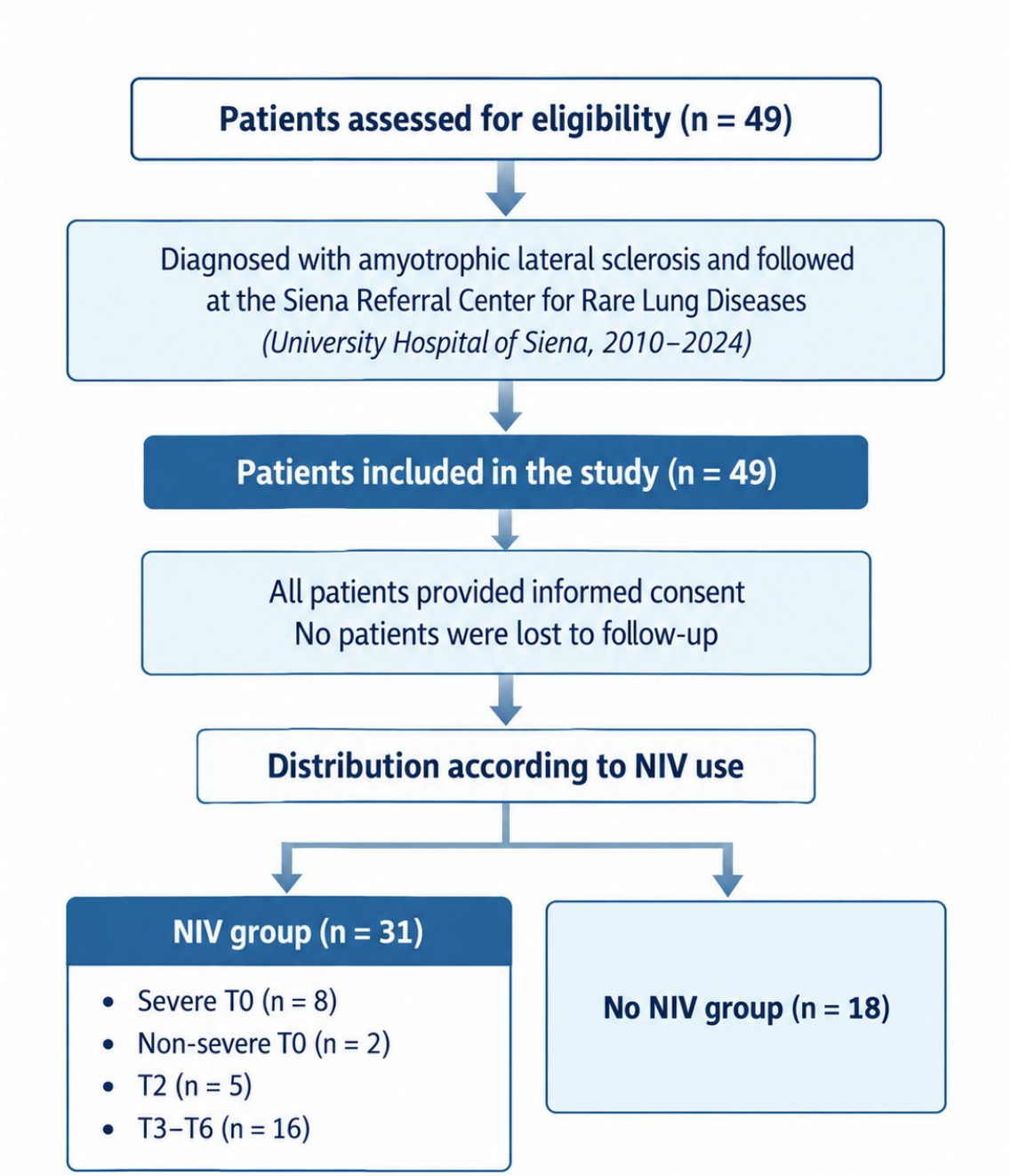


Figure 1. Flowchart illustrating the selection of 49 patients with amyotrophic lateral sclerosis and their distribution according to non-invasive ventilation (NIV) use and initiation timing. All 49 patients assessed for eligibility were included, with no exclusions or losses to follow-up. Thirty-one patients received NIV and 18 did not. Among patients receiving NIV, eight had severe baseline respiratory impairment and initiated NIV at T0, while the 23 non-severe patients initiated NIV at T0 (n=2), T2 (n=5), or T3–T6 (n=16).

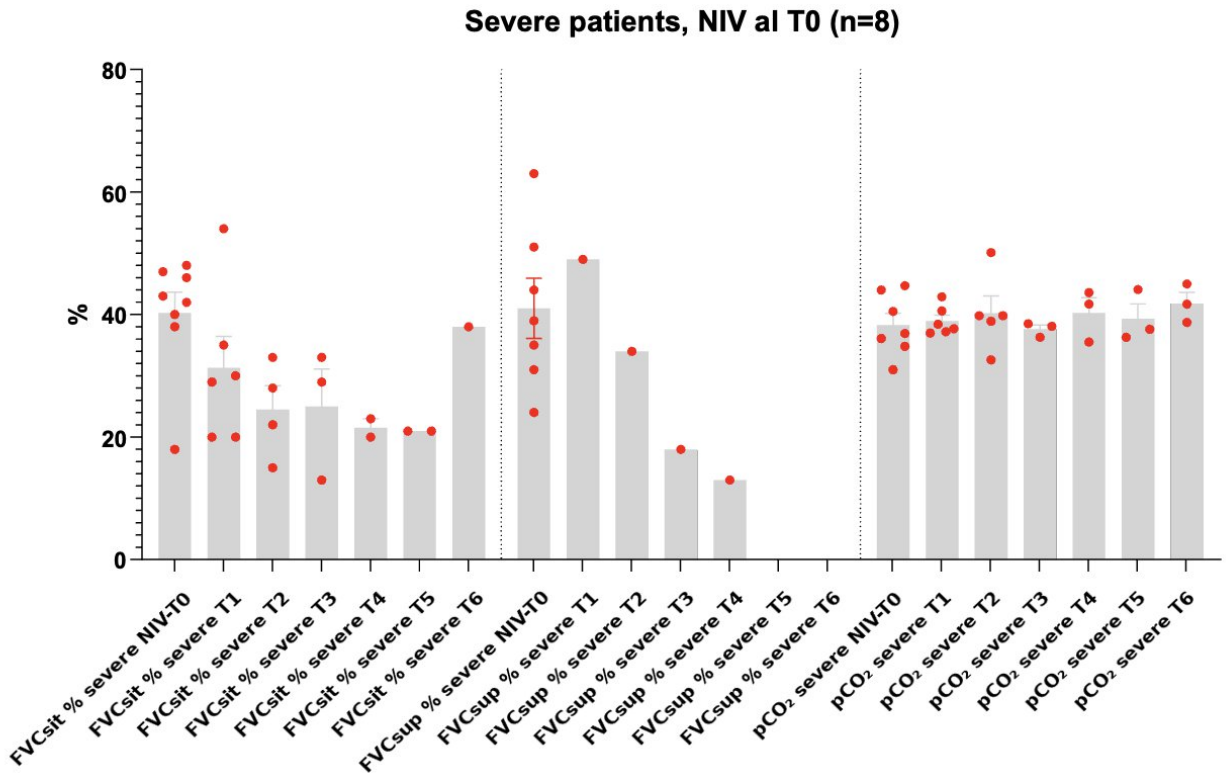


Figure 2. Longitudinal changes in sitting and supine forced vital capacity (FVCsit% and FVCsup%) among patients with severe baseline respiratory impairment initiating NIV at T0 (n=8).

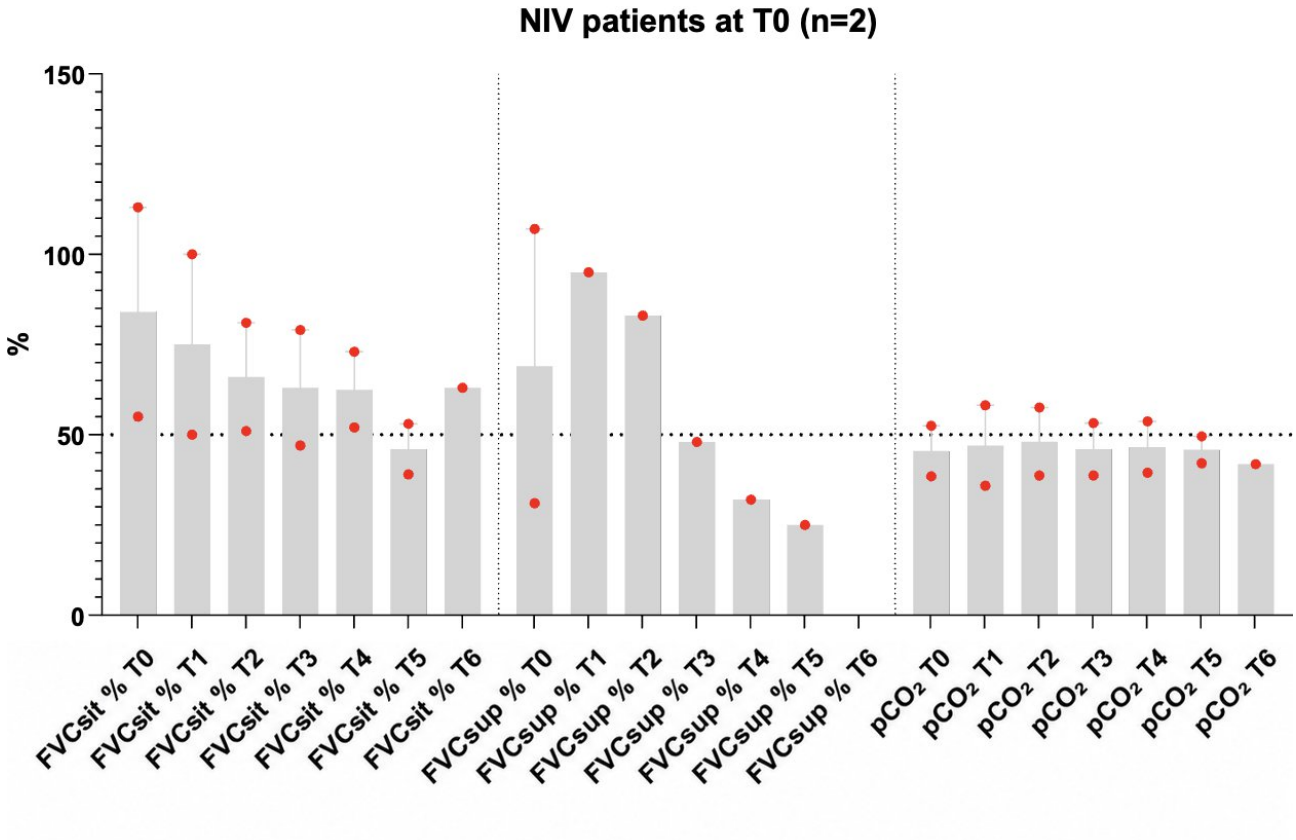


Figure 3. Longitudinal changes in sitting and supine forced vital capacity (FVCsit% and FVCsup%) among non-severe patients initiating NIV at T0 (group 1, n=2).

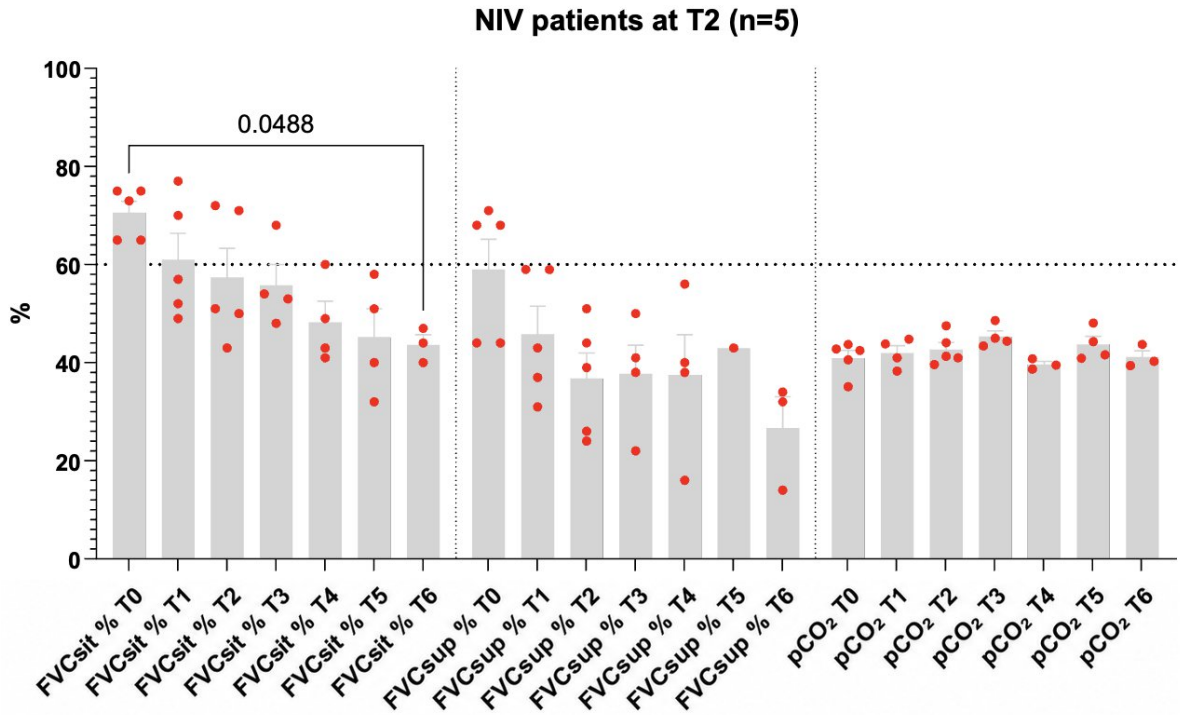


Figure 4. Longitudinal changes in sitting and supine forced vital capacity (FVCsit% and FVCsup%) among non severe patients initiating NIV at T2 (group 2, n=5).

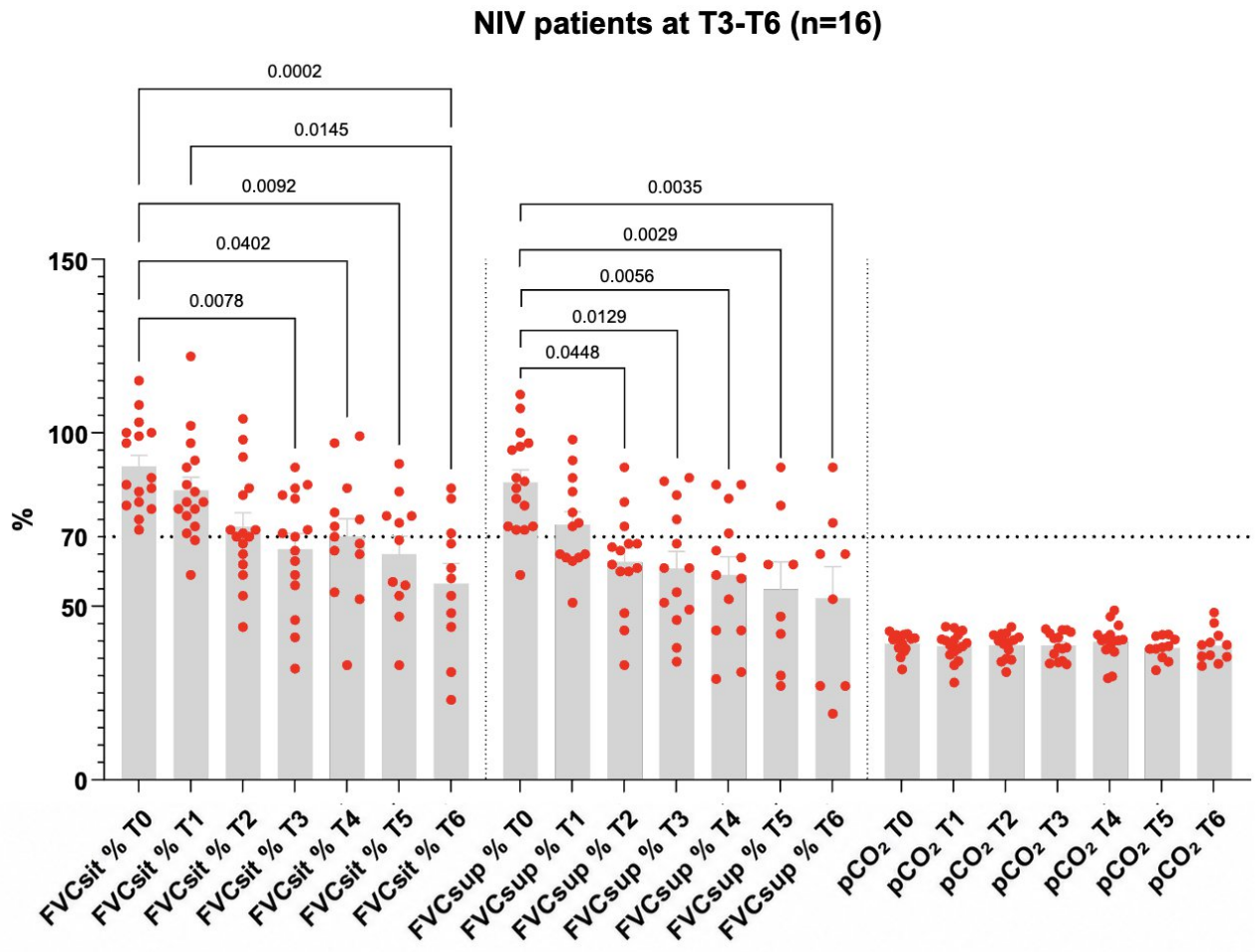


Figure 5. Longitudinal changes in sitting and supine forced vital capacity (FVCsit% and FVCsup%) among non-severe patients initiating NIV between T3 and T6 (group 3, n=16).