RESEARCH ARTICLE

Giving Breath to Motor Neurons: Noninvasive Mechanical Ventilation Slows Disease Progression in Amyotrophic Lateral Sclerosis

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Objective: Noninvasive mechanical ventilation (NIMV) improves amyotrophic lateral sclerosis (ALS) quality of life and survival. However, data about its effect on disease progression are still lacking. Here, we test whether NIMV use changed the rate of functional decline among ALS patients.

Methods: In this retrospective observational study, we included 448 ALS patients followed up at the ALS Center in Turin, Italy, who underwent NIMV during the disease course. The primary outcome was the change in functional decline after NIMV initiation adjusting for covariates. Functional decline was based on the nonrespiratory items of the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R).

Results: NIMV initiation resulted in a slower functional decline (mean improvement = 0.16 points per month, 95% confidence interval = 0.12–0.19, $p < 0.001$), with consistent effects observed across various demographic factors, including sex, age at diagnosis, and disease duration before NIMV initiation. This finding was replicated using the PRO-ACT (Pooled Resource Open-Access ALS Clinical Trials) dataset. The favorable impact of NIMV on ALSFRS-R progression was evident independently of disease stages. Notably, NIMV benefits were not dose-dependent but were particularly prominent for nighttime respiratory support.

Interpretation: NIMV significantly influences the rate of motor progression in ALS, and this effect is not determined by the nonlinearity of ALSFRS-R trajectory. The functional decline slowed following NIMV initiation, independently of the site of disease onset or disease severity at the time of NIMV initiation. Our findings underscore the importance of timely NIMV initiation for all ALS patients and highlight the need to consider NIMV-induced slowing of disease progression when evaluating clinical trial outcomes.

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that causes disability and death, usually because of respiratory failure within 3 years of onset.[1] A significant advance in the management of ALS was the demonstration of the beneficial effects of noninvasive mechanical ventilation (NIMV) on patients' survival and quality of life.[2] Therefore, the mechanical support of respiratory function is now regarded as an essential component of care.[3–5] Although several studies have reported that NIMV reduced the decline of pulmonary function, its effect on patients' functional outcome and motor progression is still controversial.[6] Here, we evaluated whether respiratory support slows the progression of functional decline in a large cohort of ALS patients.

Patients and Methods

Study Population

All patients followed up at the ALS Center in Turin, Italy and included in the Piedmont and Aosta Valley Register for ALS (PARALS) from January 1, 2007 to December 31, 2019 were considered eligible. We included in the study all ALS patients who underwent NIMV, reported adequate adherence to respiratory support, and had available Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) follow-up data after the date of NIMV initiation. The other characteristics of the PARALS have been detailed elsewhere.[7]

Criteria for NIMV Initiation

The indication for NIMV was based on current guidelines.[8,9] Briefly, patients initiated NIMV after pneumological evaluation and if vital capacity was <80% to <50% of predicted values; maximum inspiratory pressure was <40cm to <60cm H_2O; sudden nasal inspiratory pressure was <40cm H_2O; in nocturnal pulse oximetry, the percentage of time spent at <90% was >5% or >10%; and in arterial blood gas analysis, the partial pressure of CO_2 was >45mmHg.

Main Variables and Outcomes

ALSFRS-R was collected for each patient at the ALS clinic approximately every 2 to 3 months. For the analysis of motor function, we only considered the nonrespiratory items (items 1–9) of the ALSFRS-R (nonrespiratory ALSFRS-R). Additionally, the decline rates of ALSFRS-R subdomains were evaluated as secondary outcomes; the bulbar ALSFRS-R was derived from items 1 to 3 of the ALSFRS-R scale; the motor ALSFRS-R was calculated from items 4 to 9 (eMethods). Diagnosis of frontotemporal cognitive and behavioral syndromes was based on cognitive assessments and consensus criteria.[10] Additionally, King[11] and MiToS[12] stages were calculated from ALSFRS-R scores (eMethods). Clinical stage at the visit before NIMV initiation was used to determine whether the ventilatory support benefits patients across different functional stages of ALS. We defined early disease stages as MiToS stage 0 and King stage 0 or 1; MiToS stages ≥ 1 and King stages ≥ 2 were instead considered advanced disease stages. Age at symptoms onset, sex, presence of cognitive impairment, and site of disease onset were used as additional covariates.

Validation Cohort

We used the longitudinal ALSFRS-R data of patients included in the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database[13] (version December 2022, available at https://ncri1.partners.org/ProACT) to validate the effect and estimates of NIMV on functional decline in an independent cohort.

Statistical Methods

To analyze longitudinal progression and changes of the functional decline in ALS patients, we implemented univariate and multivariable mixed-effects regression models (MERs), with patients' effect fitted as random. MERs advantages over fixed-effects models are detailed in eMethods. Additionally, we performed a sensitivity analysis using the generalized least square regression, to assure the replicability of the results adopting a different statistical methodology (eMethods, eTable 1). Given the nonlinear nature of ALSFRS-R changes over time, we carefully accounted for this phenomenon in our analysis. First, we included disease staging (MiToS and King) as covariates to mitigate potential confounding effects arising from varying disease stages at the time of NIMV initiation among subjects. Moreover, we further enhanced the precision of our analysis by stratifying the study population into early and advanced disease stages based on their MiToS scores. This stratified analysis allowed us to explore potential differences in NIMV-related ALSFRS-R trajectory changes among individuals at different disease stages.

Cognitive status was included as a covariate to exclude that cognitive dysfunction could affect the response to NIMV; we additionally performed a separate analysis stratifying patients based on the presence of cognitive impairment. Furthermore, to address the impact of NIMV usage duration, we stratified patients into 3 distinct stages of NIMV usage: intermittent use, continuous nightly use, and continuous daily and nighttime use. This additional analysis provided critical insights into the potential benefits of respiratory support at different phases of NIMV utilization in slowing the progression of ALS.

Ethics Approval

This study was approved by the Comitato Etico Azienda Ospedaliero-Universitaria Città della Salute e della Scienza, Turin (#355732). All participants gave informed consent.

Results

A total of 448 patients were included in this analysis. Median age at disease diagnosis was 67.9 years (interquartile range [IQR] = 61.1–73.9), with 28.3% of patients with bulbar onset and 39.3% of patients with cognitive impairment. Patients initiated NIMV after a median 9 months (IQR = 2.32–19.2). Baseline demographic and disease characteristics of the patient cohort are summarized in eTable 2, indicating that our analysis did not exclude patients with a faster progression rate.

Effect of NIMV on Disease Progression

Longitudinal analysis revealed that initiating ventilatory support was associated with a deceleration of disease progression compared to the pre-NIMV period as measured by nonrespiratory ALSFRS-R (mean improvement = 0.16 points per month, 95% confidence interval [CI] = 0.12 to 0.19, $p < 0.001$; eTable 3). This monthly slowing remained significant in the multivariable analysis (mean improvement = 0.16 points per month, 95% CI = 0.13–0.19, $p < 0.001$; Figs 1 and 2).

Effect of NIMV according to Disease Stage

We performed additional analysis adjusting for disease stage at the time of NIMV initiation; the results revealed that NIMV usage reduced the rate of ALS progression regardless of disease severity at the time of NIMV as evaluated by either MiToS or King stage (mean improvement = 0.16 points per month, 95% CI = 0.13–0.19, $p < 0.001$; eFigure 1). A sensitivity analysis, stratifying patients into early (MiToS stage = 0) and intermediate or advanced (MiToS stages ≥ 1), demonstrated that NIMV initiation led to a significant reduction in the rate of ALSFRS-R decline. This beneficial effect was observed in both early stage patients (mean improvement = 0.16 points per month, 95% CI = 0.12–0.19, $p < 0.001$) and those in later stages of the disease (mean improvement = 0.25 points per month, 95% CI = 0.14–0.37, $p < 0.001$). This finding underscores the potential of NIMV to slow disease progression regardless of when it is initiated during the course of ALS.

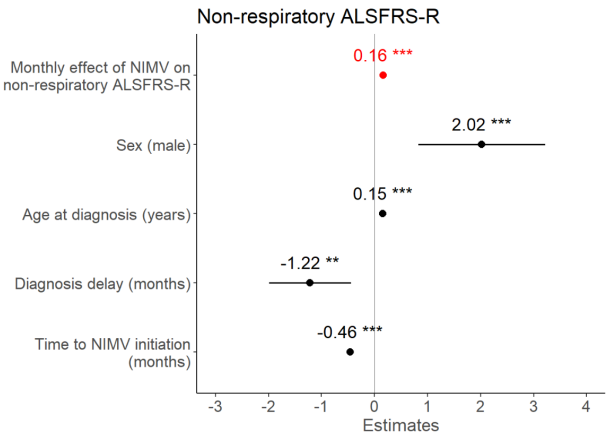

FIGURE 1: Forest plot summarizing multivariable linear mixed-effects model's fixed effects on nonrespiratory Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R). The main independent variable was noninvasive mechanical ventilation (NIMV)-related monthly ALSFRS-R change, adjusted for sex, age at diagnosis, diagnosis delay, and time to/from NIMV initiation. **$p \leq 0.01$, ***$p \leq 0.001$.

NIMV Effects on Bulbar and Spinal Function

Analysis using spinal and bulbar ALSFRS-R subdomains showed that NIMV determined a prominent deceleration in motor function decline (mean improvement = 0.13, 95% CI = 0.11–0.15, $p < 0.001$), whereas it did show a very small, even if significant, effect on bulbar symptom progression (mean improvement = 0.03 points per month, 95% CI = 0.02–0.04, $p < 0.001$; eFigure 2). However, both patients with spinal and those with bulbar disease onset experienced the NIMV-related progression slowing (eFigure 3).

Effect of NIMV Usage Duration

Upon stratifying patients based on the duration of NIMV usage, nighttime NIMV was linked to a deceleration in motor function decline compared to no or intermittent

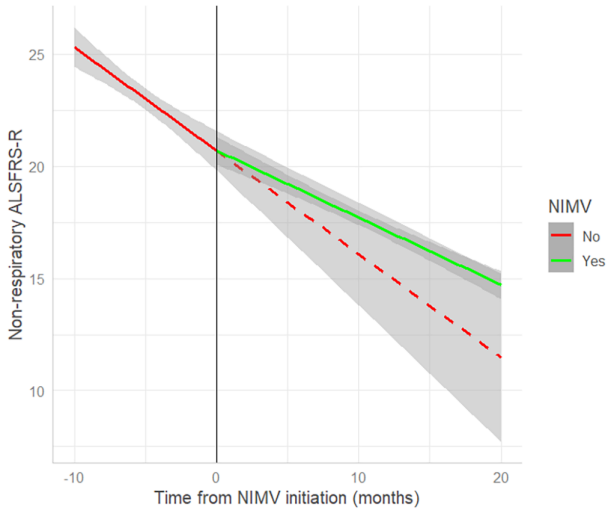

FIGURE 2: Multivariable linear mixed-effects model's predicted values of nonrespiratory Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) according to time from noninvasive mechanical ventilation (NIMV) initiation. The red line represents the predicted values based on the scores of the patients before NIMV initiation, whereas the green line represents the predicted values based on the observations after the start of NIMV. The dashed red line was also extended for time points after NIMV initiation, representing the score prediction in the case that the patients had not started NIMV. Confidence intervals (gray area) were reported for both curves. The difference in slope between the two prediction lines is representative of the monthly effect of NIMV on disease progression.

NIMV usage (mean change = 0.08 points per month, 95% CI = 0.05–0.11, $p < 0.001$). However, these benefits did not persist when NIMV usage became continuous, as compared with nightly NIMV only (mean change = −0.11 points per month, 95% CI = −0.07 to −0.16, $p < 0.001$). These results strongly suggest that the initial phases of NIMV usage are associated with the most pronounced beneficial effects, but these positive effects gradually diminish with the progression of respiratory function decline.

Replication in the PRO-ACT Cohort

We observed a similar improvement in the ALSFRS-R rate of decline associated with NIMV among patients included in the PRO-ACT cohort (in multivariate analysis: mean improvement = 0.15 points per month, 95% CI = 0.11–0.20, $p < 0.001$), thus validating the association of NIMV with a slower disease progression (eTables 7 and 8).

Discussion

Our study assessed the impact of NIMV initiation on functional decline in a large Italian ALS cohort and found that it reduced motor decline as measured by the ALSFRS-R. To the best of our knowledge, this is the first study to demonstrate that mechanical ventilation slows ALS motor progression as measured with ALSFRS-R (see Fig 2).[6] Importantly, this positive NIMV-related effect was observed across all disease stages, implying that early initiation of NIMV could significantly benefit patients' functional decline. NIMV especially helped preserve motor functions (Fig 3) with a more pronounced effect on bulbar onset patients (eFigure 3). Together, our data suggest that NIMV benefits all ALS patients, independently of age, sex, time to NIMV initiation, disease severity, and site of disease onset (eTable 4). Notably, the presence of cognitive impairment did not influence the improvement observed after NIMV initiation.

Our findings add to the well-known effects of NIMV on patients' survival and quality of life.[2] In addition, they have relevant clinical implications. First, because NIMV slows the rate of motor decline, it is increasingly crucial to perform regular respiratory evaluations even in patients without overt respiratory symptoms and initiate NIMV without delay when criteria are met.[8,9] Additionally, discussing the direct disease-slowing effect with patients and caregivers may enhance adherence to mechanical respiratory support. Third, our findings should be carefully taken into consideration in trial designs and analyses, where disease progression is a major endpoint outcome.[14] Because our models demonstrated that the positive impact of respiratory support is immediate, assessing NIMV as a potential confounder should be recommended.

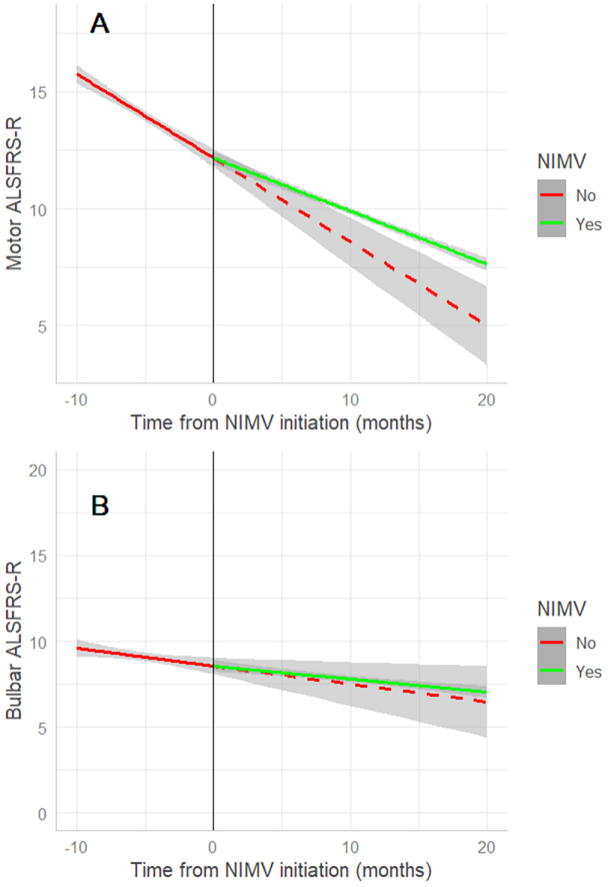

FIGURE 3: Multivariable linear mixed-effects model's predicted values of motor (A) and bulbar (B) Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) according to time from noninvasive mechanical ventilation (NIMV) initiation. The red line represents the predicted values based on the scores of the patients before NIMV, whereas the green line represents the predicted values based on the observations after the start of NIMV. The dashed red line was also extended for time points after NIMV initiation, representing the score prediction in the case that the patients had not started NIMV. Confidence intervals (gray area) were reported for both curves. The difference in slope between the two prediction lines is representative of the monthly effect of NIMV on disease progression.

Although the positive effects of NIMV on survival and quality of life are attributed to improved hypoventilation and alleviation of dyspnea,[15] the specific mechanism through which NIMV affects motor function remains uncertain. It has been proposed that NIMV usage reduces respiratory-related energy expenditure by decreasing breathing work and its consequent caloric burn, potentially ameliorating weight loss and muscle wasting due to hypermetabolism. This would, in turn, protect against further motor damage.[16] Improved respiratory function alone may also enhance patients' ability to perform tasks evaluated by the ALS-FRS scale and improve sleep quality, resulting in better overall scores. The observation that nighttime usage was especially

effective in reducing disease progression is consistent with previous findings demonstrating that improved respiratory parameters lead to reduced daytime fatigue, improved sleep, and enhanced quality of life. These improvements may be promptly noticeable to patients, although their effects may diminish over time. Considering that respiratory oligosymptomatic patients may exhibit lower treatment adherence, it becomes crucial to include in therapeutic discussions with patients the information that early initiation of NIMV provides direct disease-slowing benefits in addition to the improvement in quality of life.

Our study has some limitations. First, because of the observational setting, the quantitative effect of NIMV on ALSFRS-R progression presented here is not based on a randomized controlled trial. Nonetheless, we employed a rigorous observational design and state-of-the-art statistical methods for longitudinal data analysis, offering more realistic and generalizable real-world data from our large cohort with prospectively collected data. Importantly, our empirical evidence is reinforced by the replication in a different cohort, the PRO-ACT dataset, which further bolsters our results' generalizability and validity. Second, the variability in ALSFRS-R trajectories and the floor effect of the ALSFRS-R are inherent limitations in measuring ALS progression.[17] However, we implemented a model that predicted ALSFRS-R using the measurement immediately prior in time and included disease staging as a covariate to strengthen our findings. The incorporation of MiToS and King staging allowed us to account for baseline disease severity, providing a robust evaluation of mechanical ventilation's impact on ALSFRS-R scores and accounting for the curvilinear changes observed in the ALSFRS-R. Our findings suggest that the advantages of NIMV extend from early stage patients to those in more advanced stages and thus are not influenced by the plateauing of the functional decline during ALS final stages. This analysis highlights that NIMV may confer benefits even when patients retain a relatively high level of function, where changes in ALSFRS-R decline are initially more challenging to detect; however, this initial stage is usually followed by more rapid deterioration, underscoring the urgency of early treatment.

Moreover, initiating NIMV in early disease stages holds clinical significance and adds to the ongoing debate on the optimal timing of NIMV initiation. Our results advocate for prompt NIMV initiation and emphasize the importance of early diagnosis of respiratory symptoms in ALS.

In conclusion, our longitudinal model and sensitivity analyses provide compelling evidence of an association between NIMV and disease slowing. Optimizing respiratory support through NIMV represents a significant advancement in the effective care of ALS patients.

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Author Contributions

M.G., E.K., G.Mo., C.M., A.Cal., and A.Ch. contributed to the conception and design of the study; M.G., E.K., U.M., A.Can., R.V., F.P., G.F., P.S., G.Ma., F.C., and L.C. contributed to the acquisition and analysis of data; M.G., E.K., L.C., G.Mo., C.M., A.Cal., and A.Ch. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report.

Data Availability

Data are available to interested researchers upon motivated and reasonable request.

References

1. Chiò A, Logroscino G, Traynor BJ, et al. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. Neuroepidemiology 2013;41:118–130. https://doi.org/10.1159/000351153.

2. Bourke SC, Tomlinson M, Williams TL, et al. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. Lancet Neurol 2006;5:140–147. https://doi.org/10.1016/S1474-4422(05)70326-4.

3. Rafiq MK, Proctor AR, McDermott CJ, Shaw PJ. Respiratory management of motor neurone disease: a review of current practice and new developments. Pract Neurol 2012;12:166–176. https://doi.org/10.1136/practneurol-2011-000199.

4. Radunovic A, Annane D, Rafiq MK, et al. Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev 2017;10:CD004427. https://doi.org/10.1002/14651858.CD004427.pub4.
5. Chio A, Moglia C, Canosa A, et al. Respiratory support in a population-based ALS cohort: demographic, timing and survival determinants. J Neurol Neurosurg Psychiatry 2022;93:1024–1026. https://doi.org/10.1136/jnnp-2021-327968.
6. Atassi N, Cudkowicz ME, Schoenfeld DA. Advanced statistical methods to study the effects of gastric tube and non-invasive ventilation on functional decline and survival in amyotrophic lateral sclerosis. Amyotroph Lateral Scler 2011;12:272–277. https://doi.org/10.3109/17482968.2011.577786.
7. Chiò A, Mora G, Moglia C, et al. Secular trends of amyotrophic lateral sclerosis. JAMA Neurol 2017;74:1097–1104. https://doi.org/10.1001/jamaneurol.2017.1387.
8. Andersen PM, Borasio GD, Dengler R, et al. EFNS task force on management of amyotrophic lateral sclerosis: guidelines for diagnosing and clinical care of patients and relatives. Eur J Neurol 2005;12:921–938. https://doi.org/10.1111/j.1468-1331.2005.01351.x.
9. EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis, Andersen PM, Abrahams S, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)—revised report of an EFNS task force. Eur J Neurol 2012;19:360–375. https://doi.org/10.1111/j.1468-1331.2011.03501.x.
10. Strong MJ, Abrahams S, Goldstein LH, et al. Amyotrophic lateral sclerosis–frontotemporal spectrum disorder (ALS-FTSD): revised diagnostic criteria. Amyotroph Lateral Scler Frontotemporal Degener 2017;18:153–174. https://doi.org/10.1080/21678421.2016.1267768.
11. Balendra R, Jones A, Jivraj N, et al. Estimating clinical stage of amyotrophic lateral sclerosis from the ALS functional rating scale. Amyotroph Lateral Scler Frontotemporal Degener 2014;15:279–284. https://doi.org/10.3109/21678421.2014.897357.
12. Chiò A, Hammond ER, Mora G, et al. Development and evaluation of a clinical staging system for amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2015;86:38–44. https://doi.org/10.1136/jnnp-2013-306589.
13. Atassi N, Berry J, Shui A, et al. The PRO-ACT database: design, initial analyses, and predictive features. Neurology 2014;83:1719–1725. https://doi.org/10.1212/WNL.0000000000000951.
14. Kiernan MC, Vucic S, Talbot K, et al. Improving clinical trial outcomes in amyotrophic lateral sclerosis. Nat Rev Neurol 2021;17:104–118. https://doi.org/10.1038/s41582-020-00434-z.
15. Dorst J, Ludolph AC. Non-invasive ventilation in amyotrophic lateral sclerosis. Ther Adv Neurol Disord 2019;12:175628641985704. https://doi.org/10.1177/1756286419857040.
16. Georges M, Morélot-Panzini C, Similowski T, Gonzalez-Bermejo J. Noninvasive ventilation reduces energy expenditure in amyotrophic lateral sclerosis. BMC Pulm Med 2014;14:17. https://doi.org/10.1186/1471-2466-14-17.
17. Hartmaier SL, Rhodes T, Cook SF, et al. Qualitative measures that assess functional disability and quality of life in ALS. Health Qual Life Outcomes 2022;20:12. https://doi.org/10.1186/s12955-022-01919-9.