Non-invasive Ventilation Use is Associated with Better Survival in Amyotrophic Lateral Sclerosis

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Online Data Supplement.

Methods

Symptom onset site

Site of symptom onset was determined by the patients' report of the predominant muscle(s) involved at the time of disease onset. The attending neurologist would categorize the patient's initial site of symptom onset as either bulbar or limb. Bulbar onset indicated first symptoms were related to dysfunction of speech or swallowing, while limb onset indicated initial dysfunction included the arms or legs.

ALSFRS-R score

The ALS Functional Rating Scale-Revised (ALSFRS-R) score is a standardized, validated, widely-used method for staging functional status of an ALS patient in clinical care as well as clinical trials.(1–4) The ALSFRS-R has been shown to correlate with progression of disease and survival, as well as have validity and reliability.(3, 5) There are 12 questions covering four domains, including gross motor tasks, fine motor tasks, bulbar function, and respiratory function. Each question rates an individual's function for that domain on a scale of zero (minimal function) to four (maximal function). The range of the total ALSFRS-R score is from zero (most severe symptoms) to 48 (minimal to no symptoms). Most pertinent components to this study include two of the respiratory components of the ALSFRS-R, dyspnea and orthopnea.

Diagnosis delay

Diagnosis delay represents the time between patient-reported onset of symptoms and the date of diagnosis by an attending neurologist. It is a characteristic used in prior ALS literature to approximate the rapidity of disease progression.(6, 7)

Other missing data

Missing data from Penn were addressed using multiple imputation by chained equations with creation of 20 imputed datasets.(8, 9) We registered variables with complete data as predictors for imputation, including diagnosis age, age at symptom onset, sex, race, smoking history, and visit date.

Subgroup analyses

Primary analysis – NIV daily hourly usage

We performed several subgroup analyses. Using NIV subjects only, we performed matching and Cox proportional hazards model adjustment (described in the main body text) to estimate whether daily hourly NIV use was associated with survival. We adjusted for confounders similar to the main survival analysis. For each NIV subject, we used patient-reported NIV hourly usage for all visits post matching to create a variable for overall mean daily NIV hours. We then analyzed survival among NIV subjects, categorized by mean hourly usage.

Primary analysis – Symptom-onset site

Using NIV and non-NIV subjects, we performed the aforementioned matching and Cox proportional hazards model adjustment to estimate NIV association with survival based on ALS symptom onset site. We estimated NIV association with survival among subjects with limb-onset disease and separately among subjects with bulbar-onset disease. We adjusted for confounders similar to the main survival analysis. NIV survival effect estimates were stratified by matched groups.

Secondary analysis – Time-matched groups

FVC % predicted

Our primary analysis matched using FVC and symptom-onset site and precluded adjusting for these variables in the survival analysis. Therefore, our secondary analysis created “time-matched groups” matched with only two time variables: diagnosis delay time and follow-up time since first visit. We performed a Cox proportional hazards model that adjusted for FVC % predicted value at time of matching and baseline symptom onset site. We also adjusted for the confounders from the primary analysis.

Results

Baseline characteristics of full, unmatched Penn cohort

The Penn cohort had 864 subjects (**Table E1**). The average age at diagnosis was 64, 55% were self-reported male, and 84% were Caucasian. The majority of subjects had a normal or overweight BMI at baseline. The median diagnosis delay was 1.0 years. Seventy-six percent had limb-onset disease, while the average FVC at baseline was

75%. The mean baseline ALSFRS-R total score was 36, while the majority of subjects had no significant orthopnea or dyspnea at baseline by ALSFRS-R scores. Fifty-three percent described themselves as “never” smokers. The median survival time was 1.4 years (IQR, 0.7 – 2.5).

We compared unmatched to matched subjects in **Table E2**. Unmatched individuals tended to have a longer diagnosis delay, less Definite ALS by El Escorial criteria, higher baseline FVC, higher baseline ALSFRS-R total, higher ALSFRS-R dyspnea and orthopnea scores, and longer survival since first visit and since symptom onset. Among unmatched subjects, 73% (n=301) were non-NIV subjects and 27% (n=111) were NIV subjects. Median unadjusted survival time since first visit for NIV subjects was 23 months (IQR, 15 – 43), and for non-NIV subjects was 18 months (IQR, 7 – 41) (p=0.003). There was no significant difference in survival since symptom onset.

Table E1. Baseline characteristics of full, unmatched Penn cohort (N=864)

Variable	
Age at diagnosis, years	64 ± 12
Male sex, n (%)	473 (55)
Race, n (%)	
Caucasian	728 (84)
African American	70 (8)
Other	66 (8)
Body mass index class, n (%)	
<18.5 kg/m^2	35 (4)
18.5 – 24.9 kg/m^2	371 (43)
25 – 29.9 kg/m^2	299 (35)
≥30 kg/m^2	158 (18)
Diagnosis delay, years	1.0 (0.6, 1.8)
El Escorial criteria, n (%)	
Definite ALS	181 (21)
Possible ALS	216 (25)
Probable ALS	269 (31)
Suspected ALS	198 (23)
Symptom onset site, n (%)	
Limb	653 (76)
Bulbar	211 (24)
Forced vital capacity % predicted	75 ± 24
ALSFRS-R total score	36 ± 7
ALSFRS-R dyspnea, n (%)	
>2	721 (83)
≤2	143 (17)
ALSFRS-R orthopnea, n (%)	
>2	774 (90)
≤2	90 (10)
Smoking history, n (%)	
Current	81 (10)
Previous	323 (37)
Never	460 (53)
Coronary artery disease, n (%)	71 (8)
Diabetes mellitus, n (%)	101 (12)
Hypertension, n (%)	345 (40)

Definition of abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS functional rating scale – revised.
Data are mean ± SD or median (25th percentile, 75th percentile).

Table E2. Baseline characteristics of unmatched versus matched subjects in the Penn cohort (N=864)

Variable	Unmatched n=412	Matched n=452
Age at diagnosis, years	63 ± 12	64 ± 12
Male sex, n (%)	230 (56)	243 (54)
Race, n (%)		
Caucasian	359 (87)	369 (82)
African American	22 (5)	48 (10)
Other	31 (8)	35 (8)
Body mass index class, n (%)		
<18.5 kg/m^2	12 (3)	23 (5)
18.5 – 24.9 kg/m^2	171 (42)	200 (44)
25 – 29.9 kg/m^2	150 (36)	149 (33)
≥30 kg/m^2	79 (19)	79 (18)
Diagnosis delay, years	1.2 (0.6, 2.4)	0.9 (0.5, 1.2)
El Escorial criteria, n (%)		
Definite ALS	70 (17)	111 (25)
Possible ALS	98 (24)	118 (26)
Probable ALS	121 (29)	148 (33)
Suspected ALS	123 (30)	75 (16)
Symptom onset site, n (%)		
Limb	320 (78)	333 (74)
Bulbar	92 (22)	119 (26)
Forced vital capacity % predicted	81 ± 23	69 ± 23
ALSFRS-R total score	37 ± 7	35 ± 7
ALSFRS-R dyspnea, n (%)		
>2	367 (89)	354 (78)
≤2	45 (11)	98 (22)
ALSFRS-R orthopnea, n (%)		
>2	384 (93)	390 (86)
≤2	28 (7)	62 (14)
Smoking history, n (%)		
Current	36 (9)	45 (10)
Previous	150 (36)	173 (38)
Never	226 (55)	234 (52)
Coronary artery disease, n (%)	35 (9)	36 (8)
Diabetes mellitus, n (%)	48 (12)	53 (12)
Hypertension, n (%)	155 (38)	190 (42)

Definition of abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS functional rating scale – revised.
Data are mean ± SD or median (25th percentile, 75th percentile).

Table E3. Results of survival regression analysis for non-invasive ventilation use among limb-onset ALS patients, stratified by time-matched groups (N=333)

	Multivariate Analysis		
Variable	**HR**	**95% CI**	**P Value**
Non-invasive ventilation	0.63	0.45 – 0.87	0.006
Age at diagnosis, per decade	1.33	1.14 – 1.54	<0.001
Body mass index class (kg/m^2)			
<18.5	1.43	0.78 – 2.65	0.25
18.5 - 24.9	--	--	--
25 - 29.9	0.88	0.61 – 1.23	0.48
≥30	0.55	0.33 – 0.91	0.02
ALSFRS-R dyspnea			
>2	--	--	--
≤2	1.94	1.37 – 2.75	<0.001
Time-varying covariate			
Daily hours of non-invasive ventilation	1.00	0.998 – 1.004	0.43

Definition of abbreviations: HR = hazard ratio; CI = confidence interval; ALSFRS-R = amyotrophic lateral sclerosis functional rating scale – revised.

Figure E1. Unadjusted, unstratified survival since matching for NIV subjects versus non-NIV subjects.

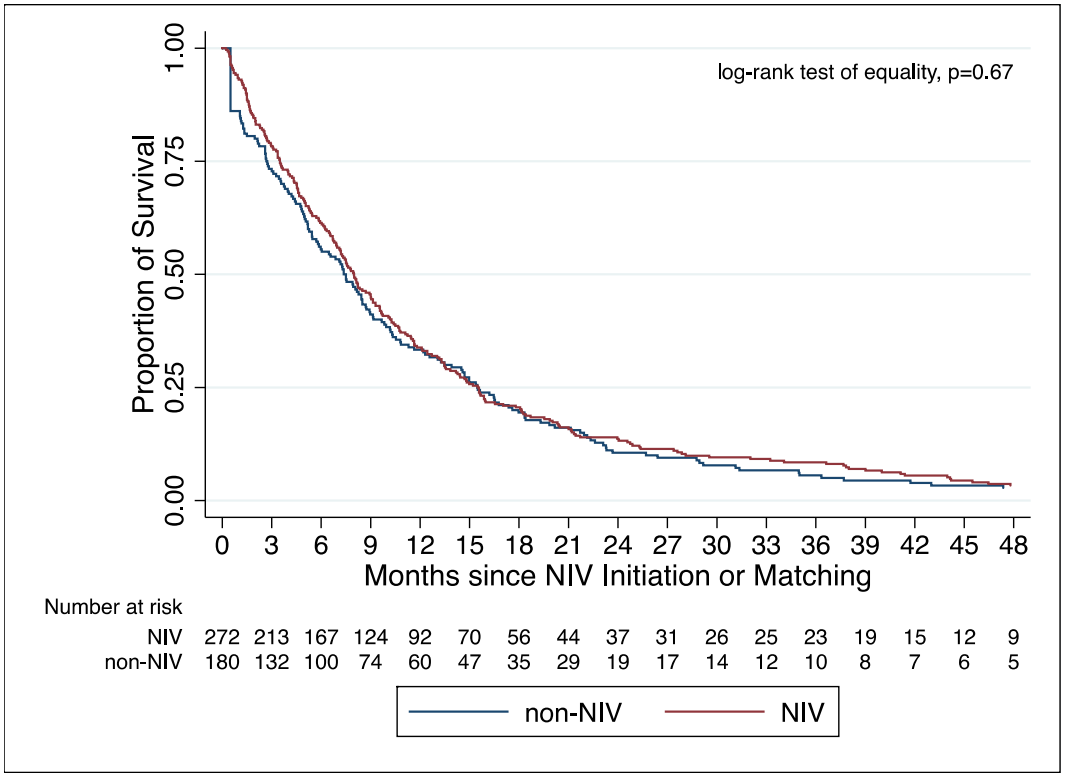
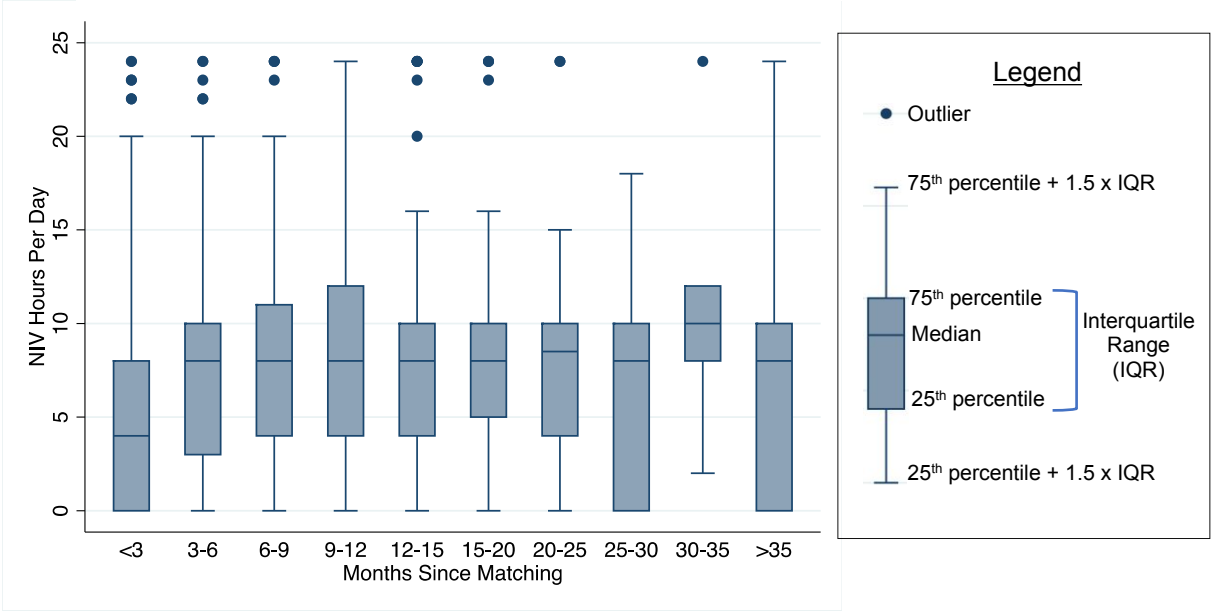


Figure E2. Patient reported daily NIV hourly usage in all NIV users (n=272), over months since matching.



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