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Non-invasive and tracheostomy invasive ventilation in amyotrophic lateral sclerosis: Utilization and survival rates in a cohort study over 12 years in Germany

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Abstract

Background and purpose: The aim of this study was to investigate utilization rates, treatment pathways and survival prognosis in patients with amyotrophic lateral sclerosis (ALS) undergoing non-invasive (NIV) and tracheostomy invasive ventilation (TIV) in a real-world setting.

Methods: A prospective cohort study using a single-centre register of 2702 ALS patients (2007 to 2019) was conducted. Utilization of NIV/TIV and survival data were analysed in three cohorts: (i) non-NIV; (ii) NIV (NIV without subsequent TIV); and (iii) TIV (including TIV preceded by NIV).

Results: A total of 1720 patients with available data were identified, 72.0% of whom (*n* = 1238) did not receive ventilation therapy. NIV was performed in 20.8% of patients (*n* = 358). TIV was performed in 9.5% of patients (*n* = 164), encompassing both primary TIV (7.2%, *n* = 124) and TIV with preceding NIV (2.3%, *n* = 40). TIV was more often utilized without previous NIV (25.7% vs. 8.3% of all ventilated patients), demonstrating that primary TIV was the prevailing pathway for invasive ventilation. The median (range) survival was significantly longer in the NIV cohort (40.8 [37.2–44.3] months) and the TIV cohort (82.1 [68.7–95.6] months) as compared to the non-NIV cohort (33.6 [31.6–35.7] months).

Conclusions: Although NIV represents the standard of care, its utilization rate was low. TIV was mainly started without preceding NIV, suggesting that TIV may not be confined to NIV treatment escalation. However, TIV was pursued in a minority of patients who had previously undergone NIV. The survival benefit observed in the patients with NIV was equal to that reported in a controlled pivotal trial, but the prognosis with TIV is highly variable. The determinants of utilization of NIV/TIV and of survival (bulbar syndrome, availability of ventilation-related home nursing, cultural factors) warrant further investigation.

KEYWORDS
amyotrophic lateral sclerosis, invasive ventilation, non-invasive ventilation, survival, utilization rates

INTRODUCTION

In amyotrophic lateral sclerosis (ALS), non-invasive ventilation (NIV) and tracheostomy invasive ventilation (TIV) constitute important and established interventions [1,2]. In NIV, a randomized and sham-ventilation controlled trial showed a benefit associated with mask ventilation in terms of quality of life and survival [3]. Based on level 1 evidence, elaborate recommendations for NIV were issued in national and multinational ALS guidelines [1,4]. However, the implementation of these guidelines, the actual utilization rate, and the survival benefit in a real-world-setting are uncertain. In contrast to NIV, the level of evidence for TIV is much lower. The reported utilization rates of TIV vary internationally [5–7]. Likewise, the influence of TIV on life prolongation varies, with particularly high median survival times in Japanese ALS patients and, by comparison, lower survival rates in Europe [5–13]. To date, there have been no systematic studies on the utilization of NIV/TIV and survival prognosis after ventilation treatment in Germany [5,14–16]. More detailed information must be obtained to monitor the current standards of care, elucidate progress in ventilation therapy and explore potential shortcomings in respiratory management. The aim of the present study, therefore, was to identify the initiation rates for NIV and TIV and the influence of ventilation support on survival in ALS in order to broaden the data basis for ventilation therapy pathways in ALS. The following hypotheses were assumed: (i) NIV is considered to be the initial ventilation therapy in ALS; (ii) the decision is made in favour of TIV when NIV is exhausted; (iii) both NIV and TIV prolong the lives of patients with ALS, with postulation of higher survival rates under TIV.

METHODS

Study design

An observational, longitudinal, single-centre register study was conducted. Data were analysed retrospectively, with an observation period from March 2007 to May 2019. The investigation was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria [17].

Participants

Subjects meeting the following criteria were included: (i) diagnosis of ALS (International Classification of Disease-10 code G12.2) according to the revised El Escorial criteria [18]; (ii) attendance at the ALS centre of the *Charité – Universitätsmedizin Berlin* as a clinical outpatient; (iii) having had a last clinical visit within the last 6 months of the observation period or before death.

Setting

Demographic and clinical data were obtained at a tertiary ALS centre ("on-site" data). In some cases, data on patient deaths were collected via a digital case management and research platform, "APST" (www.ambulanzpartner.de, "online" data). Clinical data were collected at the patient's first and at the last clinical visit (within the last 6 months of observation period or before death). The indication for NIV/TIV was established by neurologists specialized in ALS and experienced in ventilation therapy. The adaption to NIV was performed in accordance with national and European guidelines [1,19]. NIV was initiated in the presence of defined respiratory symptoms such as dyspnoea, orthopnoea, sleep disturbance, daytime sleepiness as well as respiratory parameters such as low vital capacity below 80%. In 2018, we also included a weak cough as one of the indication criteria when the peak cough flow fell below 270 L/min. TIV was indicated when NIV was exhausted or when we faced methodological barriers to NIV, such as presence of bulbar syndrome. For the purpose of ventilation therapy initiation and follow-up, patients were admitted to hospital, where pulmonologists performed the relevant procedures. Patients were discharged from hospital 5 to 10 days later. Ventilation therapy monitoring comprised an assessment of clinical symptoms, slow vital capacity, peak cough flow, as well as blood gas analysis and capnometry for individual patients. Follow-up visits took place at the outpatient ALS centre and the Department of Pulmonology, also in an outpatient setting. Challenges in connection with NIV/TIV – such as gradual ventilation adaptation, determining individual ventilation parameters and continuously motivating patients – were addressed and managed by a multidisciplinary team comprising, among others, respiratory therapists with expertise in ALS.

Protocol approvals and registrations

The study was approved by the Medical Ethics Committee of the *Charité – Universitätsmedizin Berlin*, Germany (No. EA1/219/15). A signed patient informed consent was obtained from all participating patients.

Variables and data sources

Demographic and clinical data

An overview of the patients' demographic and clinical characteristics is given in Table 1.

Functional disease status was assessed using the Amyotrophic Lateral Sclerosis Functional Rating Scale revised (ALS-FRSr), which ranges from 0 (poor function) to 48 points (full function).

TABLE 1 Demographic and clinical characteristics of patients

Characteristic	Total cohort, n = 1720	Non-NIV cohort, n = 1238	NIV cohort, n = 318	p^a	TIV cohort, n = 164	p^b
Gender, n (%)						
Female	682 (39.7)	537 (43.4)	96 (30.2)	<0.001	49 (29.9)	<0.001
Male	1038 (60.3)	701 (56.6)	222 (69.8)		115 (70.1)	
Type of onset, n (%)						
Spinal	1266 (73.6)	874 (70.6)	268 (84.3)	<0.001	124 (75.6)	<0.001
Bulbar	454 (26.4)	364 (29.4)	50 (15.7)		40 (24.4)	
Mean (SD; range) age at onset[b], years	62.8 (11.4, 21.1–88.5)	63.9 (11.4, 21.1–88.5)	61.8 (10.1, 30.2–85.8)	0.002	56.6 (11.7, 23.6–85.8)	<0.001
Mean (SD; range) disease duration[c], months	47.6 (44.7, 3.5–373.8)	42.5 (41.3, 3.5–373,8)	49.9 (39.5, 5.3–263.7)	0.004	81.4 (61.0, 8.2–347.8)	<0.001
Mean (SD; range) ALS-FRSr score						
At first visit	35.9 (8.8, 0–48)	36.8 (7.5, 11–48)	35.9 (8.3, 7–48)	0.065	29.1 (13.9, 0–47)	<0.001
At last visit	23.9 (11.2, 0–48)	27.8 (9.2, 4–48)	18.1 (7.4, 2–39)	<0.001	5.2 (7.2, 0–41)	<0.001
Dysphagia prior to NIV[d], n (%)						
Yes	n/a	n/a	68 (21.9)	n/a	n/a	n/a
No	n/a	n/a	242 (78.1)	n/a	n/a	n/a
Dysphagia prior to TIV[d], n (%)						
Yes	n/a	n/a	n/a	n/a	78 (75.7)	n/a
No	n/a	n/a	n/a	n/a	25 (24.3)	n/a
PEG, n (%)						
Yes	491 (28.5)	253 (20.4)	87 (27.4)	0.008	151 (92.1)	<0.001
No	1229 (71.5)	985 (79.6)	231 (72.6)		13 (7.9)	
Riluzole, n (%)						
Yes	1327 (77.2)	946 (76.4)	257 (80.8)	0.008	124 (75.6)	0.820
No	393 (22.8)	292 (23.6)	61 (19.2)		40 (24.4)	
FTD, n (%)						
No	1543 (89.7)	1103 (89.1)	296 (93.1)	0.035	144 (87.8)	0.620
Yes	177 (10.3)	135 (10.9)	22 (6.9)		20 (12.2)	
Mean (SD; range) BMI, kg/m^2						
At first visit	24.7 (4.1; 12.1–47.5)	24.6 (4.0, 15.1–46.3)	25.1 (4.2, 15.7–47.5)	0.065	24.7 (4.5, 12.1–38.4)	0.741
At last visit	23.4 (4.1, 9.7–38.4)	23.4 (4.0, 10.7–38.4)	23.5 (4.5, 9.7–37.7)	0.768	23.2 (3.9, 15.2–36.4)	0.804

Non-NIV cohort =patients without ventilation therapy, NIV cohort =NIV without subsequent TIV, TIV cohort =TIV, including preceded NIV.

Abbreviations: ALS-FRSr, Amyotrophic Lateral Sclerosis Functional Rating Scale revised; BMI, body mass index; FTD, frontotemporal dementia; n, number of patients; NIV, non-invasive ventilation; PEG, percutaneous endoscopic gastrostomy; SD, standard deviation; TIV, tracheostomy invasive ventilation; n/a, not applicable.

[a]Difference of frequencies between two groups were assessed by chi-squared test and between-metric data by t-test, a p value <0.05 was considered significant. Significant differences were compared with the non-NIV cohort.

[b]Age at symptom onset in years.

[c]Disease duration from symptom onset to death in months.

[d]Dysphagy is defined by ALS-FRSr item 3 (<3 score points).

Utilization rates and survival for NIV/TIV

Utilization of NIV/TIV and survival from symptom onset were analysed in three ALS cohorts: (i) a non-NIV cohort (no NIV/TIV during the course of disease); (ii) a NIV cohort (patients in whom NIV was performed without subsequent TIV); and (iii) a TIV cohort (patients in whom TIV was initiated, including TIV preceded by NIV). The utilization of NIV/TIV was defined according to the ALS-FRSr, item 12 ("respiratory insufficiency"; Figure S1).
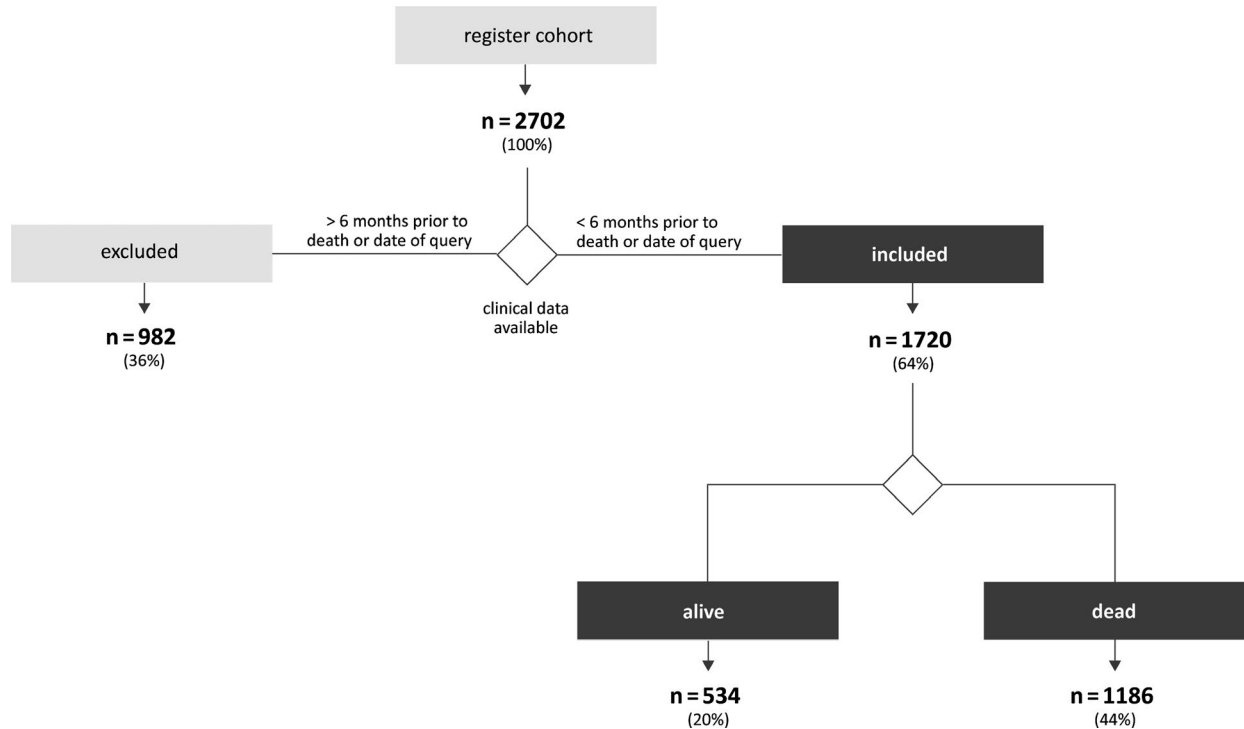
FIGURE 1 Sample characteristics. Data from a register of 2702 amyotrophic lateral sclerosis patients were selected. A subgroup of patients (total analysed cohort) with available clinical data at least 6 months prior to event (death or date of query) were included (n = 1718; 64%). Patients without clinical assessment in the last 6 months before end of observation period or death were excluded as they were regarded as lost to follow-up (n = 984, 36%). n, number of patients.

Statistical methods

Descriptive statistics were used. Group comparisons were performed using the *t*-test and chi-squared test. Kaplan–Meier estimates were obtained for the calculation of survival times. Patients whose endpoint was not death were censored at the date of their last clinical visit [20]. Group differences within the Kaplan–Meier test were compared by means of the log-rank test (univariate analysis). The Cox proportional hazards model (multiple regression analysis) was used for the investigation of potentially interacting covariates affecting survival time. The selection of covariates was based on medical expertise and literature review. The following covariates were considered: gender; type of onset; age at onset; utilization of percutaneous endoscopic gastrostomy (PEG); intake of riluzole [10]; body mass index (BMI) [21,22]; and presence of frontotemporal dementia (FTD) [23]. A *p* value of <0.05 was taken to indicate statistical significance (95% CI). The data were analysed using SPSS statistics 25.0.

RESULTS

Sample characteristics

A total of 2702 ALS patients were treated in 14,679 clinical outpatient visits. Finally, data for 1720 patients collected at least 6 months prior to the end of the observation period or death (63.7%) were

included (Figure 1). Patients without clinical assessment within the last 6 months of the observation period or death were regarded as lost to follow-up and excluded.

Demographic data and clinical characteristics

A summary of the patients' demographic and clinical data is given in Table 1.

Utilization of NIV and TIV

Non-NIV cohort

A total of 72.0% of patients did not receive NIV or TIV during their disease course (Figure 2). Patients who did not undergo ventilation were significantly older compared with the NIV and TIV cohorts (Table 1, Figure S2).

NIV cohort

A total of 20.8% of patients were treated with NIV (Figure 2). Patients with bulbar onset were significantly underrepresented in the NIV cohort (15.7% vs. 29.4% in patients without NIV; *p* < 0.001).
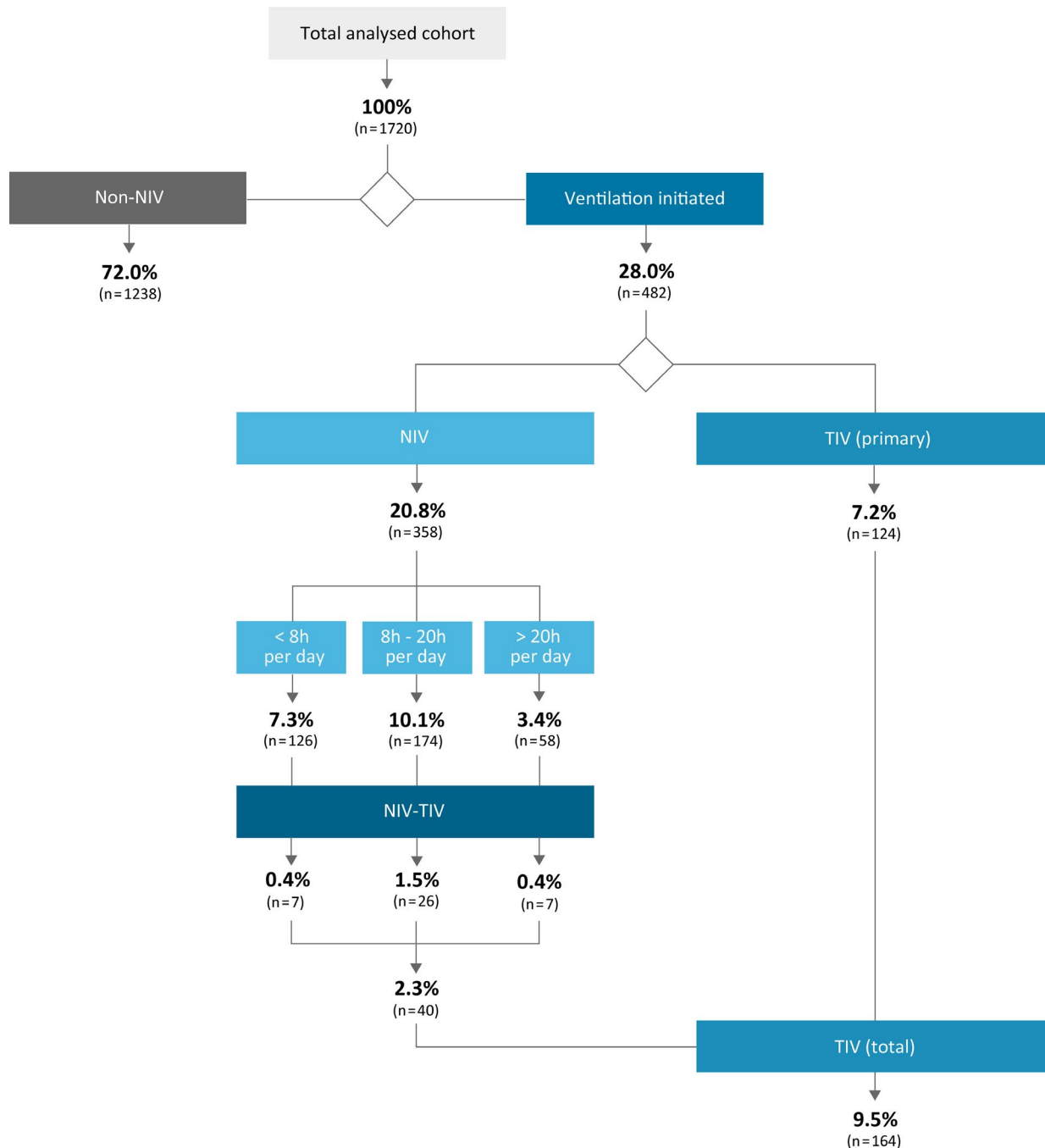
FIGURE 2 Utilization rates of non-invasive ventilation (NIV) and tracheostomy invasive ventilation (TIV). The proportion of patients with NIV and TIV was analysed using the Amyotrophic Lateral Sclerosis Functional Rating Scale revised, item 12 "respiratory insufficiency" (1 to 3 scale points = NIV; 0 scale points =TIV). Non-NIV = without NIV; NIV = NIV without subsequent TIV; TIV = TIV, including preceding NIV. *n*, number of patients.

TIV cohort

Overall, 9.5% of patients received TIV. A total of 7.2% received TIV as initial ventilation therapy without preceding NIV, and 2.3% of the total ALS cohort (11.2% of the NIV cohort) received TIV as an escalation therapy when NIV had been exhausted (Figure 2). Patients with bulbar onset were significantly underrepresented in the TIV cohort (24.4% vs. 29.4% in patients without NIV; $p < 0.001$). In contrast, bulbar onset was significantly more frequently represented in the TIV cohort compared with the NIV cohort (24.4% vs. 15.7%; $p = 0.26$). TIV was more frequently utilized in patients who died after 2013 (11.3%) as compared with the period at the beginning of the register (7.0%; $p = 0.044$ [Table 1]).

TABLE 2 Median survival from symptom onset in months.

Variable	Total cohort, (95% CI), n = 1720	p*	Non-NIV cohort (95% CI), n = 1238	p*	NIV cohort, (95% CI), n = 318	p*	TIV cohort, (95% CI), n = 164	p*
Total patients	38.09 (35.83–40.35)	n/a	33.62 (31.60–35.65)	n/a	40.76 (37.22–44.30)	n/a	82.11 (68.65–95.57)	n/a
Gender								
Female	35.79 (33.36–38.22)	0.025	33.16 (30.99–35.32)	0.222	42.43 (35.93–48.94)	0.742	60.92 (38.28–83.56)	0.030
Male	40.76 (37.32–44.19)		34.61 (30.74–38.46)		39.90 (36.09–43.72)		89.28 (64.51–114.04)	
Type of onset								
Spinal	44.44 (40.97–47.92)	<0.001	39.31 (35.07–43.55)	<0.001	43.45 (38.65–48.26)	0.003	91.23 (72.25–110.18)	0.001
Bulbar	30.03 (27.84–32.23)		27.93 (25.79–30.06)		32.01 (28.72–35.29)		58.39 (42.30–74.48)	
Age at onset								
≤60 years	59.54 (50.51–68.57)	<0.001	50.79 (42.60–58.98)	<0.001	51.58 (39.54–63.62)	<0.001	117.53 (81.24–153.83)	<0.001
>60 years	32.73 (31.06.34.40)		30.20 (28.38–32.02)		37.20 (34.16–40.25)		55.92 (47.80–64.04)	
NIV								
Yes	43.98 (39.12–48.84)	0.063	n/a (n/a-n/a)	n/a	n/a (n/a-n/a)	n/a	103.52 (86.31–120.73)	0.148
No	36.25 (33.84–38.66)		n/a (n/a-n/a)		n/a (n/a-n/a)		76.05 (58.27–93.83)	
TIV								
Yes	82.11 (68.65–95.57)	<0.001	n/a (n/a-n/a)	n/a	n/a (n/a-n/a)	n/a	n/a (n/a-n/a)	n/a
No	35.59 (33.80–37.39)		n/a (n/a-n/a)		n/a (n/a-n/a)		n/a (n/a-n/a)	
PEG								
Yes	38.45 (35.40–41.51)	0.414	30.03 (27.89–32.17)	<0.001	42.40 (36.56–48.24)	0.611	82.73 (69.64–95.82)	0.292
No	37.83 (34.71–40.94)		36.61 (32.80–40.43)		40.76 (36.30–45.21)		66.09 (40.95–91.23)	
Riluzole								
Yes	37.70 (35.36–40.04)	0.688	33.49 (31.44–35.53)	0.672	39.38 (34.86–43.89)	0.935	86.58 (68.74–104.41)	0.025
No	40.26 (35.21–45.32)		35.20 (27.17–43.22)		43.45 (37.76–49.15)		56.51 (17.03–96.00)	
BMI at last visit								
>18.5 kg/m²	39.90 (36.12–43.68)	<0.001	35.20 (30.38–40.01)	<0.001	44.38 (37.78–50.97)	0.016	110.26 (n/a-n/a)	0.525
≤18.5 kg/m²	27.93 (24.43–31.43)		26.61 (23.42–29.80)		32.17 (24.86–39.48)		n/a (na-n/a)	
FTD								
No	39.01 (36.62–41.40)	<0.001	34.77 (32.53–37.01)	0.001	41.97 (38.28–45.67)	0.245	84.87 (69.02–100.71)	0.030
Yes	31.97 (27.43–36.52)		25.99 (22.06–29.91)		38.45 (30.73–46.17)		56.22 (28.28–84.16)	

Non-NIV = without NIV, NIV = NIV without subsequent TIV, TIV = TIV, including preceded NIV.

Abbreviations: BMI, body mass index; CI, confidence interval; FTD, frontotemporal dementia; n, number of participants; NIV, non-invasive ventilation; PEG, percutaneous endoscopic gastrostomy; TIV, tracheostomy with invasive ventilation; n/a, not applicable.

*Significant differences were assessed by log-rank test; a p-value <0.05 was considered significant.
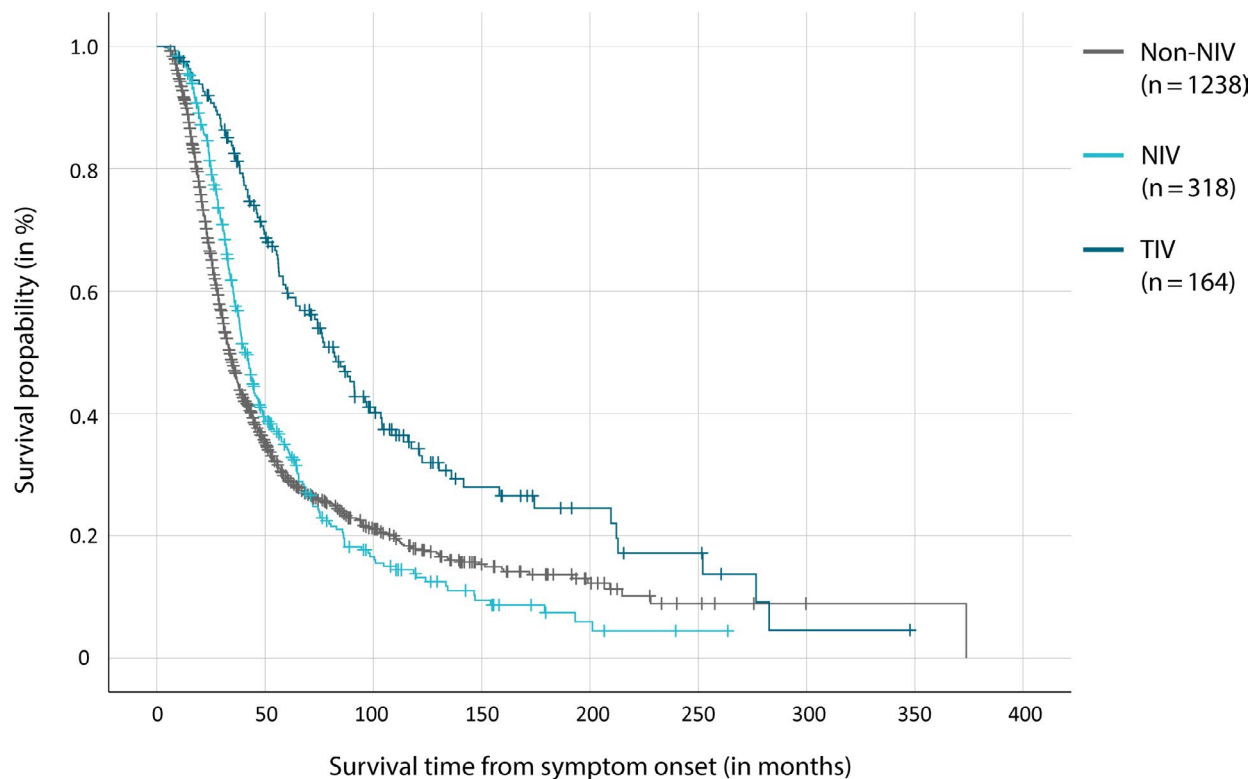
FIGURE 3 Kaplan–Meier survival probability for patients with non-invasive ventilation (NIV) and tracheostomy invasive ventilation (TIV). Non-NIV = without NIV, NIV = NIV without subsequent TIV, TIV = TIV, including preceding NIV. *n*, number of patients.

Survival prognosis

Non-NIV cohort

The median survival prognosis in the non-NIV cohort was 33.62 months (95% confidence interval [CI] 31.60–35.65; Table 2, Figure S3). The 1-, 3- and 5-year survival probabilities were 92.6% (SE 0.01), 46.7% (SE 0.02) and 29.5% (SE 0.02), respectively (Figure 3). Adjusted for potentially interacting covariates, the Cox regression analysis showed significant hazard ratios for spinal type of onset (1.38, 95% CI 1.12–1.70; *p* = 0.002), age at onset ≤60 years (2.00, 95% CI 1.63–2.44; *p* < 0.001), BMI >18.5 kg/m^2 (1.59, 95% CI 1.25–2.03; *p* < 0.001), and non-presence of FTD (1.31, 95% CI 1.02–1.69; *p* = 0.035 [Table 3]).

NIV cohort

The median survival prognosis in the NIV cohort was 40.76 months (95% CI 37.22–44.30), showing a survival difference of 7 months compared with the non-NIV cohort (Table 2, Figure S3). Correspondingly, the median survival after initiation of NIV was 13 months. The 1-, 3- and 5-year survival probability was 97.8% (SE 0.01), 57.9% (SE 0.03) and 34.1% (SE 0.03), respectively (Figure 3). Survival probability in the NIV cohort was substantially higher as compared to the non-NIV cohort (3-year survival probability of 57.9% vs. 46.7%, respectively). Adjusted for potentially interacting covariates, the Cox regression analysis showed significant hazard ratios for age at onset ≤60 years (1.82, 95% CI 1.21–2.74; *p* = 0.004) and BMI >18.5 kg/m^2 (2.70, 95% CI 1.48–4.93; *p* = 0.001 [Table 3]).

TIV cohort

The median survival prognosis in the TIV cohort was 82.11 months (95% CI 68.65–95.57), showing a survival difference of 48 months as compared with the non-NIV cohort and a median survival after initiation of TIV of 25 months (Table 2, Figure S3). The 1-, 3- and 5-year survival probabilities were 97.6% (SE 0.01), 81.9% (SE 0.03) and 59.7% (SE 0.04), respectively (Figure 3). In the TIV cohort, a significantly higher survival probability was demonstrated in comparison with both the non-NIV and the NIV cohorts (3-year survival for TIV, NIV and non-NIV of 81.9%, 57.9% and 46.7%, respectively). Adjusted for potentially interacting covariates, the Cox regression analysis showed significant hazard ratios for spinal type of onset (3.39, 95% CI 1.15–9.93; *p* = 0.026), onset age ≤60 years (2.79, 95% CI 1.03–7.59; *p* = 0.044), PEG utilization (4.89, 95% CI 1.18–20.25; *p* = 0.029), and intake of riluzole (3.84, 95% CI 1.26–11.71; *p* = 0.018 [Table 3]).

TABLE 3 Factors significantly influencing prolonged survival in multiple Cox regression

Variable	Total cohort, (95% CI), n = 1720	p*	Non-NIV cohort (95% CI), n = 1238	p*	NIV cohort, (95% CI), n = 318	p*	TIV cohort, (95% CI), n = 164	p*
Male gender	1.08 (0.92–1.27)	0.344	1.07 (0.89–1.28)	0.479	1.51 (0.96–2.36)	0.073	0.37 (0.12–1.21)	0.078
Type of onset: spinal	1.46 (1.21–1.76)	<0.001	1.38 (1.12–1.70)	0.002	1.36 (0.76–2.44)	0.298	3.39 (1.15–9.93)	0.026
Age at onset ≤60 years	2.00 (1.68–2.39)	<0.001	2.00 (1.63–2.44)	<0.001	1.82 (1.21–2.74)	0.004	2.79 (1.03–7.59)	0.044
NIV: yes	1.08 (0.88–1.32)	0.472	n/a	n/a	n/a	n/a	0.86 (0.26–2.83)	0.862
TIV: yes	2.07 (1.32–3.25)	0.001	n/a	n/a	n/a	n/a	n/a	n/a
PEG: yes	0.87 (0.71–1.07)	0.182	0.80 (0.63–1.01)	0.056	1.01 (0.60–1.68)	0.979	4.89 (1.18–20.25)	0.029
BMI^c >18.5 kg/m^2	1.66 (1.32–2.07)	<0.001	1.59 (1.25–2.03)	<0.001	2.70 (1.48–4.93)	0.001	1.19 (0.13–10.58)	0.876
Riluzole: yes	1.15 (0.97–1.36)	0.121	1.12 (0.92–1.35)	0.263	0.99 (0.64–1.55)	0.978	3.84 (1.26–11.71)	0.018
FTD: no	1.28 (1.03–1.61)	0.030	1.31 (1.02–1.69)	0.035	1.20 (0.67–2.15)	0.544	1.92 (0.47–7.82)	0.365

Non-NIV = without NIV, NIV = NIV without subsequent TIV, TIV = TIV, including preceded NIV.

Abbreviations: BMI, body mass index; CI, confidence interval; FTD, frontotemporal dementia; n, number of participants; NIV, non-invasive ventilation; PEG, percutaneous endoscopic gastrostomy; TIV, tracheostomy with invasive ventilation; n/a, not applicable.

[a]NIV was considered a covariate in total cohort and TIV cohort.

[b]TIV was considered a covariate in total cohort.

[c]Measured at last patient visit.

*Significant differences were assessed by log-rank test; a p value <0.05 was considered significant.

DISCUSSION

Sample selection

In this study, ventilation therapy was analysed in a reference ALS centre covering approximately 10% of the ALS population in Germany [24]. Systematic data assessment was facilitated by a single-centre register and the use of a digital management platform (APST) [25–29]. The digitalization of care provision via the APST platform allowed a longitudinal assessment of the journey of the disease in the largest German cohort to date, in terms of patient numbers and completeness of survival data. Survival data were either drawn from specialist ALS centres or collected by designated APST case managers. Despite these advantages, the study also has some limitations. The study was confined to a specialized ALS centre. Thus, we cannot exclude the possibility that key figures for NIV/TIV could differ outside dedicated ALS centres. It is conceivable that TIV may be overrepresented in the cohort, as decisions in favour of TIV may be linked to optimized care provision that is more likely at specialized ALS centres [7]. Moreover, the data were drawn from a single-centre database which may limit the generalizability of our results. Patients without clinical assessment within the last 6 months of the observation period or before death were logistically regarded as lost to follow-up and excluded – mainly due to travel barriers – as we were unable to assess their clinical characteristics (36%). However, we cannot exclude bias with regard to selection of more severely affected patients, and an association with a higher likelihood of loss to follow-up. Furthermore, we cannot preclude unrecorded changes in treatment for some cases in this period of time, which may lead to underreporting in the NIV/TIV cohorts.

Utilization rates for NIV and TIV

Overall, the proportion of patients receiving ventilation therapy (28%) was lower than expected. Surprisingly, NIV utilization (at 21% only) was particularly low, although evidence from a pivotal trial showed that mask ventilation is beneficial, a fact leading to recommendation for NIV in treatment guidelines [1,30]. The same NIV rate was reported in an Italian study [31] covering a cohort that was large by comparison, in a similar study setting. Also, NIV rates in Australia were similar (23%) [32]. Higher rates were reported in Japan (26%), the United States (34%) and Italy (44%–48%), while Taiwan reported lower rates (17%) [8,10,11,33,34]. It is worth discussing whether poor tolerance of NIV in patients with bulbar syndrome may account for the low provision rate [33,35,36]. The findings in our cohort contribute to this notion, as only 11% of patients with bulbar-onset ALS ended up receiving NIV. However, a significantly higher percentage of patients with spinal-onset ALS (21%) were treated with NIV (p < 0.001).

In addition to methodological limitations, reduced access to NIV provision may account for the overall low NIV utilization rate. Patient

access is closely related to the availability of home care structures as most ALS patients are dependent on nursing personnel for the handling of the mask. However, in Germany, NIV-related nursing is not covered by the (otherwise well developed) health insurance system. The potential impact of social and financial constraints on NIV utilization was also discussed in the context of other healthcare systems [11,36].

Furthermore, the counterbalancing of benefits (extended lifespan, alleviation of symptoms) and burden (e.g., perceived dependence on medical equipment and nursing, aerophagia, noise disturbance) of the mask may play a part in the rejection of NIV. In principle, the palliative concept of withholding NIV (in favour of symptomatic pharmacotherapy and other forms of palliation) have to be considered [37]. There are multiple and interdependent reasons for the rather low utilization rate for NIV and for the various challenges in connection with NIV. However, these were not elucidated in this study. Answers to such issues – at pathophysiological, healthcare and psychosocial levels – could help to counteract the low NIV provision rate. The utilization rate for TIV (9.5%) in our cohort was lower than in Japan (15%–33%), and Taiwan (21%) [34], but in the same range as rates reported in studies from Italy, 10%–11% [7,38,39]. As previously discussed in NIV, the complexity of the underlying reasons for the relatively low utilization rate of TIV also has to be considered. Methodological limitations, equivalent to the impact of bulbar syndrome in NIV, do not apply to TIV. Also, patient access to TIV and, thereby, home care nursing is not a limiting factor as TIV-related nursing is fully covered by the German healthcare system. In the light of the few procedural limitations and full coverage of TIV, the focus must be on psychosocial factors in the decision-making process for or against. The balancing of benefits (increased survival, symptom control) and downsides (e.g., loss of the speech faculty following tracheostomy, diminished autonomy and privacy in the context of 24-h home-nursing) may result in withholding of TIV [37]. Moreover, patients who have already undergone NIV treatment for months on end may not wish to escalate to TIV, as this is associated with disease progression and associated limitations. The low rate of NIV before TIV may also be influenced by the low NIV incidence in the first place. In fact, at the study centre, the decision-making process for TIV which is done electively is embedded in a multi-step Advance Care Planning (ACP) scheme. This shared decision is documented in the advanced directive and related documents. The ACP process was established to prevent TIV initiation in an emergency situation that – given the ACP concept – occurs rarely and is mostly confined to acute clinical events such as aspiration pneumonia. Although the actual number of patients who received TIV in an emergency situation was not recorded in this study, it is conceivable that the ACP concept may have contributed to the low TIV initiation rate compared with other studies [15,40–43].

Remarkably, the TIV initiation rate changed during the course of the observation period; TIV utilization was significantly higher for patients who died after 2013 (11%) than for patients who died before 2013 (7%; $p > 0.044$). Compared with earlier years, an increase in TIV initiation rates was also found in a Japanese ALS cohort [8].

Improved patient participation and associated enhancement of quality of life could be one of the reasons why ALS patients are more likely to opt for TIV nowadays. Through the increasing provision (and acceptance) of advanced communication systems and other assistive technologies for patients, and the spreading of digital communication in the societal mainstream, patients with ALS have better and more numerous options for participating in life [13,40].

Another important and equally unexpected finding related to the utilization rate of TIV following NIV was that the vast majority of patients (89%) treated with NIV were subsequently not treated with TIV. It appears that TIV did not represent a predetermined treatment escalation when NIV had been exhausted. In the TIV cohort, patients with bulbar syndrome presenting with dysphagia were overrepresented (76%) as compared with the NIV cohort (22%; Table 1). This finding supports the notion that TIV was the primary treatment option when the bulbar syndrome posed a methodological barrier for NIV. Interestingly, the proportion of patients with primary TIV (without preceding NIV) was significantly higher (26%) than the proportion of patients who had previously received NIV (8%). Strikingly, only 11% of patients treated with NIV opted for treatment escalation with TIV. A low escalation rate (<1%) from invasive ventilation was also found among NIV patients with continuous mask ventilation (>20 h of daily ventilation time; Figure 2).

Survival prognosis

Survival after symptom onset for non-NIV patients was only 34 months (Table 2). In the NIV cohort, the survival prognosis was improved (41 months). However, the survival benefit in the NIV as compared with the non-NIV cohort did not reach statistical significance. This surprising observation may be attributable to the differences in clinical characteristics between non-NIV cohorts and the intervention group. It is conceivable that patients with a slower progression rate and improved prognosis in their natural course of disease constitute a selection bias for the non-NIV group. This hypothesis is supported by the Kaplan–Meier test demonstrating that there is a subgroup of non-ventilated patients with long-term survival (Figure 3). However, no specific investigation was performed into the clinical factors that are crucial for long-time survival and absence of ventilation support, that is, topical variants, a fact that represents a limitation of this study. Better survival rates were found in other European countries (23–30 months), [44–46] but a similar rate was reported in an Italian case series, based on a large population and equal to that reported in a controlled pivotal trial [3,31]. However, a head-to-head comparison of both studies is not justified as the present study was a non-randomized study in which survival prognosis was adjusted by multiple prognostic factors of applicability (e.g., bulbar syndrome, presence of FTD), accessibility (e.g., availability of treatment options) and acceptance of NIV (e.g., withholding of treatment). Spinal onset, younger age at symptom onset and higher BMI were associated with longer survival in patients with NIV. The absence of FTD was associated with longer

survival, although not significantly so; this finding was also observed in an Italian study [23]. After adjustment for covariates, in the NIV cohort, prolonged survival was significantly correlated with younger age at symptom onset and a higher BMI (Table 3). The observation that longer survival was related to younger age at disease onset and utilization of PEG was also found to be true in the large Italian population-based study [31].

As previously reported and as expected, TIV prolonged survival significantly (82 months). Furthermore, NIV–TIV brought an additional survival benefit over TIV alone (21 months; Table 2). The results of the present study contribute to the notion that NIV in combination with subsequent TIV provided the longest survival (103.5 months) period. However, the interindividual variability of survival while on TIV was remarkable, with a range from 69 to 96 months, at a 95% CI. This variability in prognosis underlines the complexity of survival in a multivariant setting of clinical (e.g., age, ophthalmoplegia), psychosocial (e.g., individual resources, availability of assistive technology) and cultural determinants (e.g., ethical issues of discontinuation). In fact, in the TIV cohort, prolonged survival was significantly correlated with male gender, spinal type of onset, younger age at symptom onset, intake of riluzole and non-presence of FTD (Table 2). After adjustment of the covariates, spinal type of onset, younger age at symptom onset, utilization of PEG and intake of riluzole were significant influencing factors (Table 3). Accordingly, in an univariate analysis, the influence of gender and FTD on survival should be interpreted with caution. Other studies also confirmed the impact of age on survival [11,47]. In a previous study, we found that incidence of ophthalmoplegia in 41% of long-term ventilated patients was an important turning point in the patient´s decision-making process to withdraw from TIV [37].

The median survival after initiation of TIV was 25 months and comparable to reports from Italy and Denmark (19–22 months) [11,13,48], but longer than in one other Italian study, and studies from Spain and the UK (8–10 months) [7,12,42]. In contrast to our register and cohorts in other European countries, longer survival was only recently reported with TIV in Japan, with a mean survival of more than 11 years [38]. Although the reasons for differences in survival prognoses have not been analysed systematically, this finding may reflect economic and cultural differences among countries. This finding, the indication criteria and the timing of both the initiation of TIV and the discontinuation of invasive ventilation may have an important impact on survival with TIV. Acceptability of TIV withdrawal is a marked distinguishing factor in the use of TIV between Japan and Europe as well as among European countries, and needs to be duly considered.

In conclusion, the utilization rate for NIV was low, although this treatment option represents the standard of care. TIV was started predominantly without previous NIV in patients with bulbar syndrome and, to a lesser degree, as treatment escalation when NIV had been exhausted. NIV provided a significant survival benefit that was greater than previously reported. As expected, TIV added a further survival benefit, although the survival prognosis was highly variable. The reasons for refraining from ventilation therapy and the variability in survival prognosis are complex and warrant further investigation. Furthermore, real-world data on the utilization of NIV/TIV and survival prognosis in a multicentre approach may be of importance for the planning and analysis of clinical trials on disease-modifying medicines for which an impact on survival, beyond functional endpoints, is expected.

CONFLICT OF INTERESTS

T.M. and C.M. are founders of the digital management and research platform "APST" and hold shares in Ambulanzpartner Soziotechnologie APST GmbH.

AUTHOR CONTRIBUTIONS

S.S. and T.M. designed and conceptualized the study, analysed and interpreted the data, and drafted the manuscript for intellectual content. D.K. and A.M. had a major role in data acquisition, interpreted the data, and revised the manuscript for intellectual content. B.W. had a major role in data collection and preparation of data. B.K., K.K., J.N. and C.M. had a major role in data acquisition and revised the manuscript for intellectual content.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.