Prognosis of amyotrophic lateral sclerosis patients undergoing tracheostomy invasive ventilation therapy in Japan

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Abstract

OBJECTIVE: The aim of this study is to describe and clarify the factors affecting the prognosis of Japanese patients with amyotrophic lateral sclerosis (ALS) undergoing tracheostomy invasive ventilation (TIV) therapy.

METHODS: We conducted a prospective longitudinal observational case-control study using a multicenter registry. ALS patients who started TIV therapy after registration (TIV group) and those who did not receive TIV (non-TIV group) were included. We compared the survival time between the TIV group and the non-TIV group using a propensity score matching analysis and evaluated the prognostic factors in the TIV group.

RESULTS: From February 2006 to January 2018, 190 patients in the TIV group and 1093 patients in the non-TIV group were included in this study. The mean age of disease onset and usage rate of gastrostomy and non-invasive ventilation therapy differed between the groups. In the propensity score matching analysis using known prognostic factors, the median overall survival time of the TIV group was significantly greater than that of the non-TIV group (11.33 years vs. 4.61 years; $p < 0.001$). Analysis using the Cox proportional hazard model suggested that older age of onset and respiratory onset were independent factors for poor prognosis after starting TIV therapy.

CONCLUSION: We showed that there was a significant difference of approximately 7 years in life expectancy between Japanese ALS patients who did and did not receive TIV therapy.

(226 words)

Keywords: ALS, TIV

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive, paralytic disorder characterized by degeneration of the upper and lower motor neurons. It begins insidiously with focal weakness, typically in the arms or legs, and spreads relentlessly to involve most muscles, including the diaphragm.[1] Although the rate of progression of ALS varies widely among patients,[2,3] most patients die within 3 to 5 years following disease onset, mainly due to respiratory failure.[1]

Tracheostomy invasive ventilation (TIV) therapy can support ALS patients with respiratory failure and may improve prognosis. However, there are considerable differences in TIV utilization for ALS patients among countries. For example, the rate of TIV use was reported to be 4 - 8% in the United States,[4,5] 5.2% in Northern Europe,[6] 10.6% in Italy,[7] 21.0% in Taiwan,[8] and 29.3% in Japan.[9]

Although the reason for the rates (particularly high rate in Japan) being different is unclear, the cultural differences in providing informed consent, the social differences towards the use of artificial life support and the preferences of different neurologists may influence the decision-making process for introducing TIV.[10] The lack of evidence on TIV therapy for ALS patients may also contribute to this variation.[11] Deciding on artificial ventilation with appropriate informed consent is a crucial issue for ALS patients and their health professionals. To support the decision-making, it is important to provide ALS patients with the information on clinical courses and prognosis of TIV therapy. However, previous reports on the prognosis of ALS patients

with TIV are mainly from a single facility. In Italy, a population-based study investigating outcome of tracheostomy in ALS patients showed that the median survival duration after tracheostomy was less than 1 year.[7] Conversely, several studies from a single facility reported median survival times of over 3 years following initiation of TIV.[12,13]

To describe the outcome of TIV therapy and clarify factors affecting the prognosis after TIV introduction in Japanese patients with ALS, we analyzed data from a multi-center ALS registry in Japan.

METHODS

Outline of the registry

We constructed a prospective multicenter registration and follow-up system for ALS called the Japanese Consortium for Amyotrophic Lateral Sclerosis research (JaCALS), which consists of 32 medical facilities in Japan. The patients with ALS who were diagnosed in these facilities based on the revised El Escorial criteria were consecutively registered after providing written informed consent.[14] At registration, full clinical examinations were conducted by neurologists in the respective facilities. The ethics committees of all participating facilities approved the study. The onset of the disease was defined as when the patient initially recognized a weakness, a bulbar symptom or a respiration disorder. The onset type was defined by the site that was dominantly impaired at the early phase of the disease. The included patients were prospectively followed-up via telephone surveys conducted by clinical research coordinators (CRCs) every 3 months, and the degree of deterioration in physical function for performing the activities of daily living (ADL) was determined at each time-point or examined by the doctor every year. As a scale of physical function, we used

the Japanese version of the ALS functional rating scale (ALSFRS-R), which was validated by Ohashi et al.[15] We previously confirmed the reliability of this telephone survey system,[16] using a method similar to that used to confirm the English version of the telephone survey in several studies.[17,18]

Patients

From February 2006 to January 2018, 1429 patients with ALS were registered. The observation period lasted until September 2018. Among them, 62 cases were excluded due to insufficient data. There were 274 patients who used TIV and 1093 patients who did not use TIV. We excluded 84 patients who had started TIV before registration. We included 190 patients who started TIV after registration (defined as the "TIV group"), and 1093 patients who did not use TIV (defined as the "non-TIV group") as the control group. Twelve patients in the TIV group and 56 patients in the non-TIV group had a family history of ALS.

Statistics

Comparison of onset age was performed using the Mann-Whitney U test, and comparison of data between the groups was done using the chi-squared test. Data on survival was evaluated using the Kaplan-Meier method and log-rank test. Because there were significant background differences between the patients in the TIV and the non-TIV group, a propensity score matching analysis was used to adjust for the baseline features between the TIV and the non-TIV group. The variables used in the propensity score matching analysis were onset age, sex, the revised El Escorial criteria, onset type, family history, use of riluzole, use of non-invasive ventilation (NIV) and use of tube feeding nutrition. Greedy matching (ratio 1:1 without

replacement) was performed based on the propensity score. We set the caliper to 0.2 standard deviations of propensity score. After propensity score matching analysis, we also examined the survival for each age subgroup and each onset type subgroup of the TIV group and the non-TIV group. For prognostic analysis after TIV introduction we considered 7 factors (sex, onset age, onset type, duration from onset to starting TIV, use of NIV, use of feeding tube, and use of riluzole) as covariates in a multivariate cox hazard model. The analyses were conducted using the IBM SPSS Statistics 24.0 software (SPSS Inc, Chicago, Illinois, USA). A two-sided p value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

The demographic features of the included patients are shown in Table 1. After propensity score matching, 184 patients (65% male) in the TIV group and 184 patients (67% male) in the non-TIV group were included in the analysis. Average age of onset was 60.41 ± 10.72 years in the TIV group and 60.27 ± 12.44 years in the non-TIV group. The median follow-up time was 3.24 years (interquartile range: 1.55-4.68 years). There were no significant differences in all the characteristics between the groups (Table 1).

Table1: Clinical features of the included patients

	Included patients			Propensity score matching		
	TIV	Non-TIV	p value	TIV	Non-TIV	p value

number of patients	190	1093		184	184	
Sex (Male/Female)	124/ 66	636/ 457	0.067	119/ 65	123/ 61	0.742
Onset age (mean±S.D.)	60.1±10.9	62.2±12.2	**<0.001**	60.4±10.7	60.3±12.4	0.710
Family history	12(6.3%)	56(5.1%)	0.498	12(6.5%)	7(3.8%)	0.456
site of onset						
Upper Limb	67(35.3%)	424(38.8%)	0.356	66(35.8%)	65(35.3%)	0.913
Low Limb	56(29.5%)	267(24.4%)	0.139	52(28.3%)	53(28.8%)	0.908
Bulbar	45(23.6%)	257(23.5%)	0.959	44(23.9%)	40(21.7%)	0.629
Respiratory	4(2.1%)	15(1.4%)	0.307	4(2.2%)	3(1.6%)	0.500
Others(*)	18(9.5%)	130(11.9%)	0.335	18(9.8%)	23(12.5%)	0.407
The revised El Escorial criteria						
Definite	56(29.5%)	242(22.1%)	**0.027**	54(29.3%)	57(31.0%)	0.733
Probable	63(33.1%)	391(35.7%)	0.487	63(34.2%)	64(34.7%)	0.913
Probable-labo supported	51(26.8%)	304(27.8%)	0.782	51(27.7%)	46(25.0%)	0.554
Possible	9(4.7%)	91(8.3%)	0.089	9(4.9%)	9(4.9%)	1.000
Suspected	7(3.7%)	65(5.9%)	0.932	7(3.8%)	8(4.3%)	0.792
Tube feeding	177(93.1%)	371(33.9%)	**<0.001**	171(92.9%)	171(92.9%)	1.000
Riluzole	167(87.9%)	798(73.0%)	**<0.001**	162(88.0%)	161(87.5%)	0.874
NIV	96(50.5%)	275(25.2%)	**<0.001**	94(51.1%)	93(50.5%)	0.917

TIV：tracheostomy invasive ventilation, S.D.: Standard Deviation, NIV: Non-invasive ventilation

* Dropped head type, Brachial amyotrophic diplegia type, Primary lateral sclerosis type, Dementia type, and Unclassified.

Survival analysis

Figure 1 shows Kaplan-Meier curves in the TIV group and the non-TIV group. Median survival time in the TIV group was 11.33 years (interquartile range: IQR 7.83-16.84), and 4.61 years (IQR 2.59-7.75) in the non-TIV group ($p < 0.001$) (Table 2). The Cox Regression Analysis examining the factors affecting survival time after starting TIV showed significant hazard ratios of "Onset age" (1.05, 95% CI: 1.02-1.08, $p=0.004$) and "Respiratory onset type" (29.86, 95% CI: 6.62-134.60, $p<0.001$).

Table 2: Survival from onset in each age group

a: Median survival time from onset in each age group

Onset age	TIV Number	TIV Median survival time (IQR)	Non-TIV Number	Non-TIV Median survival time (IQR)	p value(*)
Under 50	32	N/C (9.00-)	38	7.20(4.09-12.59)	<0.001
From 50 to 60	45	14.58(8.42-)	38	5.50(3.42-7.75)	<0.001
From 60 to 70	76	9.25(6.92-12.25)	70	3.67(2.50-7.08)	<0.001
Over 70	31	6.33(5.91-9.09)	38	4.00(2.42-6.00)	0.003
Total	184	11.33(7.83-16.84)	184	4.61(2.59-7.75)	<0.001

b: Five-year and 10-year survival rates from onset

Onset age	TIV 5-year	TIV 10-year	Non-TIV 5-year	Non-TIV 10-year
Under 50	93.4%	74.1%	65.8%	33.4%
From 50 to 60	92.8%	67.9%	51.8%	20.8%
From 60 to 70	90.2%	41.3%	40.0%	14.5%
Over 70	79.2%	22.5%	30.5%	14.5%
Total	89.1%	53.4%	45.4%	18.9%

IQR: interquartile range, N/C: not calculated, TIV: tracheostomy invasive ventilation

We divided the patients into 4 subgroups by onset age: under 50 years, from 50 to 60 years, from 60 to 70 years, and above 70 years. The survival curves and median survival times and survival rates (5-year and 10-year) of the age groups are shown in Figure 2 and Table 2, respectively.

In all the onset age subgroups, there was a significant difference of life prognosis between the TIV and non-TIV groups, with the difference being larger in the younger onset age subgroup.

We also examined life prognosis according to the onset type (Table 3). There was no significant difference in the time from disease onset to starting TIV among the onset type subgroups (Figure 3a). The survival time after starting TIV in the respiratory onset subgroup was significantly shorter than in the other subgroups (p

< 0.001) (Figure 3b). The respiratory onset type was rare, with only 4 patients classified into this subgroup. These 4 patients were 3 males and 1 female, and the mean onset age was 61.9 ± 10.6 years old (range: 44-73). They had no family history of ALS and no past medical histories which could worsen the life prognosis. All 4 patients died during the follow-up period, and the causes of death were kidney failure, myocardial infarction, respiratory failure due to pulmonary fibrosis, and unknown.

Table3: Survival time in each group of the onset type in the TIV group.

Onset type	Number of patients	Median time from onset until starting TIV (years) (Interquartile range)	Median survival time from starting TIV (years) (Interquartile range)
Upper Limb	67	2.92 (1.92-4.50)	6.75 (4.83-NC)
Lower Limb	56	3.25 (2.25-4.42)	5.83 (3.92-9.33)
Bulbar	45	2.50 (1.51-3.90)	9.67 (2.75-NC)
Respiratory	4	2.08 (1.25-3.42)	1.00 (0.33-1.25)
Other(*)	18	2.92 (2.08-4.17)	NC (5.00-NC)

TIV: tracheostomy invasive ventilation

NC: not calculated

* Dropped head type, Brachial amyotrophic diplegia type, Primary lateral sclerosis type, Dementia type, and Unclassified.

Cause of death

During the observation period, 62 patients died in the TIV group. The most frequent cause of death was pneumonia and the second was respiratory failure due to suffocation or any other airway complications (Table 4). Non-respiratory problems, such as heart diseases or malignancy, accounted for more than half of the

causes of death in the TIV group. On the other hand, in the non-TIV group most of the causes of death were pneumonia and respiratory failure, except for the unknown causes (Table 4).

Table4: Causes of death in the TIV group and the non-TIV group

Cause of death	Number of patients	
	TIV group	Non-TIV group
Pneumoniae	16	64
Respiratory failure/suffocation	10	270
Heart disease	8	24
Multiple organ failure/Renal failure	5	10
Malignancy	3(*)	7(***)
Others	6(**)	19(****)
unknown	14	217
Total	62	611

TIV: tracheostomy invasive ventilation
(*) retroperitoneal tumor, colon cancer, cholangiocarcinoma
(**) pulmonary embolism, intestinal necrosis, cholecystitis, fungus sinusitis, accident, pulmonary fibrosis
(***) Hepatocellular carcinoma 2persons、stomach cancer, uterine cancer, multiple cancer, prostate cancer each one person
(****) Accident 4persons, stroke 3persons, ileus 3persons, FTLD, hypoxic encephalopathy, intestinal necrosis, liver failure, aortic dissection, pulmonary embolism, thyroid disease, each one person.

Physical functions before and after TIV introduction

The mean values of total ALSFRS-R scores for each onset type subgroup (excluding the respiratory scores of "Dyspnea", "Orthopnea", "Respiratory insufficiency") are shown for each month spanning 3 years before and after starting TIV (Figure 4, supplemental table). The physical functions of the patients deteriorated rapidly around the perioperative period of introduction of TIV, and most of the patients were confined to bed after starting TIV.

DISCUSSION

In this multicenter registry study, we showed that there is approximately a 7-year difference in survival time between ALS patients with TIV and those without TIV, suggesting that TIV therapy can influence life prognosis of ALS patients by ameliorating respiratory problems. Previous reports showed that the causes of death in ALS patients without TIV were mostly respiratory problems,[19,20] which was confirmed in our present study.

The length of survival extension with TIV therapy shown in this study is comparable to previous reports from facilities in Japan, however there were considerable differences compared to reports from other countries. In a survival analysis of ALS patients with TIV from a facility in Italy, TIV therapy extended median survival by 16 months (TIV, 47 months vs non-TIV, 31 months).[17] In a single-center cohort study from Denmark, the average treatment time of the group with non-invasive mechanical ventilation followed by TIV was 33.9 months more than that of the group with no mechanical ventilation (NIV + TIV, 56.8 months vs no ventilation support, 22.9 months).[18] Taken together, the life expectancy following TIV introduction in Japanese ALS patients appears to be longer than in Europeans. The evaluation and analysis methods may contribute to this difference, but the exact reason is an issue to be considered in the future.

We showed that higher age of onset was associated with poor prognosis after starting TIV therapy. The higher age of onset is commonly shown to be one of the poor prognostic factors among ALS patients with TIV or tracheostomy in previous reports from Japan and European countries.[12,17,18] The higher age of onset is also reported to be an independent risk factor of poor prognosis in ALS patients without TIV therapy.[21] The decline of available biological reserves in elderly patients was considered to be one of the reasons for

this.[22] The use of NIV therapy before starting TIV was reported to be a factor favoring survival in ALS patients using TIV,[18] however this was not confirmed in our present study. Our study also suggests that the respiratory onset type is a poor prognostic factor for survival after starting TIV, but the reason for this is unclear. Because the number of patients with respiratory onset was too small, we must interpret this result with caution. It was reported that the respiratory onset is a poor prognostic factor in ALS patients without TIV,[23] and one reason for this might be an increased energy metabolism due to disordered breathing, making patients weaker.[23,24] Our results showed that all patients with respiratory onset presented steep ADL deteriorations immediately before starting TIV, which might influence the poor prognosis following TIV introduction.

Our results showed that patients' physical function severely declined after TIV introduction. It was previously reported that over 70% of patients lost swallowing and limb function after TIV introduction.[25] In Japan, about 13% of ALS patients with TIV were classified as totally locked in state (TLS), which is defined as total paralysis of the voluntary muscles, including the ocular muscles.[26] It has been reported to take an average of 2.75 years from respiratory failure to TLS.[26] In Germany, about 19.4% of ALS patients with long-term TIV were in TLS. [27] In fact, ALS patients with TIV therapy would live in a poor ADL state. In addition, their behavioral disorder and physical function deterioration is often burdensome to the families and may cause depression to their caregivers. [28,29] If they become TLS, the burden on the caregiver is expected to increase significantly.

On the other hand, a recent observational study from Sweden showed that ALS patients in the state of complete immobility and loss of verbal communication abilities maintain a high sense of well-being and have

a strong will to live.[30] In a survey of ALS patients with emergent introduction of TIV in Italy, over 80% responded favorably to using TIV.[31] Studies from Japan also reported high patient adherence following TIV introduction.[12] In Japan, some ALS patients with TIV therapy are maintaining social activities. All this information, including life expectancy, should be provided so that patients can make an informed decision whether or not to introduce artificial ventilation. In Japan, there is no legally approved procedure to enable TIV withdrawal, which could render decision-making to start TIV even more important. From the information in this study, various effects on decision-making of ALS patients can be considered. We recommend providing quality information to those who need it.

The daily lives of ALS patients with TIV may be influenced by the medical care system, nursing care system, various socioeconomic factors or family situations. There are reports that the existence of marital relationships has an impact on the prognosis of ALS patients.[32,33] Collecting and analyzing this information and investigating the patients' quality of life are tasks to be addressed in the future.

This study has several limitations. In this survey, we could not completely evaluate the urgency and status at the time of introduction of TIV, cognitive functions of the patients, status of the patients' family, the burden of caregivers, and status of communication in the patients with TIV. These are important concerns for the future studies. We conducted a propensity score matching to adjust the effects of confounding factors using observed known prognostic factors. If unmeasured confounding factors existed, the effects were not adjusted, which could be a limitation to this study.

In conclusion, we showed that Japanese ALS patients with TIV had longer survival times than those without TIV, and there was a difference of about 7 years in median survival. The effect of TIV on prognosis

was limited in elderly patients and possibly in patients with respiratory onset type. This information will contribute to improve decision-making regarding medical care for ALS patients.

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FIGURE LEGENDS

Figure 1. Comparison of overall survival time from onset. The TIV group and the non-TIV group were matched by propensity scores. TIV: tracheostomy invasive ventilation

Figure 2. Comparison of overall survival time from onset in each onset age subgroup.

Figure 3. Comparison of survival among the onset type subgroups. Figure 3a shows time from disease onset to starting TIV. Figure 3b shows survival time following introduction of TIV.
(Others consist of Dropped head type, Brachial amyotrophic diplegia type, Primary lateral sclerosis type, Dementia type, and Unclassified.)

Figure 4. Physical functions before and after TIV introduction in the onset type subgroups. The mean values of total ALSFRS-R scores, excluding the respiratory scores (the scores of “Dyspnea”, “Orthopnea”, “Respiratory insufficiency”), are shown for each month 3 years before and after starting TIV.