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Onset of age, site and respiratory symptoms are strongly associated with respiratory decline in sporadic amyotrophic lateral sclerosis: a long-term longitudinal study

Shin-ichi Terao ,[1] Yasunobu Nosaki,[2] Atsunori Murao,[3] Ryota Torii,[4] Nanayo Ogawa,[5] Naofumi Miura,[6] Yousuke Sasaki,[7] Gen Sobue[8]

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For numbered affiliations see end of article.

Correspondence to
Dr Shin-ichi Terao;
terao@mitaki.or.jp

ABSTRACT

Objective The objective of this study is to identify factors influencing progression of respiratory decline from the onset of neurological symptoms to respiratory failure in patients with amyotrophic lateral sclerosis (ALS).

Methods In 100 patients with sporadic ALS, %vital capacity (%VC) was continuously measured from the first visit to the respiratory endpoint (REP). Cox proportional hazards model identified factors influencing the duration from onset of ALS to REP (Onset-REP). We performed Kaplan-Meier survival curve analysis for onset-REP according to identified factors.

Results Onset sites were the upper limb (U-ALS), lower limb (L-ALS), bulbar paralysis (B-ALS) and respiratory paralysis (R-ALS) in 37, 19, 32 and 12 patients, respectively. Duration from the onset of ALS to the onset of respiratory symptoms (Onset-Rp) and REP (Onset-REP) was 16.1 (SD 12.1) and 24.9 months (SD 14.6), respectively. Multivariate analysis revealed that age at onset, site of onset, Onset-Rp and %VC decline rate significantly influenced Onset-REP duration. Elderly patients had a significantly shorter Onset-REP duration. Onset-REP duration did not significantly differ between patients with U-ALS and L-ALS, but was longer in these patients than in those with B-ALS and R-ALS. Onset-REP duration was positively associated with Onset-Rp duration. The average monthly %VC decline rate was −5.6% (SD 3.3). Age at onset, onset site and Onset-Rp duration significantly influenced the %VC decline rate.

Conclusions Our findings revealed strong and independent patient-specific factors that influence the Onset-REP duration and the %VC decline rate in patients with ALS. These could inform future clinical trials and interventions considering the respiratory function and natural history of patients with ALS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Studies have investigated the natural history and survival of patients with amyotrophic lateral sclerosis (ALS), with a focus on age, sex, onset site and survival time. Compared with young and middle-aged patients, elderly patients with ALS are clinically characterised by poorer prognosis and more frequent onset of bulbar palsy. However, the decline in respiratory function over time in patients with ALS remains unclear.

WHAT THIS STUDY ADDS

⇒ To identify factors that influence the progression of respiratory decline from the onset of neurological symptoms to respiratory failure in patients with ALS. Multivariate analysis revealed that age at onset (p=0.039), site of onset, onset of ALS to the onset of respiratory symptoms (Onset-Rp) (p<0.001), and %VC decline rate (p=0.001) significantly influenced the duration from onset of ALS to respiratory endpoint (Onset-REP). The average monthly %VC decline rate was −5.6% (SD 3.3). Age at onset (p=0.029), onset site and Onset-Rp duration (p<0.001) significantly influenced the %VC decline rate.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings could inform future clinical trials and interventions that consider the respiratory function and natural history of patients with sporadic ALS.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that selectively and systematically damages cortical and spinal motor neurones, which results in systemic atrophy of muscles, including respiratory muscles. Accordingly, respiratory muscle paralysis can lead to death due to respiratory insufficiency.[1–5] Studies have investigated the natural history and survival of patients with ALS, with a focus on age, sex, onset site and survival time.[6–11] Compared with young and middle-aged patients, elderly patients with ALS are clinically characterised by poorer prognosis and more frequent onset of bulbar palsy.[9 10 12–16]

Table 1 Patient characteristics of whole patients (n=100), and those with consecutive %VC measurements (%VC decline rate) (n=53)

	Number (%)	Mean value (SD)	Number (%)	Mean value (SD)
Age at neurological onset, years	100	63.3 (11.6)	53	61.6 (11.5)
Sex, men	63 (63)		35 (66)	
Onset site	100		53	
Upper limb weakness (U-ALS)	37 (37)		20 (38)	
Lower limb weakness (L-ALS)	19 (19)		12 (23)	
Bulbar symptoms (B-ALS)	32 (32)		14 (26)	
Respiratory symptoms (R-ALS)	12 (12)		7 (13)	
Onset-FE, months	100	11.3 (7.8)	53	11.9 (8.4)
%Vital capacity at baseline, %	89	84.0 (19.8)	53	87.1 (19.8)
Onset-Rp, months	100	16.1 (12.1)	53	16.1 (10.8)
Rp-REP, months	100	8.9 (5.0)	53	10.8 (5.7)
Onset-REP, months	100	24.9 (14.6)	53	26.9 (14.4)
Onset-permanent ventilator	100	33.1 (22.7)	53	36.5 (25.9)
or heart death, months				
Ventilator: NIV	11 (11)		9 (17)	
TIV	12 (12)		3 (6)	
%VC decline rate per month			53	−5.6 (3.3)

NIV, non-invasive ventilation; Onset-FE, period from onset to first examination; Onset-REP, period from onset to respiratory endpoint; Onset-Rp, period from onset to respiratory symptoms; Rp-REP, period from respiratory symptoms to respiratory endpoint; TIV, tracheostomy and invasive ventilation.

It is important to elucidate the clinical manifestations of ALS, especially the respiratory deterioration over time, in order to allow prediction of the disease course, selection of appropriate treatment strategies and design of clinical trials. However, the decline in respiratory function over time in patients with ALS remains unclear. The prognosis of patients with ALS is dependent on the onset of respiratory failure due to respiratory muscle weakness and residual respiratory function. The present study performed a long-term sequential assessment of respiratory function until death or respiratory failure in patients with sporadic ALS. Specifically, we aimed to document the natural history of respiratory deterioration in patients with ALS with respect to various clinical features such as age at onset, onset site and onset of respiratory symptoms (Rp). Additionally, we aimed to clarify the factors that influenced the duration from the onset of illness to respiratory failure and the rate of respiratory decline in Japanese patients with sporadic ALS.

PARTICIPANTS AND METHODS

Participants

We included 100 patients with sporadic ALS who were followed over time for clinical assessments, including respiratory function, from the first examination to respiratory failure. They were selected from the Department of Internal Medicine (S-iT and NM) of Aichi Medical University between 1989 and 2004, the Department of Neurology (S-iT, YN, AM, and RT) of Kasugai Municipal Hospital between 2006 and 2019 and the Department of Neurology (S-iT and NO) of Mitaki General Hospital between 2020 and 2023. Patients were diagnosed using the revised El Escorial diagnostic criteria for ALS, which are based on the presence of progressive cortical and spinal motor neuron signs, diagnostic imaging such as MRI, electrophysiological findings and clinical course.[17] To avoid selection bias, we included not only patients with ALS with limb paralysis or bulbar palsy, but also patients with ALS with rapidly progressing acute respiratory failure. We included patients with definite, probable or probable ALS according to laboratory-supported findings. We excluded patients with a medical history of cerebrovascular disease, dementia including frontotemporal lobar degeneration or chronic lung disease.

Assessment of time of ALS onset (Onset), period until clinical respiratory symptoms (Rp) and time of respiratory endpoint (REP)

The time of ALS onset was defined as the time at which the patient became aware of subjective neurological symptoms on muscular weakness. The onset time of Rp was defined as the time when the patient experienced shortness of breath, dyspnoea or difficulty in deep breathing, and sleep disturbance. Pulmonary function testing was performed using standardised spirometry to continuously assess the forced vital capacity of the patient, which was expressed as per cent predicted vital capacity (%VC).[9 18–22] Standardised spirometry testing using a mouthpiece was

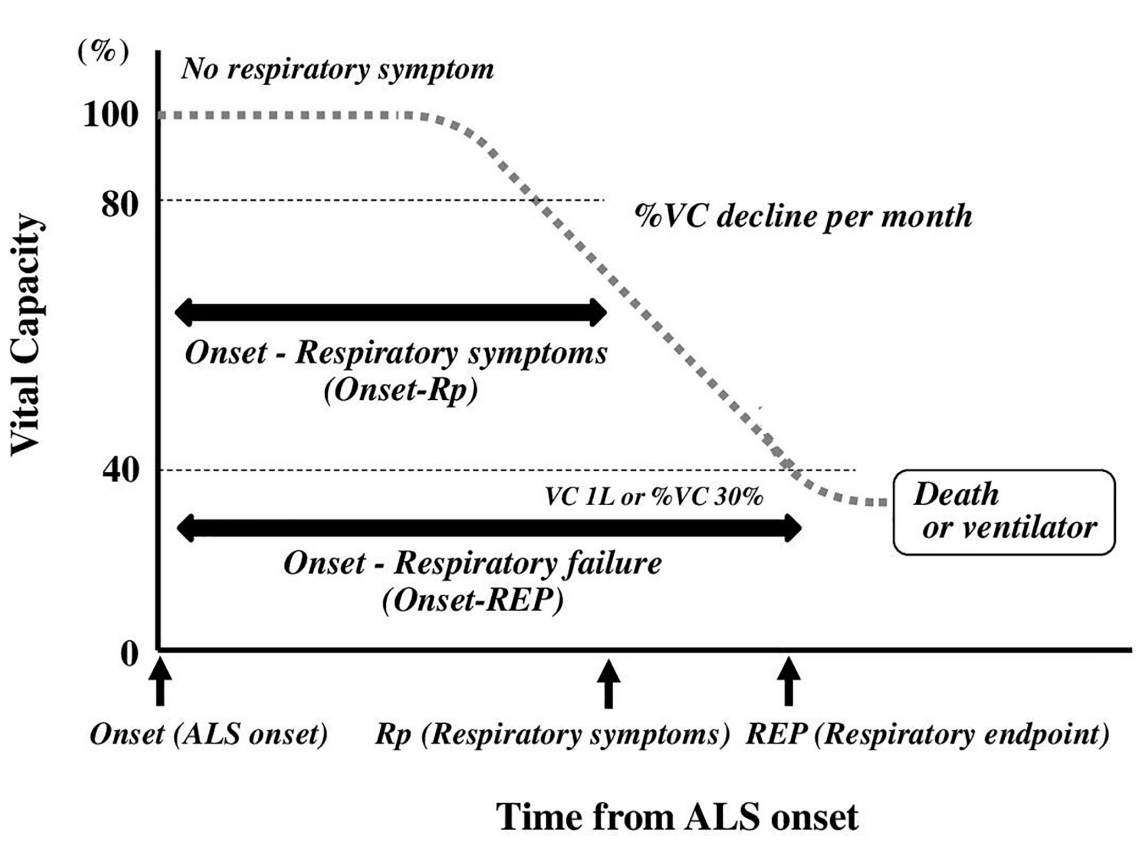

Figure 1 Schematic diagram of the course of respiratory function deterioration in patients with amyotrophic lateral sclerosis (ALS). Schematic diagram showing the time from ALS onset to a decline in vital capacity. Onset-Rp indicates the period from the onset of ALS to the onset of Rp. Onset-REP was defined as the time from the onset of ALS to respiratory failure (respiratory endpoint). The decline in respiratory function over time was shown as the monthly per cent predicted vital capacity (%VC) decline rate.

performed initially on 89 patients. Furthermore, we performed consecutive spirometry at least once a month (mean 1.9 times (SD 0.9) per month) from the initial examination to the REP in 53 patients. If the patient had difficulty holding the mouthpiece, further continuous VC measurements were discontinued. A decrease in %VC to 50% of the predicted value almost always involves Rp.[23 24] Additionally, a decrease in the VC to <30% of the

Table 2 A Cox hazard model with Onset-REP as the dependent variable

	N	HR	95% CI		P value
Multivariable analysis: forced input of significant variables					
Age at onset (per 1 year old)	100	0.971	0.944	0.998	0.039
Sex, men (vs women)	100				
Onset site	100				
U-ALS (upper limb)	37	1	Ref		
L-ALS (lower limb)	19	2.103	1.071	4.127	0.031
B-ALS (bulbar)	32	3.167	1.532	6.545	0.002
R-ALS (respiratory)	12	4.978	1.502	16.501	0.009
Onset-FE (per 1 month)	100	1.005	0.947	1.066	0.881
%Vital capacity at baseline (per 1)	89	1.008	0.994	1.026	0.351
Onset-Rp (per 1 month)	100	0.57	0.501	0.648	<0.001

95% CI, 95% confidence interval; HR, Hazard ratio.

Table 3 A Cox hazard model with Onset-REP as the dependent variable (with %VC decline rate)

	N	HR	95% CI		P value
Multivariable analysis: Forced input of significant variables					
Age at onset (per 1 year old)	53	1.037	0.998	1.079	0.065
Sex, Men (vs Women)	53	—			
Onset site	53				
U-ALS (upper limb)	20	1.000	ref		
L-ALS (lower limb)	12	0.522	0.205	1.328	0.172
B-ALS (bulbar)	14	1.354	0.551	3.327	0.508
R-ALS (respiratory)	7	1.735	0.483	6.235	0.398
Onset-FE (per 1 month)	53	1.059	0.989	1.133	0.100
%Vital capacity at baseline (per 1)	53	1.006	0.979	1.033	0.666
Onset-Rp (per 1 month)	53	0.746	0.672	0.828	< 0.001
%VC decline rate (per 1)	53	1.322	1.128	1.549	0.001

95% CI, 95% confidence interval; HR, Hazard ratio.

predicted value is an indicator of imminent respiratory failure or death.[18] Therefore, we set the REP to %VC of ≤30% or undergoing tracheostomy.

Statistical analysis

We used the Cox proportional hazard model to identify factors that influence the Onset-REP duration, which included onset age, sex, onset site, onset to first examination (Onset-FE), %VC at baseline and onset-Rp, with adjustment for confounding factors. Additionally, we performed Kaplan-Meier (K-M) survival curve analysis for onset-REP according to age at onset, onset site, onset-Rp and %VC decline rate. Further, we examined the %VC decline rate using linear regression analysis. Statistical analyses were performed using SPSS software (V.24.0; IBM Japan). Between-group comparisons were performed using the unpaired t-test (Bonferroni correction) or Fisher's exact test. Statistical significance was set at p<0.05.

RESULTS

Table 1 shows the background characteristics of the patients. The mean age at onset was 63.3 (SD 11.6) years; moreover, 63% of the patients were men. Regarding the site of onset, these were the upper limb (U-ALS) and lower limb (L-ALS) in 37 and 19 patients, respectively. Thirty-two patients had bulbar palsy (B-ALS) that caused dysarthria or dysphagia, and 12 patients had respiratory muscle palsy (R-ALS) that caused breathing difficulties. The period from ALS onset to the first examination (Onset-FE) was 11.3 (SD 7.8) months, the %VC value at the baseline was 84.0 (19.8) %, the period from the ALS onset to the onset of Rp (Onset-Rp) was 16.1 (SD 12.1) months, and the period from the onset of Rp to REP (Rp-REP) was 8.9 (SD 5.0) months. The mean Onset-REP duration was 24.9 (SD 14.6) months; further, the period from ALS onset to failure of ventilation weaning or cardiac arrest was 33.1 (SD 22.7) months. Three patients with B-ALS and one patient with R-ALS developed pneumonia at the initial examination. Among the patients with R-ALS, nine patients presented with severe weight loss preceding Rp, while four patients had acute respiratory failure. In this study, 25 patients underwent tracheostomy, and 12 patients received invasive ventilation. Five patients with U-ALS (three men) and one male patient with L-ALS survived for ≥2 years following REP until cardiac death, without respiratory management.

Based on previous reports[12 25] and our nomenclature, we have shown a schematic diagram of the progression of respiratory decline in patients with ALS (figure 1) and indicated the time of respiratory events. During early-stage ALS, Rp may not occur even if the patient presents limb weakness or bulbar symptoms. The onset time of Rp varies across patients; however, it begins with a gradual decline in respiratory function, followed by progressive deterioration and eventually respiratory failure.

Factors associated with the Onset-REP duration

In the multivariate analysis, age at onset (p=0.039), onset site (for U-ALS, L-ALS p=0.031, B-ALS p=0.002, R-ALS p=0.009) and Onset-Rp (p<0.001) were significantly associated with Onset-REP duration. Regarding the onset site, the HR for L-ALS, B-ALS and R-ALS were 2.103 (p=0.031), 3.167 (p=0.002) and 4.978 (p=0.009), respectively (table 2). A Cox proportional hazards model that used the factors identified in the multivariate analysis showed that Onset-Rp (HR 0.746, p<0.001) and %VC decline (HR 1.322, p=0.001) were significant factors for the Onset-REP duration (table 3). For table 3, more detailed results of univariate and multivariate analyses were presented in online supplemental table 1.

In the K-M survival curve analysis of onset-REP according to age at onset (figure 2a), the patients were divided into three groups: group A (≤55 years, n=29) and group B

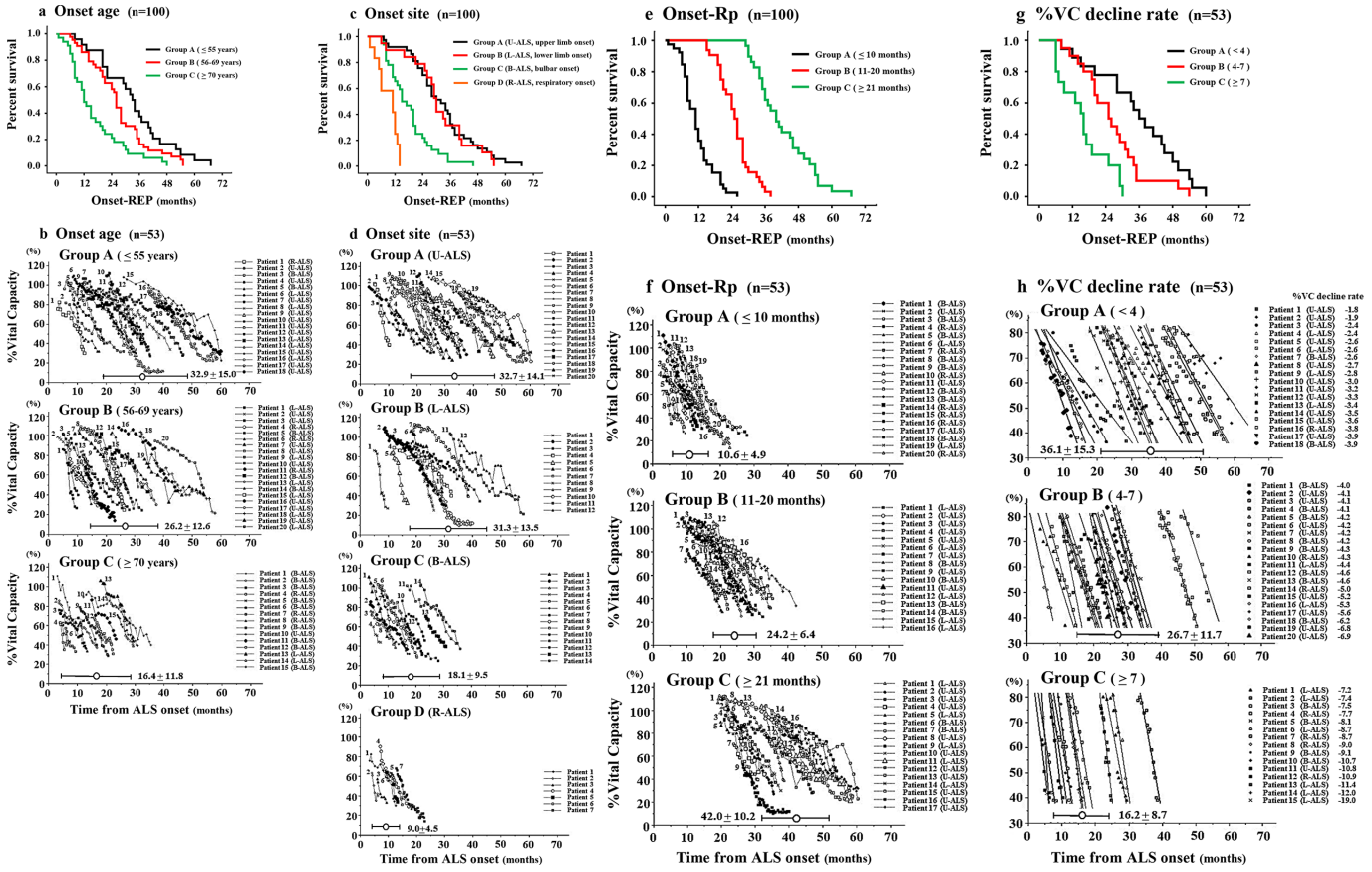

Figure 2 Kaplan-Meier survival curve analysis of Onset-respiratory endpoint (REP) and progression of respiratory function (per cent predicted vital capacity (%VC)) in patients with amyotrophic lateral sclerosis (ALS). Kaplan-Meier survival curve analysis of Onset-REP (a, c, e and g)—the age at onset was divided into three groups: group A (≤55 years, n=29), group B (56–69 years, n=38) and group C (≥70 years, n=33) (a). The onset sites were divided into four groups: group A (U-ALS, n=37), group B (L-ALS, n=19), group C (B-ALS, n=32) and group D (R-ALS, n=12) (c). Onset-Rp duration was divided into three groups: group A (≤10 months, n=34), group B (11–20 months, n=37) and group C (≥ 21 months, n=29) (e). %VC decline rate was divided into three groups: group A (<4, n=18), group B (4–7, n=20) and group C (≥7, n=15) (g). Progression of respiratory function (%VC) in patients with ALS (b, d, f and h)—the age at onset was divided into three groups: group A (≤55 years, n=18), group B (56–69 years, n=20), and group C (≥70 years, n=15) (b). The onset sites were divided into four groups: group A (U-ALS, n=20), group B (L-ALS, n=12), group C (B-ALS, n=14) and group D (R-ALS, n=7) (d). Onset-Rp duration was divided into three groups: group A (≤10 months, n=20), group B (11–20 months, n=16), and group C (≥21 months, n=17) (f). %VC decline rate for Onset-REP was divided into three groups; group A (<4, n=18), group B (4–7, n=20) and group C (≥7, n=15) (h). Onset REP values (SD) were indicated in each figure.

(56–69 years, n=38) and group C (≥70 years, n=33). The median Onset-REP durations did not significantly differ between group A (33.0 (SE=2.45) months) and group B (26.0 (SE 0.65) months) (p=0.072); however, it was significantly shorter in group C (12.0 (SE 1.64) months) than in groups A and B (p<0.001 and p=0.001, respectively). The slope of the %VC decline was nearly linear in group A with many patients showing a gentle gradient; however, it varied across the patients. In group B, patients with short and long onset-REP durations showed steep and gentle gradients, respectively. Patients in group C had a lower baseline %VC; accordingly, more patients showed steep slopes of the %VC decline (figure 2b).

In the K-M survival curve analysis of Onset-REP according to onset site (figure 2c), the patients were divided into four groups: group A (U-ALS, n=37), group B (L-ALS, n=19), group C (B-ALS, n=32) and group D (R-ALS, n=12). The median Onset-REP durations in groups A, B, C and D were 32.0 (SE 3.47), 30.0 (SE 1.08), 15.0 (SE 2.83) and 11.0 (SE 4.27) months, respectively. Groups A and B had a significantly longer Onset-REP duration than groups C and D, respectively (p<0.001). Group D had a significantly shorter Onset-REP duration than group C (p<0.001). In groups A and B, some patients showed a steep and fast %VC decline while others showed gentle and slow %VC decline. In group C, almost all patients showed a steep and fast %VC decline. Patients in group D tended to have a shorter disease course and lower baseline %VC (figure 2d).

In the K-M survival curve analysis of Onset-REP according to Onset-Rp (figure 2e), the patients were divided into three groups: group A (≤10 months, n=34), group B (11–20 months, n=37) and group C (≥21 months, n=29). The median Onset-REP durations in groups A, B

Table 4 Linear regression analysis with %vital capacity decline (logarithmic transformation) as the dependent variable

	N	Regression coefficient	SE	β	t value	P value	VIF
Univariable analysis:							
Age at onset (per 1 year old)	53	0.014	0.006	0.300	2.245	0.029	
Sex, men (vs women)	53	−0.065	0.152	−0.060	−0.429	0.669	
Onset site	53						
U-ALS (upper limb)	20	Ref					
L-ALS (lower limb)	12	0.435	0.179	0.352	2.428	0.019	
B-ALS (bulbar)	14	0.311	0.171	0.265	1.818	0.075	
R-ALS (respiratory)	7	0.553	0.215	0.362	2.566	0.013	
Onset-FE (per 1 month)	53	−0.015	0.008	−0.242	−1.779	0.081	
%Vital capacity at baseline	53	−0.004	0.004	−0.144	−1.039	0.304	
Onset-Rp (per 1 month)	53	−0.023	0.006	−0.474	−3.841	<0.001	
Onset-REP (per 1 month)	53	−0.022	0.004	−0.602	−5.378	<0.001	
Multivariable analysis: input significant variables stepwise							
Age at onset (per 1 year old)		n.e.					
Sex, men (vs women)		–					
Onset site							
U-ALS (upper limb)		Ref					
L-ALS (lower limb)		0.325	0.143	0.263	2.280	0.027	1.264
B-ALS (bulbar)		−0.065	0.153	−0.055	−0.422	0.675	1.613
R-ALS (respiratory)		0.016	0.204	0.011	0.080	0.937	1.693
Onset-FE (per 1 month)		–					
%Vital capacity at baseline		–					
Onset-Rp (per 1 month)		n.e.					
Onset-REP (per 1 month)		−0.013	0.006	0.364	−2.03	0.048	3.039

R^2 = 0.504, adjusted R^2 = 0.451. Onset site: upper limb (U-ALS), lower limb (L-ALS), bulbar (B-ALS), and respiratory (R-ALS).
Onset-FE, period from onset to first examination; Onset-Rp, period from onset to respiratory symptoms; VIF, variable inflation factor; β, standard regression coefficient.

and C were 11.0 (SE 1.24), 25.0 (SE 0.94) and 40.0 (SE 2.69) months, respectively. The Onset-REP duration was significantly shorter in group A than in groups B and C (p<0.001); further, it was shorter in group B than in group C (p<0.001). Group A comprised patients with steep and fast %VC decline. Group B included both patients with acute and mild %VC decline. Group C comprised only a few patients with steep slopes of %VC decline, with most patients showing a gentle and slow %VC decline (figure 2f).

In the K-M analysis of onset-REP according to the %VC decline rate (figure 2g), the patients were divided into three groups: group A (<4, n=18), group B (4–7, n=20) and group C (≥7, n=15). The median Onset-REP durations were 36.0 (SE 4.24) months in group A, 25.0 (SE 3.73) in group B and 16.0 (SE 1.90) in group C. Group A had a significantly longer onset-REP duration than group B or C (p=0.023 and p<0.001, respectively). Group B had a significantly longer onset-REP duration than group C (p=0.004). The onset-REP duration was negatively correlated with the %VC decline rate (figure 2h).

Factors affecting the slope of %VC decline

Furthermore, for 53 patients with ALS who underwent continuous follow-ups for respiratory function, we obtained a scatter plot showing where the %VC changed from 80% to ≤40% during the onset-REP duration (table 4). This scatter plot was used to obtain an approximate regression line, which was measured as the monthly %VC decline rate. The patient characteristics of 53 patients in which %VC was measured consecutively were shown in table 1. The population characteristics were almost same for these two groups (n=100 and n=53). The average monthly %VC decline rate among these patients was −5.6% (SD 3.3). Linear regression analysis revealed that onset age (p=0.029), onset site and Onset-Rp (p<0.001) significantly influenced the %VC decline rate.

To analyse the %VC decline rate according to the age at onset, patients were classified into the following three groups: group A (≤55 years, n=18), group B (56–69 years, n=20) and group C (≥70 years, n=15) (figure 3a). The monthly %VC decline rate

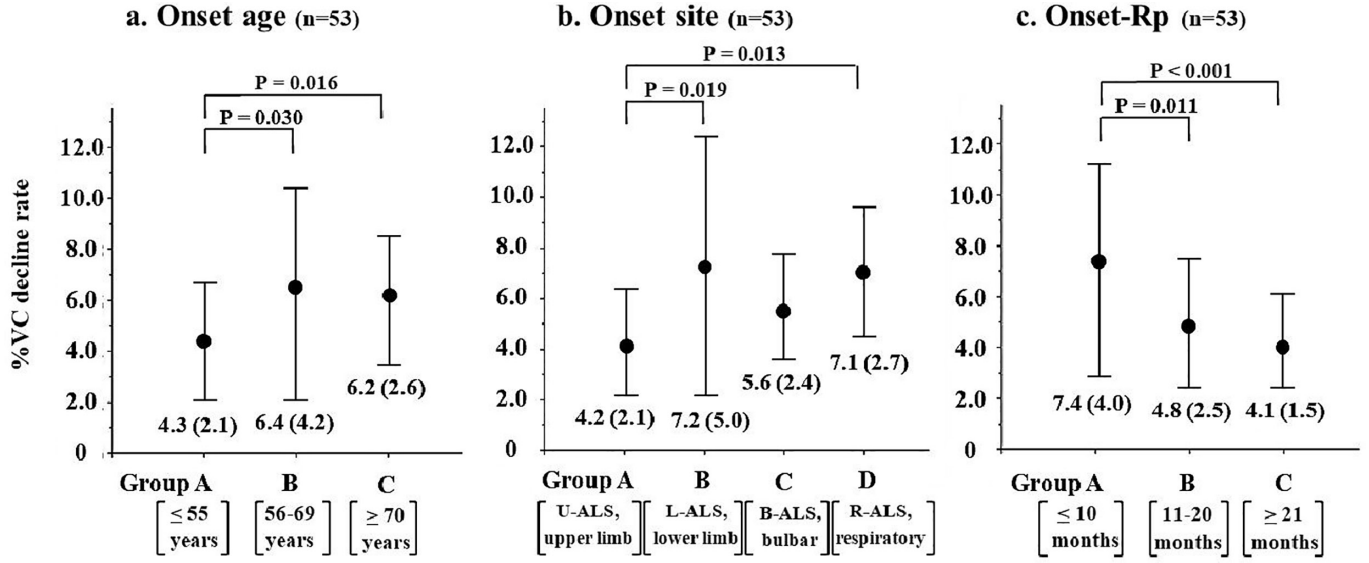

Figure 3 Factors affecting the per cent predicted vital capacity (%VC) decline rate in patients with amyotrophic lateral sclerosis (ALS). The age at onset was classified into three groups: group A (≤55 years, n=18), group B (56–69 years, n=20) and group C (≥70 years, n=15) (A). The onset sites were divided into groups A (U-ALS, n=20), B (L-ALS, n=12), C (B-ALS, n=14) and D (R-ALS, n=7) (B). Onset-Rp duration was divided into three groups: group A (≤10 months, n=21), group B (11–20 months, n=15) and group C (≥21 months, n=17) (C). The %VC decline rate (SD) indicated in each figure.

was 4.3 (SD 2.1) in group A, 6.4 (SD 4.2) in group B and 6.2 (SD 2.6) in group C. This rate was significantly smaller in group A than in groups B and C (p=0.030 and p=0.016, respectively).

To analyse the %VC decline rate according to the onset site, patients were divided into groups A (U-ALS, n=20), B (L-ALS, n=12), C (B-ALS, n=14) and D (R-ALS, n=7) (figure 3b). The monthly %VC decline rate was 4.2 (SD 2.1) in groups A, 7.2 (SD 5.0) in B, 5.6 (SD 2.4) in C and 7.1 (SD 2.7) in D. Univariable analysis revealed a significantly greater %VC decline rate in groups B and D than in group A (p=0.019, p=0.013, respectively). Multivariate analysis revealed that the %VC decline rate was significantly lower in group B than in group A (p=0.027).

To analyse the %VC decline rate according to Onset-Rp, patients were divided into groups A (≤10 months, n=21), B (11–20 months, n=15) and C (≥21 months, n=17) (figure 3c). The monthly %VC decline rate was 7.4 (SD 4.0) in groups A, 4.8 (SD 2.5) in B and 4.1 (SD 1.5) in C. Compared with groups B and C, group A had a significantly higher %VC decline rate (p=0.011, p<0.001, respectively).

The %VC decline rate was significantly lower in group A than in group C (figure 4a). The %VC decline rate was higher in groups B and D than in group A (figure 4b). Furthermore, the onset-Rp duration was negatively associated with the %VC decline rate (figure 4c).

DISCUSSION

Our study revealed that the age at onset, site of onset and onset-Rp duration significantly influenced the onset-REP duration and %VC decline rate in patients with sporadic ALS. Among them, onset-Rp duration showed the strongest influence on both onset-REP duration and %VC decline rate. The prognosis of patients with ALS is strongly determined by the REP and is correlated with the %VC decline rate. Therefore, the onset-Rp duration may be a crucial predictive factor for respiratory outcomes and prognosis in patients with ALS. Specifically, the onset-Rp duration is negatively and positively correlated with the onset-REP duration and %VC decline rate, respectively.

Consistent with our findings, the age at onset has been found to be a strong prognostic factor for ALS and to be negatively correlated with survival time.[10 14–16] Specifically, compared with young patients, elderly patients show more rapid progression to the tracheostomy positive pressure ventilation stage.[14] Our results well support these observations, the duration of Onset-REP and progression rate of %VC decline were strongly affected by the age at onset, and Onset-REP was shorter in elderly patients than in young and middle-aged patients.

Regarding the onset site, patients with B-ALS have a worse prognosis than both patients with U-ALS or L-ALS.[10] Specifically, bulbar palsy symptoms are independent prognostic factors across all ages and disease stages.[26] Furthermore, in patients with B-ALS, age is positively and negatively correlated with the %VC decline rate and survival duration, respectively. Additionally, young patients with U-ALS and L-ALS have a relatively long survival period. B-ALS and U-ALS likely occur during old and young age, respectively.[9 11] Patients with B-ALS had a significantly shorter Onset-REP duration than patients with U-ALS and L-ALS. In addition, the shorter onset-Rp period resulted in a shorter onset-REP period, and there was a significant difference between the B-ALS and the

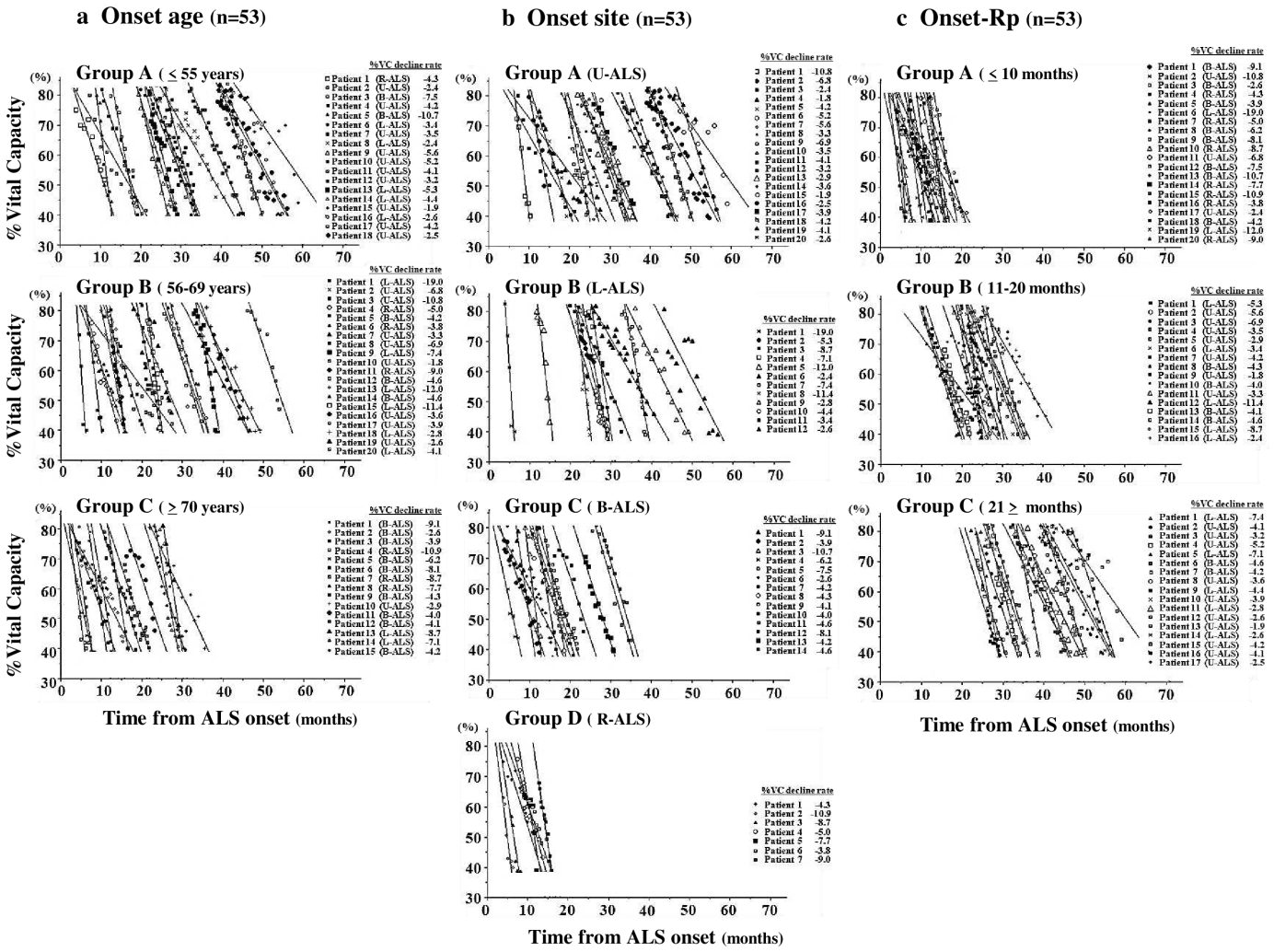

Figure 4 Factors affecting the per cent predicted vital capacity (%VC) decline in patients with amyotrophic lateral sclerosis (ALS). Onset age was classified into three groups: group A (≤55 years, n=18), group B (56–69 years, n=20) and group C (≥70 years, n=15) (A). Onset sites were divided into groups A (U-ALS, n=20), B (L-ALS, n=12), C (B-ALS, n=14) and D (R-ALS, n=7) (B). Onset-Rp duration was divided into three groups: group A (≤10 months, n=21), group B (11–20 months, n=15) and group C (≥21 months, n=17) (C).

U-ALS and L-ALS groups. Moreover, the %VC decline rate was influenced by the onset site, with patients with B-ALS showing a more %VC decline rate than patients with U-ALS and L-ALS. However, the mechanisms underlying the influence of age at onset and onset site on prognosis and Rp progression rate remain unclear. Respiratory failure is the most crucial factor influencing the prognosis of patients with ALS; accordingly, our findings provide insights into the underlying respiratory mechanisms.

Several models of diminishing respiratory patterns in patients with ALS have been recently proposed. Ackrivo *et al*[27] indicated that patients with ALS can present with stable lows, rapid progression or slow progression of respiratory decline. They noted that patients with rapid progression and stable lows had shorter diagnostic delays and a higher likelihood of presenting B-ALS. Contrastingly, a sigmoid biasymptotic model has been proposed, in which the change in the VC value accelerates after a period of stability, followed by inflection and slowing to a plateau.[28] Furthermore, the respiratory decline of the patient may accelerate when the measured value reaches about 80% of the %VC value at the time of diagnosis.[29]

Our present study provided very precise antegrade data of respiratory symptom progression and further revealed factors influencing respiratory functional decline. However, this retrospective study had a few limitations. First, there was a limited sample size. Second, respiratory function was solely assessed based on the %VC; this method may not be the most sensitive or specific test. In particular, in patients with advanced, end-stage bulbar ALS, the mouthpiece may not have been held tightly during VC measurement. Although not directly related to Onset-REP, 25 patients in this study underwent tracheostomy. In Japan, tracheostomy has been performed more frequently than European and American populations, which may be due to the national health insurance scheme and differences in cultural and religious

backgrounds. The indications for tracheostomy in patients with ALS are the development of aspiration pneumonia or respiratory failure due to bulbar paralysis. Third, although patients with obvious dementia, including frontotemporal lobar degeneration, were excluded, detailed cognitive function tests were not performed except for a small number of patients. Fourth, the genetic background of patients could not be determined.

Our findings demonstrated several factors that influence the respiratory decline in patients with sporadic ALS; however, the underlying mechanisms remain unclear despite several factors including genetic and epigenetic backgrounds being suggested.[30–35] Our findings could inform future clinical trials and daily clinical practice that consider the respiratory function and natural history of patients with sporadic ALS.

Author affiliations
[1]Neurology, Mitaki General Hospital, Yokkaichi, Mie, Japan
[2]Neurology, Toyohashi Municipal Hospital, Toyohashi, Aichi, Japan
[3]Neurology, Higashinagoya National Hospital, Nagoya, Aichi, Japan
[4]Neurology, Kasugai Municipal Hospital, Kasugai, Aichi, Japan
[5]Rehabilitation, Mitaki General Hospital, Yokkaichi, Mie, Japan
[6]Aoki Internal Medicine, Kuwana, Mie, Japan
[7]Satista Co, Kyoto, Japan
[8]Aichi Medical University, Nagakute, Aichi, Japan

Contributors S-iT and GS conceived the study. S-iT, YN, AM, RT, NO and NM collected patient data. S-iT and YS developed the statistical analysis plan and conducted statistical analyses. S-iT and GS contributed to the interpretation of the results. S-iT and GS drafted the original manuscript. S-iT is responsible for the overall content as guarantor. All authors have approved the submitted version of the manuscript and agreed to be accountable for any part of this work.

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ORCID iD
Shin-ichi Terao http://orcid.org/0000-0003-4846-4309

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