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Estimating acceleration time point of respiratory decline in ALS patients: A novel metric

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ABSTRACT

Objective: We aimed to derive and assess a novel metric for respiratory decline: the timing of acceleration of respiratory functional decline during the course of the disease in patients with amyotrophic lateral sclerosis (ALS).

Methods: In this single-center retrospective study, we reviewed consecutive definite/probable ALS patients, diagnosed and followed up at our hospital. We recorded serial slow vital capacity (percentage of predicted slow vital capacity; %VC) since diagnosis for all patients. These serial %VC data were fitted with logistic function of the time since diagnosis, and 'acceleration point' was calculated as the week in which the second derivative of the fitted logistic function had the minimum value.

Results: We included 62 patients with ALS, whose serial %VC data had been recorded for a median of 8 times over a median of 94.3 weeks. The calculated acceleration time-point was the time-point at which the %VC is becoming 0.789 times of maximum %VC, and had a strong association with the period since diagnosis to the administration of nutritional/respiratory support ($p < 0.001$). Bulbar-type ALS or lower Body Mass Index at diagnosis, both are well-known ALS prognostic factors, were also associated with more rapid arrival of the acceleration time-point.

Conclusions: We introduced the time-point of acceleration in the vital capacity decline during disease progression as a novel metric for ALS respiratory decline. Although we could not build a practically-available clinical model that directly predicts acceleration time-point due to the limited sample size, our metric may be used as one of the helpful indicators in the management during earlier disease course of ALS, such as to be careful for the potentially approaching acceleration time-point when the %VC is decreasing to approximately 0.789 times of initial %VC.

1. Introduction

Respiratory function is one of the important determinants for the progression and survival of patients with amyotrophic lateral sclerosis (ALS) [1–4]; therefore, its monitoring is necessary in the follow-up management of patients with ALS. Forced vital capacity (FVC), slow vital capacity (SVC), and their percentages to the predicted vital capacity (%VC) are the most frequently used metrics [2,5,6].

While the vital capacity gradually declines along with progression of ALS, it does not always decline linearly throughout the disease course; neurologists sometimes experience that the respiratory functional decline appears to 'accelerate' at a certain time point during the course of ALS. Since this characteristic serial decrease in the vital capacity inevitably urges the patients and neurologists to deal with the impending need for nutritional and respiratory support [7], it would be desirable to be able to estimate in advance the period of acceleration of respiratory functional decline.

However, only few earlier studies have directly addressed this metric, in contrast to the those estimating the survival period. ALS prognosticators, such as older age at onset [3,8,9], definite ALS [9], bulbar-type ALS [3], early progression rate [10], and decline in the functional ALS scores [1,11], have been intensively investigated. In addition, prognosis can also be influenced by the patients' psychosocial factors [3], and the patients' choice of whether to receive respiratory support. The acceleration of respiratory functional decline would be less likely to be influenced by these factors, and the more accurate estimation may be possible for the acceleration time point than for the overall survival.

In the current study, we aimed to estimate the acceleration point in the decline of respiratory function during the course of ALS by calculation. Using logistic function to fit to the serial %VC data in each case,

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we could calculate the theoretical time-point at which the %VC declined most severely, termed as the estimated 'acceleration' time-point. To evaluate this novel metric, we assessed the association of this metric with the known ALS metrics such as the period since diagnosis until the administration of tube-feeding or respiratory support. Furthermore, we derived the significant factors associated with the rapidity of arrival of the acceleration time-point by the acceleration-free survival analysis.

2. Methods

2.1. Data acquisition

This is a single-center retrospective observational study where, we reviewed clinical data since January 1, 2001 to September 30, 2018 of consecutive patients who were diagnosed with ALS at The University of Tokyo Hospital. We included only those with 'definite' or 'probable' ALS according to the revised El Escorial criteria [12] as confirmed throughout the disease course, and followed for their respiratory function evaluated with spirometry thrice or more, during the follow-up period of three months or more. In addition, patients diagnosed with ALS after September 30, 2015 were excluded from the study so as to secure an observational time window of at least three years. We obtained time-serial %VC data during the period since ALS diagnosis, sex, age both at the onset and diagnosis, type of ALS ('classical-type', 'bulbar-type', 'predominant upper motor neuron ALS', etc.) which is classified based on the symptoms and signs seen at-index ALS diagnosis and during the follow-up [13], certainty of ALS diagnosis according to the revised El Escorial criteria at-index diagnosis, total scores of ALS functional rating scale (ALS-FRS), body-mass index (BMI) at diagnosis, past history of smoking including Brinkman Index, medical history of diabetes mellitus and lumbar canal stenosis, serum creatinine kinase (CK) level (mg/dL) at diagnosis, and cerebrospinal fluid (CSF) total protein (TP) level (mg/dL) at diagnosis. We chose the diabetes and lumbar canal stenosis as the medical history because they are the common disease which can have influence on the level of CSF total protein [14,15]. For patients who received tube feeding or respiratory support (invasive or non-invasive) during the disease course, we also obtained the time (weeks) required since diagnosis until patients started to receive these interventions.

2.2. Model fitting

As the primary outcome measure in this study, we used the 'acceleration time-point' at which the vital capacity (%VC) decline appeared to accelerate during the follow-up since ALS diagnosis. The %VC (since ALS diagnosis) is the percentage of SVC to the predicted SVC with age, sex, and body height of normal (control). We obtained this time-series %VC data followed since ALS diagnosis. Note that here we used SVC but not FVC, because we consider the SVC might be easier to perform than the FVC is for ALS patients with orofacial weakness [16] in an attempt to cover as many ALS patients as possible, in addition the SVC has been reported as similar to FVC as a marker for ALS [17]. The time and the total number of times serial spirometry was performed on a given patient mainly depended on each case, thereby making standardized time-point analysis difficult. Therefore, we applied the logistic function [18], which is simple and widely-used for modelling increase/decrease of non-negative data with upper-limit such as natural phenomena, to fit to the time series %VC data in each case. We want to emphasize here that we used the logistic regression model only to obtain the acceleration time-point calculated from the fitted functional curve, and not applying probabilistic model (e.g. binomial distribution) for the purpose of the regression analysis. This is because the %VC at one time should depend on the preceding %VC value within the same ALS patient, and the time-serial %VC change is expected to be a unit root process, to which regression with time may lead to false-positive results.

First, let $n = N$eligible patients($N \in \mathbb{N}$) with ALS, and the i^{th} patient have completed $s_i (i = 1, 2, \ldots, N)$ times of spirometry in total during the entire observation. We denote the observed %VC value of the j^{th} spirometry ($j = 1, 2, \ldots, s_i$) of the i^{th} patient as $p(i,j)$. Then, the %VC value is normalized to $P(p(i,j))$ within the same patient so that the normalized %VC falls in the range of $0 \le P(p) \le 1$. We normalized the l^{th} %VC value of the k^{th} patient ($k = 1, 2, \ldots, N$, $l = 1, 2, \ldots, s_k$), $p(k,l)$, according to the Eq. (1) as given below:

$$P(p(k,l)) = \frac{p(k,l) - min\{p(i,j)\}}{max\{p(k,m)\} - min\{p(i,j)\}} (m = 1, 2, \ldots, s_k, \quad i = 1, 2, \ldots, N, \quad j = 1, 2, \ldots, s_i) \tag{1}$$

Then the $P(p(k))$data was fitted with generalized linear model of binomial distribution, where the fitted estimation in the k^{th} patient ($k = 1, 2, \ldots, N$) is a function of t defined in Eq. (2) given below:

$$f_k(t) = \frac{e^{a_k + b_k t}}{1 + e^{a_k + b_k t}} (t \ge 0) \tag{2}$$

The continuous variable t denotes the weeks since ALS diagnosis ($t = 0$ at the first spirometry i.e. at the time of diagnosis), and the constant a_k and b_k are determined in each case uniquely. For fitting logistic function, we excluded ALS patients whose last %VC is larger than the first %VC, since we assumed the respiratory function in ALS as monotonously-decreasing. The second derivative of the Eq. (2) is as follows:

$$\frac{d^2}{dt^2} f_k(t) = -\frac{b^2 \cdot e^{-a-bt}}{(1 + e^{-a-bt})^2} + \frac{2b^2 \cdot e^{-2a-2bt} \cdot (1 + e^{-a-bt})}{(1 + e^{-a-bt})^4} \tag{3}$$

We defined the 'acceleration' time-point as the time where the fitted logistic functional curve's slope decreased most drastically, i.e., the decline in %VC appeared to "accelerate". Therefore, the 'acceleration' time-point, t_{acc}, was obtained in each case as the t at which the above $f''_k(t)$takes its minimum value (Fig. 1, shown with a filled arrow).

In addition, we also calculated the estimated time-point at which the %VC corresponded to 50%, which is a clinically important metric in ALS [5], because the risk following Percutaneous Endoscopic Gastrostomy (PEG) tube placement increases when %VC is 50% or less, and therefore it is recommended to place PEG before the %VC becomes too

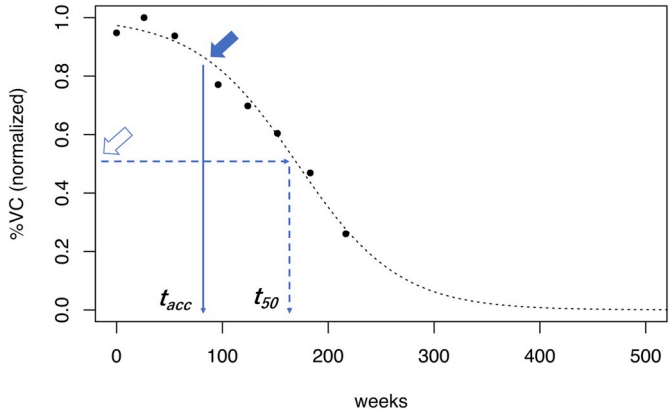

Fig. 1. Scheme for estimating the time-point at "acceleration" and "%VC equals to 50%."
An example of logistic regression model-fitting to the serial plot of %VC data in one case.
The filled arrow shows the point where the fitted logistic functional curve's slope decreases most severely as if the fitted curve decline accelerates at this point. We denote this point as the "accelerate" time-point (week at t_{acc}), and this corresponds to the point at which the second derivative of the fitted logistic function takes its minimum value.
The blank arrow shows the height of normalized %VC from 50%. We denote the "%VC equals to 50%" time-point as t_{50}, at which the value of the fitted logistic function corresponds to this arrow's height.

low [7]. In addition, non-invasive respiratory support is recommended for ALS patients whose %VC approaches 50% or less [7]. We can calculate this time-point, t_{50}, in each case by the following Eq. (4) (Fig. 1):

$$f_k(t) = P(50)\ (k = 1,, 2,..., N) \quad (4)$$

2.3. Statistical analyses

All the statistical analysis and the mathematical calculations were performed using R version 3.3.3 and its packages [19]. In summarizing data, median and interquartile range (IQR) were used for continuous variables, and frequency and percentage (%) were used for categorical variables. For two group testing, the Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical variables were used. Degree of fitness was evaluated by calculating the determinant coefficient (R^2). In the univariate acceleration-free survival analysis, the Wilcoxon test was used. In the multivariate acceleration-free survival analysis, Cox-proportional hazard test was used, and if the proportional hazardness assumption was not satisfied, restricted mean survival time (RMST) analysis was used [20,21]. RMST analysis was performed using R package '*survRM2*' (https://CRAN.R-project.org/package=survRM2).

2.4. Ethical

This study has been approved by the institutional review board (ID: 2339-(3)).

3. Results

3.1. Calculated acceleration time-point: overview

The present retrospective study included 62 patients with ALS. Many of the included patients were male in their 60's at onset and had a median time of 49 weeks from onset until diagnosis (Table 1). At index diagnosis, more than half of the patients met the 'definite' criteria (58.3%) and showed a 'classical' type (55.0%) of ALS presentation. In addition, about half of the patients showed elevated serum CK, while approximately 20% showed elevated CSF TP at diagnosis.

As demonstrated in Fig. 2, the fitting results were overlaid on the observed time-series %VC plot which included cases ($n = 61$ out of 62) whose first %VC is larger than the last %VC. The R^2 by the logistic regression across all these samples was fair, with the median of 0.9232 (IQR: 0.7439–0.9627), among whom 40/61 cases showed better fitness than by the linear regression (R^2 of median 0.8531 (IQR: 0.7294–0.9396), paired Wilcoxon rank-sum test, $p < 0.001$).

The estimated acceleration time-point (t_{acc}) and the estimated %VC equaling to 50% time-point (t_{50}) according to the Eqs. (3) and (4) was determined for 61 cases. Fig. 3 shows the t_{acc}-free survival curve (A) and t_{50}-free survival curve (B). For patients in whom we did not calculate these time-points ($n = 1$), we regarded them as censored at the timing of their last spirometry. The median $t_{acc}$was at 45.52 weeks (IQR: 25.43–88.06) since diagnosis and the median t_{50} was at 79.0 weeks (IQR: 48.7–164.6) since diagnosis. Inversely, the normalized %VC at t_{acc} was 0.789 in all calculated cases, and the minimum %VC value across all samples was 12, therefore the actual %VC value at t_{acc} can be obtained from the formula (1) as $(0.789 \cdot max\{p(k)\} + 2.532)$. The t_{50} was clearly proportional to the t_{acc}within each case linearly regressed as $t_{50} = 1.86 \cdot t_{acc} + 0.27$ ($p < 2e\text{-}16$), and the R^2 between them was 0.9059. In addition, the t_{acc} also showed a clear correlation with the period since diagnosis to the administration of nutritional support (rho = 0.765, $p < 3.5e\text{-}08$) with the R^2 of 0.5418, whereas the correlation between the t_{acc} and the period since diagnosis to the administration of respiratory support (rho = 0.550, $p < 4.3e\text{-}04$) was much lower with the R^2 of 0.3025.

Table 1
Summary of clinical features at baseline, at diagnosis, and throughout the disease course.

Variables		Median (IQR) or Frequency (%)
Sex	Female (yes)	25/60 (41.67%)
Age at onset	Age (y/o)	60.54 (54.08–70.02)
	Over 50 (yes)	53/60 (88.33%)
	Over 70 (yes)	15/60 (25%)
Age at diagnosis (y/o)		63.21 (55.67–70.81)
Weeks from onset to diagnosis (w)		48.86 (33.5–100.3)
BMI at diagnosis	BMI (kg/m^2)	22.19 (19.67–24.1)
	BMI < 22 (yes)	23/48 (47.92%)
Smoking	History (yes)	31/60 (51.67%)
	Brinkman_Index	40 (0–525)
History: DM		5/60 (8.33%)
History: LSCS		1/60 (1.67%)
El Escorial criteria	Definite	35/60 (58.33%)
	Probable	23/60 (38.33%)
	Possible	2/60 (3.33%)
ALS-FRS total score at diagnosis		43 (40–45)
Type of ALS	Bulbar	13/60 (21.67%)
	Classical	33/60 (55%)
	Flail arm	8/60 (13.33%)
	Upper-predominant	6/60 (10%)
Cranial nerve symptoms	Lower (yes)	51/60 (85%)
	Upper (yes)	36/58 (62.07%)
Total number of spirometry completed in each patient (times)		8(5–13.75)
%VC at Diagnosis	%VC	102 (84.25–109)
	< 100 (yes)	29/62 (46.77%)
Weeks from diagnosis until	Acceleration point	40.62(24.65–79.73)
	Tube feeding	48.71 (33.57–86)
	Respiratory support	67.64 (43.93–130)
	$\%VC_{50}$ point	73(42.5–146.5)
Max. followed months (m)		94.25 (55.25–158.2)
Serum CK at diagnosis	CK (mg/dL)	191 (119.8–295)
	CK elevated (yes)	29/60 (48.33%)
CSF TP at diagnosis	TP (mg/dL)	25.5 (0–43.5)
	TP elevated (yes)	13/60 (21.67%)

Summary of the clinical features at baseline, at diagnosis, and throughout the disease course. Continuous variables are summarized with median (and IQR), and categorical variables are summarized with frequency (and %).
Abbreviations: BMI, Body-Mass Index; DM, Diabetes mellitus; LSCS, Lumbar Canal Stenosis; ALS-FRS, ALS Functional Rating Scale; CK, Creatinine kinase; CSF, Cerebrospinal fluid; TP, Total Protein.

3.2. Acceleration-free survival analysis and its associated factors

The t_{acc}-free survival analysis and t_{50}-free survival analysis, with the binarized clinical variables were performed. Table 2 represents p-value results in each variable using the Wilcoxon test. Only BMI at diagnosis < 22 showed significant association with the faster arrival of t_{acc}.

The result of multivariate survival analysis is summarized in Table 3A shows the overall results before variables backward-and-forward selection procedure according to the Akaike's Information Criterion (AIC) value to select variables for constructing a better-fitting model; Table 3B shows the derived model of selected variables. These results suggest that bulbar-type ALS and higher CSF-TP at diagnosis were associated with the faster arrival of t_{acc}, while longer delay until diagnosis, higher BMI at diagnosis, and a positive history of smoking was associated with the slower arrival of the t_{acc}.

However, the proportional hazard assumption, which is the prerequisite for using Cox-proportional hazard analysis, was not satisfied in some of the included variables (as shown in Supplemental Table 1). Since the confidence of the multivariate result was thus considered as statistically uncertified one, we performed RMST analysis (Table 4). Both metrics of ratio (A) or difference (B) of RMST result shared significant factors of bulbar-type ALS, BMI at diagnosis, and CSF TP level at diagnosis. In addition, %VC at diagnosis and history of smoking were also significant factors in RMST results. Overall, these results suggest

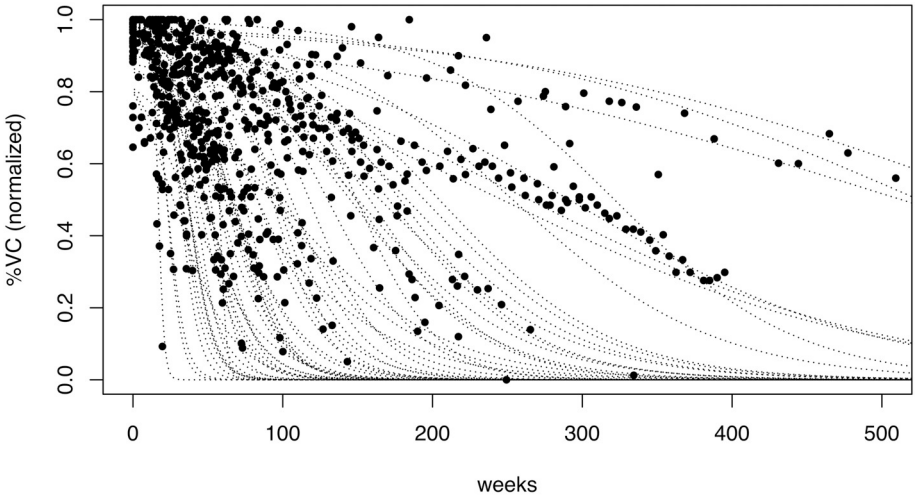

Fig. 2. Logistic regression curves fitted on the observed time-series %VC plots.
The dotted lines represent the logistic regression curves for each set of time-series data, overlaid on the plots. There is a wide variation of serial %VC changes in each case, and some cases have prolonged chronic process of respiratory decline.

that bulbar-type ALS showed lower BMI at diagnosis, and higher CSF TP at diagnosis are significantly associated with the faster arrival of the acceleration time-point.

4. Discussion

ALS patients benefit from nutritional and respiratory support for their survival [3], and such support should be started before the respiratory function severely decreases i.e. to ≤30% [7]. Therefore, it is important for neurologists involved in outpatient management to try to estimate to what degree the patient's respiratory function will decline in the near future. It would have been simpler if the respiratory decline always progressed linearly. However, this is not always the case and ALS patients sometimes show an accelerated decline in their respiratory function. Thus, the current study directly addresses the timing of this 'acceleration' by applying a logistic regression model fitted to the observed time-series data with a good level of fitness, which is one of the major strengths of this study.

The $t_{50}$was clearly proportional to the t_{acc} (approximately 1.7 times of the t_{acc},), and there was also a clear correlation between t_{acc} and the time period from diagnosis to administration of nutritional/respiratory support, suggesting that the acceleration time-point is an early indicator of the timing of administration of nutritional (and respiratory) support. In addition, because of the nature of logistic curve, the normalized %VC at t_{acc} was 0.789 in all calculated cases. And initial %VC at diagnosis records the highest value among time-serial %VC in many cases. This means that when the measured %VC value reaches approximately 80% of initial %VC, we can suspect that the patient's respiratory decline may possibly be becoming accelerated.

Table 2
Results of survival analyses (*p-value* in generalized Wilcoxon test).

	for t_{acc}	for t_{50}
Sex: Female	0.401	0.458
Age of onset: > 70	0.607	0.550
El Escorial: definite	0.745	0.618
Bulbar-type ALS	0.166	0.132
ALS-FRS: 43 or lower	0.133	0.085
BMI at onset: 22 or less	0.031	0.070
%VC at diagnosis: < 100	0.078	0.052
History of smoking	0.186	0.152
Serum CK at diagnosis: elevated	0.458	0.532
CSF TP at diagnosis: elevated	0.905	0.734

Lower BMI at diagnosis was the only factor associated with the faster arrival of t_{acc}.

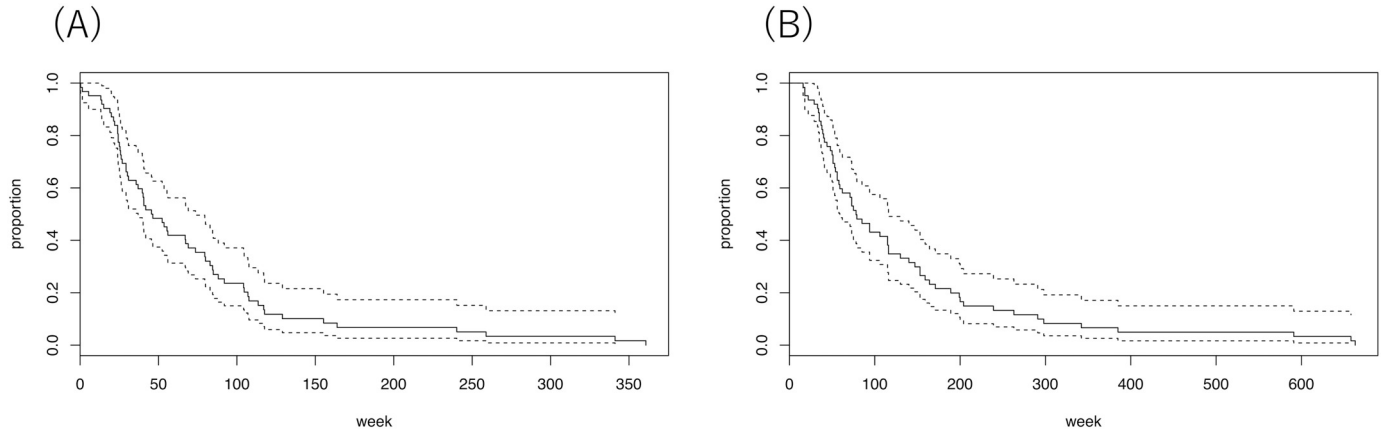

Fig. 3. Kaplan-Meier survival curves.
Kaplan-Meier survival curves and their 95% confidential intervals for the "acceleration" time-point (t_{acc}) (A) and for the "%VC equals to 50%" time-point (t_{50}) (B). These estimations were calculated only for eligible patients (n = 61 among 62), and those not included in the calculation were regarded as censored without arrival of the time-point at the last visit for spirometry. The $t_{50}$was clearly proportional to the t_{acc} in each case.

Table 3
Cox-proportional hazard analysis for acceleration-free survival

Variables	Adjusted HR	Lower 0.95	Upper 0.95	Pr (> |z|)	
(A) Before variable selection					
Sex: Male	0.752	0.294	1.924	0.553	
Age at diagnosis	1.014	0.976	1.055	0.471	
El Escorial: definite	1.015	0.502	2.050	0.967	
Bulbar-type	6.928	2.186	21.958	0.001	**
ALS-FRS at diagnosis	1.069	0.949	1.204	0.273	
Weeks since onset to diagnosis	0.993	0.987	0.999	0.020	*
BMI at diagnosis	0.851	0.743	0.974	0.019	*
%VC at diagnosis	0.982	0.958	1.007	0.157	
History of smoking	0.589	0.264	1.313	0.195	
History of DM	1.745	0.381	8.002	0.474	
Serum CK at diagnosis	1.000	0.998	1.002	0.866	
CSF TP at diagnosis	1.031	1.010	1.053	0.004	**
(B) After variables selected					
Bulbar-type	6.052	2.268	16.155	0.000	***
Weeks since onset to diagnosis	0.992	0.986	0.997	0.002	**
BMI at diagnosis	0.881	0.785	0.988	0.030	*
CSF TP at diagnosis	1.028	1.011	1.046	0.001	**

Summary of the Cox-proportional hazard analysis on the entire initial model with all the included variables (A) and the derived model with the selected variables according to the AIC (B).

Table 4
Results of the restricted mean survival time (RMST) analysis for acceleration-free survival

Ratio	Exp (coef)	Lower 0.95	Upper 0.95	*p*	
(A) RMST-ratio					
Intercept	27.883	5.698	136.450	< 0.001	
Arm ('bulbar-type' or not)	0.474	0.302	0.745	0.001	**
Sex: female	0.927	0.670	1.283	0.648	
Age at diagnosis	0.991	0.979	1.004	0.168	
El Escorial: definite	0.950	0.750	1.203	0.669	
ALS-FRS at diagnosis	0.976	0.946	1.007	0.128	
Weeks since onset to diagnosis	1.001	1.000	1.002	0.179	
BMI at diagnosis	1.040	1.005	1.077	0.027	*
%VC at diagnosis	1.014	1.004	1.024	0.004	**
History of smoking	1.440	1.059	1.957	0.020	*
History of DM	0.864	0.485	1.541	0.621	
Serum CK at diagnosis	1.000	1.000	1.000	0.917	
CSF TP at diagnosis	0.989	0.983	0.995	< 0.001	***
(B). RMST-difference					
Intercept	21.051	−56.675	98.778	0.596	
Arm ('bulbar-type' or not)	−25.316	−42.138	−8.494	0.003	**
Sex: female	−2.784	−16.629	11.060	0.693	
Age at diagnosis	−0.266	−0.808	0.276	0.336	
El Escorial: definite	−1.491	−11.566	8.584	0.772	
ALS-FRS at diagnosis	−0.842	−2.271	0.588	0.249	
Weeks since onset to diagnosis	0.039	−0.020	0.098	0.197	
BMI at diagnosis	1.698	0.139	3.256	0.033	*
%VC at diagnosis	0.486	0.102	0.870	0.013	*
History of smoking	13.657	0.598	26.717	0.040	*
History of DM	−7.762	−31.607	16.083	0.523	
Serum CK at diagnosis	−0.003	−0.024	0.019	0.789	
CSF TP at diagnosis	−0.444	−0.691	−0.197	< 0.001	***

Results of the RMST, on the ratio of RMST (A) or on the difference of RMST (B) between arm subgroups (= 'bulbar-type' or not). Tau value is 68.96 here. Other clinical variables are included as covariates. Both in (A) and (B), the variables similar to the result from Cox-proportional hazard analysis also showed statistical significance in the multivariate testing by RMST.

While we applied the logistic regression model (binomial distribution) for convenience to fit the observed %VC data in each case, the inductive reason why the data of %VC serial changes can be fitted well with the logistic functional curve is uncertain. The logistic function we used here shows an easy-to-understand curve to estimate the serial changes in %VC, which partly supports the use of this function. However, there may be other more accurate models that we have not used here, and in such cases, the t_{acc} will be calculated differently.

The factors associated with the faster arrival of the acceleration time-point were mostly understandable in association with the known ALS prognostic factors: patients with bulbar-type ALS have faster ALS progression and shorter survival time than those with other subtypes of ALS [3]. Lower BMI at diagnosis is also a known predictor of faster disease progression and shorter survival [22,23]. The decreased BMI may be due to the worsened nutritional status [24] following dysphagia, increased work in breathing [5], or hypermetabolism reported in ALS patients [25]. In addition, although statistically uncertain, a longer duration between onset and diagnosis may have contributed to the slower arrival of the acceleration time-point. This might reflect the slow disease progression by its nature, because the short time span from symptom onset to diagnosis is reported to be one of the prognostic factors [8]. Overall, being consistent with earlier studies on the ALS prognostic factors suggests that the faster acceleration time-point shares the same underlying mechanism as of the worse prognosis, at least in part.

Meanwhile, older age, which is one of the major predictors for the worse prognosis in ALS [3], was not the factor associated with the faster arrival of acceleration time-point. Although its reason is unclear, this may be due to the smaller proportion (12/60; 20.0%) of our patients with younger (e.g. < 50 years old) or older (e.g. > 75 years old) age at disease onset.

The higher CSF TP at diagnosis is also associated with the faster arrival of the acceleration time-point in our study. While a CSF TP that is too high might defer the diagnosis of ALS [26], none of our cases showed a CSF TP > 100 mg/dL. While higher CSF albumin and IgG levels in ALS patients compared to controls have been reported as early as in 1984 [27], the significance of mildly elevated CSF TP in ALS has been undetermined so far. It is believed that ALS involves neuroinflammatory processes, as suggested by the elevated levels of inflammatory proteins in the CSF of ALS patients compared to controls without neurological disease [28], findings of microglial infiltration in the brains of ALS patients [29], and the elevated macrophage-derived chitinase levels in the CSF of these patients [30]. Elevated CSF TP as an associated factor in our study may reflect the prominent neuroinflammatory processes in the brain.

Our study had some limitations: First, we included only those patients for whom follow-up for respiratory function was performed at least thrice; thus, the patients with rapid too fast progression may not have been analyzed. Second, wide-variation of serial %VC changes was observed in each case as shown in Fig. 2. Not all ALS patients show a clear acceleration in their serial %VC changes during the disease course, and some instead showed a linear decrease in serial %VC. Although the logistic function also fits well to the serial data of such changes, the significance of acceleration time-point in such cases would not be substantial. Third, each patient completed a different number of spirometry examinations at different timings. It would be inaccurate to fit with the logistic regression curve for the serial data where there is no significant decline noted in the data. Thus, to avoid this problem, we restricted the cases to calculate estimation for only patients showing a sufficient %VC decline during the disease follow-up visit (e.g. $n = 52$ with cut-off of 70%); however, this attempt may have been inadequate in some of the cases. Fourth, we did not consider medications such as Riluzole, although we consider this is permissible since Riluzole is usually prescribed to the most of ALS patients; moreover, its effect is reported to be very modest in a meta-analysis [31]. Fifth, technically low reliability of spirometry results when the patients had significantly

low vital capacity since such patients usually have weakness in orbicularis oris muscles leading to incomplete spirometry test, which can yield a bias in the normalization process. Sixth, the potential large heterogeneity among patients (e.g. bulbar-type or not) may have influenced on the results of survival analysis. Seventh, we could not build a practically-available clinical model that directly predicts acceleration time-point because of the limited sample size from a single-center, and of the nature of fitted model. Lastly, the positioning on spirometry (e.g. spine or sitting) was not assessed due to the lack of records.

In conclusion, the present study used a logistic functional curve to calculate the "acceleration" time-point of the respiratory decline in the ALS disease course. Although we could not build a direct predictive model, our metric may be used as one of the helpful indicators in the management during earlier disease course of ALS, such as to be careful for the potentially approaching acceleration time-point when the %VC is decreasing to approximately 0.789 times of initial %VC. Further evaluation is needed for the actual validity of this acceleration time-point as the short-term clinical metric of ALS compared to other long-term established metrics such as overall survival.

Conflicts of interest

The authors have no conflict of interest to disclose.

Ethical approval

This work was conducted in accordance with the ethical standards, laid down in the 1964 Helsinki declaration.

The study protocol was approved by the University of Tokyo ethics committee (ID: 2339-(3)).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.05.031.

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