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Neurophysiological index is associated with the survival of patients with amyotrophic lateral sclerosis

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HIGHLIGHTS

- ALS patients with low Neurophysiological Index (NI) had a shorter survival compared to patients with high NI.
- NI, age at disease onset, diagnostic delay and ALSFRS-R score were associated with the prognosis of ALS.
- Given that NI is easy to apply, it may be a potential biomarker in ALS clinical trials.

ABSTRACT

Objective: To investigate the association between Neurophysiological Index (NI) and the survival of patients with Amyotrophic Lateral Sclerosis (ALS).
Methods: Patients diagnosed with ALS in the Department of Neurology, West China Hospital, Sichuan University from May 2015 to May 2017 were enrolled in this study, and then were followed up every 3 months until 31st May 2018. According to the mean NI values, the participants were categorized into high NI and low NI groups. Differences between groups were compared with parametric or non-parametric test, whichever was more appropriate. Kaplan-Meier method and Cox regression model were used to calculate the survival analysis.
Results: One hundred and ninety one sporadic ALS patients including 78 female and 113 male were included in this study. Among them, 5 (2.6%) patients were lost to follow-up, 79 patients were still alive while 102 patients died at the last follow up. The median survival time from symptom onset to death was 33 months, as estimated by Kaplan-Meier analysis. ALS patients with lower NI exhibited to have shorter median survival time compared to the patients with high NI. Through multivariate Cox regression analysis, NI, the revised ALS functional rating scale (ALSFRS-R), diagnostic delay and age at disease onset were found to be associated with the survival of ALS patients.
Conclusion: Our findings indicate that NI provides a single number that seems to associate with the survival of ALS.
Significance: NI is readily available and reproducible, and it could be utilized as a potential biomarker for survival in further multicenter clinical trials in ALS.
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1. Introduction

Amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disease, which is clinically characterized by limb paralysis, muscle atrophy, dysphagia, dysarthria, shortness of breath and respiratory failure, is caused by progressive degeneration of both upper and lower motor neurons(Logroscino et al., 2008). Death of patients with ALS usually occur within 3 to 5 years after symptom onset due to respiratory failure, (Chio et al., 2009). And our previous study has demonstrated that the probabilities of survival at 3, 5 and >10 years from symptom onset are 58.4, 26.0 and 1.4%, respectively (Wei et al., 2015). The etiology of ALS are still uniden-

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tified, and there is also no cure for the disease so far. Recently, increasing attention has been focused on the predictors for survival in ALS, including age at disease onset, diagnostic delay, different onset forms, respiratory function and ALS Functional Rating Scale-Revised (ALSFRS-R) score (Chen et al., 2015, Kaufmann et al., 2005, Wei et al., 2015).

Neurophysiological index (NI) was first described in 2000, which indicated that the Abductor Digiti Minimi (ADM) strength is positively correlated with compound muscle action potential (CMAP) amplitude and F-wave frequency, while negatively correlated with distal motor latency (DML), so NI can be expressed as (CMAP amplitude/DML) × F frequency (de Carvalho and Swash, 2000). Recent research has drawn attention to the crucial role of NI in ALS. For instance, a study pointed out that NI is strongly associated with the strength of ADM in ALS patients (de Carvalho and Swash, 2000). Moreover, the weakness of ADM in ALS is correlated with lower motor neuron (LMN) loss, as indicated by different methods of investigation (Bromberg et al., 1993, Kent-Braun et al., 1998). In addition, their findings (Bromberg et al., 1993, Kent-Braun et al., 1998) suggest that NI can be a biomarker for tracking the progression of ALS, which has been confirmed in later studies (Escorcio-Bezerra et al., 2018, Swash and de Carvalho, 2004). NI is the most sensitive indicator of ALS progression compared to ALS-FRS and FVC, regardless of rapid or slow progression groups (Swash and de Carvalho, 2004). Furthermore, Escorcio-Bezerra and his colleague showed that NI is more sensitive than other clinical measures at detecting LMN loss in the pre-symptomatic limbs of ALS patients, which suggested that NI might be used as an outcome parameter for early stage ALS (Escorcio-Bezerra et al., 2018). Besides, ALS progression is highly associated with its survival time. To our knowledge, ALSFRS-R is recognized as a clinical indicator of ALS progression, which is also an independent factor for predicting survival of patients with ALS (Kollewe et al., 2008).

It is worth exploring whether NI at baseline can be used to predict the prognosis of ALS, which provides more sensitive measures and lower coefficient of variation. Therefore, the objective of our current was to explore the association between NI and survival in ALS.

2. Patients and methods

Totally, 191 sporadic ALS patients diagnosed at the Department of Neurology, West China Hospital, Sichuan University (a tertiary referral center in south-western China) from May 2015 to May 2017 were enrolled in this study. Participants were followed up regularly every 3 months with telephone or face-to-face interview by experienced neurologists until 31st May 2018. According to El Escorial revised criteria (de Carvalho et al., 2008), definite or probable ALS patients were defined as those presented with onset of weakness or dysarthria within 3 years and had an ADM strength of 4 (Medical Research Council scale) in at least one side.

Standard nerve conduction studies were performed, in which the ulnar nerve was stimulated at the wrist, and the resultant CMAPs over the ADM muscle were recorded using Viking IV Electromyography System (Nicolet Biomedical, Madison, WI, USA). Skin temperature of the examined limb was maintained above 32 °C. Specifically, the ulnar nerve was stimulated with a bipolar electrode at the wrist, 5–6 cm proximal to the recording electrode. The electrode was then placed over the motor endplate of the patient's stronger ADM muscle, as evaluated by the Medical Research Council scale. NI is calculated as (M-wave amplitude/DML) × (F-wave persistence after 20 stimuli). All electrophysiological examinations were carried out by the same board-certified neurologist.

Baseline clinical data of ALS patients including age at disease onset, diagnostic delay, ALSFRS-R score and riluzole use or not were collected. Onset forms were classified into bulbar onset, upper limb (UL) and lower limb (LL) forms. Diagnostic delay was calculated as the interval from the symptom onset to diagnosis (in months). According to the diagnostic delay, participants were divided into two groups as longer or shorter than 12 months. The severity of disease was evaluated with ALSFRS-R scale, of which the total score is 48, and higher scores indicating better function. Patients who administered with 100 mg/day riluzole for more than one month were categorized as "riluzole use".

For those patients who died, survival time was performed from disease onset to death. Moreover, for those patients who still alive, survival time is calculated from the symptom onset to the last follow up visit, and for those who lost to follow up, survival duration is determined from disease onset to the last contact. All patients were followed up by neurologists at 3-month intervals. Patients were considered to be lost to follow-up if they could not to be reached by phone twice consecutively. Ethical approvement of this study was obtained from the Ethics Committee of West China Hospital of Sichuan University. And all participants signed written informed consent before enrollment.

3. Statistical analysis

SPSS v. 19.0 were used to carry out all the statistical analysis (SPSS, Inc., Chicago, IL, USA). Based on the mean NI values, participants were classified into high and low NI groups. Comparison of continuous variables between groups were calculated with ANOVA, Student's t-tests or Mann-Whitney U-tests. Survival comparison between groups were carried out with Kaplan-Meier curves and log-rank tests. Continuous variables were categorized into adequate forms in order to fit the proportional hazards. And in order to identify the variables associated with survival in ALS patients, univariate and multivariable Cox regression analyses were performed. The data for continuous variables were exhibited as mean ± standard deviation (SD). Two-tailed p value less than 0.05 was considered to be statistically significant.

4. Results

Totally, 191 sporadic ALS patients were recruited in the current study, including 113 males and 78 females. Among them, 5 (2.6%) patients were lost to follow-up, 79 (40.8%) patients were still alive, and 102 (53.4%) patients died at the last follow up visit. According to the onset site, 82 (42.9%) patients were upper limb onset, 50 (26.2%) patients were lower limb onset and 59 (30.9%) patients were bulbar onset. The mean age of disease onset was 55.4 ± 10.9 years old. The median diagnostic delay of all patients was 12.0 ± 8.7 months. The mean ALSFRS-R score was 38.6, and the mean NI was 2.4. Notably, compared to patients with lower NI, ALSFRS-R score was significantly higher in high NI group ($p = 0.001$, Table 1). No significant difference was shown in UL, LL and bulbar onset form. There were no significant differences between the two groups with respect to gender, age of onset, BMI, diagnostic delay and riluzole use (Table 1).

The median survival time of all the participants was 33.5 months (95%CI = 28.5–38.5), as estimated by Kaplan-Meier analysis (Fig. 1). Furthermore, patients with lower NI exhibited shorter median survival when compared to patients with high NI (30.3 months vs. 40.5 months, $p = 0.019$) (Fig. 2). Several parameters were identified to be predictors of long-term survivalin the univariate Cox regression analysis (Table 2), including high BMI ($p = 0.007$), long diagnostic delay ($p = 0.0001$), high ALSFRS-R score ($p = 0.0001$) and high NI ($p = 0.026$), while bulbar onset was found

Table 1
Clinical features of ALS patients based on the NI.

	All patients	NI > 2.4	NI ≤ 2.4	*p*
Number	191	96	95	-
Gender (male/female)	113/78	57/39	56/39	0.952
Onset form (UL/LL/Bulbar)	82/50/59	40/27/29	42/23/30	0.827
Age of onset (Years)	55.4 ± 10.9	56.1 ± 10.4	54.6 ± 11.4	0.336
BMI	21.7 ± 3.2	21.3 ± 3.5	22.1 ± 2.9	0.076
Diagnostic delay (months)	12.0 ± 8.7	12.1 ± 9.7	12.0 ± 7.7	0.921
Use of riluzole (yes/no)	91/100	43/53	48/47	0.428
ALSFRS-R	38.6 ± 6.6	39.5 ± 4.8	37.6 ± 7.5	0.001

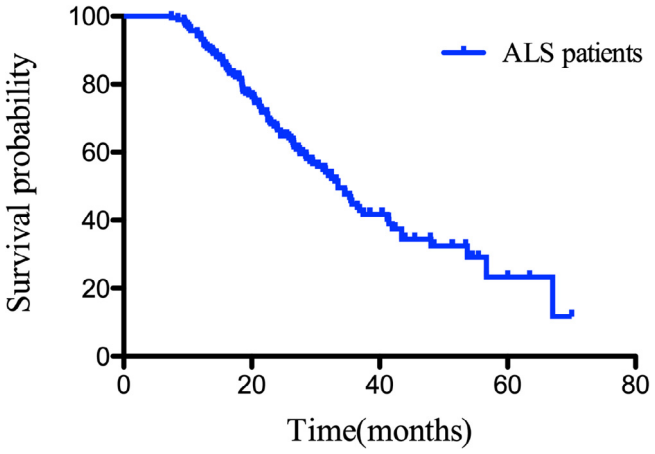

Fig. 1. Kaplan-Meier survival plot overall survival analysis in all patients from symptom onset.

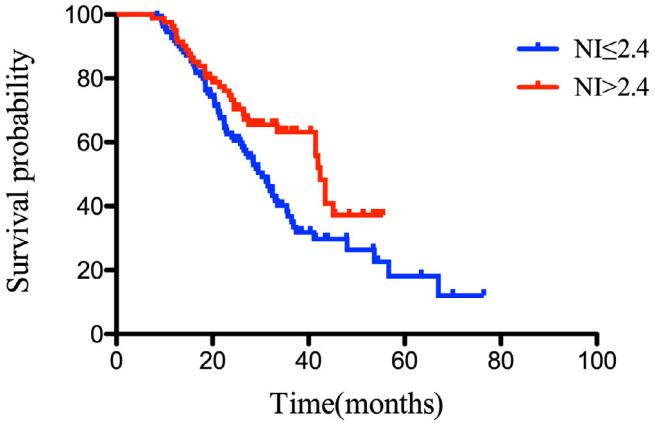

Fig. 2. Kaplan-Meier survival plot survival analysis for patients with NI ≤ 2.4 versus with NI > 2.4.

to be associated with shorter survival. Furthermore, in the multivariate Cox regression analysis, results revealed that low NI (p = 0.042), short diagnostic delay (p = 0.0001), low ALS-FRS-R score (p = 0.042) and bulbar onset (UL vs. Bulbar p = 0.010; LL vs. Bulbar p = 0.004) were significantly associated with shorter survival time of ALS patients (Table 2).

5. Discussion

The current study is the first large-scale study which explored the association between NI and survival in ALS. It may seem surprising that the parameters from only one sign of ulnar nerve can be used to predict ALS prognosis, even after multiple adjustments of age at onset, onset site and ALSFRS-R score. Additionally the strength-duration time constant tested in one nerve is related to the survival of ALS patients(Kanai et al., 2012).

A previous study (Swash and de Carvalho, 2004) has pointed out that NI value is indeed a number without sign, which can serve as a biomarker for a certain stage of ALS. Nonetheless, it does not necessarily indicate an underlying physiological, biochemical or anatomical process(Swash and de Carvalho, 2004). In addition, the study(Swash and de Carvalho, 2004) provides an example of BMI, which reflects the obesity, but the formulas and parameters of BMI did not have a direct association with the potential pathophysiological mechanism of obesity.

Nevertheless, some parameters of NI may probably explain the physiological mechanisms underlying the association between NI and ALS progression. A previous study suggests that decreased F-wave persistency can reflect the hyperexcitability of motor neuron pool (Fisher, 1992). Moreover, some studies have used other electrophysiological indices to reflect the motor neuron excitability, which support our findings. For instances, Kanai et al. (2012) have reported that the increased axonal persistent sodium current in the early stage of ALS is a strong predictor of its shorter survival, in which the increased axonal persistent sodium current represents the hyperexcitability in motor neuron. In addition, the presence of complex fasciculation potentials predicts poorer survival in ALS patients (Shimizu et al., 2014). Noticeably, the excitability of axonal membrane is relatively high, which can easily trigger the

Table 2
Univariate and Multivariate Cox survival analysis results in ALS patients.

		Univariate analysis			Multivariate analysis		
Variables		HR	95%CI	p	HR	95% CI	P
Age of onset	Higher Age of onset vs. lower age of onset than 55	2.191	1.450–4.309	0.0001	2.171	1.424–3.311	0.0001
Diagnostic delay	Longer Diagnostic delay vs. shorter diagnostic delay than 12 months	0.334	0.215–0.517	0.0001	0.293	0.187–0.461	0.0001
Onset form	UL vs. Bulbar	0.450	0.288–0.705	0.0001	0.543	0.343–0.862	0.010
	LL vs. Bulbar	0.469	0.282–0.778	0.003	0.463	0.273–0.786	0.004
ALSFRS-R	Higher ALSFRS-R vs. lower ALSFRS-R than 38	0.417	0.282–0.617	0.0001	0.348	0.231–0.524	0.0001
NI	Higher NI vs. lower NI than 2.4	0.635	0.426–0.904	0.026	0.687	0.456–0.934	0.042
Gender	Male vs. female	0.835	0.564–1.238	0.369			
BMI	Higher BMI vs. lower BMI than 21	0.582	0.394–0.859	0.007			
Use of riluzole	Yes vs. No	0.792	0.535–1.172	0.243			

complex fasciculation potentials (Shimizu et al., 2014). Besides, the CMAP amplitude is decreasing along the disease progression, although it may be preserved in the early stage due to the collateral reinnervation. There are a large number of neurophysiological biomarkers, such as motor unit number estimation (MUNE) and motor unit number index (MUNIX), which suggests that CMAP amplitude is decreasing along with the disease progression of ALS (Vucic and Rutkove, 2018). The fundamental principle underlying MUNE and MUNIX techniques is dividing the maximal CMAP amplitude by the average surface-recorded motor unit potential (SMUP) (Bromberg, 2013). Furthermore, an animal study suggests that decreased CMAP amplitude is correlated with the prognosis of ALS (Mancuso et al., 2014).

It's worth noting that there was no significant difference on NI between different onset forms patients with ALS, however the bulbar onset patients has a shorter survival time comparing to UL and LL onset group. Survival time of ALS patients with bulbar onset was shorter than in ALS patients with limb onset (Brown and Al-Chalabi, 2017) maybe means that they were different disease subtypes which had complex mechanism, rather than simple NI can explained. It also tell us the mechanism of NI maybe need more multi-factors and multi-center prospective longitudinal studies to explore.

There were some limitation in our study. Firstly, the NI was measured in the baseline, the change of NI during follow-up was absent in our study. Although we followed up the outcome of ALS patients and give us chance to use Cox model to analysis the association between NI and survival. Moreover, it was a single-centre cohort study, some results need multi-center prospective longitudinal studies to indentify.

In conclusion, our study found that NI provides a single-number parameter which seems to be associated with the survival of ALS. Given that NI can be obtained from simple and familiar measuring tools and is readily available in almost every neurological department, it has the potential to be a widely applicable and replicable biomarker for monitoring the disease progression of ALS.

Declaration of Competing Interest

None.

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