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ORIGINAL COMMUNICATION

A nerve conduction study predicts the prognosis of sporadic amyotrophic lateral sclerosis

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Abstract

Objective To clarify the relationship between nerve conduction study (NCS) and prognosis in patients with amyotrophic lateral sclerosis (ALS).

Methods We included 190 patients with sporadic ALS. We used onset age, sex, onset site (bulbar vs. spinal), revised El Escorial criteria category (definite vs. others), and the King's clinical systems, and the Milano–Torino (MiToS) functional staging systems, and decline rates of revised ALS functional rating scale (ALSFRS-R) as known prognostic factors. An NCS was performed on the median, ulnar, tibial, and sural nerves. The endpoint was death or the introduction of tracheostomy positive-pressure ventilation. Multivariate analysis for each NCS variable, known prognostic factors was performed using Cox stepwise proportional hazards analysis. Univariate analysis was performed for NCS variables that showed a significant association with prognosis in multivariate analysis. Survival was analyzed with a Kaplan–Meier curve and log-rank test.

Results The Cox model identified the compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) amplitudes of the median nerve as prognostic factors. In the log-rank test, patients with higher median nerve CMAP amplitude had a significantly better prognosis than those with lower amplitude, regardless of age. And prognosis was better in the group with lower median nerve SNAP amplitude only in patients younger than the 25th percentile (~ 57 years).

Conclusions CMAP and SNAP amplitudes of the median nerve are considered to be independent prognostic factors of sporadic ALS.

Keywords Amyotrophic lateral sclerosis · Prognosis · Nerve conduction study · Compound muscle action potential · Sensory nerve action potential · Median nerve

Introduction

Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disorder characterized by progressive muscle atrophy and muscle weakness due to the degeneration of upper and lower motor neurons. At 3–4 years after onset, patients die or need permanent mechanical ventilation due to respiratory failure [1], although there are certain subsets of patients with rapid and slow progression. The disease course of sporadic ALS subjects, accounting for 95% of patients, is rather diverse [2]; thus, the identification of prognostic factors is important for clinical studies and medical care.

Bulbar onset and older age have been consistently reported as poor prognostic factors of ALS [3–7]. Lower body mass index and shorter time from onset to diagnosis are also poor prognostic factors [5, 7, 8]. A diagnosis of definite ALS using the revised El Escorial diagnostic criteria

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has a poorer prognosis compared to all other diagnostic indices [6, 7]. The scores and decline rates of the revised ALS functional rating scale (ALSFRS-R) are also predictors of survival in ALS patients [9, 10]. As for biofluid markers, several indices, e.g., serum creatinine kinase and asymmetric dimethyl l-arginine in CSF, are potential prognostic factors of sporadic ALS [11, 12]. The most widely known staging systems include the King's systems and the Milano–Torino functional staging (MiToS) systems [13, 14]. The MiToS system predicts long-term survival in ALS [15], and King's staging was listed as an independent prognostic factor [16].

When a diagnosis of ALS is made, a nerve conduction study (NCS) is performed to rule out motor neuropathies and other ALS mimics. In ALS patients, an NCS often shows decreased compound muscle action potential (CMAP) amplitude and prolonged motor distal latency as the degree of atrophy increases. However, the relationship between an NCS and prognosis in ALS patients has not been clarified. Here, we examined whether an NCS could predict the prognosis of sporadic ALS patients.

Methods

Participants

We examined 275 consecutive patients diagnosed with sporadic ALS at Nagoya University Hospital from January 2006 to March 2018 (Fig. 1). The patients fulfilled the revised El Escorial criteria for clinically definite, probable, probable laboratory-supported, or possible ALS. Of these patients, 208 underwent an NCS within 3 months of diagnosis. We excluded 18 patients with coexisting diseases that can cause a peripheral nerve disorder as follows: diabetes ($n=15$), chemotherapy ($n=2$), and tethered cord syndrome ($n=1$). Finally, 190 patients were included in the study. The included patients were also registered and followed in Japanese Consortium for Amyotrophic Lateral Sclerosis Research (JaCALS) [17]. We also included 47 age- and gender-matched control subjects with no neurological disorders [18].

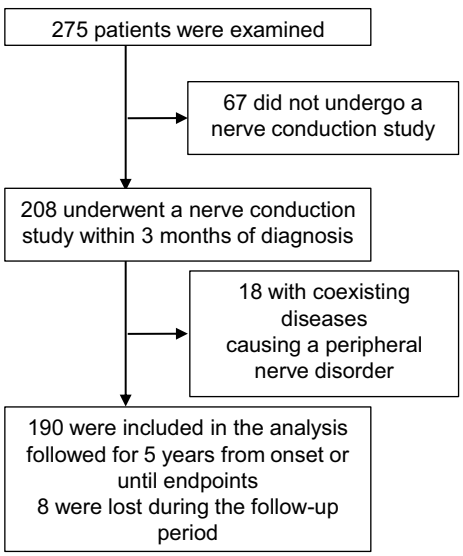

Fig. 1 Flowchart of participant recruitment

Diagnosis and follow-up period

At diagnosis, full clinical examinations were conducted by neurologists. A diagnosis of ALS was based on the revised El Escorial criteria. Disease onset was defined as the time when the first symptom was noticed by the patients. The region of disease onset was classified into bulbar or spinal. The Japanese version of the ALSFRS-R validated by Ohashi et al. [19] was used as a scale of motor function. We used King's staging and MiToS functional staging for evaluation [13, 14]. The patients were prospectively followed up with telephone surveys conducted by clinical research coordinators or via examinations by neurologists to check the prognosis every 3 months. The endpoint was defined as the time when a patient died or started tracheostomy positive-pressure ventilation. The observation period continued until 5 years after onset or until the end point [17].

NCS

An NCS was performed on the side of the body with the most severe symptoms using a standard method as described previously [18, 20–22]. Motor nerve conduction was investigated in the median, ulnar, and tibial nerves, recording from the abductor pollicis brevis (APB), abductor digiti minimi (ADM), and abductor hallucis brevis, respectively. Sensory nerve conduction was investigated in the median, ulnar, and sural nerves, recording from the proximal interphalangeal joint of the index finger, proximal interphalangeal joint of the little finger, and just behind the lateral malleolus, respectively. Diagnosis of mononeuropathies including median entrapment was made from clinical symptoms and nerve conduction study, based on the established diagnostic criteria [23].

Statistical analysis

The following NCS indices were used as variables: motor nerve conduction velocity (MCV) (wrist-elbow), distal latency, CMAP amplitude (wrist), sensory nerve conduction velocity (SCV) (wrist), and sensory nerve action potential (SNAP) amplitude (wrist) of the median nerve; MCV (wrist-elbow), distal latency, CMAP amplitude (wrist), SCV (wrist), and SNAP amplitude (wrist) of the ulnar nerve;

MCV (ankle-popliteal fossa), distal latency, and CMAP amplitude (ankle) of the tibial nerve; and SCV and SNAP amplitude of the sural nerve. Onset age, sex, onset site (bulbar vs. spinal), revised El Escorial criteria category (definite vs. others), King's staging (King's), MiToS functional staging, and ALSFRS-R decline rate were used as known prognostic factors. ALSFRS-R decline rate was defined as (48-ALSFRS-R score)/time from onset to nerve conduction study (month). We used the Mann–Whitney *U* test for two-group comparisons and analysis of variance with Bonferroni's correction to compare the variables among multiple groups. Univariate survival analyses for each NCS variable were performed using Cox proportional hazards analysis. Multivariate survival analyses for each NCS variable were also performed using Cox proportional hazards analysis including the known prognostic factors as covariates. Analysis including the variables with a P value < 0.1 in the univariate or multivariate analyses and the known prognostic factors was conducted using Cox stepwise proportional hazards analysis, using a P value < 0.05 as the entry criterion and a P value ≥ 0.05 as the removal criterion. Kaplan–Meier curve analysis was performed for NCS variables that showed a significant association with prognosis in the second multivariate analysis. The variables were divided into two groups according to the median value. The survival curves of each group were compared with the log-rank test. Given the age-dependent alterations of NCS findings, we conducted analyses with different age groups (below the 25th percentile, above the 25th percentile and below the 75th percentile, and above the 75th percentile). We also conducted analysis in the subset of patients with bulbar-onset ALS. A P value < 0.05 was considered significant. All statistical analyses were conducted using SPSS Statistics version 25.0 (IBM, Tokyo, Japan).

Results

Patient characteristics

The characteristics of the included patients were similar to those in the previous reports from Japan (Table 1) [24, 25]. They were followed for 17.48 (6.04–31.12) months (median [interquartile range]), and more than half (57.9%) of them reached the endpoint. 8 out of the 190 patients were lost during the follow-up period (Fig. 1). The CMAP amplitudes and distal latencies of motor nerves, together with median nerve MCV, were significantly different between the ALS patients and controls after Bonferroni's correction (Table 2). The SNAP amplitudes of the median and ulnar nerves were also significantly reduced in ALS subjects. NCS together with clinical examination detected no obvious mononeuropathies.

Table 1 Patient characteristics ($n = 190$)

Characteristics	
Onset age (years)	63.71 (56.92–69.46)[a]
Sex (male/female)	116/74
Time from onset to diagnosis (month)	13.7 (10.0–22.5)[a]
Time from nerve conduction study to diagnosis (month)	0.30 (0.16–0.67)[a]
Onset site [*n* (%)]	
Spinal	141 (74.2)[b]
Bulbar	49 (25.8)[b]
Revised El Escorial criteria category	
Definite ALS	42 (22.1)[b]
Probable ALS	93 (48.9)[b]
Probable laboratory-supported ALS	36 (18.9)[b]
Possible ALS	19 (10.0)[b]
ALSFRS-R score	41 (37–44)[a]
King's	2 (1–3)[a]
MiToS	0 (0–0)[a]
Event (died or introduced TPPV)	110

ALS amyotrophic lateral sclerosis, *ALSFRS-R* revised ALS functional rating scale, *IQR* interquartile range, *King's* King's staging, *MiToS* MiToS functional staging, *TPPV* tracheostomy positive pressure ventilation

[a]Data represent median (IQR)

[b]Data represent number (%)

Identification of prognostic factors

In the univariate analyses, all of the NCS indices, but the SNAP amplitude of any nerve, sural nerve SCV, and ulnar nerve MCV, and SCV showed an association with prognosis with P values < 0.1 (Table 3). In the multivariate analyses, following indices showed P values < 0.1 (Table 3); CMAP amplitude of the median and ulnar nerves, distal latency of the median, ulnar, and tibial nerves, median nerve MCV, median nerve SNAP amplitude, and sural nerve SCV. We thus included these variables and the known prognostic factors into Cox stepwise proportional hazards analysis (Table 4). The Cox model selected the median nerve CMAP and SNAP amplitudes, in addition to onset age, onset site, MiToS functional staging, and ALSFRS-R decline rate, as prognostic factors.

Relationship between NCS variables and prognosis

To verify the plausibility of the NCS as prognostic factors, we investigated Kaplan–Meier curves divided according to the median value of each parameter. The results demonstrated a significant difference in the survival curves between the groups with lower and higher median nerve CMAP amplitudes in all age groups (Fig. 2). As for the median nerve SNAP amplitude, there was a significant difference in the survival

Table 2 Nerve conduction study results

	Median (IQR)		*P* value[a]
	ALS ($n=190$)	Control ($n=47$)	
Median nerve			
MCV (m/s)	54.0 (51.0–58.0)	57.0 (54.0–59.0)	0.001
Distal latency (ms)	4.1 (3.6–4.7)	3.5 (3.3–3.7)	< 0.001
CMAP amplitude (mV)	4.0 (1.5–6.7)	8.1 (6.6–9.0)	< 0.001
SCV (m/s)	52.0 (48.0–56.2)	54.0 (50.0–58.0)	0.015
SNAP amplitude (μV)	23.9 (16.3–32.6)	20.1 (14.8–24.2)	0.013
Ulnar nerve			
MCV (m/s)	58.0 (53.0–61.0)	56.0 (53.0–61.0)	0.434
Distal latency (ms)	2.9 (2.7–3.2)	2.6 (2.4–2.8)	< 0.001
CMAP amplitude (mV)	5.7 (2.5–7.3)	6.9 (6.4–8.2)	< 0.001
SCV (m/s)	52.0 (48.8–54.6)	52.0 (49.0–55.0)	0.563
SNAP amplitude (μV)	21.8 (15.3–30.4)	18.6 (12.0–24.1)	0.014
Tibial nerve			
MCV (m/s)	44.0 (42.0–47.0)	45.0 (43.0–45.0)	0.291
Distal latency (ms)	4.7 (4.2–5.3)	4.1 (3.6–4.5)	< 0.001
CMAP amplitude (mV)	7.2 (4.2–10.2)	9.5 (7.7–12.8)	< 0.001
Sural nerve			
SCV (m/s)	50.0 (47.0–53.0)	48.0 (46.0–52.0)	0.165
SNAP amplitude (μV)	15.8 (9.5–22.1)	13.3 (9.3–22.5)	0.751

ALS amyotrophic lateral sclerosis, *CMAP* compound muscle action potential, *IQR* interquartile range, *MCV* motor nerve conduction velocity, *SCV* sensory nerve conduction velocity, *SNAP* sensory nerve action potential

[a]Mann–Whitney *U* test

curves between the groups with lower and higher median nerve CMAP amplitudes, but only in the patient population aged below the 25th percentile (56.91 years or lower), with no significant difference in any other age group (Fig. 3). As it is well known that bulbar-onset ALS patients have late onset and poor prognosis, we also performed subgroup analysis of patients whose initial symptom was bulbar palsy. Our results showed that there was a significant difference in the survival curves between the groups with lower and higher median nerve CMAP amplitudes, such difference was not found with regard to the median nerve SNAP amplitudes (Fig. 4).

Discussion

The results of the present study showed that the CMAP and SNAP amplitudes of the median nerve were independent prognostic factors of sporadic ALS. CMAP amplitude had the strongest influence on prognosis outside the onset site. The higher the median nerve CMAP amplitude, the better the prognosis in all age groups, suggesting that a high CMAP amplitude is an age-independent indicator of good prognosis. By contrast, the higher the median nerve SNAP amplitude, the worse the prognosis in young patients with sporadic ALS, implying that a low SNAP amplitude is an age-dependent indicator of good prognosis.

CMAP amplitude is construed as a rough estimation of the number of muscle fibers that are activated by nerve stimulation, and thus, an indicator of the number of nerve fibers that become excitable upon nerve stimulation as long as neuromuscular transmission is normal. A decrease of CMAP amplitude is observed in axonal degeneration, but also in segmental demyelination, albeit to a lesser degree [26]. Pathologically, the phrenic nerves of patients with ALS studied postmortem reportedly contain only 33% of the normal number of large myelinated fibers and the ratio of axonal circumference to myelin lamellae in large myelinated fibers in the distal segment was 34% greater than that in control fibers [27]. Furthermore, the large diameter of motor neuron columns were markedly and selectively decreased in ALS [28]. Axonopathy and the vulnerability of alpha fibers underlie the pathology of ALS [28], and these pathomechanisms appear to be reflected in the reduction of the CMAP amplitude of the median nerve.

Another important observation in our study was that the CMAP amplitude of the median nerve was more strongly associated with prognosis than that of the ulnar nerve. In patients with ALS, the thenar muscles (APB) and first dorsal interosseous muscle (FDI) were more severely denervated than the hypothenar muscles (ADM), and this pattern of dissociated small hand muscle atrophy has been labeled the "split hand" [29]. Kuwabara et al. [30] reported that, compared with normal controls, patients with ALS had a reduced APB/ADM amplitude ratio and FDI/ADM ratio. Prominent muscle atrophy in APB and FDI, with a relatively preserved ADM, was considered to reflect the central and peripheral pathophysiology of ALS [31]. In the present study, the CMAP amplitudes of the median and ulnar nerves were recorded from the APB and ADM, respectively. The stronger relationship between median nerve CMAP amplitude and prognosis is possibly associated with the pathological factors underlying split hand.

SNAP amplitude is considered to be a rough estimation of the number of sensory fibers of greater than 9 μm in diameter that are activated by nerve stimulation [26, 32]. A loss of approximately one-third fibers with a diameter greater than 7 μm is a requisite for a substantial drop in SNAP [26]. Although sporadic ALS selectively impairs the motor neuron system, the sensory system is also reportedly affected in certain cases. Previous studies documented electrophysiologic and pathologic findings

Table 3 Cox proportional hazards analysis of survival

	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Median nerve						
MCV (m/s)	0.932	0.901–0.965	6.1×10^{-5}	0.963	0.926–1.002	0.065
Distal latency (ms)	1.449	1.234–1.702	6.0×10^{-6}	1.360	1.142–1.619	0.001
CMAP amplitude (mV)	0.848	0.795–0.904	5.32×10^{-7}	0.822	0.763–0.887	3.52×10^{-7}
SCV (m/s)	0.971	0.943–1.000	0.049	0.997	0.967–1.028	0.841
SNAP amplitude (μV)	1.003	0.989–1.018	0.671	1.018	1.002–1.034	0.028
Ulnar nerve						
MCV (m/s)	0.975	0.946–1.005	0.104	0.998	0.962–1.305	0.901
Distal latency (ms)	1.583	1.187–2.111	0.002	1.545	1.146–2.082	0.004
CMAP amplitude (mV)	0.870	0.184–0.929	3.8×10^{-5}	0.872	0.806–0.944	0.001
SCV (m/s)	0.991	0.953–1.030	0.646	1.027	0.983–1.073	0.237
SNAP amplitude (μV)	1.008	0.992–1.024	0.345	1.013	0.994–1.033	0.176
Tibial nerve						
MCV (m/s)	0.942	0.894–0.993	0.025	0.977	0.924–1.033	0.414
Distal latency (ms)	1.211	1.002–1.465	0.048	1.184	0.971–1.444	0.094
CMAP amplitude (mV)	0.941	0.899–0.984	0.008	0.965	0.918–1.015	0.171
Sural nerve						
SCV (m/s)	0.977	0.945–1.010	0.163	0.974	0.940–1.009	0.138
SNAP amplitude (μV)	0.991	0.973–1.009	0.336	1.005	0.986–1.025	0.591

Table 4 Multivariate analysis for survival with Cox stepwise proportional hazards analysis

	HR	95% CI	*P* value
Onset age	1.049	1.025–1.074	5.4×10^{-5}
Onset site (bulbar vs spinal)	2.149	1.337–3.455	0.002
MiToS	1.576	1.047–2.371	0.029
ALSFRS-R decline rate	2.420	1.654–3.539	5.0×10^{-6}
Median nerve CMAP amplitude	0.796	0.731–0.866	1.24×10^{-7}
Median nerve SNAP amplitude	1.028	1.009–1.046	0.003

ALSFRS-R revised amyotrophic lateral sclerosis functional rating scale, *CI* confidence interval, *CMAP* compound muscle action potential, *HR* hazard ratio, *MiToS* MiToS functional staging, *SNAP* sensory nerve action potential

indicate a pattern of axonal loss predominantly affecting large-caliber myelinated fibers [33–35]. In addition, small fiber involvement is also suggested in ALS [36, 37]. SNAP amplitude decreases with age, and the age-dependent attenuation of SNAP is remarkable compared to that of CMAP amplitude [38]. This is the reason why we performed Kaplan–Meier curve analysis in different age groups. In the present study, median nerve SNAP amplitude was associated with the prognosis of young sporadic ALS patients, suggesting that there is a patient group with low median nerve SNAP amplitude and relatively good prognosis, although the underlying mechanism is elusive. Hyperexcitability underlies the neurodegenerative process of spinal and cortical motor neuron in animal models of ALS [39], and this hypothesis is supported by electrophysiogical studies in patients [40]. While glial impairment and inhibitory failure have been postulated to mediate hyperexcitability of spinal motor neurons, sensory input is another factor regulating excitability of motor neurons. In support of this view, enhanced response to peripheral sensory inputs was observed in patients with ALS [41]. These findings indicate that excitation by sensory axons has a beneficial effect on motor neuron degeneration in a mouse model of ALS [42, 43], and decreased sensory input is likely protective for motor neurons in ALS. This possibly accounts for the better prognosis of patients with low SNAP amplitudes in the present study. Given the genetic heterogeneity of sporadic ALS [44], a genomic variant may also be associated with our findings. Further clinical and basic studies are necessary to clarify the relationship between sensory nerve integrity and the prognosis of patients with ALS.

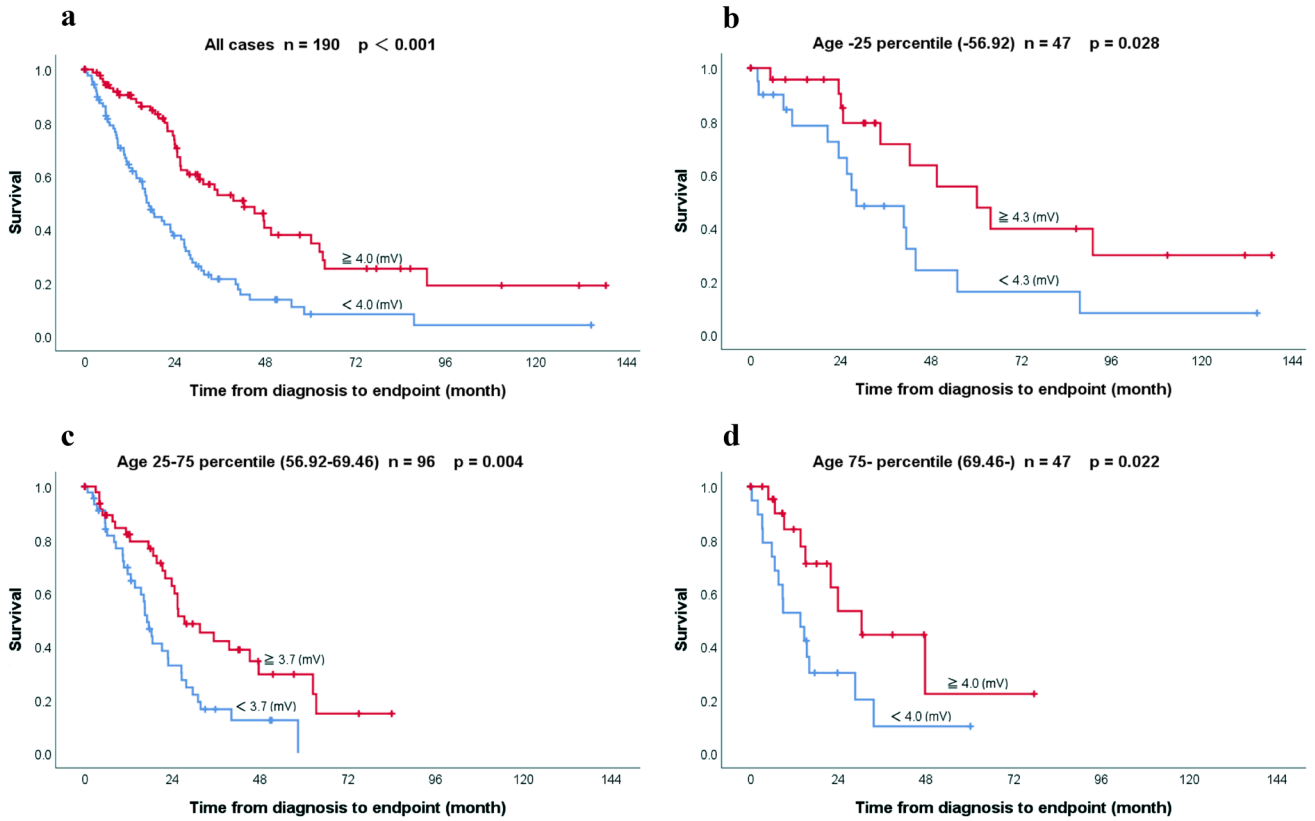

Fig. 2 Median nerve CMAP amplitude and prognosis. **a** Comparison of the survival rate between the groups with median nerve CMAP amplitude being lower and higher than the median of the total population. The median value of median nerve CMAP amplitude was 4.0 mV. **b** Comparison of the survival rate between the groups with median nerve CMAP amplitude being lower and higher than the median of the population aged below the 25th percentile (56.91 years or lower). The median value of median nerve CMAP amplitude was 4.3 mV. **c** Comparison of the survival rate between the groups with median nerve CMAP amplitude being lower and higher than the median of the population aged above the 25th percentile and below the 75th percentile (56.92–69.45 years). The median value of median nerve CMAP amplitude was 3.7 mV. **d** Comparison of the survival rate between the groups with median nerve CMAP amplitude being lower and higher than the median of the population aged above the 75th percentile (69.46 years or higher). The median value of median nerve CMAP amplitude was 4.0 mV

There are several limitations in the present study. Only a single cohort with Japanese patients was investigated in our study. Although clinical findings suggest early involvement of the first dorsal interosseous (FDI) in ALS patients [31], we did not evaluate ulnar CMAP of FDI in the present study. Neurophysiological index, an electrophysiological marker of ALS [45], was not calculated in the participants, as we did not record ulnar F-wave. Further studies evaluating FDI CMAP and neurophysiological index would thus be necessary for validating our finding.

Conclusions

Median nerve CMAP and SNAP amplitudes are independent prognostic factors of ALS. An NCS can be used as one of the composite markers for the prognosis of ALS. The association of low median CMAP with poorer prognosis in ALS patients is a much stronger and better marker than median SNAP alternations.

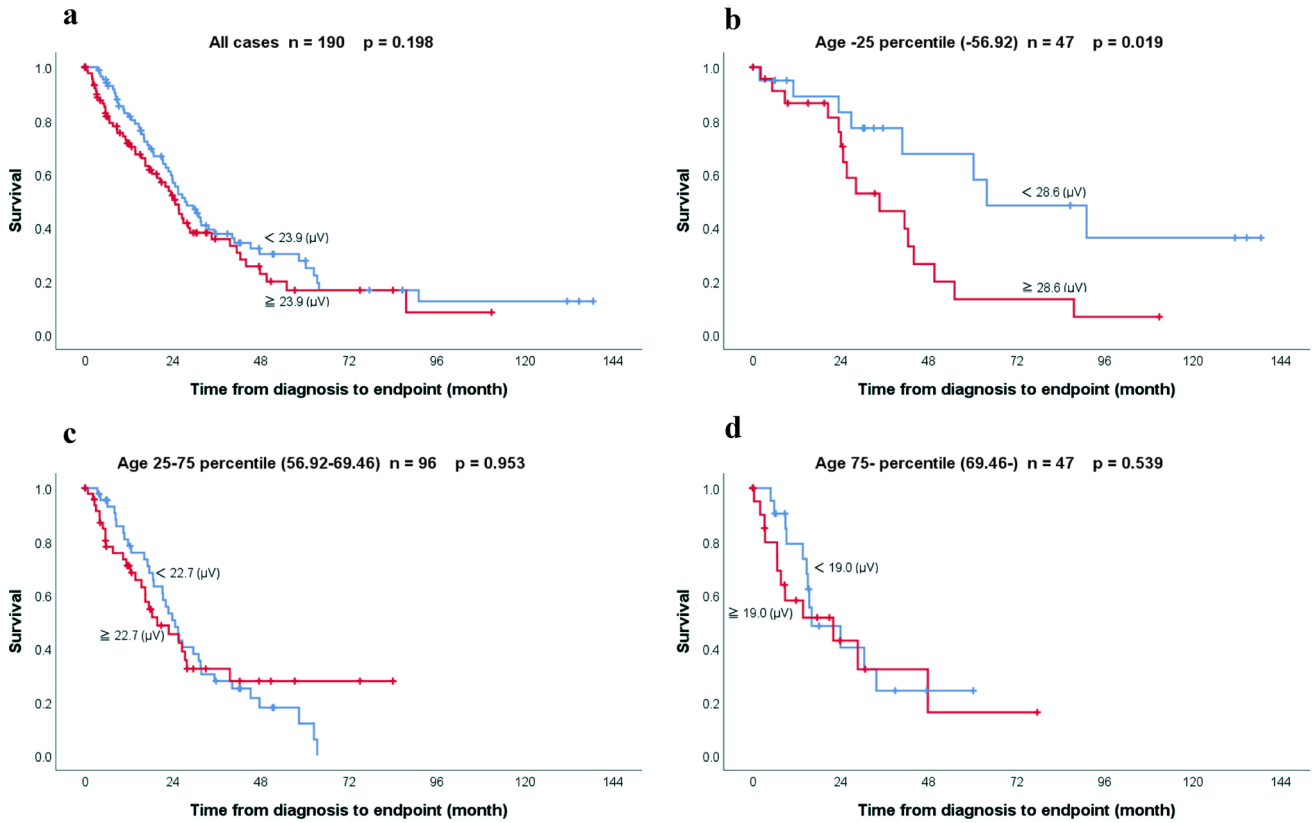

Fig. 3 Median nerve SNAP amplitude and prognosis. **a** Comparison of the survival rate between the groups with median nerve SNAP amplitude being lower and higher than the median of the total population. The median value of median nerve SNAP amplitude was 23.9 μV. **b** Comparison of the survival rate between the groups with median nerve SNAP amplitude being lower and higher than the median of the population aged below the 25th percentile. The median value of median nerve SNAP amplitude was 28.6 μV. **c** Comparison of the survival rate between the groups with median nerve SNAP amplitude being lower and higher than the median of the population aged above the 25th percentile and below the 75th percentile. The median value of median nerve SNAP amplitude was 22.7 μV. **d** Comparison of the survival rate between the groups with median nerve SNAP amplitude being lower and higher than the median of the population aged above the 75th percentile. The median value of median nerve SNAP amplitude was 19.0 μV

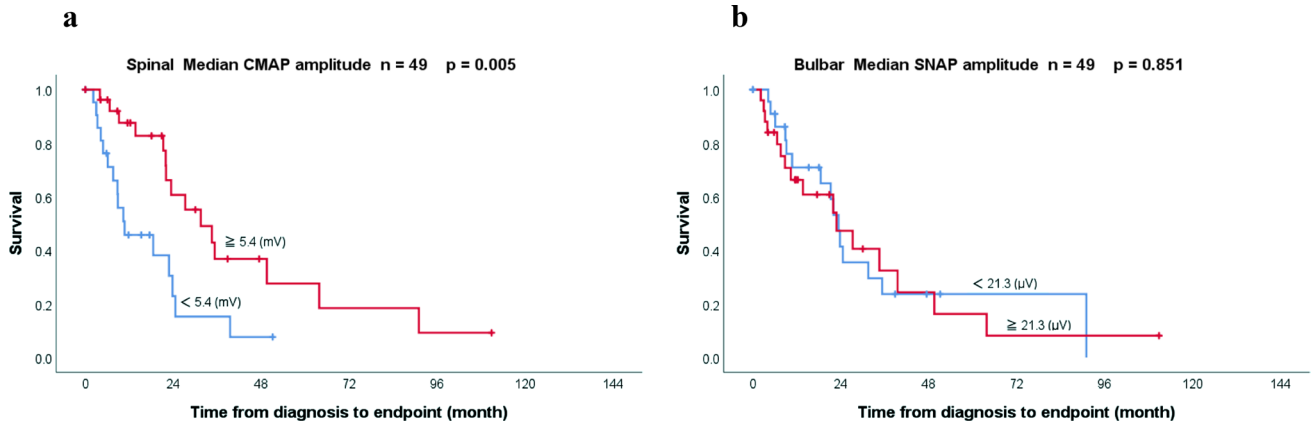

Fig. 4 Median nerve CMAP, SNAP amplitudes, and prognosis in the subset of patients with bulbar-onset ALS. **a** Comparison of the survival rate between the groups with median nerve CMAP amplitude being lower and higher than the median. The median value of median nerve CMAP amplitude was 5.4 mV. **b** Comparison of the survival rate between the groups with median nerve SNAP amplitude being lower and higher than the median. The median value of median nerve SNAP amplitude was 21.3 μV

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Author contributions EI: designed and conceptualized the study; analyzed the data; drafted the manuscript; TN, NA, and GS: interpreted the data; revised the manuscript for intellectual content; MN: analyzed and interpreted the data; MS, YH, RN, and NH: acquisition of data; MK: designed and conceptualized study; interpreted the data; revised the manuscript for intellectual content.

Compliance with ethical standards

Conflicts of interest The authors declare they have no conflict of interest.

Ethical standards This study was conducted according to the 1964 declaration of Helsinki and its later amendments, the Ethics Guidelines for Human Genome/Gene Analysis Research, and the Ethical Guidelines for Medical and Health Research Involving Human Subjects endorsed by the Japanese government. This study was approved by the Ethics Review Committee of Nagoya University Graduate School of Medicine and all participants gave written informed consent before participation.

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