Use of Bayesian MUNE to show differing rate of loss of motor units in subgroups of ALS

Running Title: Subgroups of ALS

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Summary:

To evaluate differences among patients with different clinical features of ALS, we used our Bayesian method of motor unit number estimation (MUNE). We performed serial MUNE studies on 44 subjects who fulfilled the diagnostic criteria for ALS during the course of their illness. Subjects were classified into three subgroups according to whether they had typical ALS (with upper and lower motor neurone signs) or had predominantly upper motor neurone with only minor LMN feature, or predominantly lower motor neurone signs with only minor UMN signs. In all subjects we calculated the half life of MUs, defined as the expected time for the number of MUs to halve, in one or more of the abductor digiti minimi (ADM), abductor pollicis brevis (APB) and extensor digitorum brevis (EDB) muscles. The mean half life of motor units was less in subjects who had typical ALS with both upper and lower motor neurone signs than in those with predominantly upper motor neurone weakness or predominantly lower motor neurone weakness. In 18 subjects we analysed the estimated size of the MUs and demonstrated the appearance of large MUs in subjects with upper or lower motor neurone predominant weakness. We found that the appearance of large MUs was correlated with the half life of MUs.

Key words: ALS, exponential decay, mathematical models, motor unit, MUNE
Introduction

Amyotrophic Lateral Sclerosis (ALS) is characterized by progressive loss of upper and lower motor neurones. The pathogenesis of ALS is unknown but inherited abnormalities of neuronal proteins are increasingly seen to be important [1]. The clinical picture of ALS results from dysfunction of both UMN and LMN pathways. There has been debate as to whether the death of lower motor neurones (LMNs) is secondary to dying back of axons or dying forward of upper motor neurones (UMNs) or a combination of the processes [2].

ALS is diagnosed on clinical grounds for which there are accepted criteria [3]. There are other diseases of motor neurones, which do not fulfill these criteria, with pure UMN disease (primary lateral sclerosis) or pure LMN weakness (progressive muscular atrophy). However, even when defined according to the standard criteria [3], ALS is heterogeneous with respect to whether patients have typical ALS with mixed upper and lower motor neurone signs or whether UMN or LMN signs are predominant [4-7]. Clinical distinctions are important because it is possible that subjects with different clinical features have different underlying pathophysiology.

One pathophysiological finding is that large MUs that can be demonstrated by needle EMG in ALS [8]. This is thought to occur because after denervation of muscle, there is often re-innervation due to collateral sprouting of terminal branches of surviving axons. MU size in ALS has also been studied with decomposition-based quantitative electromyography (DQEMG) [9]. However, there have been no studies of the size of
the entire population of motor unit action potentials (MUAPs) in ALS and the relationship of change in size of MUs to the rate of progression of disease.

We have developed a Bayesian statistical technique of motor unit number estimation (MUNE) that gives an estimate of the number of MUs in a muscle [10;11]. As well as estimating the number of MUs, our MUNE technique also estimates the size of all the surface-recorded MUAPs that contribute to the CMAP. We have performed a large study with serial MUNE recordings from patients with ALS, to compare the rate of loss of MUs in different clinical subtypes and different muscles and to evaluate the changes in size in MUs as disease progresses.

Methods

Subjects and clinical assessment

We recruited ALS patients who were attending the Motor Neurone Disease multidisciplinary clinic at the Royal Brisbane and Women's Hospital (RBWH). The study was approved by the Hospital Ethics Committee and all subjects gave written consent prior to testing. ALS patients met the modified El Escorial criteria for probable or definite ALS during the course of their disease [3]. We noted the age at onset of ALS, site of onset as bulbar, upper limb (UL) or lower limb (LL) and length of symptom duration before the first visit (in months).

The presence of UMN and LMN signs was evaluated. Signs of UMN involvement were taken to be spastic dysarthria, increased jaw jerk, emotional lability, hyperreflexia in the limbs, increased muscle tone, and clonus. Signs of LMN
involvement were taken to be muscle atrophy and fasciculation. Patients with typical ALS with mixed UMN and LMN signs were grouped as typical ALS (ALS-typical).

Patients with predominantly UMN signs were designated as UMN dominant type (UMN-D). Patients with UMN-D had symptoms less than 4 years, and disability due predominantly to UMN signs but with minor EMG denervation or LMN signs on examination. In these patients LMN signs of wasting and fasciculations limited to one or two muscles or minor denervation on EMG limited to sparse fibrillation potentials, positive sharp waves or minor MU potential remodelling on one or two muscles [4]. In assigning subject to UMN-D we did not include patients with clinically pure PLS [4].

Patients with predominantly LMN signs were designated LMN dominant type (LMN-D). Patients with LMN-D had symptoms and disability due to prominent lower motor signs (muscle atrophy, fasciculations) at the time of first study, with no or minor UMN signs (emotional lability, hyperreflexia, spasticity). LMN-D patients were distinguished from pure adult onset LMN syndromes such as progressive muscular atrophy (PMA) patients who have disease duration of at least 4 years and absence of UMN signs [12].

Neurophysiology
MUNE studies were performed in three different nerve/muscle combinations: median nerve / abductor pollicis brevis (APB) muscle, ulnar nerve/ abductor digiti minimi (ADM) / ulnar nerve and peroneal nerve / extensor digitorum brevis (EDB) muscle.
Lower motor neuron degeneration in ALS

Surface recordings using the belly–tendon configuration were made from APB, ADM, and EDB muscles with disposable silver pre-gelled, 20mm diameter self adhesive electrodes (Nicolet Biomedical, Madison, Wisconsin). All studies were performed using a Nicolet Viking IV machine. The recording electrode was placed over the middle of the belly of the muscle (with attention to the muscle end plate). Before placing the electrodes, the skin was cleaned to prevent high or mismatching impedance between the electrodes. In all studies, the skin temperature was recorded with a surface probe and was maintained above 31 °C for the hand and 29 °C for the foot. The muscle under testing was restrained with a Velcro strap, and the audiometer was used to detect movement [13]. The active stimulating electrode was taped approximately 7 cm from the active recording electrode. The stimulus intensity was measured as current (mA) in constant voltage mode, and stimuli were 0.1 ms in duration. The frequency of stimulation was 2 Hz.

For MUNE studies, a stimulus response curve with 1000 stimuli was first obtained as described previously [14;15]. The size of the stimulus required to produce a maximal CMAP was determined with standard NCS. For the stimulus response curve, the maximal CMAP was obtained with a stimulus strength sufficiently above the maximal (at least 10—20%) that small movements of stimulating electrodes would be unlikely to affect the maximal CMAP. For each study the minimum and maximum stimulus intensity was determined before commencing collection of the stimulus–response curve by gradually increasing the stimulus intensity with at least 1000 stimuli. A software modification supplied by Nicolet Biomedical (Madison, Wisconsin) was used to collect the stimulus response curves, by automatically evoked incremental stimuli. The CMAP amplitude measurements were automatically calculated from
baseline to negative peak. The areas and durations of the negative phase of the CMAP were measured from onset to baseline crossing.

**MUNE calculations**
Bayesian MUNE analysis was applied to the stimulus response curves, as previously published [10;11]. In the present study, on the basis of our experience with the technique, we have modified the analysis by making a direct recording of the baseline noise (rather than estimating this in the model), by making the variability of the CMAP be the same across the entire CMAP scan, rather than increasing linearly with the number of units firing, and by prohibiting MUs with excitability curves that extend across the whole stimulus range.

The MUNE method is based on mathematical model of MU activation, and uses the data from the stimulus response curve to estimate the unknown parameters of the model [16]. These parameters include the number of MUs and the size of the MUAPs. The size of the MUAPs are obtained by first obtaining the most probable number of MUs and using this as a fixed value in the model to estimate the average sizes of individual MUAPs over a further 10,000 iterations of the programme.

**Calculation of half-life**
The modal value of the posterior distribution of the number of MUs at each study was used to calculate the half life of MUs according to an exponential decay model in the nerve with more than 3 studies. The half life of the MU number was calculated as \( \log_{\text{e}2} / (\text{exponential rate of decline or decay constant}) \).
Half life according to clinical group
To determine whether the half lives of MUs in ALS was related to clinical features, the mean half lives of MUs among the three clinical groups was compared. The mean survival for these groups was also calculated.

Studies of MUAP size at different time points
In ALS subjects and healthy controls, we obtained histograms of individual estimated MU sizes for three different time points. We analysed these according to the clinical subtypes of ALS. For each study we calculated the median value of the MUAP size. We also assigned a value of size of 1000 microVms as a cut-off for large MUs, and for each study we calculated the percentage of MUs that had an area > 1000 microVms.

Statistical methods
Descriptive statistics are presented as mean and standard deviation or standard error of mean for continuous variables and proportions for categorical variables. Multiple comparisons among different nerves and clinical subtypes were made by one-way analysis of variance (ANOVA).

To see if the percentage of large MUs (defined as > 1000 microVms) was associated with the half life, we calculated the correlation co-efficient between the two measures in data from the second study at the midpoint of disease.

Results

Subjects and clinical features
We studied 44 subjects with a diagnosis of ALS. One of these patients had familial ALS with a rare SOD1 mutation with long survival [17] and the other subjects had sporadic ALS. Other results from this cohort have been published previously (Baumann et al. submitted). All subjects had MUNE studies at least 4 times at intervals of three to four months. Some patients had two muscles studied at each neurophysiology session. Table 1 shows the clinical features of ALS subjects including the age, gender, site of onset, time from onset of symptoms at the start of study and survival time. The mean (SD) age of the subjects was 59 (11) years. There were more males (n= 30) than females (n= 14).

On the basis of clinical observation, 18 patients were classified as having typical mixed ALS, 12 had predominant UMN signs (UMN-D) and 14 had predominant LMN signs (LMN-D). This classification was made prior to MUNE testing.

The half life in clinical subtypes of ALS
The mean (SD) half-life of MUs in all muscles (57 studies) in subjects with ALS-typical, those with LMN-D and those with UMN-D were 235 (151), 448 (219) and 979 (368) days, respectively. The half life of MUs was significantly less in subjects with ALS-typical than in subjects with LMN-D or UMN-D (Figure 1).

In the typical ALS group, we studied 16 ADM (55%), 7 APB and 6 EDB muscles. In LMN-D group, 12 ADM (68%), 1 APB and 4 EDB muscles were studied. In UMN – D group, 8 ADM (66%) and 4 APB muscle studies were used to calculate half life of MUs. Therefore the majority of studies were from ADM muscle in each subgroup.
The mean (SD) survival times of subjects with ALS-typical, LMN-D and UMN-D were 999 (311), 1443 (679) and 1614 (608) days, respectively. The survival time of subjects with ALS-typical was significantly shorter than those with LMN-D or UMN-D type (Figure 2).

We also compared the half lives of MUs of men (n=30) and women (n=14) as shown in Table 2 for the whole group and for each of the subgroups. There was no significant difference in half life of MUs in males (mean=419 days) and females (mean=366 days) (p=0.5).

**Studies of MUAP size at different time points:**
For this part of the study we used subjects who had serial testing of the ulnar nerve/ADM muscle. There were 8 subjects with ALS-typical, 4 with UMN-D, 4 with LMN-D and 8 healthy controls. For this analysis we used the MUNE studies at three time-points. The mean interval from onset of symptoms to the first study was 14 (SD 6) months for typical ALS, 22 (SD 6) months for UMN-D patients and 20 (SD 11) months for LMN-D patients. The second studies were done at a mean (SD) of 6 (2), 7 (4) and 8 (3) months after the first study for typical, UMN-D, and LMN-D respectively. The third studies were done at a mean of 5 (2), 9 (2) and 11 (9) months after the second study for typical, UMN-D, and LMN-D respectively.

For each subject, at each time-point the median and range in MUAP size was calculated. Figure 3 shows examples of the distribution of MUAP sizes and
representative subjects with ALS-typical, UMN-D and LMN-D types of disease, each at two time-points.

The mean values of the median MU size and the percentage of large MUs at each time-point for each type are shown in Figure 4. In the three groups of subjects with ALS, there was a large range of values for MU size, with some subjects having large median size and some subjects having a large percentage of large MUs compared to healthy subjects. This was most obvious in the UMN-D and LMN-D groups which also had larger MUs than those in the ALS-typical group. At the third study, there was a decline in the percentage of large units in 3 of the 8 subjects with typical ALS. In the groups with UMN-D and LMN-D the percentage of large units at the third study was greater than at the previous studies for all subjects.

For each subject we calculated the ratio of the values at the second and third time-points to the values at the first time-point. For each group we then calculated the mean and standard deviation of these ratios and these are shown in Table 3.

**Relationship of frequency of large MUs to rate of progression**

To determine if the percentage of large MUAPs was related to the half-life of MUs we calculated the percentage of large MUAPs (defined as being greater than 1000 microVms) at the second study. We chose to use the data from the second study because at the third study some subjects showed a decline in the number of large MUs, as can occur at the pre-terminal stage of disease. We plotted the percentage of large MUs against half life of MUs in 18 patients (Figure 5). There was a significant correlation between percentage of large MUAPs and half life of MUs (r = 0.70).
Discussion

In this study we have used our MUNE technique to show that the half-life of motor units and the accumulation of large motor units varies among subtypes of ALS. The results are based on our Bayesian MUNE method which is based on a model of motor unit activation, and leads to an estimate of the numbers and size of MUs in a muscle. We have previously explained the biological basis of our model and the underlying assumptions, and how we account for the variables in MU activation including variation in the threshold of axons and variation in the size of motor units [16;18]. We have previously shown with serial studies of the number of MUs in a muscle, that the loss of MUs is well-fitted by an exponential decay curve (Baumann et al. unpublished data). The demonstration that MU loss follows an exponential decay allows us to estimate the half-life of MUs.

We found that patients with different clinical features differ in the rate of loss of MUs. In patients with typical ALS (with UMN and LMN signs) the half life of MUs was less than in subjects with UMN or LMN predominant disease. Our study of the half-life provides electrophysiological evidence that supports clinical studies showing that patients with predominance of UMN involvement have a more benign course [19] and longer survival than subjects with typical ALS [20] and that subjects with LMN weakness have a slower rate of progression than subjects with typical ALS [12]. Although there are differences in the prevalence of ALS in men and women, and men and women differ in the site of onset of disease, with bulbar onset being more
common in older women [21] there was no difference between men and women in the half lives of MUs in the subjects that we studied.

We also used our MUNE method to study the size of MUAPs in ALS subjects, although this study has the limitation that recording from surface electrodes may underestimate the size of distant action potentials. MUs are known to vary in size from moment to moment [22], so in our model we allow MUs to vary in size, and the results we present are the average of 10,000 estimations.

There was an increase in the percentage of large motor units over time in subjects with all subtypes of ALS, with the percentage of large MUAPS correlated with the half life. This was variable among subjects reflecting the heterogeneity of disease. However, in a few of the subjects with typical ALS, there was a decline in the number of large MUs at the third study. There was an increase in the median size of MUs, particularly in subjects with UMN-D and LMN-D type of disease, and in some subjects with ALS-typical. These findings are consistent with current understanding of ALS [8;23;24] where collateral sprouting leads to an increased fibre density of MUs [25;26]. We found that the increase in MUAP size in the early stages of lesion, reflecting re-innervation, was much greater in LMN predominant subtype than typical ALS, consistent with previous reports [27]. These UMN-D and LMN-D subjects differ from typical ALS subjects in having a longer half life, and were also studied at longer times after onset of disease. We suggest that the slower and longer disease process allows collateral sprouting to occur in these subjects. We found that the percentage of large MUs was related to the half-life of MUs.
In previous studies, a modest increase in MU size was found using the multiple point stimulation MUNE method [28-30]. A previous multicentre serial MUNE study using the Poisson statistical method did not find an increase in mean MUAP size over time [31], perhaps because the effect of MU variability could not be included in the calculation. Others have shown an increase in MU size over time, using the MPS method which measures the size of a sample of MUs, rather than the whole population as is the case with our method, although in some subjects the size of the MUs declines at the end stage of disease [9;30].

These differences in length of survival, rate of progression and the accumulation of large MUs could indicate that there are underlying pathophysiological differences among these groups. Indeed, post-mortem studies have found that subjects with typical ALS differ from those with LMN predominant form of ALS in the pattern of neuronal loss, providing evidence that the clinical signs of disease reflect the pattern of neuronal loss in ALS [32]. In UMN dominant ALS, a benign LMN impairment involving only few motor units and leaving the others intact was a common feature [33]. Similarly a post-mortem study showed LMN loss was minimal in patients whose motor manifestations had been predominantly UMN type [34]. Recently subjects with UMN predominant disease have been found to have genetic variation in the KIFAP3 [35]. Although the classification into the subtypes of MND was based on clinical assessment, this reflects the clinical heterogeneity of the disease and is an approach being used by others. In summary, our MUNE analysis appears to be a feasible method to provide new insights into the pathophysiology of lower motor neuron degeneration and MU re-arrangement in ALS.
Acknowledgements

We appreciate the effort and time of the patients and their families who were involved in this study. We thank Nicole Hutchinson for her assistance in patient recruitment.

Funding

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Abbreviations

ADM - abductor digiti minimi
APB - abductor pollicis brevis
ALS – amyotrophic lateral sclerosis
CMAP – compound muscle action potential
EDB - extensor digitorum brevis
FDI – first dorsal interosseous
LMN – lower motor neurone
LL – lower limb
MN - motor neurone
MU – motor unit
MUAP – motor unit action potential
MUNE – motor unit number estimate
Lower motor neuron degeneration in ALS

PLS - primary lateral sclerosis

PMA – progressive muscular atrophy

TA – tibialis anterior

UL – upper limb

UMN - upper motor neurone
References


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Figure Legends

Figure 1. Half life of MUs according to type of ALS.
The half life of MUs among three clinical subtypes (ALS-typical, UMN-D LMN-D) was compared. There was significant difference in half lives among these three subtypes (p< 0.05).

Figure 2. Survival time according to type of ALS
The mean survival time for these groups was also calculated (D). The survival time of subjects with typical ALS was significantly shorter than those with predominantly lower (LMN-D) or predominantly upper motor neurone (UMN-D) weakness.
The bottom and top of the boxes are the 25th and 75th percentile (the lower and upper quartiles, respectively), and the band near the middle of the box is the 50th percentile (the median). The whiskers represent the minimum and maximum of all the data.

Figure 3. Frequency distribution of MU sizes
Examples of the distribution of single MUAP areas of a subjects with typical ALS (C, D), LMN-D disease (E, F) and UMN-D (G, H) type of disease, showing studies at the as the mid stage of disease (study 1) and end stage (study 2) of disease. MU size is given as area (micoVms).
Dotted lines represent the distribution curves. The LMN and UMN predominant patients had very large MUs (> 3000) at the early stages (E, G) and there were almost only large MUs (> 1000), up to 7000uVms (F,H) whereas the typical ALS patient had no large MU at the end stage (D).

**Figure 4. MUAP size in subtypes of ALS during disease progression.**

The graph of the mean of the median MUs sizes (upper panel) and the mean percentage of large MUs (lower panel) in healthy controls and three groups of ALS subjects (typical ALS, UMN-D, LMN-D) at early, mid and late stages of the disease. Error bars represent ± SD

**Figure 5. The correlation of the half life of MUs and the percentage of large MUs.** The percentage of large units (> 1000 microVms) at the second study in 18 ALS subjects was plotted against half life of MUs. There was significant correlation between percentage of large MUs and the half life of MUs (r = 0.70).
Table 1. Clinical features of ALS subjects

<table>
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<th>Number of subjects</th>
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<tr>
<td>Total number of subjects</td>
<td>44</td>
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<td>No (%) males</td>
<td>30 (68)</td>
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<table>
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<th>Age of onset and symptom duration</th>
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<tr>
<td>Mean (sd) Age of onset (yr)</td>
<td>59 (11)</td>
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<tr>
<td>Range of age of onset (yr)</td>
<td>30-81</td>
</tr>
<tr>
<td>Duration of symptoms at study entry (mo)</td>
<td>15 (11)</td>
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<td>Range of symptom onset (mo)</td>
<td>3-62</td>
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<td>No (%) bulbar onset</td>
<td>12 (27)</td>
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<tr>
<td>No (%) upper limb onset</td>
<td>15 (35)</td>
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<tr>
<td>No (%) lower limb onset</td>
<td>17 (38)</td>
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<table>
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<tr>
<td>No (%) with Typical ALS</td>
<td>18 (41)</td>
</tr>
<tr>
<td>No (%) with UMN predominant</td>
<td>14 (32)</td>
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<tr>
<td>No (%) with LMN predominant</td>
<td>12 (27)</td>
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<td>Mean (sd) survival time (mo)</td>
<td>41 (15)</td>
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<tr>
<td>Range</td>
<td>18-89</td>
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<tr>
<td>No (%) deceased at end of study</td>
<td>24 (54)</td>
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† Symptom duration is from the onset of disease to the first MUNE study
‡ Survival time is calculated from the symptom onset to death in deceased patients and to the end of study in patients who were alive at the end of the study
Table 2. Half-life of MUs according to clinical subtype and gender

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Mean half-life (days)</th>
<th>SD half-life (days)</th>
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<tr>
<td>Total group males</td>
<td>30</td>
<td>419</td>
<td>299</td>
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<tr>
<td>Total-group females</td>
<td>14</td>
<td>366</td>
<td>271</td>
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<tr>
<td>ALS-typical males</td>
<td>13</td>
<td>217</td>
<td>98</td>
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<tr>
<td>ALS-typical females</td>
<td>5</td>
<td>204</td>
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<tr>
<td>LMN-D males</td>
<td>9</td>
<td>503</td>
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<tr>
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<td>5</td>
<td>297</td>
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<td>UMN-D males</td>
<td>8</td>
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<td>397</td>
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<td>UMN-D females</td>
<td>4</td>
<td>654</td>
<td>369</td>
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### Table 3 Ratio of median size of motor units and ratio of percentage of large motor units at study 2 and study 3 to values at first study

<table>
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<tr>
<th>Patient group</th>
<th>Mean ratio of median MU size at second study to median MU size at first study</th>
<th>Mean ratio of median MU size at third study to median MU size at first study</th>
<th>Mean ratio of percent large units at second study to percent large units at first study</th>
<th>Mean ratio of percent large units at third study to percent large units at first study</th>
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<tbody>
<tr>
<td>ALS-typ</td>
<td>1.29 (0.26)</td>
<td>1.52 (1.02)</td>
<td>2.20 (3.00)</td>
<td>2.71 (4.10)</td>
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<tr>
<td>UMN-D</td>
<td>1.03 (0.27)</td>
<td>1.59 (0.47)</td>
<td>1.20 (0.17)</td>
<td>1.51 (0.33)</td>
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<td>LMN-D</td>
<td>1.79 (0.86)</td>
<td>2.66 (1.43)</td>
<td>2.0 (0.41)</td>
<td>2.98 (1.76)</td>
</tr>
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### Reference List

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