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Establishing a quantitative evaluation method for the strength of cranial muscle groups and its application in amyotrophic lateral sclerosis (ALS)

Nan Hu, Jianfeng Ding, Lei Zhang, Dongchao Shen, Xunzhe Yang, Mingsheng Liu, Liying Cui

Department of Neurology, Peking Union Medical College Hospital, Beijing, China.

Abstract

Objective: To establish a quantitative method for strength evaluation targeting cranial muscle groups and applied it in amyotrophic lateral sclerosis (ALS) patients. *Methods:* Detailed physical examination were conducted on patients with neuromuscular disorders or healthy population for the selection of the actions innervated by cranial nerves. The six-level strength by manual assessment was designed according to the Medical Research Council (MRC) score. ALS patients were consecutively recruited to explore the clinical significance of the quantitative method. *Results:* A total of fourteen actions regarding cranial muscle groups were finally involved in our quantitative evaluation method which was named the MRC cranial score, all of which showed satisfied inter-observer and intra-observer consistency. Among 58 ALS patients, 40 (68.97%) showed decrease in the MRC cranial score at baseline, mainly presenting dysfunction in cheek bulging, swallowing, speech and tongue extension. During the 3-month follow up, there was a significantly negative correlation between the baseline MRC cranial score and ALS progression rate (p<0.001). Low MRC cranial score was significantly related to the need of invasive respiratory support (p=0.005) and gastric catheterization (p=0.003). *Conclusion:* In the study, we designed the MRC cranial score, which was a easily operating evaluation method of the strength involving 14 actions innervated by cranial nerves. The MRC cranial score could quantify the involvement of cranial nerves in neuromuscular diseases comprehensively, which was negatively related to the progression rate and might be a predictor of the need of gastric tube or respiratory support in ALS patients.

Keywords: Amyotrophic lateral sclerosis, cranial nerves, muscle strength

INTRODUCTION

Lower motor neurons (LMNs) from the brainstem and upper cervical spinal cord mainly form ten pairs of cranial nerves, innervating the extraocular muscle, facial muscle, pharyngolaryngeal muscle, sternocleidomastoid muscle, and lingual muscle. Related voluntary actions include eye movement, expression variation, swallowing, speaking, neck turning, tongue movement, etc. Abnormal eye movements, facial paralysis, dysphagia are all common complaints in all kinds of diseases affecting brainstem or cranial nerves. Due to the unique nature of these actions, the commonly used MRC (Medical Research Council) score is not fully applicable to the strength assessment of the cranial muscle groups. Therefore, clinicians can only briefly describe the signs, while being unable to conduct quantitative evaluation of the strength of these muscle groups. In recent years, several studies have proposed quantitative methods for evaluating the functional status of the cranial muscle groups[1-3], yet most of which need special instruments and may not be fully feasible in clinical practice. The lack of objective and easy-operating muscle strength grading system for cranial muscle groups has caused considerable difficulties for clinicians.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease involving both upper and lower motor neurons (UMN and LMN), resulting in relentlessly progressive and extensive muscle weakness and atrophy.[4] Affected muscle groups in ALS patients are artificially divided into four body regions in diagnostic criteria[5-7]:

Address correspondence to: Mingsheng Liu and Liying Cui, Department of Neurology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100730, China. Tel: +86-13520312340. Email: Mingsheng Liu: liumingsheng_pumch@163.com; Liying Cui: cuily@pumch.cn

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bulbar region, cervical region, thoracic region and lumbosacral region. Bulbar region is the near-synonym of brainstem, dominating most of the cranial muscle groups. Bulbar onset accounts for 10-40% of ALS patients[8] and involvement of bulbar muscle groups has been identified as an independent risk factor of rapid progression and the need of the gastric tube or respiratory support.[9] Therefore, the quantitative methods of evaluating strength of bulbar muscle groups are of great significance.

In the study, we aim to develop a quantitative method for strength evaluation targeting cranial muscle groups. We will test its practicality and clinical significance in ALS patients. We hope to provide a simple and reliable scale to assessing functional status of cranial muscle groups and new insights for future ALS studies.

METHODS

Subjects

This study was an observational study conducted at the Department of neurology, Peking Union Medical College Hospital (PUMCH). Patients with neuromuscular disorders were recruited consecutively between November 2022 and October 2023 at inpatient wards and outpatient clinics. Among them, definite or probable ALS were diagnosed according to the Awaji criteria.[6] Healthy controls (HC) were recruited from the general population, medical students, and health-care workers.

The following information was collected for each patient at baseline: (1) general information [name, gender, contact information, body mass index (BMI) and disease duration]; (2) detailed neurological examinations; (3) ancillary results including electrophysiological studies; (4) clinical diagnosis. The Medical Research Council (MRC) score, including bilateral assessment of shoulder abduction, elbow flexion, elbow extension, wrist flexion, wrist extension, finger flexion, finger extension, thumb abduction, little finger abduction, hip flexion, knee flexion, knee extension, ankle dorsal flexion, ankle plantar flexion, toe dorsal flexion, and toe plantar flexion was calculated. The total MRC score was 160.

For ALS patients, the revised ALS functional rating scale (ALSFRS-R) was used for the assessment of functional status.[10] The maximum of ALSFRS-R score was 48. The sum score of item 4-9 in ALSFRS-R scale was considered as ALSFRS-R limb score. Based on the staging system proposed by Roche *et al*. in 2012[11], we divided included ALS patients into 4 clinical stages. Pulmonary function test was conducted and we focused on forced vital capacity percent (FVC%) predicted of included ALS patients. A follow-up interview was performed three months later either by phone call or in our outpatient clinic to collect a follow-up ALSFRS-R score. The progression rate was calculated by the difference of the ALSFRS-R score between two visits divided by the time interval between these two visits in months (decrease of ALSFRS-R per month).[10]

This study was approved by the Ethics Committee of the PUMCH (JS1210). All enrolled subjects provided written, informed consent to be included in the study.

Manual assessment of the strength of cranial muscle groups

For each subject, detailed physical examination would be conducted by one author (HN) for twice or two authors (JFD, LZ) respectively to explore the consistency of inter-observer and intra-observer. Authors did not know the evaluation results of others to ensure blinding. For actions that needed bilateral examination, we took the muscle strength of the weaker side as the final result. The materials required for the assessment to each patient included a tongue depressor, a glass of water, and a small piece of paper, which were all easily available. Any issues encountered during the assessment would be discussed with one of senior professors (MSL or LYC) and recorded in detail. We defined the results of the assessment as the MRC cranial score.

Statistics

The Shapiro-Wilk test was used to assess whether data exhibited a normal distribution. Normally distributed variables were expressed as means (standard deviation, SD) and non-normally distributed ones were expressed as median (range). Paired t-tests and Cohen's kappa agreement were used to test the consistency inter-observer and intra-observer. Cohen's kappa coefficient >0.40 was considered moderate consistency and >0.80 was considered strong consistency. Spearman correlation coefficient was applied to reflect the correlation among MRC cranial score, total MRC score, ALSFRS-R score, ALSFRS-R limb score, progression rate, FVC%. One-way analysis of variance (ANOVA) was used to compare studied variables among different clinical stages. Two-sided p-values were calculated for all analyses and

a value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS, version 23.0.

RESULTS

Establishing the quantitative methods for strength evaluation of cranial muscle groups

We randomly recruited a total of thirty subjects in our ward and outpatient department (age: mean±SD, 47.31±14.41 years old; 19 male and 11 female), which included five healthy medical workers, twenty patients with ALS, two patients with acute inflammatory demyelinating polyneuropathy (AIDP), one with clinically-suspected Hirayama Disease and the other two patients with spinal muscular atrophy (SMA). After thorough discussion, we designed a six-level-muscle-strength list of sixteen voluntary actions related to cranial nerves based on the scoring system of MRC muscle strength (Supplementary Table 1). Among them, some actions that were not solely controlled by cranial nerves were also included. The actions of swallowing, speech, and breathing were referred to water swallow test[12] and ALSFRS-R scale.[10] Due to the difficulty in the operation, result judgment and impact of nystagmus in some patients, eye movements were not included in the list. The results of inter-observer and intra-observer's consistency were presented in Table 1. Due to the low consistency of intra-observer, shrug was excluded from further analysis. Finally, a total of fourteen items were selected for further analysis: (1) eye opening (oculomotor nerve); (2) eye closing (facial nerve); (3) chewing (trigeminal nerve); (4) forehead wrinkling or eyebrow raising (facial nerve); (5) mouth opening (trigeminal nerve); (6) teeth showing (facial nerve); (7) cheek bulging (facial nerve, vagus nerve, phrenic nerve); (8) swallowing (glossopharyngeal nerve); (9) speech (glossopharyngeal nerve, vagus nerve); (10) neck rotation (accessory nerve); (11) neck flexion (glossopharyngeal nerve, accessory nerve); (12) neck extension (accessory nerve, C1-4 level); (13) tongue extension (hypoglossal nerve); (14) breathing (phrenic nerve, vagus nerve, glossopharyngeal nerve). (Figure 1). No subject reported obvious discomfort during the examination.

Application of the MRC cranial score in amyotrophic lateral sclerosis

We consecutively recruited a total of 58 ALS patients to test the practicality of the above

Table 1: The consistency of inter-observer and intra-observer regarding the MRC cranial score

Items	Intra-observer's consistency			Inter-observer's consistency		
	Paired t-tests	Cohen's kappa agreement		Paired t-tests	Cohen's kappa agreement	
		Coefficient	*p*		Coefficient	*p*
Eye opening	**<0.001**	0.964	**<0.001**	**0.001**	0.474	**0.002**
Eye closing	**0.002**	0.904	**<0.001**	**<0.001**	1.000	**<0.001**
Chewing	**<0.001**	1.000	**<0.001**	**<0.001**	0.464	**0.011**
Forehead wrinkling and eyebrow raising	**<0.001**	1.000	**<0.001**	**<0.001**	0.787	**<0.001**
Mouth opening	**<0.001**	1.000	**<0.001**	**<0.001**	0.651	**<0.001**
Teeth showing	**<0.001**	1.000	**<0.001**	**<0.001**	0.679	**<0.001**
Cheek bulging	**<0.001**	1.000	**<0.001**	**<0.001**	0.612	**<0.001**
Swallowing	**<0.001**	1.000	**<0.001**	**<0.001**	0.525	**<0.001**
Speech	**<0.001**	1.000	**<0.001**	**<0.001**	0.483	**<0.001**
Neck rotation	**<0.001**	1.000	**<0.001**	**<0.001**	0.871	**<0.001**
Neck flexion	**<0.001**	1.000	**<0.001**	**<0.001**	0.651	**<0.001**
Neck extension	**<0.001**	1.000	**<0.001**	**<0.001**	0.820	**<0.001**
Tongue extension	**<0.001**	1.000	**<0.001**	**<0.001**	1.000	**<0.001**
Breathing	**<0.001**	1.000	**<0.001**	**<0.001**	0.511	**<0.001**
Shrugging	**0.020**	0.470	**0.003**	**0.032**	0.302	0.204

Note: Paired t-tests and Cohen's kappa agreement were used to test the consistency inter-observer and intra-observer. Cohen's kappa coefficient >0.40 was considered moderate consistency and >0.80 was considered strong consistency. A value of $p < 0.05$ was considered statistical significance, which was bold.

Abbreviations: the MRC the Medical Research Council.

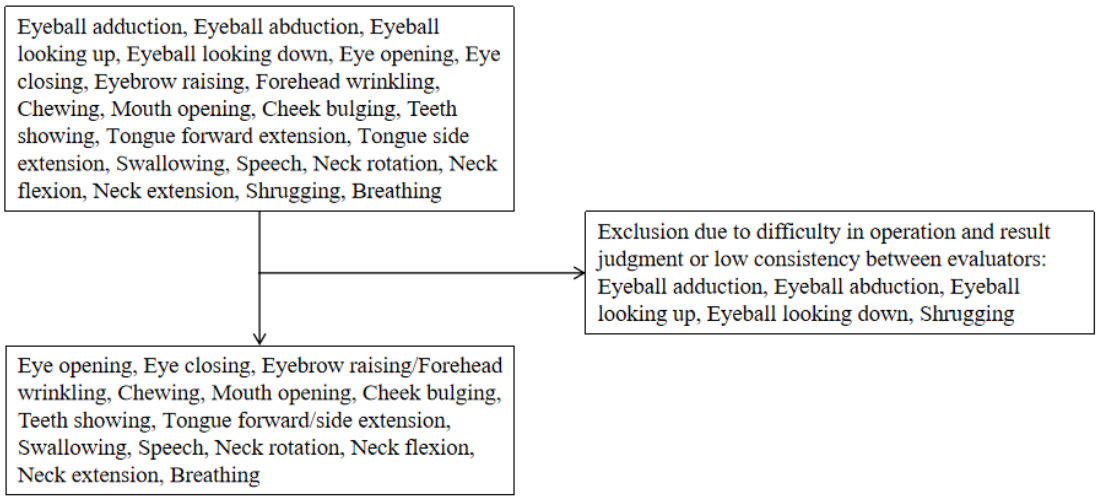

Figure 1. Selection of actions involved in the Medical Research Council (MRC) cranial score.

quantitative method for strength of cranial muscle groups. The demographic characteristics of included ALS patients were presented in Supplementary Table 2.

The mean (SD) baseline MRC cranial score was 65.93 (4.40) and ANOVA analysis showed that the MRC cranial score presented a continued decline along with the disease progression (p=0.004) (Supplementary Table 3). A total of 40 (68.97%) included patients showed decrease in the MRC cranial score at baseline. As presented in Figure 2, cranial involvement in ALS patients mainly manifested weakness in cheek bulging, swallowing, speech, tongue extension and breathing.

As showed in Table 1, our results suggested that there was no significant relationship between the total MRC cranial score and the total MRC score (p=0.183) or ALSFRS-R limb score (p=0.335). However, several items were remarkably correlated to the total MRC score or ALSFRS-R limb score, such as the strength of teeth showing and neck rotation. The total MRC cranial score was positively related to the baseline ALSFRS-R score (p<0.001), so were the MRC strength of eye closing (p=0.014), cheek bulging (p=0.006), speech (p<0.001), neck rotation (p=0.015), neck flexion (p<0.001), neck extension (p=0.002) and breathing (p=0.041). We found no vital correlation between the total MRC cranial score and baseline FVC%.

To reveal the correlation between the MRC cranial score and progression rate, we firstly calculated the previous progression rate by (48-the baseline ALSFRS-R score)/disease duration in months of included ALS patients. It was noteworthy that we only included patients with bulbar involvement in the analysis (n=40). Our results indicated a weakly negative relationship between the MRC cranial score and previous progression rate (p=0.048). Also, we found that the strength of eye closing (p=0.029), cheek bulging (p=0.048), swallowing (p=0.009), neck rotation (p=0.025), neck flexion (p=0.008) and breathing (p=0.047) were negatively related to previous progression rate.

A follow-up study was conducted to get the progression rate in the next 3 months among included patients. A total of 54 patients were successfully contacted by phone call (the missed follow-up rate: 6.90%) and finished the ALSFRS-R assessment. Among them, none died, ten (18.52%) patients received invasive respiratory support, and twelve ones (22.22%) received gastric catheterization. The 40 patients with bulbar involvement at the baseline all completed the follow-up. As showed in Table 2, there was a significantly negative correlation between the MRC cranial score and follow-up progression rate (p<0.001). The strength of eye closing (p=0.046), eye closing (p=0.018), cheek bulging (p<0.001), swallowing (p=0.012), speech (p=0.017), neck rotation (p=0.042), neck flexion (p=0.007), neck extension (p=0.014) and tongue extension (p=0.028) were negatively related to the ALS progression rate. Besides, low MRC cranial score might be risk factors of the need of invasive respiratory support (p=0.005) and gastric catheterization (p=0.003) in the next 3 months among ALS population.

Table 2. The correlation between MRC cranial score and other indicators among ALS population

Items	Total MRC score		ALSFRS-R score		ALSFRS-R limb score		FVC%		Pre progression rate		Future progression rate	
	Coefficient	*p*	Coefficient	*p*	Coefficient	*p*	Coefficient	*p*	Coefficient	*p*	Coefficient	*p*
Eye opening	-0.213	0.109	0.215	0.105	0.026	0.848	0.197	0.145	-0.108	0.507	-0.245	**0.046**
Eye closing	-0.066	0.623	0.320	**0.014**	0.205	0.122	0.225	0.096	-0.346	**0.029**	-0.322	**0.018**
Chewing	-0.051	0.703	0.151	0.256	0.180	0.177	0.159	0.240	0.280	0.081	0.090	0.532
Forehead wrinkling and eyebrow raising	0.017	0.900	0.113	0.398	-0.057	0.673	-0.006	0.965	0.293	0.066	0.058	0.677
Mouth opening	0.209	0.116	0.051	0.704	0.082	0.540	0.113	0.406	-0.089	0.583	0.005	0.981
Teeth showing	-0.577	**<0.001**	-0.019	0.885	-0.333	**0.011**	0.063	0.646	-0.063	0.710	-0.262	0.056
Cheek bulging	-0.066	0.623	0.354	**0.006**	0.092	0.493	-0.136	0.317	-0.264	**0.048**	-0.442	**<0.001**
Swallowing	-0.230	0.082	0.207	0.119	-0.058	0.665	-0.013	0.923	-0.410	**0.009**	-0.339	**0.012**
Speech	-0.261	**0.048**	0.425	**<0.001**	0.076	0.570	0.087	0.526	-0.292	0.068	-0.323	**0.017**
Neck rotation	0.302	**0.021**	0.317	**0.015**	0.320	**0.014**	0.086	0.529	-0.355	**0.025**	-0.267	**0.042**
Neck flexion	0.216	0.103	0.444	**<0.001**	0.427	**<0.001**	0.126	0.348	-0.343	**0.008**	-0.363	**0.007**
Neck extension	0.244	0.065	0.390	**0.002**	0.348	**0.007**	0.380	**0.004**	-0.252	0.117	-0.333	**0.014**
Tongue extension	-0.330	**0.011**	0.218	0.110	-0.157	0.241	0.044	0.748	-0.101	0.534	-0.299	**0.028**
Breathing	0.031	0.816	0.270	**0.041**	0.173	0.194	0.280	**0.037**	-0.316	**0.047**	0.018	0.893
MRC cranial score	-0.177	0.183	0.577	**<0.001**	0.124	0.335	0.114	0.402	-0.266	**0.044**	-0.483	**<0.001**

Note: Spearman coefficient was applied for the correlation analysis. A value of $p < 0.05$ was considered statistical significance, which was bold. Only ALS patients with bulbar involvement were included in the analysis regarding progression rate.

Abbreviations: ALS amyotrophic lateral sclerosis; ALSFRS-R the revised ALS functional rating; FVC% forced vital capacity percent; MRC the Medical Research Council.

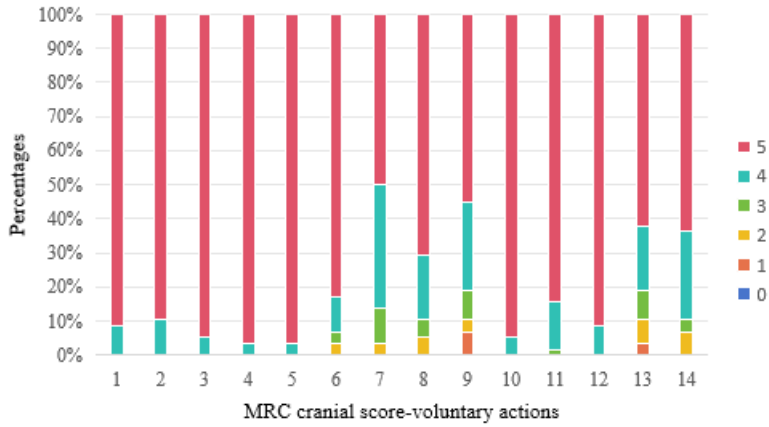

Figure 2. The distribution of the items in MRC cranial score among ALS population.

DISCUSSION

Cranial nerve or bulbar involvement was not uncommon in neuromuscular disorders, and its resulting bulbar paralysis and respiratory dysfunction remained challenging problems in clinical practice, which were usually considered as the indicators of poor prognosis.[13-15] In the study, we tried to establish a quantitative evaluation method for the strength of the bulbar muscle groups by manual examination. Based on the definition of MRC grading system, we designed a six-level strength of each autonomous activity related to cranial nerves. Due to the difficulty in manual assessment or discomfort to the patients, some actions such as eye movements were excluded from our scale. For these actions, objective description of anomalies might be more feasible. The consistency analysis suggested satisfied inter-observer and intra-observer consistency, except for the assessment of shrugging. The complexity of involved muscle groups and the limitation of articulatio humeri activity might be one of the explanations. Finally, a total of 14 movements were included in our method, which was named as the MRC cranial score. The required examination time for each patient was within 5 minutes with easily accessible tools and no subjective discomfort reported.

We consecutively recruited 58 patients to explore the practicality of the MRC cranial score in ALS population. Consistent with the relentless progression of ALS, the total MRC cranial score showed a continued decline with the increase of the clinical stages, which needed the validation of prospective studies. Nearly 70% patients showed bulbar involvement evaluating by the MRC cranial score, which was significantly more common than that by self-report and slightly more common than that by ALSFRS-R score (around 60%). Perry et al. reported that changes in lingual and jaw motor performance during a simple water swallow task (a 3-mL water swallow) were present in persons with ALS who were pre-symptomatic of clinically detectable bulbar impairment.[8] Through precise instrument measurement on SOD1-G93A rats, Smittkamp *et al*. found that a persistent tongue motility deficit might already become apparent in the early phase of the ALS[9], which did not get enough attention in the ALSFRS-R score. These all suggested mildly dysfunction in bulbar region was easily neglected by clinicians and the MRC cranial score might be able to reflect the cranial impairment in ALS earlier and more comprehensively.

Air leakage when cheek bulging, dysphagia, dysarthria and tongue stiffness or weakness were common complaints of ALS patients with bulbar involvement, which were conformed to our results. Weakness in eye opening or closing, chewing and mouth opening was common in patients with myasthenia gravis (MG)[16], AIDP[17], facial onset sensory and motor neuronopathy (FOSMN) syndrome[18], but rarely reported by ALS patients. Pathological studies have reported the marked neuron loss in nucleus ambiguous and facial nucleus, while all the components of the nerve roots of the oculomotor, trochlear, and abducent nerves tended to be completely preserved in ALS.[19,20] Our results revealed that nearly half of involved ALS patients might present one specific pattern of facial weakness in ALS patients, characterized by preferential weakness of the buccinator muscles with relative sparing of the orbicularis oculi muscle, which were both

dominated by the facial nerve. Similar patterns of paresis regarding muscle groups in hands and legs have widely reported in ALS patients, which were known as split hand, split elbow, etc.[21,22] It was generally believed that these split phenomena were characteristics of ALS, reflected the potential pathogenesis of ALS and might play a role in the differential diagnosis of ALS.[23] Here we found split phenomenon also exists in facial muscle groups (split face), and the diagnosis of ALS should be cautious for patients with early onset of blepharoptosis, weakness in eye closure or chewing.

Correlation analyses between the MRC cranial score and other indicators were conducted to further explore its clinical significance. Our results indicated a significantly positive relationship between the MRC cranial score and baseline ALSFRS-R score, which might be caused by the overlap between the items of two scales, mainly regarding the speech, swallowing and breathing. No statistically significant relationship between the MRC cranial score and functional status or muscle strength of limbs were revealed. This was not surprising, as a considerable number of ALS patients could manifest severe bulbar paralysis with relatively preserved function of the limbs, some of which even manifested as isolated bulbar paralysis.[24,25] FVC% was one of the most concerning indexes of lung function tests among ALS patients, which has been considered as an indicator of survival and disease progression.[26] However, we failed to find a predominant association between the MRC cranial score and FVC%. The high proportion of weakness in cheek bulging among the included population might be significantly influence the accuracy of FVC%, which remained one main limitation of lung function tests in neuromuscular diseases. The positive correlation between the strength of breathing and FVC% suggested that our design was reasonable and might be able to reflect the respiratory dysfunction in ALS patients.

For patients with ALS and relevant clinicians, the most concerning thing might be the progression rate or estimated survival time. Our results showed a weak correlation between the MRC cranial score and past progression rate, while there was a significantly negative association between the total MRC cranial score and subsequent progression rate during follow-up. Excluding the impacts of reporting or recall biases, we believed that the results indicated the significance of the MRC cranial score in predicting the ALS progression rate. Most of items in the MRC cranial score showed negative association with ALS progression rate, except for the strength of chewing, forehead wrinkling, mouth opening and teeth showing, which might not need key attention during the physical examination on ALS patients. Besides, we found that low MRC cranial score was a risk factor for the need of gastric tube or respiratory support in the next 3 months. All these were in accord with clinical consensus that bulbar involvement symbolized rapid progression and poor prognosis [9] for ALS patients. Due to the limited number of included patients and short follow-up time, we failed to conduct survival analysis to elucidate the impact of the MRC cranial score on ALS survival, which deserved more studies.

We admitted the following limitations of our study. Firstly, the sample size was small. Therefore, there might be inaccuracies or omissions in selection of the actions regarding cranial nerves and design of the six-level of muscle strength. Secondly, the cross-sectional design failed us to explore the dynamic changes in the MRC cranial score among ALS patients. Thirdly, only ALS patients were included in the application of the MRC cranial score. Studies on the validation of the MRC cranial score on other neuromuscular disorders might be needed to further explore the clinical significance of the MRC cranial score. We believed that through future investigations and revisions, the MRC cranial score could play an important role in the diagnosis and surveillance of neuromuscular disorders.

In conclusion, in this study, we designed an easily operating evaluation method of muscle strength involving 14 actions innervated by cranial nerves and named it the MRC cranial score. The MRC cranial score could quantify the involvement of cranial nerves in neuromuscular diseases earlier and more comprehensively, which was negatively related to the progression rate and might be a predictor of the need of gastric tube or respiratory support in ALS patients.

DISCLOSURE

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Conflict of interest: None

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Supplementary Table 1. The list of Medical Research Council (MRC) cranial score (I-XV).

1. Eye opening (oculomotor nerve) Instruct the patient to open the eyes and look straight ahead. V Normally open the eyes, without compensation for frontal muscle contraction IV Opening the eyes requires compensation from frontal muscle contraction, while able to fully open the eyes III Unable to fully open the eyes, with drooping upper eyelids covering less than half of the pupils II Unable to fully open the eyes, with drooping upper eyelids covering no less than half of the pupils (9-3 o'clock) I Unable to open eyes, visible eyelid contraction movement 0 No visible eyelid contraction movement	**9. Speech (glossopharyngeal nerve, vagus nerve)** Observe during communication with the patient. V Normal speech processes, able to speak long sentences (over 10 words) IV Detectable speech disturbance III Intelligible with repearing II Speech combined with non-vocal communication I Loss of useful speech, able to produce sound 0 Unable to produce sound
2. Eye closing (facial nerve) Instruct the patient to close the eyes and place your right thumb and index finger on both sides of the patient's upper eyelid to lift upwards. V Normally closed the eyes, able to completely resist resistance IV Weak eye closure but still able to easily close the eyes, partially resistant to resistance III Barely close the eyes, positive ciliary sign, unable to resist resistance II Unable to completely close the eyes I Unable to close eyes but visible eye closure movement 0 No visible eye closing movement	**10. Neck rotation (accessory nerve)** Instruct the patient to turn the head to both sides and place your hands on the same cheek to confront the patient. V Normally turn the neck, completely resistant to resistance IV Able to turn the neck, partially resistant to resistance III Able to turn the neck, unable to resist resistance II Unable to fully rotate the neck I Unable to rotate the neck, but able to touch the contraction of the sternocleidomastoid muscle 0 Unable to touch the contraction of the sternocleidomastoid muscle
3. Chewing (trigeminal nerve) Prepare a tongue depressor and place it between the patient's upper and lower molars. Instruct the patient to chew and engage with force, observing and touching the bilateral masseter muscles. V Able to leave tooth marks on the tongue depressor, which is unable to be easily pulled out IV Able to bite the tongue depressor tightly, which is able to be easily pulled out III Able to engage in chewing movements, but unable to bite the tongue depressor, visible masseter contraction movement II Slight chewing movements, able to clearly touch the masseter contraction movement I No visible masseter contraction movement, able to touch the masseter contraction movement 0 Unable to touch masseter contraction movement	**11. Neck flexion (glossopharyngeal nerve, accessory nerve)** Instruct the patient to bend the neck and place your hands on the forehead to apply resistance upwards. V Normal neck flexion, completely resistant to resistance IV Complete neck flexion, partially resistant to resistance III Complete neck flexion, unable to resist resistance II Partially neck flexion I Able to touch the contraction of the anterior cervical muscle group, unable to complete the neck flexion 0 Unable to touch the contraction of the anterior cervical muscle group

4. Forehead wrinkling and eyebrow raising (facial nerve) Instruct the patient to raise the eyebrows or wrinkle forehead and place your right thumb and index finger between the patient's eyebrows to exert downward resistance. V Normally lift the eyebrows, completely resistant to resistance IV Able to lift the eyebrows, partially resistant to resistance III Able to lift the eyebrows until forehead lines appear, unable to resist resistance II Unable to lift the eyebrows completely I Unable to lift the eyebrows, visible eyebrow raising movements 0 No visible eyebrow raising movements	**12. Neck extension (accessory nerve, C1-4)** Instruct the patient to extend the neck and place your hands on the occipital region to apply resistance upwards. V Normal neck extension, completely resistant to resistance IV Complete neck extension, partially resistant to resistance III Complete neck extension, unable to resist resistance II Partially neck extension I Touch the contraction of the posterior cervical muscle group, but cannot complete the neck extension 0 Unable to touch the contraction of the the posterior cervical muscle group
5. Mouth opening (trigeminal nerve) Instruct the patient to open the mouth, fix the head with your left hand, and place your right hand on the lower edge of the patient's mandible with upward force. Be careful to prevent the patient's biting the tongue. V Normally open the mouth, completely resistant to resistance IV Able to open the mouth, partially resistant to resistance III Able to open the mouth, unable to resist resistance II Unable to fully open the mouth I Unable to open the mouth, able to touch the contraction of the infratemporal fossa muscle, slightly visible temporomandibular joint movements 0 Completely unable to open mouth, unable to touch the contraction of the infratemporal fossa muscle	**13. Tongue extension (hypoglossal nerve)** Instruct the patient to extend the tongue forward, left and right. Use the tongue depressor or your fingers to apply resistance in all directions. V Normal tongue forward extension and lateral extension, completely resistant to resistance IV Able to conduct completely resistant to resistance, partially resistant to resistance III Able to extend the tongue outlet, and laterally touch the cheek mucosa, unable to resist resistance II Visible forward and lateral extension movements of the tongue, unable to extend the tongue outlet or laterally touch the cheek mucosa I Visible forward and lateral extension movements of the tongue, unable to produce forward or lateral extension movements 0 No visible forward and lateral extension movements of the tongue
6. Teeth showing (facial nerve) Instruct the patient to show the teeth and place your right hand on both sides of the mouth to exert force inward. V Normally expose the teeth, completely resistant to resistance IV Completely expose the teeth, partially resistant to resistance III Completely expose the teeth, unable to resist resistance II Partially expose the teeth I Unable to show the teeth, able to touch the contraction of the perioral muscles 0 Unable to touch the contraction of the perioral muscles	**14. Breathing (phrenic nerve, vagus nerve, glossopharyngeal nerve)** Ask the patient if he/she feel dyspnea. Prepare a 2cm wide small piece of paper and place it about 30cm in front of the patient's flat lip. Instruct the patient to blow and inhale. V No dyspnea IV Dyspnea when walking III Dyspnea with one or more of the following: eating, bathing, dressing II Dyspnea while sitting, able to constantly blow a small piece of paper I Dyspnea while sitting, unable to constantly blow a small piece of paper 0 Significant dyspnea, considering mechanical support

7. Cheek bulging (facial nerve, vagus nerve, phrenic nerve) Instruct the patient to puff the cheeks and press on both cheeks with your right thumb and index finger. V Normal bulge the cheeks, no air leakage when pressed IV Completely puff the cheeks, partial air leakage when pressed III Weakly puff the cheeks, air leakage with no need to press the cheeks, easily pout II Completely pouting with effort I Unable to pout, visible contraction of the perioral muscles 0 No visible contraction of the perioral muscles	**15. Shrugging (accessory nerve)** Instruct the patient to give a shrug and place your hands on the shoulders to apply resistance downwards. V Normal shrug, completely resistant to resistance IV Complete shrug, partially resistant to resistance III Complete shrug, unable to resist resistance II Partial shrug I Unable to shrug but able to touch the contraction of trapezius muscle 0 Unable to touch the contraction of trapezius muscle
8. Swallowing (glossopharyngeal nerve) Instruct the patient to sit upright, drink approximately 30ml of warm water, and observe the patient's coughing. V Able to swallow water smoothly once IV Able to swallow water in twice, without choking or coughing III Able to swallow once, with choking or coughing II Swallow water in twice or more, with choking or coughing I Frequent coughing, unable to swallow all water 0 Unable to orally drink water	

Note: For actions that needed bilateral examination, we took the muscle strength of the weaker side as the final result.

Supplementary Table 2. Baseline characteristics of included ALS patients

Items	ALS patients (N=58)
Onset age (years)	52.93±8.91
Gender (M/F)	34/24
BMI (kg/m^2)	22.17±2.63
Disease duration (months)	12 (3-98)
Onset region (n, %)	
Bulbar	18 (31.03%)
Upper limbs	20 (34.48%)
Lower limbs	18 (31.03%)
Others	2 (3.46%)
Total MRC score	133.70±24.93
ALSFRS-R score	37.78±6.21

Note: Normally distributed variables were expressed as means±SD and non-normally distributed ones were expressed as median (range).
Abbreviations: ALS amyotrophic lateral sclerosis; ALSFRS-R the revised ALS functional rating; BMI body mass index; F female; M male; MRC the Medical Research Council; SD standard deviation.

Supplementary Table 3. Changes in MRC cranial score along with clinical stages in ALS patients

	Stage 1	Stage 2	Stage 3	Stage 4	ANOVAComparisons
N	15	21	21	1	
MRC cranial score	67.73±4.03	66.57±3.22	64.57±4.65	54.00	0.004

Abbreviations: ALS amyotrophic lateral sclerosis; ANOVA one-way analysis of variance; MRC the Medical Research Council.