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ORIGINAL ARTICLE

Diaphragm ultrasonography in amyotrophic lateral sclerosis: a diagnostic tool to assess ventilatory dysfunction and disease severity

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Abstract

Background Respiratory failure represents an unavoidable step in patients with amyotrophic lateral sclerosis (ALS) and other motor neuron diseases (MND). The development of diaphragm ultrasonography (DUS) provides an alternative useful and risk-free tool to supply clinical, functional, and neurophysiological assessment of respiratory muscle weakness. Our aim was to evaluate if sonographic changes (thickness and echogenicity in the costal portion of the diaphragm, at rest and during respiratory movements) may be used in ALS patients to assess disease severity over time, to rule out any risk or discomfort due to traditional neurophysiological investigations.

Methods Twenty ALS patients (mean age, 64.6 ± 10.5 years) were enrolled and data were compared with age-matched healthy volunteers; DUS data were correlated with respiratory function and disease severity scale. Examinations were performed using Telemed Echo-wave II or Esaote MyLabGamma devices in conventional B-Mode.

Results Mean resting thickness was reduced in all cases; changes in thickness during inspiration and expiration were also reduced ($p < 0.0001$) and lost in severe cases ($n = 3$). In bulbar-onset disease, respiratory scores were strictly correlated with the difference in diaphragm thickness between full inspiration—and expiration—as well as on the diaphragm thickness in expiration ($p < 0.001$).

Conclusions DUS represents a simple, painless, and risk-free tool; moreover, it provides useful functional and structural insights to the understanding of diaphragm function and the degree of respiratory failure in ALS.

Keywords Neuromuscular ultrasonography (NMUS) · Diaphragm assessment · Respiratory function · Amyotrophic lateral sclerosis (ALS) · Motor neuron disease (MND) · Prognosis

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Introduction

Amyotrophic lateral sclerosis (ALS), first described by Jean-Martin Charcot in the 1870s, is a degenerative and fatal disease, characterized by degeneration of both upper and lower motor neurons (MNs) [1–3]. The estimate prevalence throughout the word is 6/100,000, with an incidence peak in the 65- to the 74-year-old age bracket. The mean ALS duration since clinical onset ranges from 22 to 52 months, and the delay between the clinical onset and the confirmed diagnosis is usually about 13–18 months [4]. Pathogenesis is still unknown and there is a dearth of any effective disease-modifying treatment [5]. The diagnosis is almost based on clinical history, physical examination, and follow-up; several investigations, including blood tests, electrodiagnostic examination [6–8], motor evoked potentials [9–11], and neuroimaging, are mandatory.

Respiratory failure represents an unavoidable step in all the patients and a common cause of death [12]. It may represent an early sign of disease and its evaluation requires patient's cooperation and operator ability to assess breathing pattern [13]. Commonly, tests such as forced vital capacity (FVC), ALS Functional Rating Scale (ALSFRS), and Motor Unit Number Estimation (MUNE) are employed [14].

Recently, muscle high-resolution sonography (US), combined with the classical EMG, has been proposed as a new promising diagnostic tool; it represents an easily accessible and painless method to detect structural muscle changes caused by neuromuscular disorders [15, 16].

The primary aim of this study was to evaluate if diaphragmatic US (DUS) changes at rest and during respiratory phases could be employed to assess respiratory impairment in ALS patients; these modifications were compared with those observed in healthy subjects and during disease progression. We assessed DUS changes (thickness and echogenicity) in the costal portion of the diaphragm at rest and during inspiration and expiration, as well as the phrenic nerve size ("cross section area," CSA); data were then correlated with respiratory function and disease severity.

Materials and methods

Subjects

Fifteen ALS patients (5 males and 10 females; mean age 65.0 + 12.42 years; range 48–81 years) and five second motor neuron disease (4 males and 1 female; mean age 67.0 + 11.1; range 56–78 years) were enrolled starting January 2017; among them, five were newly diagnosed and therapy-naive, even if the disease onset was more than 3 years before. Demographic and clinical features are summarized in Table 1.

All subjects were followed at the Neurophysiopathology Unit of the Department of Clinical and Experimental Medicine of Pisa University Medical School or the Department Section of Severe Brain Injuries (Azienda Ospedaliero-Universitaria Pisana) and DUS was performed at the Neurophysiopathology Unit by one of the authors (F.S.). The investigator was unaware of the clinical findings and disease form or duration. We then included an inter-observer concordance strategy with another examiner evaluating the same subject.

Inclusion criteria were the following: diagnosis of defined or probable ALS or diagnosis of defined or probable second motor neuron disease ("El Escorial-Revised criteria" and "Awaji electrodiagnostic algorithm"; [6, 17]); disease duration at least 1 year and age > 18 years. Exclusion criteria were the following: dementia, diabetes, respiratory or lung diseases, noninvasive ventilation (NIV), or tracheostomy. Ability to perform spirometry examination was not considered at the time of enrolment.

Mean age + S.D. at disease onset was 58 + 12.02 years (range 27–77 years). The disease form was spinal in 10 (7 upper limb dominant) and bulbar in 5 cases. At the time of enrolment, all the patients with second motor neuron disease fulfilled the criteria for "possible ALS."

As concerns the evaluation in the respiratory subscores of the ALS-FRSR, patients exhibited a forced vital capacity (FVC) determination less than normal values.

As controls, we used a group of 30 healthy volunteers, age- and sex-matched with patients, recruited among the unit's staff, and their relatives.

Informed consent was preliminarily obtained from all patients and controls before their inclusion in the study. Furthermore, the Pisa Hospital-University's institutional review board approved the study.

Respiratory function

Respiratory function was assessed using an electronic autospirometer immediately before or after the DUS. The following parameters were assessed: vital capacity (VC), forced vital capacity (FVC), and forced expired volume (FEV). For the evaluation of hypoventilation, at the same time as the spirometry, arterial blood gas analyses, including blood O_2 (BO_2) and CO_2 (BCO_2), pH, and bicarbonate ions (HCO_3) concentration, were carried out.

Ultrasonography

All investigations were performed using an Esaote MyLabGamma or a Telemed Echo-wave II device in conventional B-Mode, with a standard protocol [18]. Diaphragm was evaluated with patient sitting on a wheelchair or comfortably lying on a cot. The extent of movement and the muscle thickness were measured at the zone of apposition, using a broad spectrum linear probe (6–19 MHz): the probe was applied over the right intercostal space, between the antero-axillary and mid-axillary lines, to identify the apposition area of the diaphragm in conventional B-Mode ultrasound; this area, parallel to the body axis, thickens and shortens accordingly to breathing phases. The apposition zone is defined as the intercostal space at which the diaphragm was most easily visualized (with the transducer spanning 2 ribs), typically the ninth intercostal space [19, 20]. Size changes during inspiratory effort reflect the diaphragm muscle strength, the primary determinant of the inspiratory force. It is important to define the intercostal space where diaphragm thickness is measured as it changes, with diaphragm inferior portions being thicker than the upper ones [12]. Measurements were made at the area of apposition, inferiorly to the costophrenic angle, where the diaphragm contacts the inner aspect of the chest wall (Fig. 1). Once the apposition zone was correctly identified, each patient was instructed to breathe quietly while three images were captured at the end of quiet

Table 1 Demographic characteristics of patients and controls. Data are shown as mean ± standard deviation (SD)

	ALS ($n = 20$)	Second MND	Controls ($n = 30$)
Gender (M/F)	5/10	4/1	15/15
Age (years)	64.6 ± 10.5	67.0 ± 11.1	62.5 ± 9.8
Disease duration (months)	85.6 + 63.6	75.6 ± 49.8	N.A.
Bulbar-onset	5 (33%)		
Spinal-onset	10 (66%)		

M, males; *F*, females; *N.A.*, not applicable

expiration. The subject was then instructed to take slow deep breaths in and out, and three images were captured at the point of maximum diaphragm thickening [20].

Thickness measurements had been performed with visualization of both pleural and peritoneal membranes, with an angle of incidence of the ultrasound beam close to 90 degrees. It has been established that 0.2 cm is the cutoff below which diaphragm atrophy is defined [12, 16].

Amyotrophic lateral sclerosis functional rating scale revisited

ALSFRS is a validated clinical rating scale to track progression in ALS [202]. Progression was defined by the loss of independence in four-key domains of the ALSFRS: swallowing, walking/self-care, communicating, and breathing.

The revised scale, amyotrophic lateral sclerosis functional rating scale revisited (ALSFRS-R), is a more sensitive tool for pulmonary and diaphragmatic weakness evaluation, and it is widely used in clinical trials and setting [21, 22]. Kollewe and co-workers found a significant correlation between higher ALSFRS-R scores and survival; therefore, we decided to use also this revised scale [23]. We have especially considered the respiratory part of the ALSFRS-R to look for correlations with diaphragm thicknesses during breathing.

Statistical analysis

Nonparametric analyses were used, as datasets did not successfully passed the Shapiro-Wilk test for normality ($p < 0.05$). A nonparametric *t* test was used to compare the age between the two groups, patients, and controls.

At baseline, the Mann-Whitney *U* test compared ultrasonographic values between patients and controls.

Spearman's correlation coefficient was then used in patients to correlate sonographic variables both with the respiratory function and motor scores, in spinal- and in bulbar-onset disease.

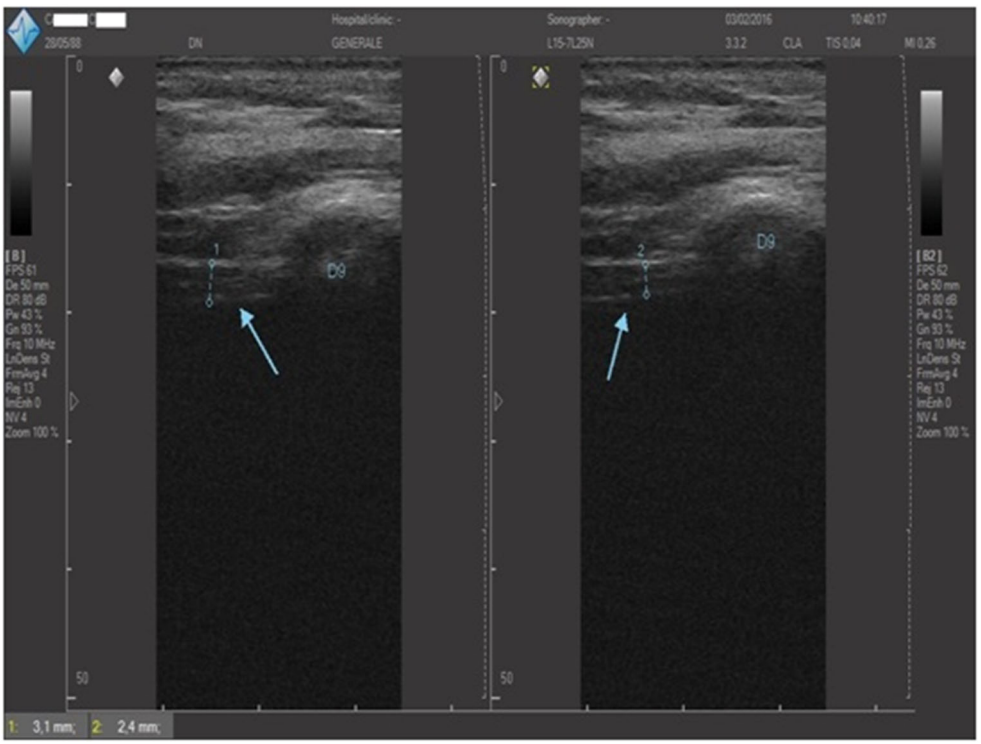

Fig. 1 Exemplificative pattern of diaphragm ultrasonographic thickness changes at the point of full inspiration and expiration in a healthy subject: note that the normal diaphragm (arrow) is seen between the ribs (C_9–C_{10}), deep to the abdominal and intercostal muscles during exhalation (right side), thicker during maximal inhalation (left side; thickness changes from 2.4 to 3.1 mm)

Table 2 Sonographic values in controls and patients, both in spinal- and bulbar-onset disease

	IT	ET	$\Delta_{ins\text{-}exp}$
Controls	4.51 ± 0.44	1.97 ± 0.38	2.68 ± 0.41
ALS (total)	1.88 ± 0.12	1.57 ± 0.13	0.33 ± 0.06
Spinal-onset	1.93 ± 0.146	1.60 ± 0.1	0.33 ± 0.07
Bulbar-onset	1.66 ± 0.33	1.38 ± 0.28	0.34 ± 0.17

IT, inspiratory thickness; *ET*, expiratory thickness; $\Delta_{ins\text{-}exp}$, difference in thickness between inspiratory and expiratory phase

Finally, a multiple linear regression analysis model (backward method) was used to test significant independent associations.

Statistical significance was set at $p < 0.05$. Data were analyzed using SPSS v. 21.0 for Windows (SPSS Inc.).

Results

The diaphragm in the area of apposition was clearly identified in all cases. Mean values of ultrasonographic measurements are reported in Table 2.

During breathing, the diaphragm changed its thickness, and measurements showed a mean coefficient of variation less than 10% [12]. A normal diaphragm thickness at rest and in full inspiration in one healthy subject is shown in Fig. 1, whereas Fig. 2 shows sonography in a patient.

Mean resting thickness was reduced when compared with the healthy volunteers (1.76 ± 0.45versus 3.45 ± 0.9 mm); thickness changes during inspiration ($p < 0.0001$, Mann-Whitney *U* test; Table 2) and expiration were also reduced ($p = 0.0004$) and lost in the most severe cases (three patients). In all cases, we found in limb muscles an increased echogenicity with decreased muscle thickness; in some patients, fasciculations were detected (55.5% of s-ALS and in 100% of b-ALS), but it was not possible to clearly identify fibrillation potentials.

A significant linear correlation was found between $\Delta_{ins\text{-}exp}$ and respiratory function scales (versus FEV, VC, and FVC; $p < 0.0001$); similarly, $\Delta_{ins\text{-}exp}$ correlated with clinical scores (versus ALSFRS and ALSFRS-R; $p < 0.0001$, see Fig. 3 and Supplementary Table 1). When patients with a bulbar-onset disease were analyzed alone, remarkable correlations were found between $\Delta_{ins\text{-}exp}$ and clinical scores (versus ALSFRS, $p = 0.029$ and versus ALSFRS-R, $p = 0.004$).

In bulbar-onset disease, the multiple linear regression model showed that FEV, VC, and FVC were dependant on the difference in diaphragm thickness between full inspiration—and expiration (and on the diaphragm thickness in expiration) ($p < 0.0001$, $p = 0.003$, and $p < 0.0001$, respectively).

Discussion

Our data are consistent with a significant reduction of diaphragm thickness in ALS, during full inspiration and expiration, when compared with the controls.

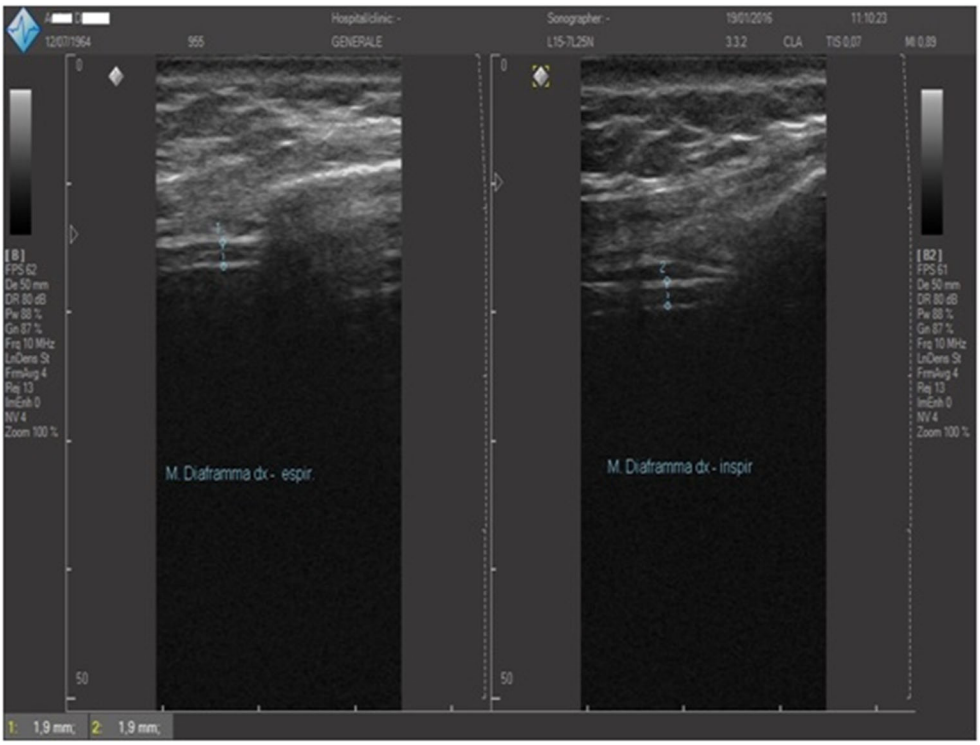

Fig. 2 Pattern of diaphragm ultrasonographic thickness changes at the point of expiration and full inspiration in a patient with ALS/MND and respiratory insufficiency: note the lack of diaphragm (arrow) thickening on inspiration (right side; 1.9 mm, the thickness remains unchanged)

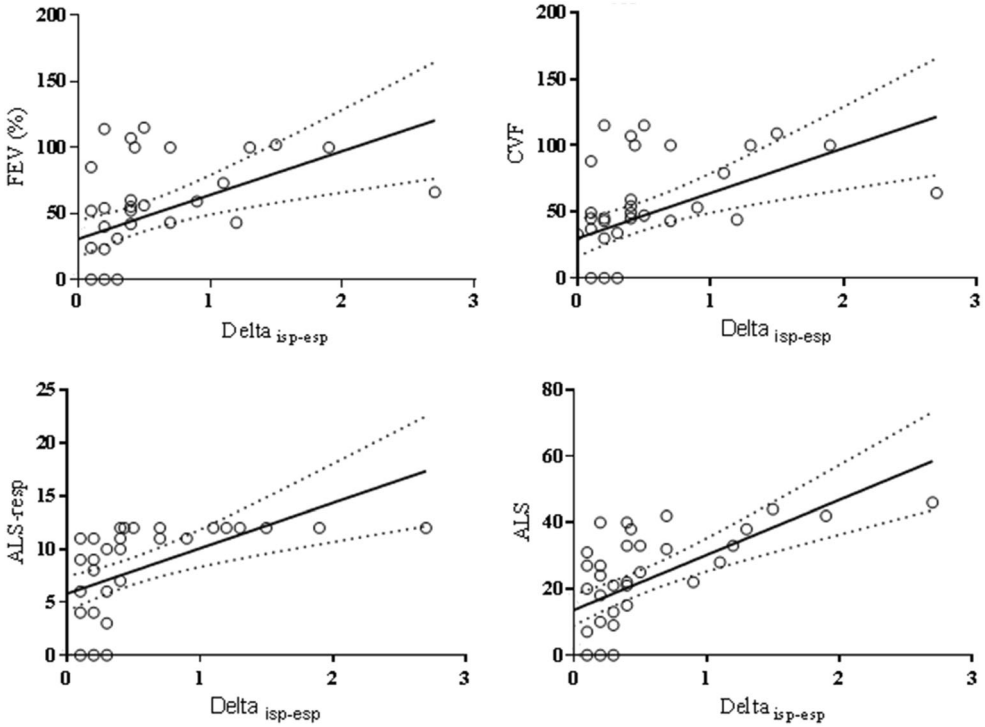

Fig. 3 Linear correlation between $\Delta_{ins\text{-}exp}$ and clinical scores. Note that $\Delta_{ins\text{-}exp}$ is highly correlated with changes both in respiratory function, as assessed by FEV and FVC (at the top), and clinical scores (ALSFRS and ALSFRS-R, at the bottom)

Our results also proved a significant correlation between DUS parameters, especially $\Delta_{ins\text{-}exp,}$ and respiratory function both in spinal- and bulbar-onset disease [12]. In bulbar ALS, multiple linear regression analysis showed that the difference in diaphragm thickness between full inspiration—and expiration—as well as the diaphragm thickness in expiration, is independently related to respiratory scores, possibly predicting disease's evolution over time. The main novelty introduced by the present data is the strong correlation between sonography and respiratory function in bulbar-onset disease; previous papers reported conflicting results about bulbar ALS, showing no correlation between changes in diaphragm thickness and respiratory scores [12].

The natural history of the disease is strongly influenced by the onset of respiratory dysfunction, which is the most common cause of death [23–25].

Muscle ultrasonography (MUS) can provide additional information about specific muscles, thus improving the diagnostic yield [26]. Furthermore, MUS can investigate the irreversible consequences of denervation, basing on muscular changes, such as diminished thickness, increased echointensity, and fasciculations [27].

Arts and colleagues showed that increased muscled echointensity could predict survival in ALS and it could be adopted as an additional prognostic tool, combined with common clinical scores [27, 28].

Moreover, the degree of respiratory involvement is an important prognostic factor and determines when to apply NIV [29]. There is no single test that can predict the presence of hypoventilation. Usually, respiratory muscle strength (RMS) is studied by spirometry, which has some limitations: cognitive decline, reduced motivation, orofacial muscles weakness, and abnormalities in the upper airways [30, 31]. Another method is diaphragm needle electromyography; however, it is technically demanding, moderately invasive, and shows large inter-individual differences.

Evidences demonstrated that the use of noninvasive ventilation improves survival and quality of life [24]; therefore, management strategies have to underline clinical and instrumental options to grade ventilation. Despite these strong evidences, respiratory function is not often regularly performed. Along this view, DUS may represent as a simple, easy, painless, and well-tolerated tool to understand diaphragm function and the degree of respiratory impairment in ALS.

Conclusions

MUS represents a simple, fast, and easy method, is painless and risk-free, and is able to provide useful functional and structural information in ALS patients. Furthermore, DUS may allow to point out concomitant respiratory failure. It is desirable that MUS become an indispensable tool of the diagnostic armamentarium of the neuromuscular physician in patients with ALS.

DUS, instead, is a simple, fast, and easy method, painless and risk-free, devoid of EMG complications, particularly pneumothorax, and able to provide useful functional and structural insights into the degree of respiratory failure in ALS.

Authors' contribution All the authors have contributed to the conception and design of the study, analysis, and interpretation of data and drafting of the manuscript.

Compliance with ethical standards

Ethical publication statement We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this study is consistent with those guidelines.

Disclosure of conflicts of interest The authors declare that they have no conflict of interest.

References

1. Salameh JS, Brown RH Jr, Berry JD (2015) Amyotrophic lateral sclerosis: review. Semin Neurol 35(4):469–476
2. de Carvalho M, Swash M (2016) Lower motor neuron dysfunction in ALS. Clin Neurophysiol 127(7):2670–2681
3. Huynh W, Simon NG, Grosskreutz J, Turner MR, Vucic S, Kiernan MC (2016) Assessment of the upper motor neuron in amyotrophic lateral sclerosis. Clin Neurophysiol 127(7):2643–2660
4. Logroscino G, Traynor BJ, Hardiman O, Chio' A, Couratier P, Mitchell JD, Swingler RJ, Beghi E, EURALS (2008) Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. J Neurol Neurosurg Psychiatry 79(1):6–11
5. Bensimon G, Lacomblez L, Meininger VA (1994) Controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. N Engl J Med 330(9):585–591
6. de Carvalho M, Dengler R, Eisen A, England JD, Kaji R, Kimura J, Mills K, Mitsumoto H, Nodera H, Shefner J, Swash M (2008) Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol 119(3):497–503
7. Sartucci F, Moscato G, Rossi C, Caleo M, Bocci T, Murri L, Giannini F, Rossi A (2010) Macro-EMG and MUNE changes in patients with amyotrophic lateral sclerosis: one-year follow up. Int J Neurosci 121(5):257–266
8. Bocci T, Pecori C, Giorli E, Briscese L, Tognazzi S, Caleo M, Sartucci F (2011) Differential motor neuron impairment and axonal regeneration in sporadic and familiar amyotrophic lateral sclerosis with SOD-1 mutations: lessons from neurophysiology. Int J Mol Sci 12:9203–9215
9. Vucic S, Ziemann U, Eisen A, Hallett M, Kiernan MC (2013) Transcranial magnetic stimulation and amyotrophic lateral sclerosis: pathophysiological insights. J Neurol Neurosurg Psychiatry 84(10):1161–1170
10. Geevasinga N, Loy CT, Menon P, de Carvalho M, Swash M, Schrooten M, Van Damme P, Gawel M, Sonoo M, Higashihara M, Noto Y, Kuwabara S, Kiernan MC, Macaskill P, Vucic S (2016) Awaji criteria improves the diagnostic sensitivity in amyotrophic lateral sclerosis: a systematic review using individual patient data. Clin Neurophysiol 127(7):2684–2691
11. Bocci T, Briscese L, Giorli E, Pecori C, Sartucci F (2012) Tongue's motor evoked potentials in the diagnosis of primary lateral sclerosis (PLS): preliminary report. J Neurol Sci 316:67–71
12. Pinto S, Alves P, Pimentel B, Swash M, de Carvalho M (2016) Ultrasound for assessment of diaphragm in ALS. Clin Neurophysiol 127(1):892–897
13. Shoesmith CL, Findlater K, Rowe A, Strong MJ (2007) Prognosis of amyotrophic lateral sclerosis with respiratory onset. J Neurol Neurosurg Psychiatry 78(6):629–631
14. de Carvalho M, Costa J, Swash M (2005) Clinical trials in ALS: a review of the role of clinical and neurophysiological measurements. Amyotroph Lateral Scler Other Motor Neuron Disord 6(4):202–212
15. Tsuji Y, Noto YI, Shiga K, Teramukai S, Nakagawa M, Mizuno T (2017) A muscle ultrasound score in the diagnosis of amyotrophic lateral sclerosis. Clin Neurophysiol 128(6):1069–1074
16. Walker FO, Cartwright MS, Alter KE, Visser LH, Hobson-Webb LD, Padua L, Strakowski JA, Preston DC, Boon AJ, Axer H, van Alfen N, Tawfik EA, Wilder-Smith E, Yoon JS, Kim BJ, Breiner A, Bland JDP, Grimm A, Zaidman CM (2018) Indications for neuromuscular ultrasound: expert opinion and review of the literature. Clin Neurophysiol S1388–2457(18):31234–31233
17. Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron Diseases (2000) El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 1(5):293–299
18. Arts IM, van Rooij FG, Overeem S, Pillen S, Janssen HM, Schelhaas HJ, Zwarts MJ (2008) Quantitative muscle ultrasonography in amyotrophic lateral sclerosis. Ultrasound Med Biol 34(3):354–361
19. Baldwin CE, Paratz JD, Bersten AD (2011) Diaphragm and peripheral muscle thickness on ultrasound: intra-rater reliability and variability of a methodology using non-standard recumbent positions. Respirology 16(7):1136–1143
20. Boon AJ, Harper CJ, Ghahfarokhi LS, Strommen JA, Watson JC, Sorenson EJ (2013) Two-dimensional ultrasound imaging of the diaphragm: quantitative values in normal subjects. Muscle Nerve 47(6):884–889
21. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, Nakanishi A (1999) The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (phase III). J Neurol Sci 169(1–2):13–21
22. Kaufmann P, Levy G, Thompson JL, Delbene ML, Battista V, Gordon PH, Rowland LP, Levin B, Mitsumoto H (2005) The ALSFRSr predicts survival time in an ALS clinic population. Neurology 64(1):38–43
23. Kollewe K, Mauss U, Krampfl K, Petri S, Dengler R, Mohammadi (2008) ALSFRS-R score and its ratio: a useful predictor for ALS-progression. J Neurol Sci 275(1–2):69–73
24. Janssens AI, Ruytings M, Al-Chalabi A, Chio A, Hardiman O, Mcdermott CJ, Meyer T, Mora G, Van Damme P, Van Den Berg LH, Vanhaecht K, Winkler AS, Sermeus W, ALS-CARE Consortium (2016) A mapping review of international guidance on the management and care of amyotrophic lateral sclerosis (ALS). Amyotroph Lateral Scler Frontotemporal Degener 17(5–6):325–336
25. Gil J, Funalot B, Verschueren A, Danel-Brunaud V, Camu W, Vandenberghe N, Desnuelle C, Guy N, Camdessanche JP, Cintas P, Carluer L, Pittion S, Nicolas G, Corcia P, Fleury MC, Maugras C, Besson G, Le Masson G, Couratier P (2008) Causes of death amongst French patients with amyotrophic lateral sclerosis: a prospective study. Eur J Neurol 15(11):1245–1251
26. Grimm A, Prell T, Décard BF, Schumacher U, Witte OW, Axer H, Grosskreutz J (2015) Muscle ultrasonography as an additional diagnostic tool for the diagnosis of amyotrophic lateral sclerosis. Clin Neurophysiol 126(4):820–827

27. Arts IM, Overeem S, Pillen S, Schelhaas HJ, Zwarts MJ (2011) Muscle ultrasonography to predict survival in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 82(5):552–554
28. Fantini R, Mandrioli J, Zona S, Antenora F, Iattoni A, Monelli M, Fini N, Tonelli R, Clini E, Marchioni A (2016) Ultrasound assessment of diaphragmatic function in patients with amyotrophic lateral sclerosis. Respirology 21(5):932–938
29. Miller RG, Anderson FA Jr, Bradley WG, Brooks BR, Mitsumoto H, Munsat TL, Ringel SP (2000) The ALS patient care database: goals, design, and early results. ALS C.A.R.E. Study Group. Neurology 54(1):53–57
30. Lyall RA, Donaldson N, Polkey MI, Leigh PN, Moxham J (2001) Respiratory muscle strength and ventilatory failure in amyotrophic lateral sclerosis. Brain 124(Pt 10):2000–2013
31. Fregonezi G, Araújo PR, Macêdo TL, Dourado Junior ME, Resqueti VR, Andrade Ade F (2013) Monitoring respiratory muscle strength assists in early diagnosis of respiratory dysfunction as opposed to the isolated use of pulmonary function evaluation in amyotrophic lateral sclerosis. Arq Neuropsiquiatr 71(3):146–152

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