Neurology Asia 2025; 30(2) : 447 – 454

Early diaphragmatic dysfunction in mild ALS patients: Ultrasound evaluation as a key tool for assessing pulmonary impairment

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Abstract

Background: This study aims to evaluate ultrasound-based measures for detecting early diaphragmatic dysfunction in patients with mild amyotrophic lateral sclerosis (ALS), providing valuable indicators for ultrasound assessment. *Methods:* A total of 36 ALS patients and 25 healthy controls were included. All participants underwent B-mode diaphragm ultrasound (DUS), recording indices such as diaphragm thickness and excursion. Clinical data, pulmonary function tests, and ALS Functional Rating Scale-Revised (ALSFRS-R) scores were collected for the ALS group. DUS indices were compared between the ALS group and controls, as well as between mild and non-mild ALS patients. Correlation analyses and Receiver Operating Characteristic (ROC) curve analysis were performed. *Results:* Compared to the control group, the study group showed significantly lower Tdi-rest, Tdi-ins, Δins-exp, ΔTdi, DE-quiet, and significantly higher ΔTmax ($P<0.05$). In comparison to healthy controls, the mild ALS group had significantly lower ΔTdi and Δins-exp ($P<0.05$). The mild ALS group had significantly higher Tdi-rest, Tdi-ins, Δins-exp, ΔTdi, DE-quiet, and DE-max than the non-mild ALS group ($P<0.05$), while ΔTmax was significantly lower ($P<0.05$). The indices Tdi-rest, Tdi-ins, Δins-exp, ΔTdi, and DE-max were positively correlated with FVC, MVV, the ALSFRS-R score, and the respiratory subscore ($P<0.05$). ROC curve analysis demonstrated that these indices had high accuracy in monitoring pulmonary insufficiency ($AUC \geq 0.811$, $P \leq 0.003$).
Conclusion: DUS can identify pulmonary impairment in ALS patients and assess disease severity. Early pulmonary insufficiency exists in mild ALS patients, primarily assessed by ΔTdi and Δins-exp, with high accuracy in monitoring pulmonary dysfunction.

Keywords: Amyotrophic lateral sclerosis, diaphragm ultrasonography, respiratory function, pulmonary function tests

INTRODUCTION

Most ALS patients die within 3-5 years due to respiratory failure and malnutrition, with early respiratory muscle involvement being a significant risk factor for poor prognosis.[1,2] Initiation of noninvasive positive pressure ventilation (NPPV) during the early stages of respiratory muscle weakness in ALS patients can slow the progressive decline of forced vital capacity (FVC), mitigate disease progression, and improve quality of life.[3-5] However, early respiratory muscle dysfunction in ALS patients often goes undetected, making its quantification crucial for early identification. Routine monitoring of respiratory function using the ALSFRS-R and pulmonary function tests may not yield reliable results in patients with severe bulbar involvement, dementia, or poor cooperation due to cognitive decline or oral muscle weakness.[6] Furthermore, standard pulmonary function tests are often insensitive for early detection of respiratory muscle involvement in ALS, offering limited information.[7-9] Diaphragmatic dysfunction is a primary cause of respiratory muscle impairment

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Date of Submission: 10 December 2024; Date of Acceptance: 16 February 2025
https://doi.org/10.54029/2025vvk

in ALS patients.[10] DUS is a well-tolerated, noninvasive technique that can be used to assess respiratory function in ALS patients.[11-15] However, there is limited research involving ultrasound assessments of the diaphragm in ALS patients, and consensus on the clinical characteristics of DUS indicators in this population, particularly regarding diaphragmatic functional changes in patients with mild respiratory impairment, is lacking. This study aims to identify ultrasound indicators that can predict respiratory dysfunction in patients with mild ALS.

METHODS

This study was conducted at the Neurology Department of Nanchang University Second Affiliated Hospital from July 2020 to December 2023, focusing on clinically diagnosed and suspected ALS patients based on the revised El Escorial diagnostic criteria.[16]

The inclusion criteria of the study subjects were: 1. Clinically diagnosed sporadic ALS; 2. Age > 18 years; 3. Able to cooperate with diaphragm ultrasound and pulmonary function tests; 4. Signed informed consent. The exclusion criteria were: 1. Patients diagnosed as possible ALS; 2. Those unable to cooperate with ultrasound or pulmonary function tests; 3. Patients with respiratory distress, tracheostomy, or already using NPPV; 4. Familial ALS patients; 5. Patients with other neurological disorders such as cervical or lumbar spondylosis, multifocal motor neuropathy, or myasthenia gravis; 6. Patients with unrelated respiratory or lung diseases affecting pulmonary and diaphragm function; 7. Cognitive impairment or poor cooperation; 8. Pregnant or breastfeeding individuals.

ALS patients meeting three additional criteria were categorized as the mild ALS group: 1. Limb onset affecting ≤2 limbs or bulbar onset limited to the bulbar region; 2. No significant respiratory symptoms, including dyspnea and orthopnea, as indicated by an ALSFRS-R item 10 score > 3; 3. FVC ≥ 70%.

The control group consisted of healthy individuals with demographic characteristics matched to those of the ALS population, recruited from the same hospital between July 2020 and December 2023. The inclusion criteria were: 1. No diaphragm dysfunction; 2. No lung or thoracic diseases; 3. No severe health issues such as fatty liver or abdominal effusion; 4. No history of chest or abdominal surgeries; 5. No dementia or cognitive impairments; 6. Voluntary participation in diaphragm ultrasound.

Clinical data collection

Clinical data for ALS patients included gender, age, height, weight, body mass index (BMI), onset time, ALS type (limb or bulbar onset), current treatment strategies, family history, and medical history. Data for the control group included age, gender, height, weight, BMI, and medical history.

Neurological function assessment

The ALSFRS-R was employed to evaluate the severity of neurological function in all enrolled ALS patients. This scale consists of 12 items, with scores ranging from 4 (normal) to 0 (severe impairment), encompassing four domains: bulbar, upper limb, lower limb, and respiratory function, with a total score range of 0 to 48. The respiratory subscore is derived from the last three items of the scale.[17]

Pulmonary function testing

Pulmonary function assessments were conducted by an experienced respiratory physician using a pulmonary function testing device (Mediq D9, Finland). Each parameter was measured three times, and the best result was used for analysis. The acceptability and repeatability of the lung function tests were ensured according to the standard criteria outlined by the American Thoracic Society, which includes the assessment of the quality of the effort and the consistency of the results across trials.[18] The key measurements included FVC, vital capacity (VC), and maximal voluntary ventilation (MVV), which represents the maximum amount of air that can be inhaled and exhaled in one minute. Maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and sniff nasal inspiratory pressure (SNIP) were not included in this study. An FVC of <70% was considered indicative of pulmonary dysfunction in ALS patients.[19]

Diaphragm ultrasound

Diaphragm ultrasound examinations were conducted by an experienced ultrasound physician using the TOSHIBA Aplio500 ultrasound diagnostic device, set at 6-18 MHz, with subjects in supine position.[8] Diaphragm thickness was measured at the 8th to 9th intercostal space along the right anterior axillary line, in B-mode, as the distance between the pleural and peritoneal membranes (excluding the membranes themselves), taken perpendicular to the fiber direction of the diaphragm.[12] Measurements

Table 1: Baseline indicators comparison between study group and control group (Mean ± SD)

Indicator	Study Group (n=36)	Control Group (n=25)	P-value
Age (years)	60.00 ± 10.18	58.96 ± 11.03	0.706
Gender (M/F)	23/13	11/14	0.124
BMI (kg/m^2)	21.59 ± 3.45	22.31 ± 2.60	0.380

included diaphragm thickness at the apposition zone during resting tidal inspiration (Tdi-rest), maximum diaphragm thickness at the end of maximal inspiration (Tdi-ins), and minimum diaphragm thickness at the end of maximal expiration (Tdi-exp). Calculations were made for the difference in thickness between full inspiration and expiration (Δins-exp = Tdi-ins – Tdi-exp), the ratio of rest to maximum inspiratory thickness (ΔTmax = Tdi-rest / Tdi-ins × 100%), and the diaphragm thickening fraction (ΔTdi = (Tdi-ins – Tdi-exp) / Tdi-exp × 100%). Diaphragm mobility was assessed using a convex array transducer in the subcostal region, recording diaphragmatic excursion during quiet (DE-quiet) and forced (DE-max) breathing in M-mode. Each parameter was measured three times, with the best result utilized for analysis.

Statistical analysis

All data were analyzed using SPSS version 29.0. Continuous variables are presented as mean ± standard deviation. The Kolmogorov-Smirnov test was utilized to assess the normality of the data. For variables that exhibited a normal distribution, independent samples t-tests and one-way analysis of variance (ANOVA) were applied, followed by Duncan's multiple comparison test. Categorical data were evaluated using the chi-square test. Pearson correlation analysis was conducted to examine the relationships between diaphragm ultrasound parameters and pulmonary function, ALSFRS-R scores, disease duration, and age. Furthermore, the sensitivity and specificity of diaphragm ultrasound parameters in predicting pulmonary insufficiency (FVC < 70%) were determined using ROC curve analysis. A P-value of < 0.05 was regarded as statistically significant.

RESULTS

Baseline characteristics

The baseline characteristics of the study group (ALS patients) and the healthy control group were compared. No significant differences were found between the two groups regarding age, gender distribution, and BMI (P > 0.05). Details are summarized in Table 1.

Comparison of DUS indicators

A comparative analysis of DUS indicators revealed significant reductions in Tdi-rest, Tdi-ins, Δins-exp, ΔTdi, and DE-quiet in the ALS group compared to controls (P < 0.05). Notably, ΔTmax displayed a significant increase in the ALS group compared to controls (P = 0.016). However, no significant differences were observed in Tdi-exp and DE-max (P > 0.05). These findings are presented in Table 2.

Comparison of DUS indicators among mild ALS, control, and non-mild ALS groups

Patients were categorized into mild ALS (n=24) and non-mild ALS (n=12) groups. The mild ALS group exhibited significant reductions in ΔTdi

Table 2: Comparison of DUS indicators between study group and control group (Mean ± SD)

DUS Indicator	Study Group	Control Group	P-value
Tdi-rest (mm)	2.21 ± 0.44	2.54 ± 0.49	0.008
Tdi-ins (mm)	3.49 ± 1.15	4.36 ± 0.95	0.003
Tdi-exp (mm)	2.16 ± 0.61	2.28 ± 0.50	0.430
Δins-exp (mm)	1.33 ± 0.78	2.08 ± 0.67	<0.001
ΔTdi (%)	62.32 ± 29.91	93.31 ± 27.31	<0.001
ΔTmax (%)	67.17 ± 15.55	59.26 ± 9.41	0.016
DE-max (mm)	51.64 ± 18.43	57.60 ± 8.73	0.098
DE-quiet (mm)	22.23 ± 7.84	26.96 ± 5.71	0.013

Table 3: Comparison of DUS indicators among mild ALS group, control group, and non-mild ALS Group (Mean ± SD)

DUS Indicator	Mild ALS Group (n=24)	Control Group (n=25)	Non-Mild ALS Group (n=12)
Tdi-rest (mm)	2.39 ± 0.31[b]	2.54 ± 0.49	1.82 ± 0.42
Tdi-ins (mm)	3.87 ± 1.12[b]	4.36 ± 0.95	2.72 ± 0.78
Tdi-exp (mm)	2.24 ± 0.52	2.28 ± 0.50	2.00 ± 0.76
Δins-exp (mm)	1.64 ± 0.76[ab]	2.08 ± 0.67	0.72 ± 0.32
ΔTdi (%)	72.83 ± 27.30[ab]	93.32 ± 27.31	41.30 ± 23.75
ΔTmax (%)	63.37 ± 14.05[b]	59.26 ± 9.41	73.15 ± 16.38
DE-max (mm)	59.25 ± 15.84[b]	57.60 ± 8.73	36.43 ± 13.33
DE-quiet (mm)	24.39 ± 7.88[b]	26.96 ± 5.71	17.92 ± 5.71

Note: [a] indicates a significant difference between the mild ALS group and the control group ($P < 0.05$); [b] indicates a significant difference between the mild ALS group and the non-mild ALS group ($P < 0.05$). For correlations of DUS indicators with respiratory subscores and other pulmonary metrics, please refer to Table 5.

and Δins-exp compared to the healthy control group ($P < 0.05$). Moreover, the mild ALS group demonstrated significantly higher values for Tdi-rest, Tdi-ins, Δins-exp, ΔTdi, DE-quiet, and DE-max in comparison to the non-mild ALS group ($P < 0.05$). ΔTmax was significantly lower in the mild ALS group. No significant differences in Tdi-exp were found between groups. The results are summarized in Table 3.

Comparison between bulbar-onset and limb-onset ALS groups

Of the 36 ALS patients, 18 were categorized into limb-onset and 18 into bulbar-onset groups. Comparison of various indicators revealed no significant differences in ALSFRS-R scores, respiratory subscores, DUS indicators, and FVC ($P > 0.05$). Only the MVV was significantly reduced in the bulbar-onset group ($P = 0.038$). The detailed results are provided in Table 4.

Correlation analysis of DUS indicators

Correlation analysis of diaphragm DUS indicators revealed positive correlations with FVC, MVV, ALSFRS-R scores, and respiratory subscores for Tdi-rest, Tdi-ins, Δins-exp, ΔTdi, and DE-max, all with $P < 0.05$. Notably, DE-max demonstrated a negative correlation with age ($r = -0.272$, $P = 0.034$). However, no significant correlations were found between DUS indicators and disease duration ($P > 0.05$). Additionally, ΔTmax did not show significant correlations with pulmonary function metrics, ALSFRS-R scores, respiratory subscores, or disease duration ($P > 0.05$). The detailed results are provided in Table 5.

ROC curve analysis for prediction of pulmonary insufficiency

ROC curve analysis was conducted to evaluate the predictive value of DUS indicators for pulmonary insufficiency, defined as FVC <70%. In this analysis, we included 24 subjects with FVC ≥70% and 12 subjects with FVC <70%. The results demonstrated that Tdi-rest, Tdi-ins, Δins-exp, ΔTdi, and DE-max had high areas under the curve (AUC), indicating strong predictive capabilities. Specifically, Δins-exp exhibited the highest AUC (0.901), while ΔTmax showed the lowest AUC (0.391), suggesting limited predictive utility. The detailed results are in Table 6.

Table 4: Comparison between bulbar-onset ALS group and limb-onset ALS group (Mean ± SD)

Variable	Limb-Onset (n=18)	Bulbar-Onset (n=18)	P-value
Age (years)	58.83 ± 9.39	61.17 ± 11.05	0.499
Gender (M/F)	13/5	10/8	0.298
Disease Duration (months)	16.44 ± 10.97	14.17 ± 12.52	0.565
ALSFRS-R Score	35.33 ± 6.31	39.33 ± 5.94	0.058
MVV (%)	75.81 ± 30.28	56.77 ± 22.14	0.038

Table 5: Correlation analysis between DUS indicators and related factors

DUS Indicator	FVC	MVV	ALSFRS-R Score	RofALSFRS-R Score	Disease Duration	Age	BMI
Tdi-rest	r=0.727**	r=0.583**	r=0.342*	r=0.557**	r=-0.147	r=-0.039	r=0.394**
	P=0.000	P=0.000	P=0.041	P=0.000	P=0.392	P=0.763	P=0.002
Tdi-ins	r=0.531**	r=0.428**	r=0.185	r=0.387*	r=-0.023	r=-0.045	r=0.291*
	P=0.001	P=0.009	P=0.281	P=0.020	P=0.895	P=0.730	P=0.023
Tdi-exp	r=0.182	r=0.161	r=-0.101	r=0.053	r=0.108	r=-0.061	r=0.043
	P=0.289	P=0.350	P=0.557	P=0.759	P=0.532	P=0.638	P=0.743
DE-max	r=0.480**	r=0.461**	r=0.502**	r=0.587**	r=-0.335	r=-0.272*	r=0.358**
	P=0.003	P=0.005	P=0.002	P=0.000	P=0.046	P=0.034	P=0.005
Δins-exp	r=0.642**	r=0.507**	r=0.353*	r=0.531**	r=-0.119	r=-0.021	r=0.377**
	P=0.000	P=0.002	P=0.035	P=0.001	P=0.491	P=0.875	P=0.003
ΔTdi	r=0.567**	r=0.429**	r=0.387*	r=0.511**	r=-0.146	r=0.000	r=0.341**
	P=0.000	P=0.009	P=0.020	P=0.001	P=0.395	P=0.997	P=0.007
ΔTmax	r=-0.101	r=-0.064	r=0.078	r=-0.047	r=-0.193	r=0.060	r=-0.045
	P=0.559	P=0.710	P=0.649	P=0.786	P=0.260	P=0.644	P=0.733

Note: *Correlation is significant at the 0.05 level (2-tailed); **Correlation is significant at the 0.01 level (2-tailed).

DISCUSSION

In this study, we compared the DUS indices between the study group and the control group, as well as between mild ALS patients and non-mild ALS patients. Our findings indicate significant differences in Tdi-rest, Tdi-ins, Δins-exp, ΔTdi, DE-quiet, ΔTmax, and DE-max between these groups. Notably, Tdi-rest, Tdi-ins, Δins-exp, ΔTdi, and DE-max exhibited higher accuracy in monitoring lung dysfunction, making them particularly useful in clinical settings.

Among mild ALS patients, only ΔTdi and Δins-exp demonstrated significant differences, underscoring their critical role in monitoring milder cases of the disease. In routine clinical practice, pulmonary function tests are commonly employed to assess respiratory function; however, these tests require patient cooperation and significant muscle coordination, often leading to insufficient information.[9,20] In contrast, DUS has fewer operational requirements and can effectively assess diaphragm function by evaluating diaphragm thickness and mobility, showing a stronger correlation with diaphragm dysfunction than FVC.[21] Our study found significant differences in Tdi-rest, Tdi-ins, Δins-exp, ΔTdi, and DE-quiet between ALS patients evaluated through DUS and healthy controls; however, DE-max did not show a significant decline, likely due to the predominance of mild cases in our cohort.

The mild ALS group exhibited significantly higher values for Tdi-rest, Tdi-ins, Δins-exp, ΔTdi, DE-quiet, and DE-max compared to the non-mild ALS group, while ΔTmax was notably lower in the mild ALS group. This indicates that these indices correlate with disease severity. When

Table 6: ROC curve analysis of DUS indicators in the study group (FVC < 70%)

DUS Indicator	AUC Value	P-value	95% CI
Tdi-rest	0.840	0.001	0.684-0.997
Tdi-ins	0.811	0.003	0.671-0.951
Δins-exp	0.901	<0.001	0.804-0.998
ΔTdi	0.814	0.002	0.657-0.972
ΔTmax	0.391	0.290	0.183-0.598
DE-max	0.844	0.001	0.697-0.990

compared to the healthy control group, the mild ALS group showed only a significant decrease in ΔTdi and Δins-exp, suggesting that diaphragm involvement in ALS primarily manifests as changes in thickness between maximal inspiration and expiration. Fantini et al. demonstrated the value of ΔTmax in predicting altered pulmonary function tests, showing higher accuracy than changes in diaphragm thickness after maximal inspiration when considering FVC < 50%.[22] Wen *et al*. indicated that ΔTmax is the most accurate measure of ventilatory function among DUS parameters in ALS patients, while ΔTdi has no diagnostic value for pulmonary dysfunction.[23] Our findings differ, with Δins-exp showing the highest AUC value of 0.901, indicating its extremely high accuracy in predicting respiratory insufficiency, with a highly significant P-value of 0.000. DE-max, Tdi-rest, and ΔTdi followed, while ΔTmax had the lowest AUC value at 0.391 compared to the other values. The discrepancies observed in our results compared to previous studies may be attributable to several factors, particularly the heterogeneity in the severity of ALS patients across different studies and the varying thresholds employed for predicting respiratory insufficiency in ROC curve analysis.

De Carvalho *et al*. reported that although there are no significant changes in maximum inspiratory pressure and sniff nasal inspiratory pressure in early-stage ALS patients, a marked decline in MVV has been observed.[24] In our study, when comparing the bulbar-onset ALS group with the limb-onset ALS group, only MVV showed a significant decrease. This may be attributed to bulbar-onset ALS patients experiencing involvement of the medullary muscles, leading to symptoms such as oral weakness and air leak during exhalation. These findings suggest that MVV could serve as a potential biomarker for assessing pulmonary insufficiency in patients with bulbar-onset ALS.

Carrié *et al*. found that when ALS patients have an FVC of ≤ 50%, DE-max significantly decreases.[25] In our study, ALS patients showed a marked reduction in DE-quiet compared to the healthy control group, while the decline in DE-max was less pronounced. Notably, in the non-mild ALS group, both DE-quiet and DE-max were significantly lower than in the mild ALS group and the healthy control group. However, no significant differences were observed between the mild ALS group and the healthy control group. These findings indicate that diaphragm mobility remains relatively unchanged in the early, mild stages of ALS but significantly decreases in the later, non-mild stages.

Our results confirm a significant correlation between ultrasound-assessed diaphragm thickness (Tdi-rest, Tdi-ins, Δins-exp, ΔTdi, DE-max) and FVC, MVV, ALSFRS-R scores, as well as respiratory subscores. However, an unexpected finding was that ΔTmax did not show a significant correlation with lung function parameters, ALSFRS-R scores, respiratory subscores, or disease duration, likely due to the majority of our patients being in the mild stage of the disease. Sartucci *et al*. reported that Δins-exp and Tdi-exp are independently associated with respiratory scores and may predict disease progression.[26] In our study, Tdi-exp did not show significant differences between the study group and the control group, nor between the mild ALS group and the control group, or between the non-mild ALS group. Therefore, further research is needed to verify these results.

This study has several limitations. First, the sample size is limited, with mild cases accounting for approximately two-thirds, potentially introducing selection bias. Second, while we established inclusion criteria for the mild ALS group to delineate characteristics clearly, these criteria were not referenced against published literature, which may limit their generalizability and scientific validity. Despite these limitations, our findings indicate that DUS serves as a viable alternative for identifying pulmonary dysfunction in ALS patients.

In conclusion, this study findings elucidate that DUS, as a non-invasive diagnostic technique, not only facilitates the identification of pulmonary dysfunction in ALS patients but also serves as an initial modality for assessing disease severity. Notably, even in the early stages of ALS, where clinical manifestations may be subtle, diaphragmatic dysfunction can manifest. The parameters ΔTdi and Δins-exp have been validated as indicators of significant accuracy in the assessment and monitoring of respiratory insufficiency. This discovery not only provides clinicians with a convenient diagnostic tool but also presents novel perspectives for tracking disease progression.

DISCLOSURE

Ethic: This study was approval by the research ethics committee of The Second Affiliated Hospital of Nanchang University.

Data availability: Further inquiries can be directed to the corresponding author.

Financial support: None

Conflicts of interest: None

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