

The Quantitative Assessment of Respiratory Muscles by Computed Tomography in Patients of Amyotrophic Lateral Sclerosis

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Abstract

Objectives Progressive weakness of respiratory muscle is common to patients with amyotrophic lateral sclerosis, which leads to respiratory failure, even death. The evaluation of respiratory muscle is essential to evaluate the severity during the progression of the disease and choose appropriate interventions. This study aimed to evaluate the respiratory muscles change of the patients with amyotrophic lateral sclerosis by regular chest computed tomography.

Methods The cross-sectional area of respiratory muscles in amyotrophic lateral sclerosis patients was retrospectively reviewed. The severity of the disease was determined by the value of the amyotrophic lateral sclerosis function score scale. A healthy control group was selected with well-matched to the amyotrophic lateral sclerosis patients.

Results Compared with the healthy control group, the cross-sectional area of the diaphragm muscle was lower in amyotrophic lateral sclerosis patients. The reduced cross-sectional area of respiratory muscles has a positive correlation with a lower amyotrophic lateral sclerosis function score. Patients with amyotrophic lateral sclerosis further showed a significant reduction in the cross-sectional area of respiratory muscles after 6-8 months.

Conclusions

The single-slice axial computed tomography is a fast and reliable method to quantitatively assess the cross-sectional area of respiratory muscles, especially diaphragm muscle, in disease progression.

Key Points

High Resolution Computed Tomography helps clinicians to assess respiratory muscle of the patients with ALS.

Patients with ALS showed a significant reduction in the cross-sectional area of respiratory muscles during follow-up.

The reduced cross-sectional area of respiratory muscles in ALS has a positive correlation with a lower amyotrophic lateral sclerosis function score.

Background

Amyotrophic lateral sclerosis (ALS) is the motor neuron disease characterized by progressive muscle atrophy and weakness. In ALS, progressive weakness is common for respiratory muscles, which leads to respiratory failure, even death. The assessment of respiratory muscle is essential to evaluate the severity of the progression and choose appropriate interventions in time [1–3]. Thereby, different tests are necessary to provide a global view of the respiratory function of diseased subjects.

Single-slice axial computed tomography (CT) scans, as a quantitative assessment method, have been used to measure local skeletal muscle parameters quantitatively, including muscle volume, content, and distribution of adipose tissue [3]. It was considered as one of the gold-standard measurements for muscle size [2], and widely used in the diagnosis and monitoring of muscle changes in some conditions, such as myopathies, chronic obstructive pulmonary disorder, diabetes, Cushing syndrome, sepsis, inactivity, denervation, fasting, malnutrition, cancer-associated cachexia, renal failure, and cardiac failure. In contrast to dual X-ray absorptiometry and B-mode ultrasound, CT is a fast and objective method, which provides the spatially resolved distribution of muscle and adipose tissue. Compared with magnetic resonance imaging (MRI), the grey values of the muscle voxels from CT scaled in a known way with the intramuscular fat content accurately [4]. In neuromuscular disorder, diaphragm thickness was measured in 34 patients with ALS using CT before the diaphragm pacing system implantation. The diaphragm thickness was 4.6 mm (interquartile range 2.95–6.00) on the right side and 4.1 mm (interquartile range 2.77–6.00) on the left side. Significantly, diaphragm thickness below 3.5 mm was associated with higher mortality after diaphragm pacing system implantation [5]. However, there was no evaluation of CSA and attenuation in ALS.

This study evaluated the changes in CSA and attenuation of respiratory muscles in patients with ALS. It was hypothesized that the above indicators could measure the impairment of respiratory function in ALS.

Materials And Methods

The Research Ethics Committee approved this cross-sectional study. All individuals involved in the study signed informed consent from the Department of Neurology, *BLINDED HOSPITAL*. We investigated 16 patients with ALS, who were diagnosed by more than two neurologists according to the El Escorial criteria as “definite” in this retrospective study from August 2015 to December 2018. All subjects with ALS underwent chest CT and amyotrophic lateral sclerosis function score scale (ALS-FRS). 10 follow-up patients with ALS (ALS-f) were conducted chest CT-scan 6-8 months later. The exclusion criteria included cardiovascular, pulmonary, the other neuromuscular diseases, and history of chest surgery and trauma, which may affect respiratory muscle content, usage of drugs that may affect skeletal muscle mass (statins, sulfonyleureas, glinides). A healthy control (HC) group was selected from the health examination center of *BLINDED HOSPITAL*, who conducted chest CT scanning and was well-matched with age and sex to the patient groups.

Chest CT Scanning scheme and data analysis

All CT examinations were performed with high-resolution CT (Discovery CT750 HD scanner GE Healthcare, GE MEDICAL SYSTEM, *BLINDED HOSPITAL*, ct99; MHELICAL MODE; software Versions sles_hde3.5). Chest CT scans were performed with the parameters as follows, 120 kVp; 260 mA under automatic exposure control; and a rotation time of 1.0 seconds. The CT scan was reconstructed with a section width of 5mm. Subjects were requested to hold their breath while performing a chest CT scan.

NIH Image J software (Wayne Rasband National Institutes of Health) was used to quantify both muscle mass and content as the earlier guide [6]. The levels and regions of interest (ROIs) of respiratory muscles were modulated, referring to previous study [7] as Fig1. A) ROI on the 2nd thoracic vertebrae (T2) level was defined as the slice on the level of clavicolomanubrial joint on the axial scan, including the pectoralis major and minor. B) ROI on the 8th thoracic vertebrae (T8) level was defined as the slice on the right inferior pulmonary vein into the left atrium, including latissimus dorsi and serratus anterior muscle. C) ROI on the 12th thoracic vertebrae (T12) level was on the origin of the celiac trunk, where can select the diaphragm muscle between the anterior vertebral body and the pedicle of the vertebral arch. The ROIs were obtained by limiting HU range -29 to 190, and the boundary of ROIs was adjusted manually by a neuromuscular specialist. All images were performed under the same height × width (512 pixels × 512 pixels), color mode (RGB mode), pixel format (16-bit), and window & level set (window center 90, window width 350). The mean cross-sectional area (CSA) and attenuation of ROIs at the level of T2, T8, and T12 were calculated automatically. The pixel numbers were extracted corresponding to each grey level.

Statistical analysis

The CSA and attenuation of ROIs were expressed as the mean ± standard error. The independent-samples t-test was used for comparison between ALS and controls. Linear regression analysis was used to analyze its correlation with the ALS-FRS score by controlling age. Paired t-test compared with baseline and follow-up muscle parameters of ALS. Statistical analysis was performed with GraphPad InStat software ver. 8.3, and the significance level was set at $p < 0.05$. The pixel numbers corresponding to each grey level were fitted a polynomial trendline to the 6th order.

Result

16 patients with ALS and 16 age and sex-matched HCs were recruited. There was no statistical difference in age between the ALS patients and the HC groups. 10 patients (males = 9 and females = 1) were assessed longitudinally after 6-8 months later. Clinical and demographic data are summarized in Table 1 and Supplements Table 1 for each patient.

5 cases of ALS group and 3 cases of HCs could not be delineated diaphragm ROI attributing to lack 12th thoracic vertebrae level in chest CT scan. The comparison of ROIs CSA and attenuation between ALS and control group was shown in Fig.2. The CSA of ROIs on T2, T8 showed no differences between the two groups, while the CSA of diaphragm muscle was found to be lower in a patient with ALS (302.9 ± 131.7) than in HCs (501.6 ± 113.3) significantly ($t = 3.977, p < 0.001$). Interestingly, 3 higher pots of ALS group in figure 2.E represented the younger male patients with higher ALS-FRS scores. By displaying the box plots of the trends and the degree of dispersion in the data set, it could find that the ALS group showed more considerable intragroup differences of ROIs CSA on 3 levels. There were no statistically significant differences in the attenuation of respiratory muscles on 3 levels between the two groups. Linear regression models of CT parameters with the ALS-FRS were shown in Table 2. The ROIs CSA of T2, T8,

and T12 consistently demonstrated a positive correlation with ALS-FRS when age was controlled. We derived a curve fitting to histogram data of the pixel number distribution according to the grey value. The pixels of the lower grey value in diaphragm muscle and posterior auxiliary respiratory muscles were reduced, and pixels of higher grey value increased in ALS patients (Fig.3).

The comparison of ROIs CSA and attenuation between ALS and ALS-f were shown in table 4 and figure 4. 6-8 months later, the patients with ALS showed a significant reduction in ROIs CSA at all 3 levels, and no changes were found in attenuation (Fig.4).

Discussion

The study found that the CSA of the diaphragm is significantly lower in patients with ALS than those in HC controls, and the CSA of the diaphragm and other auxiliary respiratory muscles positively correlated with the clinical severity of ALS consistently. With the progress of the conditions, the CSA of the diaphragm and other auxiliary respiratory muscles reduced significantly.

The ALS group showed considerable intragroup differences in CSA of auxiliary respiratory muscles. It may be due to the ALS patients recruited in the study with different disease progression, various disease phenotypes, and unique genotype. But changes of the diaphragm are comparable to some previous studies findings using ultrasound assessment of muscle quantity and quality. The absolute diaphragm thickness at maximal inhalation and end-expiration, along with the thickening ratio, were all reduced in patients with ALS compared with the age-matched control group, which were negatively correlated with the partial pressure of carbon dioxide [8, 9]. But it is not sensitive to detect the changes of diaphragm thickness by ultrasound. One study enrolled 40 patients with ALS at baseline and 4 months later, showed that diaphragmatic compound muscle action potential amplitude provided a better measure of change over the study period, while diaphragmatic thickness showed no changes [10]. The single-slice axial CT scans are rapid and objective in muscle evaluations. In addition to the diagnostic value, the results provided a significant decline either in diaphragm CSA or in other auxiliary respiratory muscles 6–8 months later. Our study also showed that the decline of all respiratory muscles CSA positively correlates with the severity of disease significantly at baseline. These findings thus open new perspectives in using the single-slice axial CT scans to diagnosis diaphragmatic impairment in patients with ALS. In particular, the patients could not perform traditional lung function tests or electromyography tests, which require cooperation and operative skill to produce reliable measurement.

The attenuation on 3 levels at baseline and follow-up assessments showed no differences from HC and changes with the progression of the disease. It is supposed that the grey values of muscle pixels from CT scaled in a known way with the intramuscular fat content accurately. There were no significant fat content changes in the research of diaphragm biopsies[11] and other muscle biopsies [12] in the early processing of ALS. So, the attenuation of CT should not be a valuable biomarker for evaluating the respiratory muscles of patients with ALS. Interestingly, although the mean grey value of muscles on 3 levels was not different, the pattern of distribution changed. The normal distribution of diaphragmatic

grey value disappeared in patients with ALS and the low-density muscle reduced, and high-density muscle increased in posterior auxiliary respiratory muscles. The results could reflect the changing progression of muscle pathology in ALS.

Certain limitations of this study are taken into account. As a retrospective study, there was no lung function monitoring and diaphragm muscle electromyography data to compare sensitivity and specificity. Second, a fixed slice was selected based on the anatomy position in each subject, but the position of the respiratory muscle could have subtle variations. The third limitation is the relatively small number of patients. Finally, although the delineation of muscles was followed the guidelines and adjusted by a neuromuscular specialist, an automated postprocessing software would be preferable to improve accuracy to avoid the interference of other components on CT [13].

The study found that single-slice axial CT assessment of the CSA of respiratory muscle, especially the diaphragm, is a fast and reliable method to diagnose and evaluate respiratory muscle status in disease progression.

Conclusions

This study shows that the dyspnea and its severity of ALS patients can be distinguished by the cross-sectional area of the respiratory muscles of the chest CT, which is also suitable for follow-up of ALS patients.

Abbreviations

ALS Amyotrophic lateral sclerosis

CT Computed Tomography

MRI Magnetic Resonance Imaging

ALS-FRS Amyotrophic Lateral Sclerosis Function Rating Scale

ALS-f Follow-up patients with ALS

HC Healthy Control

ROIs Regions of Interest

CSA Cross-Sectional Area

Declarations

Ethics approval and consent to participate

This study was approved by Zhongda Hospital Affiliated to Southeast University. Reference number 2019ZDKYSB098 for the prospective study for which all patients gave their written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices) will be available together with the study protocol beginning 9 months and ending 12 months following article publication. Data will be available with investigators whose proposed use of the data has been approved by an independent review committee (“learned intermediary”) identified for this purpose. Data could be used for individual participant data meta-analysis. Proposals may be submitted up to 12 months following article publication. After 12 months the data will be available in our university’s data warehouse but without investigator support other than deposited metadata.

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Conflicts of Interest

Di Wu, Yujia Cao, Yan Cui, Xiaoli Li, Baoyu Yuan, Yijing Guo, Zhijun Zhang have no competing interests.

Authors' contributions

Study concepts/study design or data acquisition or data analysis/interpretation: Di Wu, Yujia Cao, Baoyu Yuan. Manuscript drafting or manuscript revision for important intellectual content: Baoyu Yuan, Yijing Guo, Zhijun Zhang. Manuscript final version approval: all authors. Agrees to ensure any questions related to the work are appropriately resolved: all authors. Literature research: Di Wu, Yujia Cao, Baoyu Yuan, Zhijun Zhang. Clinical studies: Yan Cui, Xiaoli Li, Baoyu Yuan, Yijing Guo. Data analysis: Di Wu, Yujia Cao, Zhijun Zhang. CALIPER quantification and stratification: Yan Cui, Xiaoli Li, Baoyu Yuan, Yijing Guo, Zhijun Zhang. Manuscript editing, Di Wu, Yujia Cao, Yan Cui, Xiaoli Li, Baoyu Yuan, Yijing Guo, Zhijun Zhang . All authors read and approved the final manuscript.

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Tables

Tables are not available in this version

Supplemental Data

Supplemental Tables are not available in this version

Figures

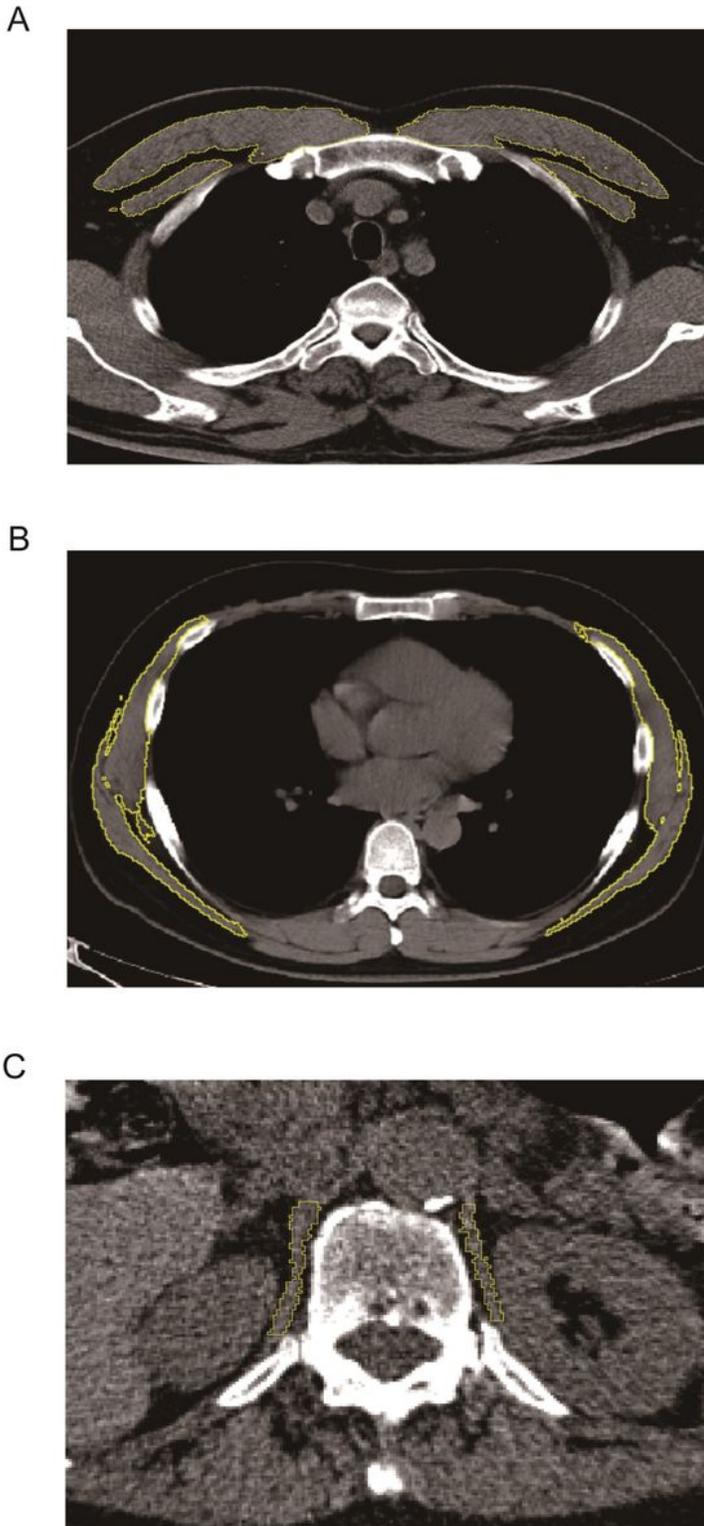


Figure 1

The delineation of ROIs. A) ROI on the 2nd thoracic vertebrae (T2) level was defined as the slice at the level of clavicolomanubrial joint on the axial scan, including pectoralis major and minor, were acquired. B) ROI on the 8th thoracic vertebrae (T8) level was defined as the slice at the level of the right inferior pulmonary vein into the left atrium, including latissimus dorsi, serratus anterior muscle. C) ROI on the

12th thoracic vertebrae (T12) level was at the level of the origin of the celiac trunk, where can select the diaphragm muscle between the level of the anterior vertebral body to the pedicle of the vertebral arch.

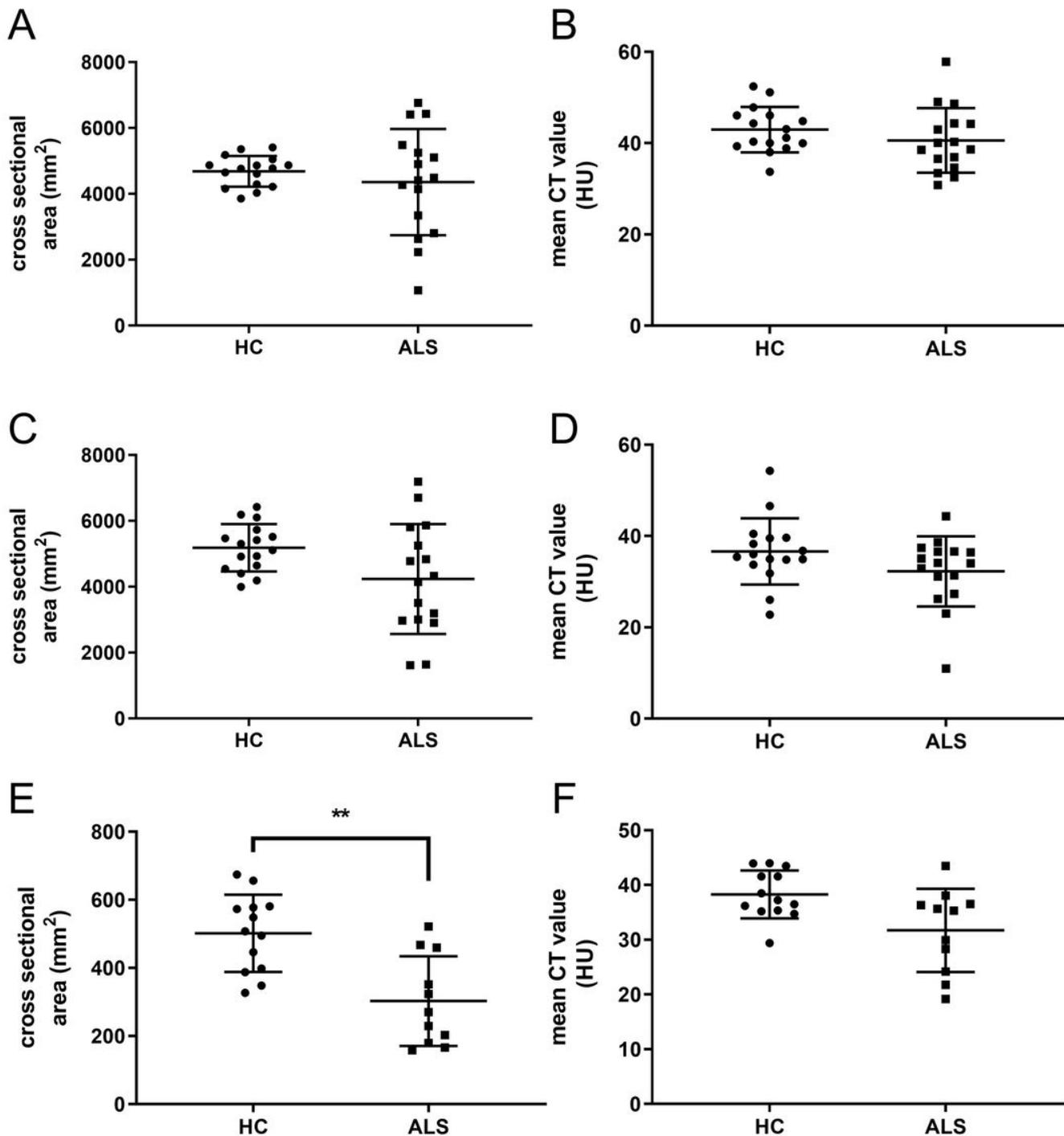


Figure 2

Comparison of cross-sectional area (CSA) and CT value of the ROIs on T2, T8, and T12 level between ALS and HC group. A, C) The CSA of ROIs on T2, T8 showed no differences between 2 groups (n=16), E) while the CSA of diaphragm muscle was found to be lower in the patient with ALS (302.88 ± 39.72 , n=11)

than in HCs (501.65 ± 31.41 , $n=13$) significantly ($t = 3.977$, $p < 0.001$). B, D, F) There were no statistically significant differences in the attenuation of respiratory muscles on 3 levels between groups. **, $p < 0.01$

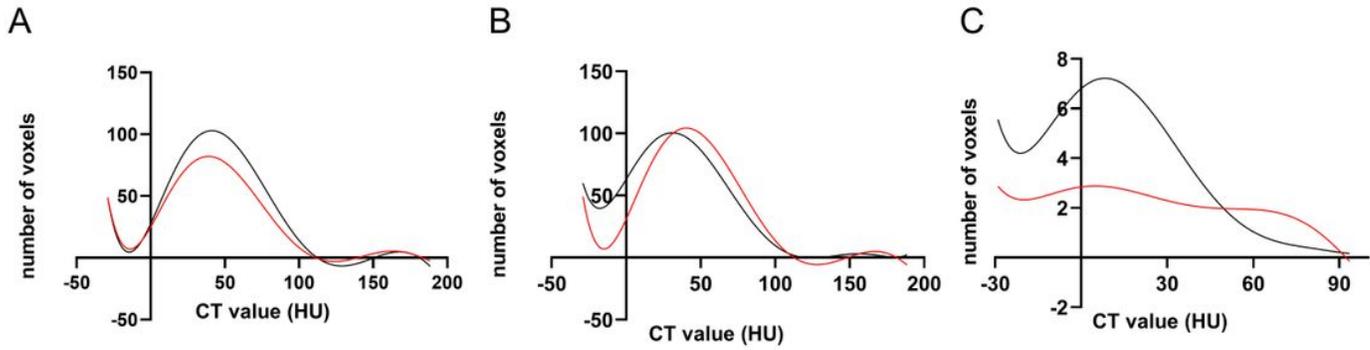


Figure 3

The curve fitting to histogram data of the pixel number distribution according to the grey value. A B C) The ROIs on T2, T8, and T12 level. The red line represents the ALS group; the black line represents the HC group.

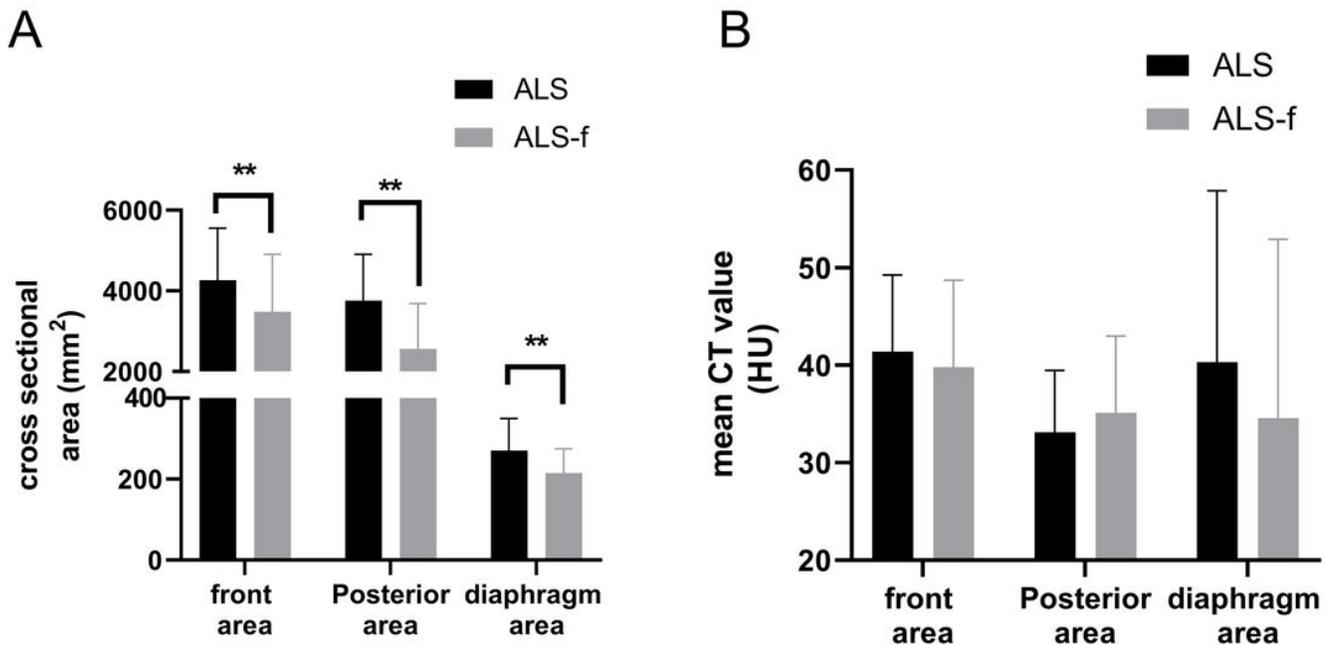


Figure 4

Comparison of the cross-sectional area (CSA) and attenuation of ROIs on T2, T8 and T12 level between ALS and ALS-f group ($n=10$). A) 6-8 months later, the patients with ALS showed that significant reduction in CSA on T2 level ($t = 3.971$, $p = 0.003$), T8 level ($t = 5.154$, $p = 0.001$) and T12 level ($t = 3.853$, $p = 0.004$). B) there were no changes found in attenuation on all levels. **, $p < 0.01$.