Association Between Fat Depletion and Prognosis of Amyotrophic Lateral Sclerosis: CT-Based Body Composition Analysis

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Objective: The purpose of this study was to present the results of our investigation of the prognostic value of adipopenia and sarcopenia in patients with amyotrophic lateral sclerosis (ALS).
Methods: Consecutive patients with ALS with abdominal computed tomography (CT) were retrospectively identified at a single tertiary hospital between January 2010 and July 2021. Deep learning-based volumetric CT body composition analysis software was used to obtain abdominal waist fat volume, fat attenuation, and skeletal muscle area at the L3 level, then normalized to the fat volume index (FVI) and skeletal muscle index (SMI). Adipopenia and sarcopenia were defined as the sex-specific lowest quartile and SMI reference values, respectively. The associations of CT-derived body composition parameters with clinical variables, such as body mass index (BMI) and creatinine, were evaluated by Pearson correlation analyses, and associations with survival were assessed using the multivariable Cox regression analysis.
Results: Eighty subjects (40 men, 65.5 ± 9.4 years of age) were investigated (median interval between disease onset and CT examination = 25 months). The mean BMI at the CT examination was 20.3 ± 4.3 kg/m^2. The BMI showed a positive correlation with both FVI ($R = 0.70$, $p < 0.001$) and SMI ($R = 0.63$, $p < 0.001$), and the serum creatinine level was associated with SMI ($R = 0.68$, $p < 0.001$). After adjusting for sex, age, King's stage, BMI, creatinine, progression rate, and sarcopenia, adipopenia was associated with shorter survival (hazard ratio [HR] = 5.94, 95% confidence interval [CI] = 1.01, 35.0, $p = 0.049$). In a subgroup analysis for subjects with nutritional failure (stage 4a), the HR of adipopenia was 15.1 (95% CI = 2.45, 93.4, $p = 0.003$).
Interpretation: Deep learning-based CT-derived adipopenia in patients with ALS is an independent poor prognostic factor for survival.

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Abbreviations

ALS amyotrophic lateral sclerosis
BMI body mass index
FVI fat volume index
SMI skeletal muscle index

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by the degeneration of motor neurons, resulting in progressive motor impairment and muscle atrophy.[1] During disease progression, both skeletal muscles and adipose tissues develop wasting due

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to muscle denervation, decreased dietary intake, and metabolic perturbations.[1–3] Rapid weight loss and a low body mass index (BMI) at diagnosis are associated with faster progression and shorter survival.[4,5] Unsurprisingly, a high baseline BMI has been reported to be associated with a low risk of ALS occurrence several decades later.[6] However, body weight or BMI changes do not reflect specific alterations of body composition. The BMI is only a measure of weight (i.e., a sum of body fat, muscles, bones, and organs), not body fat alone.[7] Indeed, the BMI has been criticized given its high specificity (97%) but low sensitivity (42%) in detecting body fat.[8]

Several studies have assessed body composition, including fat mass and fat-free mass, by bioelectrical impedance analysis (BIA) or dual-energy x-ray absorptiometry (DXA).[9–12] DXA is considered a gold standard for measuring body composition, but requires a costly machine, and patients must lie flat for over 10 minutes.[13] Although the usefulness of BIA in patients with ALS has been validated,[14] the formula for calculating the fat mass and fat-free mass relies on a few assumptions and measures body composition indirectly. A subsequent study showed that anthropometric measures are not reliable indicators of fat mass in patients with ALS.[15]

CT images directly quantify skeletal muscles and adipose tissues, and body composition in the abdomen represents the whole-body composition.[16] In addition, a deep neural network has been developed that reliably enables the volumetric segmentation of CT images for body composition assessment.[17] Thus, body composition has been analyzed using CT images in studies targeting asymptomatic screening cohorts and certain disease groups. However, whether the body composition analysis has prognostic implications in rare diseases, such as ALS, is unknown. In this study, we investigated associations between CT-derived body composition parameters and clinical variables, as well as their prognostic value for long-term survival in patients with ALS.

Methods

This retrospective study was approved by the Institutional Review Board of Seoul National University Hospital, and the requirement for written informed consent was waived (institutional review board [IRB] No.: H-2108-096-1245). Part of the study population (16.3%, 13 of 80) was reported in a previous study investigating the prognostic value of the neutrophil-to-lymphocyte ratio in patients with ALS.[18] In contrast, the present study investigated the prognostic implications of CT-derived body composition analysis.

Study Participants

We retrospectively reviewed the medical records of consecutive patients with ALS diagnosed at a single tertiary hospital between January 2010 and July 2021 who underwent abdominal CT. Patients were diagnosed with definite, probable, or possible ALS according to the revised El Escorial criteria. In those with multiple CT scans, we selected only the CT scan taken closest to the onset of ALS. Among these patients, we only included those with an abdominal CT scan after the diagnosis of ALS. The diagram of patient selection is shown in Figure 1.

Data Collection

We collected demographic data (sex, age, height, weight, and BMI), date of onset, region of onset, ALS Functional Rating Scale-Revised (ALSFRS-R) score, progression rate ([48 ALSFRS-R]/[time from onset to clinical assessment]), King's clinical stage, date of gastrostomy, date of tracheostomy, statin use, forced vital capacity (% predicted), arterial partial pressure of carbon dioxide, total cholesterol, triglyceride, high−/low-density lipoprotein cholesterol, uric acid, creatinine, hemoglobin A1C, CT examination date, and the indications of CT. The King's staging system was used with minor modifications, for which clinical data were retrospectively retrieved from the medical records: stage 1 = involvement of the first region, stage 2 = involvement of the second region, stage 3 = involvement of the third region, stage 4a = needing nutritional support (gastrostomy), stage 4b = needing respiratory support (tracheostomy), and stage 5 = death. To determine whether each anatomic segment was involved, we used both clinical and electrophysiological evidence. The date of death was obtained from a database of the Ministry of the Interior and Safety, Korea.

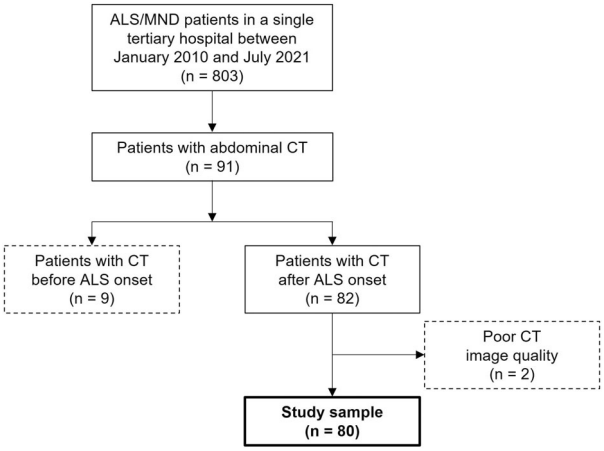

Figure 1: A diagram of subject selection. ALS = amyotrophic lateral sclerosis; CT = computed tomography; MND = motor neuron disease.

Image Acquisition and Body Composition Analysis

The routine abdominal CT protocol of our institution used the following parameters: section thickness = 2.5 to 3.0 mm, reconstruction interval = 2.0 to 3.0 mm, rotation time = 0.50 to 0.75 seconds, peak voltage = 100 to 120 kVp, and tube current = 150 to 250 mAs. After the acquisition of precontrast axial images, an intravenous nonionic contrast medium (iobitridol [Xenetix 350, Guerbet] or iohexol [Bonorex 350, Central Medical Service]) was injected at a dose of 1.6 mL/kg at a rate of 3 to 5 mL/s followed by a 20 to 40 mL saline flush using an automatic power injector. Using the bolus tracking technique, portal venous phase axial images were obtained with a scan delay of 55 to 70 seconds, starting from the threshold enhancement of 100 to 150 (Hounsfield units [HU]) in the distal thoracic aorta.

Abdominal CT images were imported into commercially available deep learning-based body composition analysis software (DEEPCATCH, version 1.0.0.0, MEDICALIP Co. Ltd.). Two authors (J.H.L. and S.H.Y., with 10 and 17 years of experience in body images, respectively) confirmed the completeness of the segmentation of the software in consensus and adjusted the segmentation results if necessary. The software calculated CT-derived parameters, including total fat volume (cm^3), visceral fat volume (cm^3), subcutaneous fat volume (cm^3), visceral fat attenuation (HU), and subcutaneous fat attenuation (HU) at the abdominal waist level (World Health Organization definition; between the 12th rib and iliac crest), and skeletal muscle area at L3 (cm^2).[19] Detailed information about the software has been described in a previous study.[17] The total, visceral, and subcutaneous fat volumes and skeletal muscle area were normalized for height squared to calculate the total fat volume index (FVI), visceral FVI, subcutaneous FVI, and skeletal muscle index (SMI).

Definition of Sarcopenia and Adipopenia

The cutoff value of SMI for sarcopenia was 55 cm^2/m^2 for men and 39 cm^2/m^2 for women.[20] Adipopenia has no widely accepted reference value; thus, we divided the FVI into quartiles by sex and operationally defined adipopenia as the lowest quartile of the FVI. Accordingly, the cutoff value of FVI for adipopenia was set to be 627.9 cm^3/m^2 for men and 627.7 cm^3/m^2 for women.

Statistical Analysis

Continuous variables are presented as mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables are shown as the frequency with percentage. Differences in body composition parameters according to the King's stage were assessed using logistic regression analyses. Associations between clinical variables, such as BMI, creatinine, ALSFRS-R score, and body composition parameters, were evaluated by the Pearson correlation analyses. For survival analysis, the proportional hazard assumption was assessed by the Schoenfeld residual test, and, as a result, the onset region was excluded. The functional endpoint was defined as either death from any cause or the introduction of tracheostomy-invasive ventilation. Kaplan–Meier curves were generated and compared using the log-rank test. Univariable and multivariable Cox regression analyses were performed. For multivariable analyses, we used variables with $p < 0.10$ in the univariable analyses (King's stage, BMI, creatinine, and progression rate). We also included well-established prognostic factors that may affect body composition, such as sex and age. For subgroup analysis, we analyzed the characteristics of subjects with nutritional failure who had yet to undergo tracheostomy (stage 4a). Additional survival analyses, including Kaplan–Meier curves with the log-rank test and Cox regression, were performed. We separately performed Cox regression analyses with categorical (adipopenia; model 1) and continuous (FVI; model 2) input variables. A 2-tailed $p < 0.05$ was considered statistically significant. All statistical analyses were performed using R version 4.1.2. (R Project for Statistical Computing, Vienna, Austria).

Results

Clinical Characteristics

Of 803 patients with ALS or motor neuron disease, 91 patients with ALS (11.3%) were identified as having undergone abdominal CT for any reason. Among them, 9 subjects were excluded because CT was taken before the onset of ALS. Two subjects were excluded because the image quality of the CT scans was poor for analyzing body composition. Thus, 80 subjects were included in the final analysis (40 men and 40 women; mean age = 65.5 ± 9.4 years). The median interval between disease onset and CT examination was 25 months (IQR = 11.8–42.5 months). The proportion of bulbar-onset ALS was 33.8% (27 of 80 subjects). The ALSFRS-R score was 26.5 ± 10.9. The progression rate was calculated as 1.19 ± 1.05 per month. The distribution of the King's clinical stages was as follows: 6 subjects in stage 1 (7.5%), 3 in stage 2 (3.8%), 25 in Stage 3 (31.3%), 29 in stage 4a (36.3%), and 17 in stage 4b (21.3%). Forty-six subjects (57.5%) underwent gastrostomy, and 20 (25%) were on tracheostomy-invasive ventilation. Demographics and clinical characteristics are summarized in Table 1.

TABLE 1. Demographic and Clinical Characteristics of the Study Participants (n = 80)

Characteristic	Value
Sex (M/F)	40/40
Age at CT examination, yr[a]	65.5 ±9.4
Time from onset to CT examination, mo[b]	25.0 (11.8–42.5)
Onset region (%)	
Bulbar	27 (33.8)
Cervical	31 (38.8)
Lumbosacral	20 (25.0)
Respiratory	1 (1.3)
Unclear	1 (1.3)
ALSFRS-R[a], n = 55	26.5 ± 10.9
King's clinical stage (%)[c]	
Stage 1	6 (7.5)
Stage 2	3 (3.8)
Stage 3	25 (31.3)
Stage 4a	29 (36.3)
Stage 4b	17 (21.3)
Progression rate[a], n = 55	1.19 ± 1.05
BMI (kg/m^2)[a], n = 74	20.3 ± 4.3
FVC (% predicted)[b], n = 34	53.0 (22.3–70.8)
$PaCO_2$ (mmHg)[a], n = 56	46.5 ± 11.1
Statin (%), n = 79	19 (23.8)
Total cholesterol (mg/dL)[a], n = 60	168.7 ± 44.3
HbA1c (%)[a], n = 45	5.94 ± 0.70
Creatinine (mg/dL)[a], n = 73	0.59 ± 0.24
Uric acid (mg/dL)[a], n = 76	4.19 ±1.64
Gastrostomy (%)	46 (57.5)
Tracheostomy (%)	20 (25.0)

Note: Data are shown as number and frequency.

Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; BMI = body mass index; CT = computed tomography; FVC = forced vital capacity; HbA1c = hemoglobin A1c; $PaCO_2$, = arterial partial pressure of carbon dioxide.

[a]Data are shown as mean and standard deviation.

[b]Data are shown as median and interquartile range.

[c]King's clinical staging system is as follows: stage 1 = involvement of first region, stage 2 = involvement of second region, stage 3 = involvement of third region, stage 4a = need for nutritional support (gastrostomy), stage 4b = need for respiratory support (tracheostomy), and stage 5 = death. The serum creatinine level of one subject with chronic kidney disease (1.95 mg/dL) was excluded from the analysis. One subject underwent per-oral endoscopic myotomy due to achalasia. The date of the procedure was unknown in one subject who underwent gastrostomy. The date of the procedure was unknown in one subject who underwent tracheostomy.

Indications of Abdominal CT

The most common indication of abdominal CT was related to gastrostomy (33.8%, 27 of 80): evaluations for post-gastrostomy complications in 19 subjects (23.8%, 19 of 80) and evaluations before gastrostomy in 8 subjects (10%, 8 of 80). Cancer screening for weight loss (31.3%, 25 of 80) was the second most common cause. Other indications included fever (13.8%, 11 of 80), gastrointestinal symptoms (10%, 8 of 80), follow-up studies (8.8%, 7 of 80), x-ray image abnormalities (1.3%, 1 of 80), and myalgia (1.3%, 1 of 80). The CT images used to analyze body composition consisted of both CT examinations with and without contrast medium (with contrast medium = 63.8%, 51 of 80, and without contrast medium = 36.2%, 29 of 80).

Association Between Clinical Variables and Body Composition Parameters

We found a linear association between the SMI and King's clinical stage in regression analyses. The median SMI was 63.0 (IQR = 51.6–77.2), 59.5 (IQR = 45.9–62.6), and 39.4 (IQR = 35.6–49.5) in stages 1 to 3, 4a, and 4b, respectively (odds ratio [OR] = 0.954, 95% confidence interval [CI] = 0.923, 0.982, $p = 0.003$). After splitting stages 1 to 2 and 3, this linear tendency was maintained, although it did not reach statistical significance ($p = 0.068$). In contrast to subcutaneous FVI, visceral FVI gradually decreased with disease progression: the median visceral FVI was 438.4 (IQR = 201.5–745.5), 249.1 (IQR = 71.2–541.0), and 171.8 (IQR = 21.7–336.0) in stages 1 to 3, 4a, and 4b, respectively (OR = 0.998, 95% CI = 0.995, 0.999, $p = 0.006$). The proportion of subjects with sarcopenia progressively increased with disease progression, but this association was not seen in subjects with adipopenia (Fig 2). Both subcutaneous and visceral fat attenuation consistently increased as the disease progressed. Further details on the associations between King's clinical stage and body composition parameters are summarized in Table 2 and Table S1. In an analysis according to the onset region, subjects with limb-onset disease showed a lower SMI and a higher prevalence of sarcopenia than those with bulbar-onset disease. However, no significant difference was observed in the FVI or the proportion of adipopenia between the 2 groups (Table S2).

The SMI was strongly correlated with BMI ($R = 0.63$, $p < 0.001$) and the serum creatinine level ($R = 0.68$, $p < 0.001$), and moderately with the ALSFRS-R score ($R = 0.35$, $p = 0.009$), respectively. The SMI seemed modestly associated with the level of serum uric acid ($R = 0.20$, $p = 0.078$), but without statistical significance. The total FVI was strongly correlated

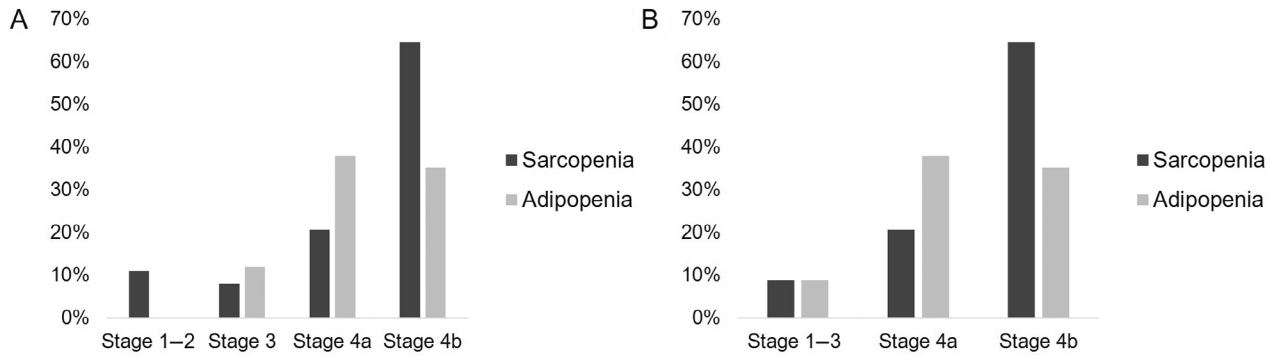

Figure 2: The proportion of subjects with sarcopenia and adipopenia according to the King's clinical stage. (A) Stages 1 to 3 were merged into a single entity, (B) stages 1 to 2 and 3 were split.

with BMI ($R = 0.7$, $p < 0.001$) and modestly with the serum uric acid level ($R = 0.26$, $p = 0.022$), respectively. The FVI tended to increase along with the ALSFRS-R score ($R = 0.25$, $p = 0.061$), but it did not reach statistical significance. Neither the FVI nor SMI was correlated with the progression rate. Figure 3 shows the correlation plots between clinical variables and the SMI and FVI, respectively.

Survival Analyses

In univariable Cox regression analyses for survival, the King's clinical stage, progression rate, BMI, FVI, and adipopenia were found to be statistically significant ($p < 0.05$). In multivariable analyses, sex (hazard ratio [HR] = 8.01, 95% CI = 1.91, 33.7, $p = 0.005$ in model 1; and HR = 5.84, 95% CI = 1.48, 23.0, $p = 0.01$ in model 2), age (HR = 1.07, 95% CI = 1.01, 1.14, $p = 0.03$ in model 1; and HR = 1.07, 95% CI = 1.01, 1.14, $p = 0.03$ in model 2), progression rate (HR = 2.72, 95% CI = 1.49, 4.97, $p = 0.001$ in model 1; and HR = 2.10, 95% CI = 1.27, 3.46, $p = 0.004$ in model 2), and adipopenia (HR = 5.94, 95% CI = 1.01, 35.0, $p = 0.049$ in model 1) were identified as independent prognostic factors for survival (Table 3). Kaplan–Meier curves showed a significant difference in overall survival rates according to adipopenia status ($p < 0.001$; Fig 4). In a subgroup of subjects with nutritional failure (Table S3), sex (HR = 11.6, 95% CI = 1.82, 73.7, $p = 0.01$ in model 1; and HR = 8.03, 95% CI = 1.49, 43.3, $p = 0.02$ in model 2), progression rate (HR = 6.01, 95% CI = 1.75, 20.7, $p = 0.004$ in model 1; and HR = 2.95, 95% CI = 1.19, 7.33, $p = 0.02$ in model 2), adipopenia (HR = 15.1, 95% CI = 2.45, 93.4, $p = 0.003$ in model 1), and total FVI (HR = 0.99, 95% CI = 0.99, 1.00, $p = 0.01$ in model 2) were independent prognostic factors for survival (Table S4). Images of representative cases are shown in Figure 5.

Discussion

This study corroborated that deep learning-based volumetric CT body composition analysis is an appropriate approach to represent patients' body composition, as it

TABLE 2. Association Between King's Clinical Stage and Body Composition Parameters (n = 80)

Body composition parameters	Stage 1–3 (n = 34)	Stage 4a (n = 29)	Stage 4b (n = 17)	OR (95% CI)	*p*
Skeletal muscle index (cm^2/m^2)	63.0 [51.6, 77.2]	59.5 [45.9, 62.6]	39.4 [35.6, 49.5]	0.954 (0.923, 0.982)	0.003
Fat volume index (cm^3/m^2)	1152.7 [782.3, 1688.0]	762.8 [436.5, 1279.6]	859.4 [352.7, 985.4]	0.999 (0.998, 0.999)	0.017
Subcutaneous fat volume index (cm^3/m^2)	601.7 [439.8, 976.0]	611.5 [304.1, 869.5]	546.9 [228.8, 638.7]	0.999 (0.997, 1.000)	0.113
Visceral fat volume index (cm^3/m^2)	438.4 [201.5, 745.5]	249.1 [71.2, 541.0]	171.8 [21.7, 336.0]	0.998 (0.996, 0.999)	0.006
Subcutaneous/visceral fat volume	1.51 [0.88, 2.81]	3.02 [1.63, 3.89]	2.19 [1.33, 4.39]	1.289 (1.051, 1.682)	0.033
Subcutaneous fat attenuation (HU)	−96.5 [−106.5, −89.2]	−91.1 [−102.2, −72.2]	−84.9 [−89.5, −74.5]	1.056 (1.022, 1.097)	0.003
Visceral fat attenuation (HU)	−91.6 [−95.7, −84.6]	−83.1 [−94.7, −72.2]	−79.4 [−90.5, −67.4]	1.044 (1.009, 1.084)	0.017

Note: King's clinical staging system is as follows: stage 1 = involvement of first region, stage 2 = involvement of second region, stage 3 = involvement of third region, stage 4a = need for nutritional support (gastrostomy), stage 4b = need for respiratory support (tracheostomy), and stage 5 = death. Data are shown as median and interquartile range.
Abbreviations: CI = confidence interval; HU = Hounsfield unit; OR = odds ratio.

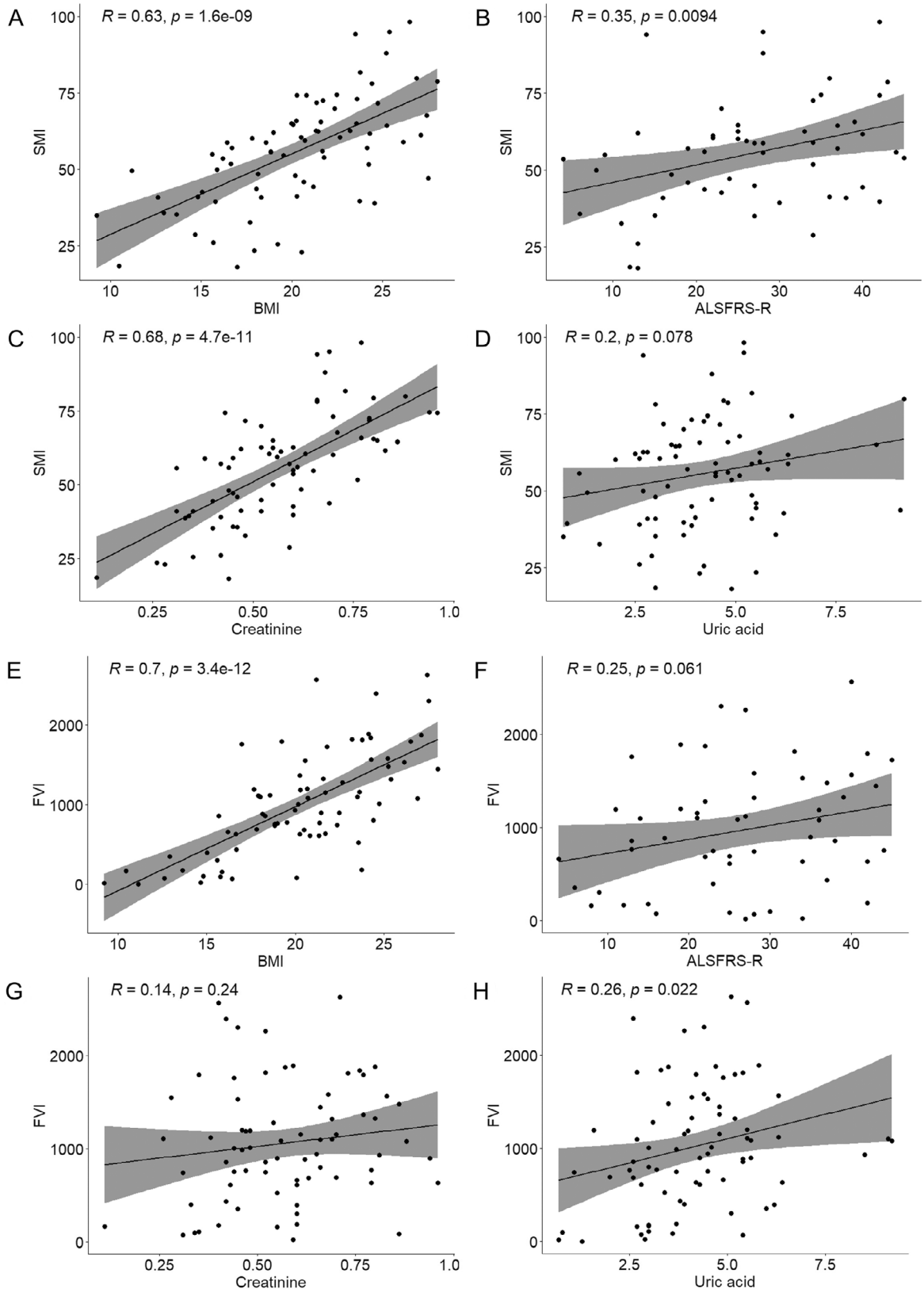

Figure 3: Correlation plots between clinical features and SMI or FVI: (A) between BMI and SMI ($R = 0.63$, $p < 0.001$), (B) between ALSFRS-R and SMI ($R = 0.35$, $p = 0.009$), (C) between creatinine and SMI ($R = 0.68$, $p < 0.001$), (D) between uric acid and SMI, (E) between BMI and FVI ($R = 0.70$, $p < 0.001$), (F) between ALSFRS-R and FVI ($R = 0.25$, $p = 0.061$), (G) between creatinine and FVI ($R = 0.14$, $p = 0.24$), and (H) between uric acid and FVI ($R = 0.26$, $p = 0.022$). ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; BMI, body mass index; FVI, fat volume index; SMI, skeletal muscle index.

TABLE 3. Univariable and Multivariable Cox Regression Analyses in All Subjects (Exclusion of Stage 4b, n = 63)

	Univariable		Multivariable			
			Model 1		Model 2	
Body composition parameters	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Sex (M)	1.37 (0.68–2.76)	0.38	8.01 (1.91–33.7)	0.005	5.84 (1.48–23.0)	0.01
Age, yr	1.02 (0.98–1.06)	0.36	1.07 (1.01–1.14)	0.03	1.07 (1.01–1.14)	0.03
Onset region (bulbar)	0.83 (0.39–1.78)	0.63				
King's clinical stage (stage 4a/stage 1–3)	2.73 (1.31–5.70)	0.008	2.09 (0.64–6.85)	0.22	2.31 (0.72–7.43)	0.16
BMI (kg/m^2)	0.90 (0.83–0.99)	0.02	0.98 (0.77–1.24)	0.87	0.87 (0.64–1.18)	0.38
Creatinine (mg/dL)	0.15 (0.02–1.22)	0.08	0.02 (0.00–1.32)	0.07	0.04 (0.00–2.87)	0.14
Progression rate	1.44 (1.01–2.05)	0.046	2.72 (1.49–4.97)	0.001	2.10 (1.27–3.46)	0.004
Skeletal muscle index (cm^2/m^2)	0.99 (0.97–1.01)	0.23				
Fat volume index (cm^3/m^2)	0.99 (0.99–1.00)	0.04			0.99 (0.99–1.00)	0.83
Sarcopenia	2.26 (0.97–5.29)	0.06	0.68 (0.12–3.90)	0.66	0.72 (0.11–4.57)	0.73
Adipopenia	4.57 (2.09–9.98)	<0.001	5.94 (1.01–35.0)	0.049		

Note: Survival time was defined as the time from the abdominal CT scan to the functional endpoint (death or tracheostomy). The cutoff value of the skeletal muscle index for sarcopenia was 55 cm^2/m^2 for men and 39 cm^2/m^2 for women. The cutoff value of the fat volume index for adipopenia was 627.9 cm^3/m^2 for men and 627.7 cm^3/m^2 for women. Model 1 and model 2 used adipopenia (categorical variable) and fat volume index (continuous variable) as an input variable, respectively.

Abbreviations: BMI = body mass index; CI = confidence interval; CT = computed tomography; HR = hazard ratio.

showed correlations with pre-established indices of body composition (e.g., serum creatinine) and the prognosis of patients with ALS. That is, CT body composition analysis was proven to be a proxy to represent body composition and had prognostic implication even in a rare disease. Specifically, skeletal muscle mass, represented by the SMI, progressively diminishes as ALS progresses. The serum creatinine level was positively correlated with the SMI, but not with the FVI. In contrast, BMI showed positive associations with both SMI and FVI. The visceral FVI, but not the subcutaneous FVI, declined during disease progression. After adjustment for other clinicoradiological factors in multivariable Cox regression, adipopenia was identified as an independent prognostic factor for survival in patients with ALS. As a result, deep learning-based volumetric CT body composition analysis has a prognostic role even in this rare neurodegenerative disease.

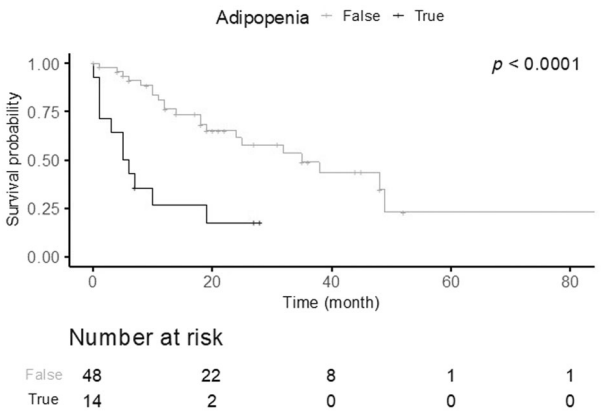

Figure 4: Kaplan–Meier survival curves according to adipopenia status. Subjects with adipopenia had significantly shorter survival than those without (median survival = 5.5 vs 35.0 months, $p < 0.001$).

Based on the long-standing clinical observation that ALS frequently develops in lean and physically fit adults,[21–23] ALS researchers have focused on the contribution of metabolic and nutritional factors to its pathogenesis. The following hypotheses have been proposed: (A) a common oligo- or polygenic genetic background predisposes individuals to be both lean and fit and to be at increased risk of ALS; and (B) body fat has a protective effect on the risk of developing ALS. Several observational studies have demonstrated that BMI is negatively associated with the risk of developing ALS and positively correlated with survival after ALS diagnosis.[4,6,24] A Mendelian randomization study and longitudinal cohort studies have consistently shown that the baseline body fat (%) and

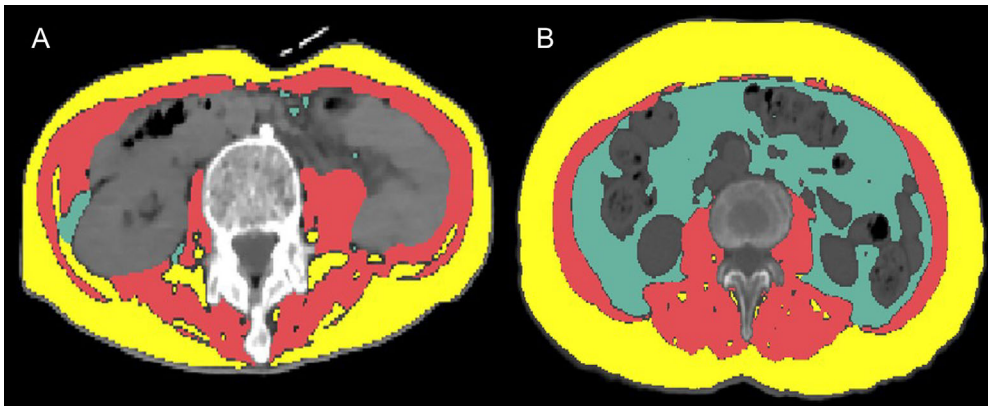

Figure 5: Representative images of low visceral fat volume (adipopenia) predicting mortality in subjects with amyotrophic lateral sclerosis. (A) CT images of a 53-year-old woman diagnosed with amyotrophic lateral sclerosis. Segmentation-overlaid images from body composition analysis of unenhanced axial CT images show the segmentation results of visceral fat (green), subcutaneous fat (yellow), and skeletal muscle (red). The fat volume index is 352.7 cm^3/m^2, included in the lowest quartile (threshold: 627.7 cm^3/m^2), suggesting adipopenia. A month after the examination, the subject died. (B) CT images in a 72-year-old woman diagnosed with amyotrophic lateral sclerosis. Segmentation-overlaid images from body composition analysis of unenhanced axial CT images show the segmentation results of visceral fat (green), subcutaneous fat (yellow), and skeletal muscle (red). The fat volume index is 1530.6 cm^3/m^2, falling into the higher three quartiles (threshold: 627.7 cm^3/m^2). She survived as of May 2022 (38 months later). CT = computed tomography.

waist-to-hip ratio are associated with a decreased risk of developing ALS and post-diagnosis survival.[25–27] However, because conventional anthropometry does not accurately measure fat mass in ALS,[15] the true role of body fat as a prognostic indicator for survival remains unclear. Therefore, this study made an original contribution by quantitatively calculating body composition and establishing a positive relationship between fat volume and survival length.

Neurodegeneration might affect adipose tissue and energy homeostasis through diverse mechanisms or vice versa. Epidemiological studies have shown that patients with ALS experience catabolism and lose weight more than 10 years before disease onset.[23,28] Weight loss is associated with structural defects in the hypothalamus, the integration center of energy metabolism.[29] Catabolism may also result from the combination of dysphagia and intrinsic hypermetabolism in patients with ALS.[2] The fat distribution has been reported to be closely linked to metabolic disease risk. In particular, increased visceral fat is associated with type 2 diabetes and insulin resistance, whereas increased subcutaneous fat is associated with a lower risk of metabolic syndrome, diabetes, and atherosclerosis.[30–33] A mouse study suggested that 24-hour fasting induces the subcutaneous adipose tissues to acquire key properties of visceral fat, mediated by microRNA (miRNA)-149-3p and suppression of *PRDM16*.[15] In our study, as the disease progressed, both visceral and subcutaneous fat attenuation increased, but only the visceral FVI was significantly associated with the King's clinical stage. Because adipose tissue fibrosis increases attenuation in CT images,[34,35] these findings may point to a close link between visceral fat fibrosis and chronic inflammation according to motor neuronal death in ALS or possibly reflect changes in the metabolic properties of adipose tissue in patients undergoing significant malnutrition.[18,36,37] Further experimental investigations are warranted.

The serum creatinine level, which is proportional to skeletal muscle mass, was strongly correlated with the SMI, but not with the FVI. In a recent study using data from multiple ALS cohorts of clinical trial participants, the rates of decline of plasma creatinine were shown to have considerably lower between-patient variability than the ALSFRS-R score,[38] and plasma creatinine was highly predictive of functional status and survival.[38] Furthermore, serum/plasma creatinine declines with a decrease in fat-free mass over the disease course in ALS and thus can be a useful biomarker for monitoring the change of fat-free mass.[39] The high correlation coefficient ($R = 0.68$, $p < 0.001$) between the SMI and creatinine shows that deep learning-based body composition analysis can robustly discriminate fat-free mass and fat mass.

Insufficient nutrition has been recognized as an independent and modifiable risk factor for disease progression and survival in ALS.[22,40] Therefore, several studies and clinical trials have been conducted to assess the efficacy of gastrostomy tube feeding and nutritional interventions.[12,41] A recent randomized, double-blind, placebo-controlled trial (the LIPCAL-ALS study) provided no clear evidence for a life-prolonging effect of high-caloric fatty diet for the overall ALS population; however, a post hoc analysis of the LIPCAL-ALS study showed that using high-caloric fatty supplements demonstrated a significant survival benefit and weight stabilization in fast-progressing patients (progression rate = > 0.62 points of ALSFRS-R per month).[42] In

addition, in a subsequent randomized, parallel-group, controlled trial comparing effects of various high-caloric food supplements as an add-on therapy in patients with ALS (the TOLCAL-ALS study), it appeared that interventions rich in fat offered a greater potential for weight gain.[43] These studies support the need to identify patients who might benefit from nutritional intervention. Given the mean progression rate in our ALS cohort, most patients included in our study were fast progressors (mean progression rate = 1.19) who may benefit from high-caloric fatty diet supplementation. Because fat-free and fat mass changes are not accurately reflected in the BMI, CT-based deep learning-based body composition analysis may help to identify patients requiring an early nutritional intervention and would benefit from fat-rich nutritional support.

This study has several limitations. First, the number of study patients was relatively small, and the patients were retrospectively identified at a single institution. Further studies involving more patients are warranted to investigate the prevalence of adipopenia in patients with ALS of different races and from various countries. Second, more than half of the patients had advanced disease (King's stage 4), and the proportion of those with fast progression was relatively high. Third, we utilized the King's clinical staging system with minor modifications based on individual retrospective chart review, instead of relying on ALSFRS-R subscores, for the following reasons: (1) ALSFRS-R scores were available for only 55 out of 80 patients (68.7%) because the remaining 25 patients did not have ALSFRS-R scores assessed within 6 months of the CT scan date. (2) There was a buffer of up to 6 months between the assessment of ALSFRS-R scores and CT examinations. Consequently, some patients with nutritional failure were incorrectly categorized as Stage 3 (n = 14). (3) Interventional procedures, such as gastrostomy and noninvasive positive pressure ventilation, were implemented relatively late compared to the recommended guidelines for Korean patients with ALS; therefore, stages 4a and 4b estimated from the ALSFRS-R subscores were highly likely to be inaccurate in our cohort. Fourth, the number of patients undergoing follow-up CT scans was limited; thus, we could not analyze longitudinal changes in body composition parameters according to the disease progression. Nonetheless, we assessed correlations of fat-free and fat mass with clinical measures, enabling future research on the contributions of fat metabolism to the pathogenesis of ALS, with implications for therapeutic interventions in the future.

In conclusion, deep learning-based CT-derived adipopenia is an independent poor prognostic factor for survival in patients with ALS. Differences were found in body composition parameters derived from CT images according to the clinical stages, potentially stratifying patients who require nutritional intervention. Further prospective studies with more patients are warranted to validate our findings and investigate the associations between fat depletion and other potential contributors to the pathogenesis such as metabolic and inflammatory biomarkers.

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Author Contributions

S.C. and J.H.L. contributed to the conception and design of the study. S.C., S.H.Y., J.S., and J.H.L. contributed to the acquisition and analysis of data. S.C., S.H.Y., J.S., and J.H.L. contributed to the drafting a significant portion of the manuscript text and figures.

Potential Conflicts of Interest

S.H.Y. is a chief medical officer for Medical IP, and holds stock of the firm, which software (DEEPCATCH) is tested in this study.

Data Availability Statement

The data sets generated or analyzed during the study are available from the corresponding authors on reasonable request.

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