Journal of Neurology (2019) 266:1412–1420
https://doi.org/10.1007/s00415-019-09276-2

ORIGINAL COMMUNICATION

Prognostic significance of body weight variation after diagnosis in ALS: a single-centre prospective cohort study

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Received: 18 January 2019 / Revised: 28 February 2019 / Accepted: 7 March 2019 / Published online: 13 March 2019

Abstract

Background Body weight reduction after disease onset is an independent predictor of survival in amyotrophic lateral sclerosis (ALS), but significance of weight variation after diagnosis remains to be established.

Objective To investigate weight variation after diagnosis and its prognostic significance in patients with ALS as a prospective cohort study.

Methods Seventy-nine patients with ALS were enrolled in this study. At the time of diagnosis and about 1 year later, we evaluated the following parameters: age, sex, onset age, onset region, body mass index (BMI) and premorbid BMI, forced vital capacity and the revised ALS functional rating scale. Annual BMI decline rates (ΔBMI) from onset to diagnosis and from diagnosis to about 1 year later were calculated. Patients were followed to the endpoints (death or tracheostomy), and the relationships between ΔBMIs and survival were investigated.

Results Patients with post-diagnostic ΔBMI ≥ 2.0 kg/m^2/year showed shorter survival length than those with < 2.0 kg/m^2/year (log-rank test, $p < 0.0001$), and multivariate analysis using the Cox model revealed post-diagnostic ΔBMI as an independent prognostic factor. No correlation was identified between pre- and post-diagnostic ΔBMIs. Female patients with post-diagnostic ΔBMI < pre-diagnostic ΔBMI showed longer survival than those with the opposite ΔBMI trend (log-rank test, $p = 0.0147$). Female patients with post-diagnostic weight increase showed longer survival than those with weight decrease (log-rank test, $p = 0.0228$).

Conclusion Body weight changes after diagnosis strongly predicts survival in ALS, and weight gain after diagnosis may improve survival prognosis, particularly in female ALS patients.

Keywords Amyotrophic lateral sclerosis · Body weight · Survival · Sex difference · Nutritional intervention

Abbreviations

ALS	Amyotrophic lateral sclerosis
ALSFRS-R	Revised Amyotrophic Lateral Sclerosis Functional Rating Scale
BMI	Body mass index
ΔBMI	Body mass index decline rate
FVC	Forced vital capacity
IQR	Interquartile range
PEG	Percutaneous endoscopic gastrostomy
PMA	Progressive muscular atrophy
POMC	Pro-opiomelanocortin
TDP-43	TAR DNA-binding protein-43

Introduction

Patients with amyotrophic lateral sclerosis (ALS) frequently exhibit body weight reduction during the initial stage of the disease [1]. Weight reduction is multifactorial and originates from muscle wasting, dysphagia, anorexia [2], sympathetic hyperactivity [3], respiratory insufficiency, and hypermetabolism that might be specific to ALS [4–7]. Weight variation or body mass index (BMI) at the time of diagnosis has been established as an independent prognostic factor

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for survival [8–11]. In this context, nutritional education has been emphasized as an important intervention during early-stage ALS, and maintaining the body weight of a patient as much as possible using a high-calorie diet and early placement of gastrostomy is recommended [12–14].

In a model mouse for superoxide dismutase 1-related ALS, high-fat or ketogenic diets were effective for preventing reduction in body weight and prolongation of survival [15]. In patients with ALS, however, evidence for the effects of a high-calorie diet have been limited [14, 16]. A randomized phase 2 trial of hypercaloric enteral nutrition showed a significant effect of a high-carbohydrate hypercaloric diet on survival despite a small sample of patients, suggesting a bright future for nutritional intervention studies for ALS patients [14, 16].

The simplest outcome of nutritional intervention is body weight gain, particularly for patients who show progressive weight reduction. Actually, previous studies have focused on whether body weight could be stabilized or increased by diet therapy [17–19]. However, some clinical questions remain unsolved: (1) can ALS patients with progressive weight reduction in the early stage achieve weight increase after nutritional education in clinical practice, or can the natural course of weight variation in ALS patients be changed? (2) Can suppression of weight reduction or increasing body weight prolong survival? (3) Do sex differences exist in the effects of body weight changes on survival? To answer such questions, we evaluated pre-diagnostic and post-diagnostic body weight changes in the same cohort, and investigated the relationships of these changes with survival and sex.

Methods

Patients

A total of 145 patients (76 men and 69 women) with sporadic ALS or progressive muscular atrophy (PMA) were enrolled [20]. All of them has been referred to the neurophysiology laboratory of Tokyo Metropolitan Neurological Hospital between January 2010 and December 2015 for examination of needle EMG and somatosensory-evoked potential for the diagnosis of ALS. Patients' characteristics have been reported elsewhere [20]. We included patients with definite ($n=21$), probable ($n=76$), or possible ($n=22$) ALS according to the Awaji criteria based on the revised El Escorial criteria [21, 22]. We also included patients with PMA ($n=26$) because PMA shares a common pathophysiology with ALS [23]. All patients showed relentlessly progressive muscle wasting and bulbar palsy or respiratory paralysis. No patients were diagnosed as having any other neurological diseases or malignancy-related, diabetic, or vasculitic complications during follow-up.

Patients were clinically staged on the basis of the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) at the time of diagnosis [24], and were classified according to the site of disease onset as showing bulbar or spinal onset. Sex, age at onset, forced vital capacity (FVC, percentage of the predicted value), body mass index (BMI, kg/m^2) and premorbid BMI were recorded. Disease onset was defined as the time of appearance of the first motor disability or weakness other than fasciculation, cramp and nonspecific pain. Premorbid BMI was defined as the BMI at a stable period of body weight before onset, as reported by the patients or their family. All patients received nutritional education from clinicians or dieticians to eat as much as possible and to maintain or even increase their body weight. In particular, patients were instructed not to worry about obesity or metabolic syndrome. The details of nutritional education, however, were not standardized, since physical, nutritional, social and economic situations varied across individual patients, but a common instruction in the nutritional education for all patients was to maintain or increase body weight as possible.

All patients were followed-up until an endpoint or censoring time of the study. Endpoints were defined as the time of death or tracheotomy. The censoring time for the follow-up was the end of March 2017. Overall survival was calculated as the disease duration between onset and endpoint, and we also calculated the duration from the time of diagnosis to the endpoint as post-diagnostic survival.

The study was approved by the ethics committee at Tokyo Metropolitan Neurological Hospital (TS-H29-048). All patients provided informed consent to participate in the study.

BMI

The pre-diagnostic BMI decline rate (ΔBMI) was calculated using the following formula: pre-diagnostic ΔBMI (kg/m^2/year) = (premorbid BMI–BMI at diagnosis)/interval from disease onset to the time of diagnosis (years) [11, 20]. During follow-up after diagnosis, BMI was repeatedly but irregularly measured by clinical indications. We generally adopted values of BMI (post-diagnostic BMI) at the time of about 0.5–2 years after diagnosis for individual patients. BMI was unable to be followed-up in patients who showed very rapid progression or transferred to other hospitals before the second BMI measurement for individual reasons. In one patient, post-diagnostic BMI was evaluated at 4 years after the diagnosis, since he showed very slow progression. Post-diagnostic ΔBMI was calculated using the following formula: post-diagnostic ΔBMI (kg/m^2/year) = (BMI at diagnosis–post-diagnostic BMI)/interval from diagnosis to second BMI measurement (years). In total, data for both

pre-diagnostic and post-diagnostic ΔBMI were available for 79 patients.

Percutaneous endoscopic gastrostomy (PEG) was performed in 59 out of these 79 patients during follow-up. PEG was usually performed because of progressive weight loss or dysphagia although the timing of PEG was not standardized. The amount of energy intake through gastrostomy was variable across the patients, and we could not control the energy intake.

Statistical analysis

For the comparison of data between groups, we used Welch's *t* test and the paired *t* test. For correlation analysis, we used Pearson's correlation coefficient. Survivals were analysed using the log-rank test, whereas the Kaplan–Meier method was used to estimate the absolute risk of an event for each group. In the log-rank test for overall survival from onset or post-diagnostic survival, we determined the cutoff levels of ΔBMI as 2.0 kg/m^2/year, around of the median patient value; median values for pre- and post-diagnostic ΔBMI for the 79 patients were 2.3 kg/m^2/year and 2.4 kg/m^2/year, respectively. For post-diagnostic survival analyses, we classified the patients into two subgroups according to pre-diagnostic ΔBMI ≥ or < post-diagnostic ΔBMI. We also analysed the difference in post-diagnostic survival between patients with body weight decrease or increase after diagnosis (i.e., post-diagnostic ΔBMI < 0 and ≥ 0 kg/m^2/year; log-rank test). Last, for post-diagnostic survival analyses, we performed uni- and multivariate analyses using the Cox proportional hazard model. For multivariate analysis, we included parameters that were identified as significant from univariate analyses.

Statistical analyses were two sided, and values of $p < 0.05$ were considered significant. Data from patient profiles are expressed as mean (SD). Survival times were expressed as the median value and interquartile range (IQR). All statistical analyses were performed using JMP for Macintosh version 13.0.0 (SAS Institute, Cary, NC, USA).

Results

Summary of characteristics in the total patient cohort ($N = 145$) was reported elsewhere [20]. In the present study, we focused on the 79 patients with both premorbid and post-diagnostic BMI values available (Fig. 1), and all the results described below were for these 79 patients. Mean age at onset was 64.0 (SD 9.1) years, 63.8 (9.5) years in male patients, and 64.2 (8.7) years in female patients. Age at diagnosis was 65.8 (9.0) years. Fourteen patients (17.7%) showed bulbar onset. Interval from onset to diagnosis (diagnostic delay) was 1.7 (1.5) years. The relatively long

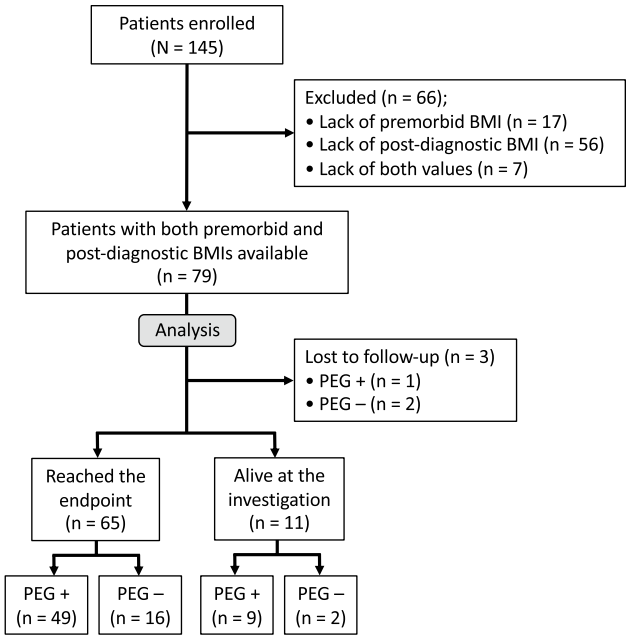

Fig. 1 Flowchart of patient enrollment and study sample. *BMI* body mass index, *PEG* percutaneous endoscopic gastrostomy

diagnostic delay was due to the fact that our hospital is a tertiary centre and many ALS patients are transferred from other hospitals and clinics for confirmation of diagnosis, further assessment of disease and therapeutic intervention. ALSFRS-R at diagnosis was 40.0 (6.9). FVC at diagnosis was 84.0 (25.4) % of the predicted. An endpoint was reached in 65 patients. Median overall survival time from onset was 2.9 (IQR 1.7–4.8) years, and post-diagnostic survival was 1.4 (0.8–2.2) years. All of these data were not significantly different from the data of the excluded 66 patients from the total patient cohort. Three patients were lost to follow-up, and 11 patients were alive at the time of investigation (Fig. 1).

Premorbid BMI and BMI at diagnosis were 23.0 (3.1) kg/m^2 and 20.7 (3.5) kg/m^2, respectively, showing a significant difference between both values ($p < 0.0001$, paired *t* test). Interval from diagnosis to second BMI measurement was 1.0 (0.6) year, and the post-diagnostic BMI was 19.0 (3.6) kg/m^2. We also found a significant difference between BMI at diagnosis and the post-diagnostic BMI ($p < 0.0001$, paired *t* test), indicating progressive weight loss through disease course. No correlation was identified between the pre-diagnostic difference of BMI value (premorbid BMI—BMI at diagnosis) and post-diagnostic difference of BMI value (BMI at diagnosis—post-diagnostic BMI) ($p = 0.2711$, Pearson's correlation coefficient; Fig. 2a).

Pre-diagnostic and post-diagnostic ΔBMIs were 2.3 (3.3) kg/m^2/year and 2.4 (3.0) kg/m^2/year, respectively, showing no significant difference between them ($p = 0.7938$, paired

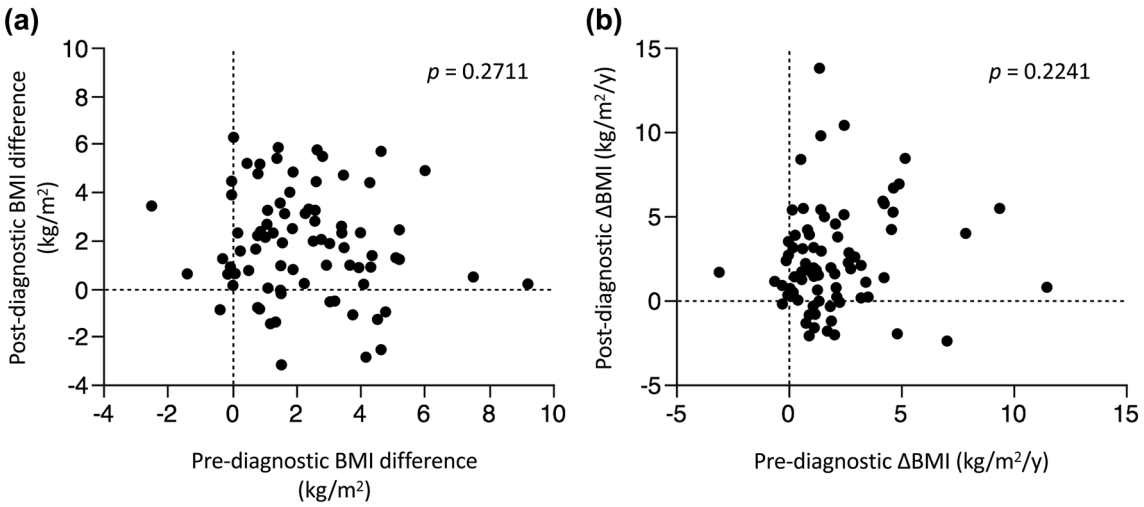

Fig. 2 Relationship between pre-diagnostic difference in BMI (premorbid BMI—BMI at diagnosis) and post-diagnostic difference in BMI (BMI at diagnosis—BMI at the time of follow-up) (**a**), and relationship between pre-diagnostic ΔBMI and post-diagnostic ΔBMI (**b**). Both figures indicate no significant correlations ($p=0.2711$ for Fig. 2a, $p=0.2241$ for Fig. 2b, Pearson's correlation coefficient)

t test). We unexpectedly found no significant correlation between pre- and post-diagnostic ΔBMIs ($p=0.2241$; Fig. 2b). Pre-diagnostic ΔBMI showed a positive correlation with age at onset ($p=0.0280$, Pearson's correlation coefficient) and negative correlations with diagnostic delay (duration from onset to diagnosis; $p=0.0257$). Post-diagnostic ΔBMI showed a positive correlation with age at onset ($p<0.0001$), but showed no correlations with diagnostic delay ($p=0.1957$).

When we defined the cutoff level as 2.0 kg/m^2/year for ΔBMI, Kaplan–Meier analysis showed that patients with pre-diagnostic ΔBMI ≥ 2.0 kg/m^2/year had shorter overall survival than those with pre-diagnostic ΔBMI < 2.0 kg/m^2/year (log-rank test, $p=0.0020$; Fig. 3a). When looking at sex difference, pre-diagnostic ΔBMIs were 2.6 (4.1) kg/m^2/year in male patients and 1.9 (2.0) kg/m^2/year in female patients, showing no significant difference ($p=0.3315$, Welch's *t* test). Male patients showed a significant difference in overall survival between pre-diagnostic ΔBMI ≥ 2.0 and < 2.0 kg/m^2/year ($p=0.0036$; Fig. 3b), whereas female patients showed no significant difference ($p=0.2027$; Fig. 3c).

Focusing on post-diagnostic ΔBMI, Kaplan–Meier analysis showed that patients with post-diagnostic ΔBMI ≥ 2.0 kg/m^2/year had shorter post-diagnostic survival than those with post-diagnostic ΔBMI < 2.0 kg/m^2/year (log-rank test, $p<0.0001$; Fig. 4a). Regarding sex

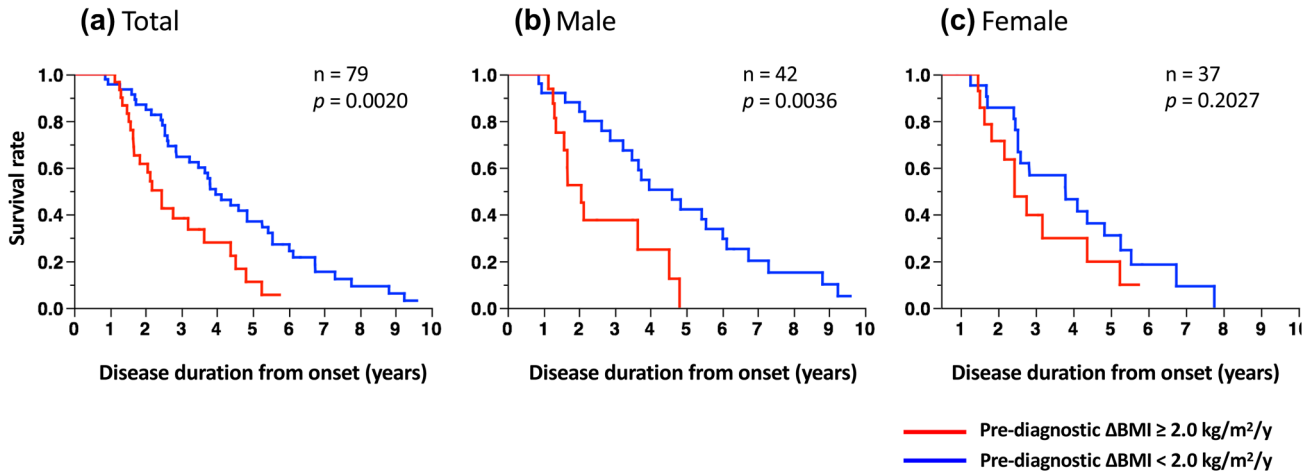

Fig. 3 Comparison of survival rate between ALS patients with pre-diagnostic ΔBMI ≥ 2.0 and < 2.0 kg/m^2/year for the total cohort patient group (**a**), male patient group (**b**), and female patient group (**c**). Kaplan–Meier analyses showed significant differences in the total cohort patient group (log-rank test, $p=0.0020$) and male patient group ($p=0.0036$), but not in the female patient group ($p=0.2027$)

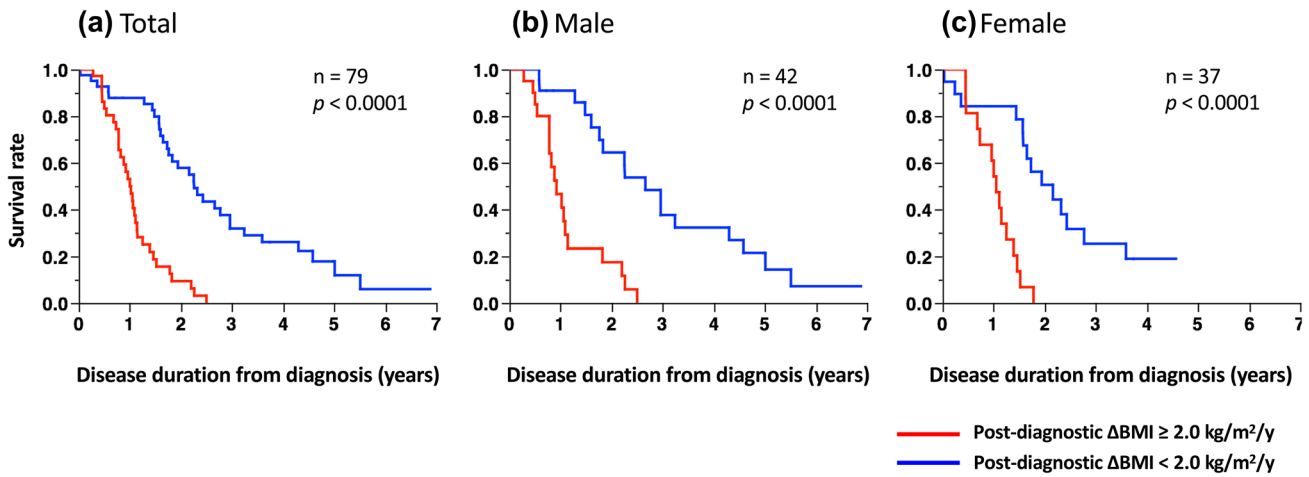

Fig. 4 Comparison of survival rate between ALS patients with post-diagnostic ΔBMI ≥ 2.0 and ≤ 2.0 kg/m^2/year for the total cohort patient group (**a**), male patient group (**b**), and female patient group (**c**). Kaplan–Meier analyses showed significant differences in the total cohort patient group (log-rank test, $p < 0.0001$), male patient group ($p < 0.0001$), and female patient group ($p < 0.0001$)

differences, we found a significant difference in post-diagnostic ΔBMIs between male and female patients [3.1 (3.2) and 1.7 (2.7) kg/m2/year, respectively; $p = 0.0395$, Welch's *t* test]. Post-diagnostic survivals differed between patients with ΔBMI ≥ 2.0 and < 2.0 kg/m^2/year for both male and female patients (log-rank test, $p < 0.0001$ for both sexes; Fig. 4b, c). Univariate analysis by the Cox model for post-diagnostic survival showed that onset age and post-diagnostic ΔBMI were significantly associated with post-diagnostic survival, and multivariate analysis identified that post-diagnostic ΔBMI was a significantly strong predictor of post-diagnostic survival (Table 1).

When patients were classified into two subgroups with post-diagnostic ΔBMI ≥ and < pre-diagnostic ΔBMI, patients with post-diagnostic ΔBMI < pre-diagnostic ΔBMI showed longer post-diagnostic survival (log-rank test, $p = 0.0414$; Fig. 5a). This difference was prominent in female patients (log-rank test, $p = 0.0147$; Fig. 5c), whereas the male patients showed no difference (log-rank test, $p = 0.2512$; Fig. 5b). Furthermore, we created another classification of patients in which BMI was decreased or increased after diagnosis (i.e., post-diagnostic ΔBMI ≥ 0 and < 0 kg/m^2/year). Fifteen patients (12 females) showed increased BMI after diagnosis (Fig. 2a, b). Kaplan–Meier

Table 1 Uni- and multivariate analyses of prognostic factors for survival after diagnosis

Category	Univariate analysis		Multivariate analysis	
	Crude HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
Sex				
Male vs. female	0.82 (0.50–1.37)	0.4491		
Age at onset				
≥ 65 vs. < 65 years	2.23 (1.35–3.74)	0.0018	1.65 (0.95–2.86)	0.0743
Onset region				
Bulbar vs. spinal	0.92 (0.42–1.79)	0.8264		
FVC				
< 70 vs. ≥ 70%	1.55 (0.89–2.61)	0.1172		
ALSFRS-R				
< 40 vs. ≥ 40	1.84 (0.95–3.51)	0.0693		
PEG				
Yes vs. no	0.76 (0.44–1.40)	0.3708		
Post-diagnostic ΔBMI				
≥ 2 vs. < 2 kg/m^2/year	5.19 (2.91–9.45)	< 0.0001	4.63 (2.52–8.61)	< 0.0001

ALSFRS-R revised Amyotrophic Lateral Sclerosis Functional Rating Scale, *FVC* forced vital capacity, *ΔBMI* body mass index decline ratio, *PEG* percutaneous endoscopic gastrostomy

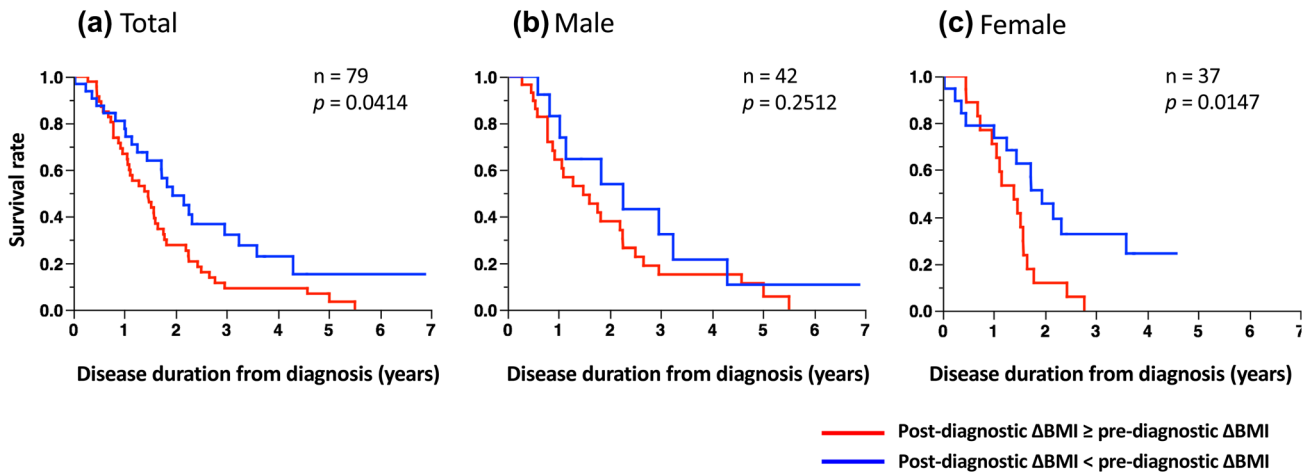

Fig. 5 Comparison of survival rate between ALS patients with post-diagnostic ΔBMI ≥ and < pre-diagnostic ΔBMI for the total cohort patient group (**a**), male patient group (**b**), and female patient group (**c**). Kaplan–Meier analyses showed significant differences in the total cohort patient group (log-rank test, $p = 0.0414$) and female patient group ($p = 0.0147$), but not in the male patient group ($p = 0.2512$)

analysis showed that patients with increased BMI after diagnosis survived longer than those with decreased BMI after diagnosis (log-rank test, $p = 0.0274$; Fig. 6a) This difference was distinct for female patients (log-rank test, $p = 0.0228$; Fig. 6c), whereas the number of male patients were insufficient for analysis (Fig. 6b).

In patients who underwent PEG, the time interval between the second BMI evaluation and PEG was 0.9 (12.5) months. Comparison between patients with and without PEG showed no differences in overall survival from onset ($p = 0.1559$, log-rank test) and in post-diagnostic survival ($p = 0.4154$, log-rank test). We found no difference in post-diagnostic ΔBMI between patients with and without PEG [1.6 (1.1) vs. 1.6 (1.2) kg/m^2/year, respectively, $p = 0.9560$, log-rank test]. Univariate analysis also showed no association between PEG and post-diagnostic survival (Table 1).

Discussion

Our study showed that post-diagnostic BMI decline was a strong predictor for survival along with pre-diagnostic BMI decline, and that patients with slower post-diagnostic BMI decline or with weight increase after diagnosis showed better survival prognosis. The latter finding was prominent among female patients. Although we did not investigate precise

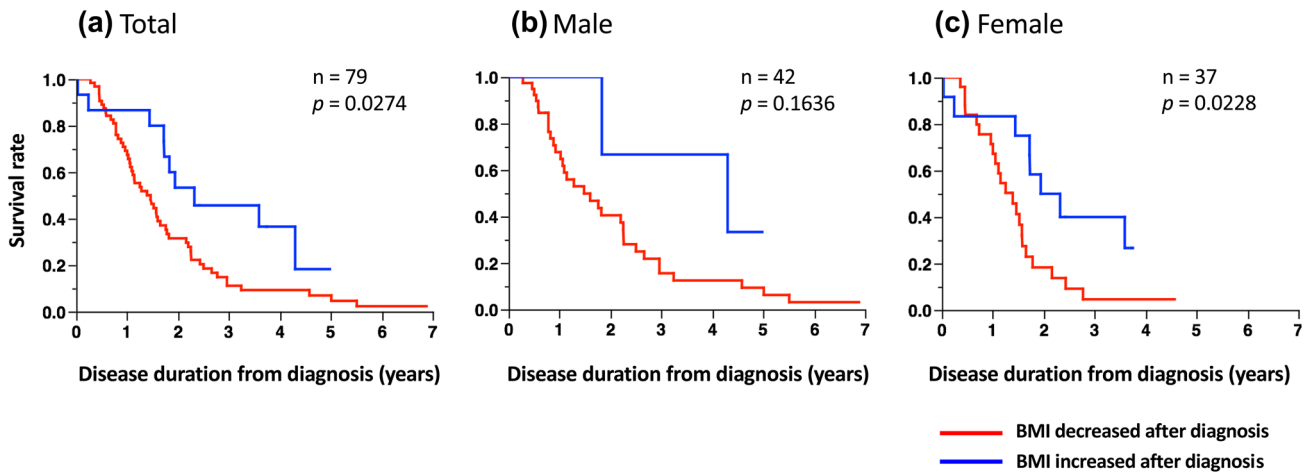

Fig. 6 Comparison of survival rate between ALS patients with increase and decrease in post-diagnostic BMI for the total cohort patient group (**a**), male patient group (**b**), and female patient group (**c**). Kaplan–Meier analyses showed significant differences in the total cohort patient group (log-rank test, $p = 0.0274$) and female patient group ($p = 0.0228$). The male patient group did not show any significant difference because of the small sample size ($p = 0.1636$)

factors explaining the sex difference, such as amount of food intake, appetite and sex hormones, our results might suggest a difference of the ALS-specific metabolic pathophysiology between male and female patients.

Our finding on the effect of pre-diagnostic ΔBMI on survival is consistent with previous evidence [11]. Unexpectedly, however, we could not find a significant correlation between pre- and post-diagnostic ΔBMIs. Considering that ALS is a progressive neurodegenerative disease, the results suggest that BMI variation does not always correlate with disease stage or severity. Our findings are partly in accordance with a recent paper that reported that survival after PEG was influenced by the weight reduction from the time of diagnosis to the time of PEG and the degree of weight increase after PEG [17]. In our study, since the time of second BMI evaluation was around the time of PEG in patients who underwent PEG, the parenteral energy intake through gastrostomy would have had no effect on the results. The slowing of weight decline or increase in weight shown in this study might be possibly the result of increased oral energy intake by patients themselves. Weight variations in ALS can be changed, and our findings suggest that nutritional intervention to stabilize or increase weight has potential therapeutic effects that may improve survival.

Female patients did not show significant effects of pre-diagnostic ΔBMI on survival (Fig. 3c), but the effect of slowing post-diagnostic ΔBMI on survival was prominent in female patients (Fig. 5c). Twelve of the 15 patients with weight increase were female (Fig. 6c). Male-to-female ratio in ALS patients has been reported to be within a range of 1.1–2 [25], and this ratio is high in younger patients before menopause and drops to 1.4 in older patients after menopause [26], suggesting a protective role of oestrogen against ALS. According to an investigation of reproductive history in female patients, the lifetime endogenous oestrogen exposure is significantly associated with survival [27]. However, when considering the relationship between body weight and oestrogen, the story is rather complicated. Oestrogen usually reduces body weight, and menopause is a risk factor for obesity [28]. Many of our female patients were considered to have experienced onset of ALS after menopause, and the weight stabilization or increase after diagnosis seems unlikely to have been directly influenced by endogenous oestrogen. This hormone acts in the hypothalamus including pro-opiomelanocortin (POMC) neurons in relation to energy metabolism [28]. POMC neurons inhibit food intake and modulate energy expenditure, leading to weight loss. In the absence of oestrogen, POMC neurons are not activated, and body weight should thus increase. This hypothalamic melanocortin pathway is disrupted in ALS [29, 30], but, in female ALS patients with menopause, the melanocortin pathway might be relatively preserved compared with male ALS patients. Further study is needed to elucidate the relationship between female sexuality, menopause and weight variation in ALS.

Causative factors that could directly influence weight variation other than sex yet remain unclear. A previous study of a large cohort of ALS patients reported four subtypes of ALS according to the progression mode [31], and a low expression of titin, a large sarcomere protein, was associated with rapid functional decline. Modifier genes or proteins might be playing a role in regulating disease progression, including weight variation. The aetiology of ALS-specific hypermetabolism also remains unknown. Metabolic analyses using indirect calorimetry have revealed that about 40–50% of patients with ALS show hypermetabolism with poorer survival than patients with normometabolism [7, 32]. Recent evidence has suggested involvement of the hypothalamus in weight loss in ALS [29, 30, 33]. A neuropathological study of a mouse model of ALS has shown that inclusions of TAR DNA-binding protein-43 (TDP-43) accumulate in the hypothalamus [34]. In a clinical study, TDP-43 pathology in the lateral hypothalamus was associated with weight reduction in ALS patients [35], suggesting a relationship between hypothalamic lesions and hypermetabolism. Nutritional intervention targeting weight gain may have therapeutic effects in normometabolic patients without the hypothalamic lesions. In addition, cognitive function and eating behaviours in ALS are associated with calorie intake and BMI, and affect survival [36]. Given this context, the specific types of patients who could achieve therapeutic efficacy from nutritional intervention need to be elucidated [37].

The key limitations of this study were first that the number of patients examined was small and the study was performed at a single centre, which might have lead to some bias in patient enrollment. In particular, relatively few patients showed weight increase, and no clear conclusions could be reached regarding the effects of weight increase on survival. Second, the time of post-diagnostic BMI measurement varied between patients, and those patients with the most rapid progression were excluded from the study. Third, the amount of oral energy intake was not controlled, although this would be very difficult in clinical practice. Nutritional education should be standardized, including not only the amount of energy, but also the ratios of fat and carbohydrate in meals [14]. Recently reported ALS-specific formulae to calculate the necessary energy demand would be useful for future nutritional studies of ALS [5, 6, 38].

Despite all the above limitations, the results clearly indicate differences between the significance of pre- and post-diagnostic weight variations and suggest sex differences in the metabolic pathology of ALS. Further study is required to elucidate the efficacy of nutritional therapy, particularly in view of a sex difference in ALS.

Acknowledgements This study was supported by JSPS KAKENHI [Grant-in-Aid for Scientific Research (B) Nos. 25293449, 16H05583 and 16H03044] from the Ministry of Education, Culture, Sports, Science and Technology of Japan and by the Joint Program for ALS Research (2015–2018) from the Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan.

Compliance with ethical standards

Conflicts of interest Dr. Shimizu reports speaker honoraria from Tanabe Mitsubishi Pharma. The other authors declare that they have no conflict of interest.

Ethical approval The study was approved by the ethics committee at Tokyo Metropolitan Neurological Hospital (TS-H29-048). All patients provided informed consent to participate in the study, in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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