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Benoît Marin, Jean-Claude Desport, Patrick Kajeu, Pierre Jésus, Blerta Nicolaud, Marie Nicol, Pierre-Marie Preux, Philippe Couratier

### ► **To cite this version:**

Benoît Marin, Jean-Claude Desport, Patrick Kajeu, Pierre Jésus, Blerta Nicolaud, et al.. Alteration of nutritional status at diagnosis is a prognostic factor for survival of ALS patients.. Journal of Neurology, Neurosurgery and Psychiatry, 2010, 82 (6), pp.628. 10.1136/jnnp.2010.211474 . hal-00594142

**HAL Id: hal-00594142**

**<https://hal.science/hal-00594142>**

Submitted on 19 May 2011

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## **TITLE PAGE**

### **Alteration of nutritional status at diagnosis is a prognostic factor for survival of ALS patients.**

Marin B <sup>1,2</sup> (MD, MSc), Desport JC <sup>1,3</sup> (MD, PhD), Kajeu P <sup>1</sup> (MSc), Jesus P <sup>3</sup>, Nicolaud B <sup>4</sup> (MD), Nicol M <sup>4</sup>, Preux PM <sup>1,2</sup> (MD, PhD), Couratier P <sup>1,4</sup> (MD, PhD).

1 Université de Limoges ; IFR 145 GEIST ; Institut d'Epidémiologie Neurologique et de Neurologie Tropicale ; EA 3174 NeuroEpidémiologie Tropicale et Comparée, Limoges, F-87025, France.

2 CHU Limoges, Unité Fonctionnelle de Recherche Clinique et Biostatistique, F-87042 Limoges, France.

3 CHU Limoges ; Service d'Hépatogastro-Entérologie, Unité Fonctionnelle de Nutrition, Limoges, F-87042, France.

4 CHU Limoges, Service de Neurologie, Centre Expert SLA, F-87042 Limoges, France.

Abstract: 248 words; Main text: 3466 words

Number of Tables: 3; Number of supplementary Tables: 2; Number of Figures: 2

Correspondence to:

Prof. Philippe Couratier

Institut de NeuroEpidémiologie et Neurologie Tropicale (EA 3174)

Faculté de Médecine, 2 rue du Docteur Marcland

87025 Limoges, France

Tel : +335 55 43 58 20, Fax : +335 55 43 58 21

E-mail : philippe.couratier@unilim.fr

Keywords : Amyotrophic Lateral Sclerosis, Epidemiology, Cohort Studies, Prognosis, weight loss.

## ABSTRACT

**Objectives:** The aims were to analyze changes in nutritional parameters from diagnosis of ALS to death and to assess their relationships with survival at the time of diagnosis and during follow-up.

**Methods:** Ninety-two ALS patients were included and clinically assessed every three months (ALS FRS, MMT, forced vital capacity, weight, BMI, percent weight loss). Bioimpedance was performed to evaluate body composition (fat-free mass, fat mass and hydration status) and phase angle. Survival analyses were performed from diagnosis to death or censoring date using a Cox model.

**Results:** The evolution of nutritional parameters in ALS patients was marked by significant decreases in weight, BMI, fat-free mass and phase angle, and increased fat mass. We identified an adjusted 30% increased risk of death for a 5% decrease from usual weight at time of diagnosis (Relative Risk (RR): 1.30 95% CI 1.08-1.56). During follow-up, we identified adjusted 34% (95% CI 18-51) and 24% (95% CI 13-36) increased risks of death associated with each 5% decrease in usual weight and each unit decrease in usual BMI, respectively ( $p < 0.0001$ ). Malnutrition during the course was related to shorter survival ( $p = 0.01$ ), and fat mass level was associated with a better outcome (RR 0.90 for each 2.5-kg fat mass increment).

**Conclusions:** Nutritional parameters of ALS patients worsened during evolution of the disease and worse nutritional status (at time of diagnosis or during the course) was associated with higher mortality. This study offers some justification for studying the use of therapeutic nutritional intervention to modify the survival of ALS patients.

## INTRODUCTION

Alteration of nutritional status among patients suffering from amyotrophic lateral sclerosis (ALS) is multifactorial involving: dysphagia, chewing difficulties, difficulty moving the extremities, reduced caloric intake (1) and hypermetabolism (2, 3).

Malnutrition is an independent prognostic factor for survival during the course of ALS, with an eight-fold increased risk of death (4). **Body mass index** (BMI) has been identified as a prognostic factor for survival at time of gastrostomy placement (5) and indications for **non-invasive** ventilation (6), and a recent study identified longer survival in ALS patients with a high blood LDL/HDL cholesterol level (7).

**To date, studies on relationships between nutritional status and survival of ALS patients have considered nutritional status only during the course of the disease. There is a need to obtain further information on the relationships between survival and nutritional status at the time of diagnosis. It would also be of great interest to evaluate this relationship during follow-up, and to describe the evolution of nutritional parameters during the course of the disease.** The aims of this study were to collect the following data at the time of diagnosis and during subsequent follow-up, to analyze changes that occur and to assess their relationships with survival: anthropometric nutritional parameters (percentage of weight lost, BMI, triceps skinfold thickness representing **fat mass**, mid-arm muscular circumference representing **fat-free mass**) and paraclinical parameters (**fat mass, fat-free mass**, phase angle, extracellular/intracellular fluid volumes measured by total body impedance analysis (BIA)).

## **METHODS**

### **Eligibility criteria**

This study was performed within the Limoges ALS expert centre. A total of 92 ALS patients diagnosed between 1997 and 2007 according to Airlie House criteria were enrolled. They included patients with a definite, probable or probable laboratory-supported form either at time of diagnosis or during follow-up. Subjects had to be followed at least twice during the course by the nutritional unit of the centre, with the first nutritional evaluation performed at the time of diagnosis.

### **Data collection**

Socio-demographic and neurological data were extracted from the computerized database of the ALS centre, which contains prospectively gathered clinical data on all ALS patients. The database was approved by the CNIL (Commission nationale de l'informatique et des Libertés) and patients gave their informed consent for data collection. End of data collection was March 1<sup>st</sup> 2009. Clinical assessments were performed every 3 months.

### **Neurological and respiratory assessments**

These consisted of manual muscular testing (MMT) of all extremities and neck, as defined by the Medical Research Council (maximal value 150) and the ALS Functional Rating Scale (ALS FRS), (maximal value 40). The neurologist specified the date of onset of the first disease symptom, and the site of onset (bulbar or spinal). Diagnosis delay was calculated as the time between the dates of first symptoms and of diagnosis. Forced respiratory vital capacity was measured using a Hans Rudolph pneumotachograph, integrated in a body plethysmography system 1085 (CPF Medical Graphics, St Paul, MN, USA). Results were expressed in relation to a theoretical calculated index value.

### **Nutritional assessment**

Patients were weighed in their underwear in a seated position on an electronic SECA chair scale (Vogel & Halke, Hamburg, Germany) recording to 0.1 kg. Height was obtained standing upright for all the patients at the first evaluation, using a SECA gauge recording to 0.2 cm (Vogel & Halke, Hamburg, Germany). BMI was calculated according to the formula  $BMI = \text{weight}/\text{height}^2$ . Patients were classified for nutritional status using BMI as follows: (i) malnutrition:  $BMI < 18.5$  if age  $< 70$  years and  $BMI < 21$  if age  $\geq 70$  years; (ii) normal status:  $18.5 \leq BMI < 25$  if age  $< 70$  years and  $21 \leq BMI < 27$  if age  $\geq 70$  years; (iii) overweight:  $25 \leq BMI < 30$  if age  $< 70$  years and  $27 \leq BMI < 30$  if age  $\geq 70$  years; (iv) obesity:  $BMI \geq 30$  (8, 9). Percentage of weight lost was calculated as compared to usual weight as recorded 6 months before the first symptoms. Units of BMI lost were accordingly calculated using usual weight.

**Triceps skinfold thickness** (mm) was measured using a Harpenden caliper. Three measurements were performed on each side of the body, and the retained value was the mean of all. **Mid-arm muscular circumference (MAMC)**, (cm), was calculated using **triceps skinfold thickness (TSF)** and the mean mid-arm circumference (MAC, cm) measured on each side of the body, using the equation:  $MAMC = MAC - 0.314 \times TSF$  (10). BIA was performed using an Analycor3 instrument with surface electrodes (Spengler, Paris, France) according to standard methods, at 50 kHz, 5 kHz and 100 kHz (11), (median number of evaluations: 3, interquartile range (IQR): 2-4). Monofrequency BIA measured phase angle (in degrees) which is directly related to cell membranes (amount and functional status of cells) and whose normal value is considered to be  $6^\circ$  and over in healthy subjects (12), **fat mass** (kg) and **fat-free mass** (kg), and bifrequency estimated extracellular and intracellular fluid volumes (in liters) and their ratio which gives a picture of the cell membrane status (12). Phase angle **(PA)** was obtained using the formula:  $PA = \arctan(Xc/R)$  (in degrees), where Xc is the body reactance (resistive effect due to capacities induced by tissue interfaces and cell membrane in ohms) and R is the bioelectrical resistance (linked to bodily extracellular hydration, in ohms).

### **Power assessment**

When the total number of events is 74, a 0.050 level two-sided log-rank test for equality of survival curves will have 80% power to detect the difference between a group 1 survival probability at time  $t$  (24 months, for example) of 0.40, and a group 2 survival probability at time  $t$  of 0.62 (constant hazard ratio of 1.92).

### **Statistical analysis**

Quantitative variables were described using median and IQR. Qualitative variables were described using frequency and percentage. Normality for distribution of quantitative variables was assessed using the Shapiro-Wilk test. Paired quantitative variables were compared using the Wilcoxon rank signed test. Quantitative variables were compared between groups using the Kruskal-Wallis test and pairwise comparisons used the Wilcoxon test. Paired proportions were compared using the Mac Nemar Chi-square test. Evolution of nutritional markers was plotted against time, using time until death as baseline. Means ( $\pm$  1 standard deviation) are depicted on the graphs. We calculated means ( $\pm$  standard deviation) of nutritional markers for all patients at two common time points: time of death and time of diagnosis. At intermediate time points (at least 6 months, 12 months, and 18 months before death) the numbers of patients may be lower than the total due to death over time. Survival was analysed from date of diagnosis until the death of the patient or the censoring date - the date of last neurological consultation. The Kaplan–Meier method was used to estimate survival function and the log rank test was used to compare survival distribution among groups. Univariate and multivariate analyses were performed using the Cox proportional hazard model. To identify the prognostic value of nutritional variables measured at diagnosis, we adjusted our analyses according to clinical markers measured at diagnosis: ALS FRS (five-unit increment), MMT

(five-unit increment), Airlie House Criteria (definite, probable, probable laboratory-supported ALS vs possible ALS), FVC ( $\geq 80\%$  of theoretical value vs  $< 80\%$ ) and diagnostic delay (1-month increment). To identify the prognostic value of nutritional variables measured over the entire follow-up we used time-varying covariates for nutritional variables and for other neurological or respiratory adjustment variables: ALS FRS (five-unit increment), MMT (five-unit increment), Airlie House criteria (definite ALS vs other categories) and FVC (10% increment) and diagnostic delay (1-month increment). Those adjustment variables were forced in the first multivariable model, which was simplified using a backward stepwise procedure. Survival analyses for nutritional variables were performed separately. Relevant interactions between variables in each final multivariate model were tested. Respect for hypotheses of loglinearities effects of quantitative variables were checked graphically and hypotheses for proportional hazard were tested using an interaction term between time and variables. P value  $< 0.05$  was considered statistically significant. We complied with STROBE guidelines (13). Analyses were performed using SAS<sup>®</sup>, Version 9.1.2 (SAS Institute, Cary, NC).



## RESULTS

### Baseline demographic and clinical characteristics

Median age at diagnosis was 65.6 years (IQR 56.5-73.3) and the sex ratio was 1. Bulbar form at onset represented 48% of cases. Supplementary baseline clinical characteristics are depicted in Table e-1 (supplementary file). The median weight variation at diagnosis according to usual weight was -2.32% (IQR -7.76-0.68) and median BMI variation at diagnosis according to usual BMI was -0.55 unit (IQR -1.99-0.15) (Table e-2, supplementary file). The two latter values were significantly different from 0 ( $p=0.0001$ ). At the time of diagnosis, 8.70% of patients were malnourished according to BMI category.

**Supplementary file : Table e-1: Demographic, neurological and respiratory characteristics of ALS patients at time of diagnosis**

Characteristics	Median or frequencies	IQR or %	N
Age at diagnosis, years	65.64	(56.46-73.35)	92
Gender Male/female	46/46	(50.00/50.00)	92
Diagnosis delay, months	7.93	(6.05-12.22)	92
Form at onset Bulbar/Spinal	44/48	(47.83/52.17)	92
Airlie House criteria at diagnosis			92
Definite	8	8.70	
Probable	53	57.61	
Probable laboratory-supported	3	3.26	
Possible	28	30.43	
ALS FRS score at diagnosis /40	33	(30-36)	92
MMT score at diagnosis /150	135	(125-145)	92
FVC (percent of theoretical value)	92	(73-108)	92

Legend: IQR: Interquartile range; ALS FRS: Amyotrophic Lateral Sclerosis Functional Rating Score; MMT: manual muscular testing; FVC : forced vital capacity.

**Supplementary file : Table e-2: Nutritional variables at time of diagnosis**

Nutritional variables	Median or frequencies	IQR or %	N
Weight, kg	66.15	(56.95-75.00)	92
Body mass index	24.17	(21.63-26.91)	92
Rate of weight loss from usual weight (% / month)	-0.32	(-1.04-0.08)	92
Rate of BMI loss from usual BMI (unit / month)	-0.08	(-0.25-0.02)	92
BMI categories*			92
Malnourished	8	8.70	
Normal	50	54.30	
Overweight	23	25.00	
Obese	11	12.00	
Weight variation from usual weight (%)	-2.32*	(-7.76-0.68)	92
BMI variation from usual BMI (unit)	-0.55*	(-1.99-0.15)	92
Mid-arm muscle circumference, cm	23.89	(21.97-26.57)	92
Triceps skinfold thickness, mm	12.47	(9.61-16.78)	92
Phase angle, °	3.38	(2.61-4.34)	83†
Extracellular fluid/intracellular fluid volume	0.91	(0.83-1.01)	89†
Lean mass, kg	45.11	(36.20-52.74)	86†
Fat mass, kg	19.97	(14.83-24.28)	86†

Legend: IQR: Interquartile range. BMI categorization: (i) Malnutrition: BMI <18.5 if age <70 years and BMI<21 if age ≥70 years; (ii) Normal status 18.5≤BMI<25 if age <70 years and 21≤BMI<27 if

age  $\geq 70$  years; (iii) Overweight:  $25 \leq \text{BMI} < 30$  if age  $< 70$  years and  $27 \leq \text{BMI} < 30$  if age  $\geq 70$  years;

(iv) Obese  $\text{BMI} \geq 30$ .

\* At time of diagnosis variation statistically different from 0 ( $p < 0.0001$ ).

† Less than 92 due to impossible body impedance analysis or missing value

### **Medical care and outcome**

During follow-up, 39.10% of patients underwent non-invasive ventilation and 57.60% were gastrostomised. All patients were treated with riluzole. The proportion of gastrostomy was significantly higher in patients malnourished at the time of diagnosis (75.00%) as compared to patients with a normal BMI (59.50%), overweight patients (64.50%) and obese patients (18.20%), ( $p=0.036$ ). Median time between diagnosis and gastrostomy placement was 10.00 months (IQR 6.10-15.20). During follow-up, 74 patients died (80.40%), median survival time being 27.80 months, (95% confidence interval (95% CI), 19.50-30.40).

### **Evolution of nutritional markers between diagnosis and death**

All nutritional markers varied between diagnosis and death (Table 1). Accordingly, weight, BMI, percentage of weight, BMI variation (as regards usual weight) and lean mass showed a significant worsening from diagnosis to death (Figures 1.a, 1.b, 1.c). Before death, median percent weight loss reached 7.05% (IQR 14.36-1.16) and median BMI loss 1.70 (3.62-.25). Fat-free mass also significantly decreased using bioimpedance (Figure 1.d) or mid-arm muscular circumference. Conversely, fat mass and triceps skinfold thickness significantly increased. Phase angle dramatically decreased (median value from  $3.37^\circ$  to  $2.29^\circ$ ) and the ratio of extracellular fluid volume over intracellular fluid volume increased (median value from 0.93 to 1.00) (Figure 1.e). During follow up, the proportion of malnourished patients increased to 15.2%, though non-significantly (Mac Nemar Chi-square test  $p=0.058$ ); the proportions of patients with normal BMI and who were overweight appeared stable (56.5% and 22.8%, respectively) and the proportion with obesity was reduced (5.5%).

**Table 1: Nutritional variables at diagnosis and last evaluation for people who died during follow up**

Nutritional variables	At diagnosis		Before death		P value*	N
	Median	IQR	Median	IQR		
Weight, kg	65.60	(56.70-75.00)	63.10	(54.20-71.60)	0.02	74
BMI	24.13	(21.20-26.96)	23.48	(20.86-26.60)	0.02	74
Weight variation from usual weight (%)	-2.29†	(-8.40-0.50)	-7.05	(-14.36- -1.16)	0.02	74
BMI variation from usual BMI (unit)	-0.53†	(-2.24-0.10)	-1.70	(-3.62- -0.25)	0.03	74
Mid-arm muscle circumference, cm	23.89	(22.16-26.47)	22.02	(19.70-24.18)	<0.0001	74
Triceps skinfold thickness, mm	12.47	(9.30-16.30)	13.53	(9.92-19.33)	0.048	74
Phase angle, °	3.37	(2.57-4.34)	2.29	(1.69-2.97)	<0.0001	66‡
Extracellular fluid/intracellular fluid volume	0.93	(0.84-1.02)	1.00	(0.90-1.11)	<0.0001	72‡
Fat-free mass, kg	44.94	(36.20-52.74)	42.13	(33.99-48.65)	<0.0001	69‡
Fat mass, kg	20.11	(14.10-24.28)	21.24	(14.50-28.36)	0.04	69‡

Legend: IQR: Interquartile range.

\* Comparisons between time of diagnosis and before death

† At time of diagnosis variation statistically different from 0 ( $p < 0.0001$ )

‡ Less than 74 due to impossible body impedance analysis or missing values.

### **Prognostic value of nutritional markers at the time of diagnosis**

At the time of diagnosis, the percentage of weight lost from usual weight was significantly associated with survival. After adjustment for age, gender, bulbar form at onset, ALS FRS, MMT, FVC and diagnostic delay, we identified a 30% increase in the risk of death (95% CI 8-56%) for each 5% decrease in weight (Table 2). We identified a significant difference in survival between ALS patients with a weight loss of 5% and over at the time of diagnosis (median survival time : 20.6 months (95% CI 12.4-29.0)) as compared to patients whose weight was stable or dropped by less than 5% (median survival time: 29.0 months (95% CI 21.2-38.5)), Log rank test  $p=0.01$ , (Figure 2). Patients with a weight loss of 5% or over experienced an adjusted 1.92 Relative Risk (RR) of death (95% CI 1.15-3.18). Each BMI unit lost from the usual BMI was associated with an adjusted 20% increased risk of death (95% CI 6-36%). Rate of weight loss (% per month) and rate of BMI loss (unit per month) between first symptoms and diagnosis were also independently associated with survival. Malnutrition at baseline and other nutritional variables including phase angle and ratio of extracellular fluid volume over intracellular fluid volume were not associated with survival in multivariate analysis.



**Table 2: Relative risks of death associated with nutritional variables measured at diagnosis in univariate and multivariate analysis. Each nutritional variable has been analysed independently from other nutritional variables.**

Nutritional variables at diagnosis*	Univariate analysis			Multivariate analysis		
	cHR	95% CI	P value	aHR <sup>†</sup>	95% CI	P value
Weight variation from usual weight (for 5% decrease)	1.28	1.06-1.54	<b>0.009</b>	<b>1.31</b>	<b>1.08-1.60</b>	<b>0.006</b>
BMI variation from usual BMI (for one unit decrease)	1.20	1.06-1.36	<b>0.005</b>	<b>1.23</b>	<b>1.07-1.41</b>	<b>0.003</b>
Rate of weight loss from usual weight (% / month)	<b>1.09</b>	<b>1.04-1.14</b>	<b>0.0002</b>	<b>1.07</b>	<b>1.02-1.12</b>	<b>0.003</b>
Rate of BMI loss from usual BMI (unit / month)	<b>1.35</b>	<b>1.16-1.58</b>	<b>0.0001</b>	<b>1.28</b>	<b>1.09-1.50</b>	<b>0.003</b>
Malnutrition at diagnosis vs other BMI categories	1.67	0.79-3.50	0.18	<b>1.32</b>	<b>0.62-2.80</b>	<b>0.47</b>
Mid-arm muscle circumference, cm (for one unit increase)	0.96	0.90-1.03	0.23	<b>0.95</b>	<b>0.89-1.01</b>	<b>0.12</b>
Triceps skinfold thickness, cm (for one unit increase)	0.99	0.96-1.03	0.81	<b>1.00</b>	<b>0.96-1.03</b>	<b>0.78</b>
Phase angle, ° (for one unit decrease)	1.29	1.02-1.63	<b>0.03</b>	<b>1.15</b>	<b>0.87-1.52</b>	<b>0.33</b>
Extracellular fluid/intracellular fluid volume (for 0.2 unit increase)	1.40	0.98-2.00	0.06	<b>1.34</b>	<b>0.92-1.97</b>	<b>0.12</b>
Lean mass, kg (for 2.5 unit increase)	0.97	0.92-1.03	0.33	<b>1.00</b>	<b>0.94-1.07</b>	<b>0.90</b>
Fat mass, kg (for 2.5 unit increase)	0.99	0.92-1.06	0.81	<b>0.96</b>	<b>0.89-1.03</b>	<b>0.21</b>

Legend : cHR: crude Hazard Ratio; aHR: adjusted Hazard Ratio.

\* Survival analyses were performed separately for each nutritional variable.

† Adjustment on age, gender, bulbar form at onset, ALS FRS at diagnosis, manual muscular testing at diagnosis, forced vital capacity at diagnosis  $\geq 80$  vs  $< 80$ , Airlie House criteria at diagnosis definite, probable or probable laboratory-supported vs possible and diagnostic delay.

### **Prognostic value of nutritional markers over the entire follow-up**

While considering nutritional status over the entire follow-up, we identified a 34% increased risk of death for each 5% decrease from usual weight and a 24% increased risk for each unit decrease from usual BMI (Table 3). Rate of weight loss during the course of the disease did not appear to be significantly associated with survival. Malnutrition also appeared significantly associated with survival ( $p=0.01$ ). As compared to patients in the normal range of BMI, malnourished patients experienced a 2.15 (IC95% 1.09-4.25) increased risk of death, whereas overweight and obese patients tended to have reduced risk of death RR: 0.71 (IC95% 0.40-1.28) and 0.36 (IC95% 0.11-1.19) respectively. An increase in fat mass using triceps skinfold thickness or bioimpedance was significantly associated with a better outcome. An increase in ratio of extracellular fluid volume over intracellular fluid volume was significantly associated with a shorter survival in multivariate analysis ( $p=0.02$ ). In survival analyses there was no significant interaction between bulbar form at onset and BMI or weight loss at diagnosis or in subsequent follow-up.

**Table 3: Relative risks of death associated with nutritional variables measured over the entire follow-up in univariate and multivariate analysis. Each nutritional variable has been analysed independently from other nutritional variables.**

During follow-up nutritional variables*	Univariate analysis			Multivariate analysis		
	cHR	95% CI	P value	aHR†	95% CI	P value
Weight variation from usual weight (for 5% decrease)	1.40	1.23-1.59	<0.0001	1.34	1.18-1.51	<0.0001
BMI variation from usual BMI (for one unit decrease)	1.30	1.18-1.42	<0.0001	1.24	1.13-1.36	<0.0001
Rate of weight loss from usual weight (% / month)	1.11	1.02-1.20	0.01	1.07	0.98-1.17	0.11
Rate of BMI loss from usual BMI (unit / month)	1.44	1.08-1.93	0.01	1.28	0.94-1.74	0.11
Malnutrition vs other BMI categories	2.32	1.25-4.29	0.007	2.56	1.33-4.94	0.005
BMI categories			0.03			0.01
Malnutrition	2.15	1.14-4.08		2.15	1.09-4.25	
Normality (reference)	1.00			1.00		
Overweight	0.98	0.56-1.72		0.71	0.40-1.28	
Obesity	0.43	0.13-1.40		0.36	0.11-1.19	
Mid-arm muscle circumference, cm (for one unit increase)	0.89	0.82-0.95	0.001	0.93	0.86-1.005	0.07
Triceps skinfold thickness, cm (for one unit increase)	0.99	0.96-1.03	0.66	0.94	0.90-0.98	0.003

Phase angle, ° (for one unit decrease)	1.68	1.27-2.23	<b>0.0003</b>	1.27	0.92-1.75	0.15
Extracellular fluid/intracellular fluid volume (for 0.2 unit increase)	1.76	1.26-2.46	<b>0.0009</b>	1.67	1.07-2.61	<b>0.02</b>
Lean mass, kg (for 2.5 unit increase)	0.94	0.89-1.002	0.06	1.00	0.94-1.07	0.97
Fat mass, kg (for 2.5 unit increase)	0.98	0.91-1.04	0.46	0.90	0.83-0.96	<b>0.003</b>

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Legend : cHR: crude Hazard Ratio; aHR: adjusted Hazard Ratio; . BMI categorization: (i) Malnutrition: BMI <18.5 if age <70 years and BMI<21 if age ≥70 years; (ii) Normal status 18.5≤BMI<25 if age <70 years and 21≤BMI<27 if age ≥70 years; (iii) Overweight: 25≤BMI<30 if age <70 years and 27≤BMI<30 if age ≥70 years; (iv) Obesity BMI≥30.

\* Survival analyses were performed separately for each nutritional variable.

† Adjustment on age, gender, bulbar form at onset, ALS FRS, manual muscular testing, forced vital capacity, Airlie House criteria during follow-up and diagnostic delay.

## **DISCUSSION**

We have shown that patients with a weight loss from usual of 5% and over at the time of diagnosis experience a 2-fold increase in the risk of death (median survival time: 20.6 months (95% CI 12.4-29.0)) as compared to patients whose weight remains stable or drops by less than 5% (median survival time: 29.0 months (95% CI 21.2-38.5)). Weight loss at diagnosis was identified as an independent prognostic factor with an adjusted 30% increased risk of death for a 5% decrease from usual weight. We also identified during the course of ALS a decrease in weight, BMI, fat-free mass, and phase angle, and an increase in fat mass. We observed an adjusted 34% increased risk of death associated with each 5% decrease from usual weight during follow-up. Malnutrition during the course was associated with a shorter survival (p=0.01) and fat mass level was associated with a better outcome (RR 0.90 for each 2.5-kg fat mass increment).

This work is, to our knowledge, the first demonstration of the prognostic value for survival of the nutritional status of ALS patients at time of diagnosis. Other authors have reported the prognostic significance of BMI for survival, but only if it is assessed at the time of gastrostomy placement (5), or an indication for non-invasive ventilation, (6) or during the course of the disease (14). A correlation analysis performed by Kasarskis et al. also found an association between BMI and proximity of death (15).

Concerning malnutrition assessed by BMI during the follow-up, our results are in agreement with Desport et al. who, in 1999, (4) showed that malnutrition was an independent prognostic factor for survival. In that study, the mean delay between first symptoms and nutritional assessment (29±25 months) was longer than in our work where assessment was performed at time of diagnosis (median time between first symptoms and diagnosis 7.9 months (IQR 6.0-

12.2)) and in subsequent follow-up. The absence of an association between malnutrition at diagnosis and survival here could be due to a lack of power caused by the low initial percentage (8.7%) of malnourished patients.

In a seminal paper, Slowie et al. reported that for a limited number of ALS patients during a large range of times between diagnosis and assessment (6 months to 11 years) 25% of patients lost 10% of their weight (1). According to our data, at time of diagnosis, the nutritional status of patients is already highly altered: 50% lost more than 2.3% of weight and 25% lost more than 7.8% and 2 units of BMI. It has to be acknowledged that alteration of nutritional status is multifactorial: progressive muscular wasting due to denervation (1), swallowing or salivary disorders and dysphagia present at the time of diagnosis in patients with the bulbar form or appearing during the course are also implicated (4). In addition, anorexia, digestive disorders and upper limb motor difficulties contribute to low intake. Moreover, an increase in energy requirement sufficient to exceed intake has been demonstrated in 50% of patients (2-3). The reason for this hypermetabolism is not known. Our study was not designed to explore the respective contributions of these factors. A further study looking at that point could also assess the link between mobility and the weight/body composition of ALS patients.

Following the literature, only 9% of patients were malnourished according to BMI at the time of diagnosis, reaching 15% at the last nutritional evaluation (4, 16, 17). This alteration is also highlighted by the dramatic reduction in phase angle at time of diagnosis and before death. The early decrease of phase angle during ALS reflects alteration of the body composition, and general health and function. Similar patterns are displayed by the ratio of extracellular fluid volume over intracellular fluid volume.

In common with Nau et al (18) and other authors (19), we identified modifications of body compartments in ALS patients, with a loss of fat-free mass and a gain of fat mass during the course. Our study shows for the first time that a higher fat mass is beneficial for survival of ALS patients. Similar results have already been reported in chronic obstructive pulmonary disease (20), cardiac insufficiency (21), and in hemodialysis patients (22) suggesting that in several chronic diseases a moderate excess of weight could aid survival. In ALS patients, Dupuis et al. (7) have shown that patients with high LDL/HDL cholesterol have longer survival confirming previous results in mice (23). It is worth considering whether high LDL/HDL may be associated in many cases with either a sustained nutritional status or a weight excess with higher fat storage. In accord with Patel et al. (24), our results suggest that enhanced fat storage through an energy enriched diet may improve patient survival. This hypothesis is also supported by animal models showing better outcome for SOD1-G93A transgenic ALS mice fed with a ketogenic diet (25). This concept is opposed to previous suggestions that modest weight loss may be desirable early in the course of the disease in order to obviate unnecessary accumulation of fat (26).

We have to acknowledge that usual predictions from hospital-based study may have limited validity for population-based patients. Rapidly deteriorating patients may not survive until referral to an academic centre or may be too ill to go there whereas younger patients are more likely to seek a second opinion. Although our study is hospital-based, our ALS centre is the only multidisciplinary care centre in our region and our incidence profile (2.0/100 000 inhabitants for the 1997-2007 period and 4.4/100 000 in the 45-74 age group) is highly consistent with data from American or European registries (27). It can be convincingly argued that our centre is representative of the ALS population. Moreover, due to the inclusion criteria (follow-up by our nutrition unit), half the patients had a bulbar form at onset. We think our



results provide valuable information relevant to the whole ALS population because our study population is probably better followed from a nutritional point of view than the ALS population overall.

This result has three main implications. First, our findings provide important support for a reevaluation of daily routine nutritional management and for considering early nutritional intervention to improve survival of ALS patients. The prognostic value of weight loss at the time of diagnosis and quite late nutritional interventions allow us to propose close monitoring of nutritional status following a diagnosis of ALS. Despite the value of BIA in monitoring body composition, our results and their clinical application support weight assessment as the first priority. We propose a weight loss of 5% from usual be considered a threshold for systematic dietary recall, nutritional assessment, and BIA evaluation of fat mass and fat-free mass. For people without such a weight loss, close monitoring every 3 months of weight at least could be appropriate.

Our results have other implications for epidemiological and clinical research. Weight loss at the time of diagnosis is an independent prognostic factor for survival of ALS patients, therefore observational studies should adjust their estimations accordingly. Those conducting clinical trials might use percentage weight loss as a stratification criterion because a slight disequilibrium between groups for this strong prognostic factor could mask the modest efficacy of a new treatment.

Finally, in contrast to other recognised prognostic factors at diagnosis, the nutritional status of patients can be modified using oral or enteral procedures. It is interesting to consider that the correction of weight loss at diagnosis could exceed the effect of riluzole on survival (28).

Consequently, trials to investigate such interventions are needed. Early enteral nutrition could be a challenge because studies showed that percutaneous endoscopic gastrostomy (PEG) is effective in stabilizing body weight/BMI. According to the American guidelines for management of ALS patients, there is level B evidence that PEG should be considered for prolonging survival in patients with ALS, but the optimum time for PEG insertion is still unknown (29). There is however growing evidence that PEG placement should be performed before  $FCV < 50\%$  to prevent respiratory deficiency during insertion, and radiological inserted gastrostomy has been shown to be a safe alternative below this threshold (30). Although European guidelines for care of ALS patients state that PEG placement should be envisaged early in the course of the disease (31), patients have difficulty accepting it then. The median delay between diagnosis and gastrostomy placement in our study (10 months) can be considered as early, but is probably late as far as nutritional status and improvement of survival are concerned. Another trial could investigate the effects of nutritional supplementation enriched in energy and lipids close to diagnosis as compared with a diet adapted for caloric needs.

**AUTHORS AND CONTRIBUTIONS:**

All authors significantly contributed to this paper. Philippe Couratier, Jean Claude Desport, Pierre Marie Preux and Benoît Marin wrote the first draft of the study protocol (scientific hypothesis, objective, choice of study design and statistical methods). All authors contributed to the final version of the Protocol. Benoît Marin and Patrick Kajeu performed statistical analyses. All authors contributed to interpretation of the results. Benoît Marin and Philippe Couratier wrote the first draft of the manuscript. All authors contributed to the final text and to editing. William Francis (medical writer) contributed to editing.

**COMPETING INTERESTS:**

Authors have no conflict of interest to declare.

**ACKNOWLEDGEMENTS:**

Acknowledgement: We thank William Francis for reviewing the manuscript.

**FUNDING:**

None

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## FIGURE LEGEND

### Figure 1

No Legend

Title : Figure 1: Evolution of nutritional factors from time of diagnosis to time of death

### Figure 2

No Legend

Title : Figure 2. Survival functions of ALS patients according to percentage of weight loss at time of diagnosis

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