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Predictive factors for gastrostomy at time of diagnosis and impact on survival in patients with amyotrophic lateral sclerosis

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Running head: Survival in ALS patients with gastrostomy indication.

Abbreviation list: ALS: Amyotrophic lateral sclerosis, ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised version, BFS: Norris Bulbar Score, BMI: Body

Mass Index, CI: Confident interval; CNIL: Commission Nationale de l'Informatique et des Libertés, FM: Fat Mass, FFM: Fat-Free Mass, FTD: Fronto-Temporal Dementia, FVC: Forced Vital Capacity, HR: Hazard ratio, IQR: Interquartile range, MD: missing data, MMT: Manual Muscular Testing, n: number of observations, NIV: Non Invasive Ventilation, OR: Odds ratio, p: probability, PA: Phase Angle, PEG: Percutaneous Endoscopic Gastrostomy, PRG: Percutaneous Radiological Gastrostomy.

ABSTRACT:

Background: Gastrostomy is recommended in patients with Amyotrophic Lateral Sclerosis (ALS) in the presence of weight loss over 10% as compared to usual weight, repeated aspirations or meal time duration longer than 45 minutes. Currently, the impact of gastrostomy on survival of ALS patients is not clear.

Aims: i) to describe diagnosis factors associated with the indication for gastrostomy ii) to evaluate survival of ALS patients with gastrostomy indication according to their acceptance of feeding tube placement.

Methods: Patients with ALS were included and followed in the ALS referral centre of Limoges's teaching hospital between 2006 and 2017. Neurological, nutritional and respiratory status was assessed prospectively from diagnosis to death. Statistical analysis was performed using Mann-Whitney test, Chi^2 tests, Cox model and multivariate logistic regression.

Results: Two hundred and eighty-five patients were included. Among the 182 for whom gastrostomy was indicated, 63.7% accepted the placement. The median time was 7.3 months [IQR: 3.2 – 15.0] and 2.7 months [IQR: 0.9 – 5.8] respectively from diagnosis to indication and from indication to placement. Weight loss > 5% significantly increased the risk of death by 17% ($p < 0.0001$). At time of diagnosis, bulbar onset, a loss of one point in the body mass index or on the bulbar functional scale were all positively associated with indication for gastrostomy (aOR = 10.0 [95%CI: 1.96-25.0]; p = 0.002, aOR = 1.17 [95%CI: 1.02-1.36]; p = 0.025 and aOR = 1.19 [95%CI: 1.06-1.32]; p = 0.002, respectively). However, gastrostomy placement did not have any impact on survival (aHR = 1.25 [95%CI: 0.88-1.79]; p = 0.22).

Conclusion: Both neurological and nutritional criteria were associated with an indication for gastrostomy at diagnosis. Gastrostomy placement had no impact on survival. The study of earlier gastrostomy placement might be of interest in further prospective studies.

Key words: Amyotrophic lateral sclerosis, gastrostomy recommendation, weight loss, survival, diagnosis indicators

Introduction:

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease in adults (1). Nutritional status alteration of is related to survival in patients with ALS (2–4). The causes of the energetic imbalance are multifactorial, mainly due to an increase in resting energy expenditure or to a decrease in food intake linked to hypersalivation, dysphagia, loss of dexterity, respiratory insufficiency and depression.

During the follow-up, different nutritional strategies may be proposed in case of an alteration of the nutritional status like splitting meals, texture adaptation, nutritional supplements, speech therapy or enteral nutrition with a gastrostomy feeding tube (5). According to the guidelines, gastrostomy is recommended in case of insufficient food intake with weight loss over 10%, meal time duration over 45 min and repeated aspirations (6–11).

Gastrostomy plays a role in the improvement of the quality of life; however, its impact on survival is not clear. Some studies have shown a decrease in the risk of death (12,13) while others found no significant benefit (14,15). These controversial results may be due to methodological differences in the selection of patients, the primary outcome and the statistical analysis. The ProGas study demonstrated that weight loss over 10% in gastrostomized patients between diagnosis and placement time was a negative prognostic factor for survival (aHR= 2.51 [95%CI: 1.49-4.24]; p= 0.001) (16).

The aims of this study were i) to describe associated factors related to gastrostomy indication at time of diagnosis, and ii) to evaluate post-diagnosis and post-gastrostomy survival according to these factors.

Materials and Methods

Study design

This observational cohort included ALS patients followed in the ALS referral centre of Limoges's teaching hospital (CHU) between April 2006 and December 2017. According to the revised-El Escorial criteria, each patient was classified into definite, probable, laboratory-supported probable or possible ALS at time of diagnosis. All the patients had been treated with riluzole since diagnosis. Patients with fronto-temporal dementia (FTD), with parenteral or enteral nutrition before diagnosis, and patients with missing data on their usual weight, Body mass index (BMI) at diagnosis, time for indication of gastrostomy placement, Forced Vital Capacity (FVC) value and the modified Norris bulbar score (BFS) during the follow-up were not included. Informed consent was obtained from the patients to retrieve prospective clinical data from the French national database, which approved by the French Commission (Commission Nationale de l'Informatique et des Libertés). The data collection is described below.

Nutritional assessment:

During the follow-up, every three months, at each clinical consultation, current weight and usual weight (in kg, six months before the first symptoms) are prospectively collected. Patients are weighted in their underwear on an 0.1 kg electronic SECA scale (Vogel & Halke, Hamburg, Germany), in either a standing or a seated position for those who cannot stand up. Height (in m) is measured in the upright position with a 0.2 cm SECA gauge (Vogel & Halke, Hamburg, Germany), or with the Chumlea formula for patients over 60 years who could not stand up (17). Body mass index (BMI), in kg/m², is calculated, which allowed to classify patients as follows: (i) undernutrition: BMI <18.5 for age <70 years and BMI <21 for age ≥70 years; (ii) normal: 18.5≤BMI<25 for age <70 years and 21≤BMI<27 for age ≥70 years; (iii) overweight: 25≤BMI<30 for age <70 years and 27≤BMI<30 for age ≥70 years; (iv) obesity:

BMI≥30 (10,18,19). The percentages of weight loss and units of BMI lost were calculated in comparison with the usual weight. The waist circumference (in cm) is measured with a measuring tape. The triceps skinfold thickness (TSF, in mm) is measured obtained from the average of three measurements on each side with Harpenden's caliper (Baty International, Burgess Hill, UK). Body composition is evaluated using total body impedance measurement at 50 kHz with the Analycor® device (Eugédia, Chambly, France), in a supine position after five minutes at rest. Fat Free Mass (FFM) and Fat Mass (FM) (in kg and %) are calculated with the validated Desport et al. formula (20). Phase angle (PA) (in degrees) was obtained by impedancemetry measurements (21). Time and indication related to gastrostomy were collected to determine time from diagnosis to indication and time from indication to placement. Then, according to the guidelines, gastrostomy was recommended in case of insufficient food intake with a weight loss over 10%, meal time duration over 45 min and repeated aspirations (6–11).

Neurological and respiratory assessments:

Functional decline is recorded on the Amyotrophic Lateral Sclerosis Functional Rating Scale revised version (ALSFRS-R) and the ALSFRS-R slope was calculated according to the formula: (48-ALSFRS-R at time of diagnosis) / (duration from onset to diagnosis) (22). The modified Norris bulbar score (39 points maximum) and Manual Muscular Testing (MMT) (150 points maximum) are also collected (10,23). The date of the first symptom and the site of onset are recorded. FVC expressed as percentage of theoretical value is measured at each visit every three months and the presence of non-invasive ventilation had been collected during the follow-up.

Statistical methods:

Results were expressed as median and interquartile range (IQR) for quantitative variables, and number and percentage (%) for qualitative variables. Quantitative variables

were compared thanks to Mann-Whitney's or Student's t tests, and qualitative variables by using the Chi-squared test. To identify factors associated with gastrostomy indication, variables with a $p < 0.20$ in the univariate model were included in the logistic regression model. The final model was simplified with the backward procedure method. Sex and age were forced-in covariates in the final model.

The crude mortality-rate one month post-intervention (gastrostomy placement) was calculated. Furthermore, the Cox proportional hazard method was used to evaluate the impact of gastrostomy on survival of ALS patients with indication for gastrostomy placement. Variables with a $p < 0.20$ in the univariate model were included final multivariate model by backward procedure method. Survival time was analysed from the date of diagnosis until the death of the patient or tracheostomy placement or the censoring date. Weight, FFM, FM, PA, MMT, BFS, ALSFRS-R, and FVC covariates had been also collected during all the follow-up and used for adjustment. Relevant interactions between variables in the final multivariate model were tested. The proportional hazard assumptions were tested using an interaction-with-time method. No data computational method was used. For all statistical analysis, the significance threshold was 0.05. Statistical analysis was performed with SAS® (SAS institute NC, Cary, USA) and Stata® 15.1 (Statacorp, Lakeway, USA).

Results:

Overall, 285 ALS patients were included in the study (Figure 1) and their characteristics are presented in Table 1.

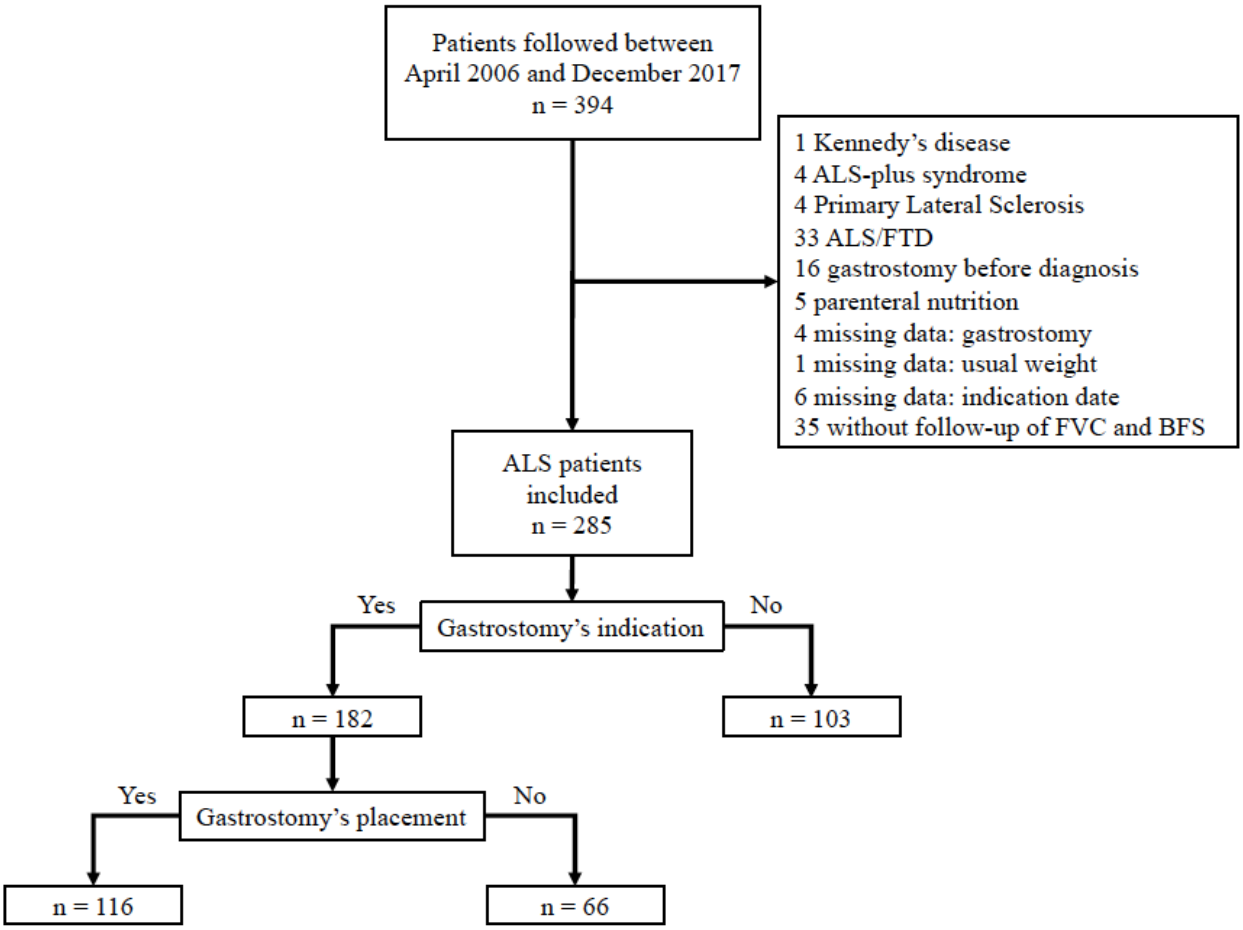

Figure 1: Flowchart of included ALS patients (n = 285)

ALS: Amyotrophic Lateral Sclerosis ; BFS: Bulbar Functional Scale; FTD: Fronto-Temporal Dementia; FVC: Forced Vital Capacity; n: number

At time of diagnosis, the median age was 66.0 years [IQR 57.7 – 74.5] and the M/F sex-ratio was 1.19. 30.9% of ALS patients had bulbar onset.

During the follow-up, 117 (62.1%) had Non-Invasive Ventilation (NIV) and 182 (63.9%) had indication for gastrostomy. Mean time from diagnosis to gastrostomy indication was 7.3 months [IQR: 3.2 – 15.0]. The characteristics of patients with and without gastrostomy indication are presented in Table 1.

Table 1: Characteristics of ALS patients at diagnosis (n = 285) and comparison between patients with (n = 182) and without (n = 103) indication for gastrostomy placement

Variables	TOTAL	INDICATION		MD	p
	(n= 285)	***Yes*** *(n=182)*	***No*** *(n=103)*		
	n (%) or Median [IQR]	n (%) or Median [IQR]	n (%) or Median [IQR]		
Age (years)	66.0 [57.7-74.5]	66.8 [58.9-74.7]	64.6 [54.5-73.9]	0	0.139[b]
Sex				0	**0.026**[a]
Male	155 (54.4)	90 (49.5)	65 (63.1)		
Female	130 (45.6)	92 (50.5)	38 (36.9)		
Time to diagnosis (months)	9.3 [6.0-13.9]	8.4 [5.9-12.8]	10.9 [6.8-17.5]	0	**0.036**[b]
Type of onset				0	**<0.0001**[a]
Bulbar	88 (30.9)	83 (45.6)	5 (4.9)		
Spinal	197 (69.1)	99 (54.4)	98 (95.1)		
Airlie House criteria				0	**0.007**[a]
Possible	68 (23.8)	44 (24.2)	24 (23.3)		
Laboratory-supported probable	78 (27.4)	39 (21.4)	39 (37.9)		
Probable	105 (36.8)	71 (39.0)	34 (33.0)		
Definite	34 (12.0)	28 (15.4)	6 (5.8)		
ALSFRS-R (/48 points)	40.8 [36.0-43.2]	40.0 [36.0-43.2]	41.0 [38.0-43.2]	6	0.218[b]
ALSFRS-R slope (units/month)	-0.7 [-1.4- -0.4]	-0.8 [-1.5- -0.5]	-0.7 [-1.1- -0.4]	0	**0.008**[b]
MMT (/150 points)	138.0 [125.0-145.0]	139.0 [125.0-146.0]	136.0 [128.0-143.0]	8	**0.037**[b]
BFS (/39 points)	37.0 [31.0-39.0]	33.0 [27.0-39.0]	39.0 [38.0-39.0]	5	**<0.0001**[b]
FVC (% of theoretical value)	94.0 [73.0-109.0]	88.0 [70.0-105.0]	99.0 [83.5-111.5]	58	**0.012**[b]
Weight (kg)	65.8 [58.6-75.2]	63.5 [56.5-72.7]	71.1 [63.4-79.2]	0	**<0.0001**[c]
BMI (kg/m²)	24.6 [22.3-27.6]	24.1 [22.0-26.2]	25.8 [23.4-28.0]	0	**<0.0001**[b]
Nutritional status				0	**0.002**[a]
Undernutrition	32 (11.2)	27 (14.8)	5 (4.9)		
Normal	161 (56.5)	109 (59.9)	52 (50.5)		
Overweight	66 (23.2)	32 (17.6)	34 (33.0)		
Obesity	26 (9.1)	14 (7.7)	12 (11.6)		
Weight loss (%)	3.8 [0.0-9.4]	4.5 [0.0-11.1]	2.1 [0.0-7.4]	0	**0.011**[b]
Phase angle (°)	3.1 [2.6-3.9]	3.1 [2.5-3.8]	3.1 [2.6-4.3]	12	0.195[b]
Fat mass (kg)	20.6 [15.5-25.0]	20.1 [14.5-23.5]	22.7 [17.6-26.7]	16	**0.006**[b]
Fat mass (%)	30.3 [24.1-37.7]	30.2 [23.0-37.2]	30.6 [25.6-38.8]	16	0.516[b]
Fat free mass (kg)	45.8 [38.0-52.7]	42.9 [37.2-51.3]	49.8 [39.8-55.4]	16	**0.002**[b]
Fat free mass (%)	69.7 [62.3-75.9]	69.8 [62.8-77.0]	69.4 [61.2-74.4]	16	0.516[b]
Waist circumference (cm)	90.0 [81.0-99.0]	87.0 [80.0-95.0]	94.0 [87.0-102.0]	6	**<0.0001**[c]

ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised; BFS: Bulbar Functional Scale; BMI: Body Mass Index; FVC: Forced Vital Capacity; IQR: Interquartile range, MD: Missing data; MMT: Manual Muscle Test ; n: number ; p: probability

a: Chi^2 test; b: Mann-Whitney test; c: Student test; in bold: $p < 0.05$

After adjustment, the factors associated with a gastrostomy indication at time of diagnosis were bulbar onset (aOR = 10.00 [95%CI: 1.96 – 25.0]), loss of 1 point on the BFS (aOR: 1.19 [95%CI: 1.06-1.32]), weight loss of 1 kg (aOR = 1.03 [95%CI: 1.01 – 1.06]) and loss of 1 point of BMI (aOR = 1.17 [95%CI: 1.02-1.36]) (Table 2). During the follow up, the placement of NIV was also associated with the indication for gastrostomy (aOR = 4.58 [95%CI: 2.36 – 8.88]).

Table 2: Factors associated with indication for gastrostomy placement in univariate and multivariate analysis with binary logistic regression (n= 285)

Explanatory variables	**Univariate analysis**		**Multivariate analysis**	
	cOR [95%CI]	p	aOR [95%CI]	p
Age* (+1 year)	1.01 [1.00-1.04]	0.13	0.98 [0.96-1.01]	0.170
Sex				
Male	1.00		1.00	
Female	1.75 [1.07-2.86]	**0.027**	1.23 [0.61-2.50]	0.547
Non-invasive ventilation#				
No	1.00		1.00	
Yes	3.40 [2.05-5.65]	**0.0001**	**4.58** [2.36-8.88]	**0.0001**
Time onset - diagnosis (+1 year)	0.98 [0.97-1.00]	0.10	-	-
Type of onset				
Spinal	1.00		1.00	
Bulbar	16.67 [6.25-50]	**0.0001**	**10.00** [1.96-25.0]	**0.002**
ALSFRS-R slope* (-1 point/month)	1.47 [1.08-2.00]	**0.016**	-	-
BFS* (-1 point)	1.35 [1.23-1.47]	**0.0001**	**1.19** [1.06-1.32]	**0.002**
Weight* (-1 kg)	1.04 [1.02-1.06]	**0.0001**	**1.03** [1.01-1.06]	**0.037**
BMI loss* (-1 kg/m²)	1.25 [1.12-1.40]	**0.0001**	**1.17** [1.02-1.36]	**0.025**
Fat mass* (-1 kg)	1.03 [1.01-1.06]	**0.032**	-	-
Phase angle* (-1°)	1.23 [0.97-1.59]	0.098	-	-

ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised; aOR: adjusted Odds Ratio; BFS: Bulbar Functional Scale; BMI: Body Mass Index; cOR: crude Odds Ratio; p: probability; 95%CI: 95% confidence interval. *: on diagnostic examination; #: during follow-up. In bold: $p < 0.05$

For the 285 patients with ALS, the median survival from diagnosis was 18.7 months [IQR: 16.2 – 21.2] and the crude mortality rate by December 31st 2017 was 77.9%. Among the 182 patients with indication for gastrostomy placement, 116 (63.7%) patients accepted the placement of the feeding tube. Characteristics of ALS patients at gastrostomy indication, comparing patients who declined or accepted gastrostomy placement, are presented in Appendix A. The mean time from indication to placement was 2.7 months [0.9 – 5.8]. The crude mortality rate was 8.6%, one month after gastrostomy placement. Nevertheless, multivariate survival analysis showed that gastrostomy placement during the follow-up had no significant impact on survival (Table 3). At time of diagnosis, each 5% of weight loss increased the risk of death by 17%. There was no interaction between gastrostomy placement and weight loss ($p = 0.30$).

Table 3: Impact of gastrostomy on survival of patients with an indication of gastrostomy placement, univariate and multivariate analysis with Cox proportional hazard model (n = 182)

Variables	**Univariate analysis**			**Multivariate analysis**		
	cHR	95%CI	p	aHR	95%CI	p
Time onset – diagnosis (+6 months)	0.91	[0.84-0.99]	**0.024**			
Time diagnosis - indication (+6 months)	0.95	[0.88-1.02]	0.15			
Age* (+5 years)	1.10	[1.04-1.18]	**0.002**	**1.16**	[1.09-1.24]	**<0.0001**
MMT[#] (– 10 points)	1.15	[1.10-1.21]	**<0.0001**			
ALSFRS-R[#] (– 5 points)	1.40	[1.27-1.54]	**<0.0001**	**1.43**	[1.26-1.57]	**<0.0001**
BFS[#] (– 5 points)	1.08	[0.99-1.16]	0.058			
FVC[#] (– 10% of theoretical value)	1.05	[0.99-1.12]	0.01			
Weight loss[#] (– 5%)	1.13	[1.05-1.21]	**0.0006**	**1.17**	[1.09-1.26]	**<0.0001**
Sex			0.57			
Male	1.00					
Female	1.10	[0.80-1.52]				
Type of onset			0.09			
Spinal	1.00					
Bulbar	1.32	[0.95-1.82]				
Airlie House criteria*			**<0.0001**			
Possible	1.00					
Laboratory-supported probable	1.30	[0.80-2.10]				
Probable	2.13	[1.39-3.26]				
Definite	3.41	[2.02-5.76]				
Gastrostomy[#]			**0.002**			0.216
No	1.00			1.00		
Yes	1.74	[1.23-2.45]		1.25	[0.88-1.79]	
NIV[#]			**<0.0001**			**0.03**
No	1.00			1.00		
Yes	2.33	[1.61-3.36]		**1.54**	[1.04-2.27]	

aHR: adjusted Hazard Ratio; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised; BFS: Bulbar Functional Scale; cHR: crude Hazard Ratio; FVC: Forced Vital Capacity; MMT: Manual Muscle Testing; NIV: Non-invasive Ventilation; p: probability ; 95%CI: Confidence Interval at 95%. *: on diagnostic examination; [#]: during follow-up. In bold: $p < 0.05$

Discussion:

This study focused on factors associated with gastrostomy indication at time of diagnosis in patients with ALS. For the 63.9% patients who reached the indication of gastrostomy placement during the follow-up, the clinical characteristics at diagnosis showed greater neurological decline over a shorter time from the first symptom to diagnosis and a more pronounced alteration of nutritional status than those of patients who did not reach indication. For clinicians, bulbar impairments and weight loss are signs for an indication of gastrostomy placement (6–11).

Jackson-Tarlton et al., have demonstrated that the presence of moderate swallowing troubles scoring 3 on the swallowing item of the ALSFRS-R (maximum 4 points) was associated with indication for percutaneous endoscopic gastrostomy (PEG) placement with an OR at 4.24 [95% CI 1.47-12.23]. When swallowing function was evaluated between 0 was 2, the OR dramatically increased at 52.23 [95% CI 19.12-142.69] (24). According to Conde et al., PEG could be performed following sensitive indicators like FVC $\leq$ 74%, Cough Peak Flow $\leq$ 205 l/min, ALSFRS-R $<$ 29 or bulbar sub-score of ALSFRS-R $\leq$ 8 (25). In their population, 75% of patients who accepted PEG had a bulbar onset. Similarly, in our study, 55.2% of patients who accepted PEG had a bulbar onset.

Early gastrostomy feeding tube placement should be considered as soon as possible to avoid rapid weight loss. The latter is an important risk factor for death in ALS and seems to be irreversible in clinical practice as there was no interaction between weight loss and gastrostomy placement ($p = 0.30$). Some studies have demonstrated a decrease in the instantaneous risk of death for patients with gastrostomy (HR = 0.75; $p = 0.003$) and an increase for patients without gastrostomy (HR = 3.89, $p = 0.0004$) (12,13). On the contrary, some studies have shown no significant improvement in survival in patients with or without gastrostomy (47.0 months vs 58.0 months; $p = 0.33$, 25.0 months vs 24.7 months; $p = 0.52$)

(14,15). These contradictory results may be explained by the difficulty to compare the group of ALS patients accepting tube feeding with those who refuse it (Appendix B).

According to this methodological aspect, survival was assessed not only considering patients with or without gastrostomy, but taking into account patients who needed and then accepted or not the feeding tube placement. This study allowed to identify a 17% increase in the risk of death for each 5% of weight loss based on usual weight as previously reported (26). Moreover, in the ProGas study, patients with a weight loss greater than 10% between diagnosis and gastrostomy placement had a risk of death increased by 151% (aHR = 2.51; p = 0.0011) compared with those who lost less than 10% of body weight. According to the European guidelines for ALS nutritional management, the aim of nutritional care is to stabilize the weight if BMI is between 25 and 35kg/m^2 and to improve nutritional status if BMI is under 25kg/m^2 (11). It remains essential to assess the nutritional status and to adapt nutritional care since time of diagnosis using oral nutritional supplements and texture adaptation in order to have a positive impact on functional evolution and survival. In this sense, the placement of gastrostomy could improve ALS patients' survival. Unfortunately, our study did not find any impact of gastrostomy on survival of probable ALS patients because the placement occurred too late as we observed in our study with a median delay of 10 months after diagnosis whereas the median survival was 17.5 months (26).

The choice of the method of gastrostomy placement could also have an impact. Percutaneous radiological gastrostomy (PRG) was used for most of our patients, because it has been shown that PRG may be performed in patients with more severe respiratory dysfunction (11). When comparing PRG and PEG on survival, a study has failed to show a significant difference between the two methods (p = 0.28) (27). Two studies have shown 3% and 6%mortality rates thirty days after the placement of a PRG (16,28) contrasting with a higher mortality rate of 8.6% in our study. But, with time procedures have improved, in

particular the use of the non-invasive ventilation during PRG placement reducing the risk of acute respiratory insufficiency during the following days.

Our study has strengths ; it is the first to assess survival of ALS patients according to the indication for gastrostomy placement using a multivariate analysis adjusted on longitudinal data (MMT, ALSFRS-R, BFS, FVC…). However, further studies could be performed taking into account inter-individuals and inter-examinations variabilities using a mixed statistical model with supplementary variables collected during all the follow-up (Airlie House criteria, Age…). To promote a good homogeneity of the clinical characteristics of ALS patients, we included subjects diagnosed after the publication date of the French guidelines for management of patients with ALS (Haute Autorité de Santé, 2006) (18).

Our study has also some limitations : our ALS population was selected from the referral centre and not from the French register of ALS in Limousin (FRALim), which could have induced some selection bias (26). Another limit is the absence of use concerning the daily food intake data at diagnosis and during follow-up, the results of the DePippo test (29,30) and the value of resting energy expenditure. These parameters would have allowed to clarify the causes of early weight loss in our patients. Daily food intake data are difficult to obtain mainly at diagnosis. Furthermore, food surveys can be biased. The De Pippo test is performed at each nutritional examination. However, data are not systematically entered in the database or in medical records and therefore induce a high number of missing data at diagnosis (n=212) and at gastrostomy indication (n=260). Concerning the resting energy expenditure, also to limit missing data and the non-inclusion of patients we did not study this parameter. Moreover, a recent study has demonstrated that mean time until the feeding tube placement is not statistically different between patients with or without hypermetabolism (31).

Clinical trials are needed to evaluate the effect of early gastrostomy placement as compared to classical care. Current nutritional strategy trials aim to demonstrate if early

supplementation in calories or in lipids may improve the functional status and survival of patients with ALS (NUTRALS / LIPCAL-ALS).

Conflicts of interest

No conflicts are declared

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Author contributions

MV, PJ, PC, JCD, GL and PF designed the research project. BM and PMP had a role in running the protocol. MP, HS and MV collected data. MV and BM analysed the data. Then, MV, PJ, PC, JCD provided writing assistance and language help.

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REFERENCES:

1. Swinnen B, Robberecht W. The phenotypic variability of amyotrophic lateral sclerosis. Nat Rev Neurol. 2014;10:661–70. DOI: 10.1038/nrneurol.2014.184

2. Desport JC, Preux PM, Truong TC, Vallat JM, Sautereau D, Couratier P. Nutritional status is a prognostic factor for survival in ALS patients. Neurology. 1999;53:1059–63. DOI: 10.1212/wnl.53.5.1059

3. Marin B, Desport JC, Kajeu P, Jesus P, Nicolaud B, Nicol M, et al. Alteration of nutritional status at diagnosis is a prognostic factor for survival of amyotrophic lateral sclerosis patients. J Neurol Neurosurg Psychiatry. 2011;82:628–34. DOI: 10.1136/jnnp.2010.211474

4. Genton L, Viatte V, Janssens J-P, Héritier A-C, Pichard C. Nutritional state, energy intakes and energy expenditure of amyotrophic lateral sclerosis (ALS) patients. Clin Nutr. 2011;30:553–9. DOI: 10.1016/j.clnu.2011.06.004

5. Couratier P, Desport J-C, Antonini M-T, Mabrouk T, Perna A, Vincent F, et al. Prise en charge nutritionnelle et respiratoire des patients atteints de Sclérose Latérale Amyotrophique (SLA). Rev Neurol (Paris). 2004;160:243–50. DOI: 10.1016/S0035-3787(04)70898-X

6. Andersen PM, Borasio GD, Dengler R, Hardiman O, Kollewe K, Leigh PN, et al. Good practice in the management of amyotrophic lateral sclerosis: Clinical guidelines. An evidence-based review with good practice points. EALSC Working Group. Amyotroph Lateral Scler. 2007;8:195–213. DOI: 10.1080/17482960701262376

7. Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, et al. Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Drug, nutritional, and respiratory therapies (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009;73:1227–33. DOI: 10.1212/WNL.0b013e3181bc01a4

8. Greenwood DI. Nutrition management of amyotrophic lateral sclerosis. Nutr Clin Pract Off Publ Am Soc Parenter Enter Nutr. 2013;28:392–9. DOI: 10.1177/0884533613476554

9. EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis:, Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)--revised report of an EFNS task force. Eur J Neurol. 2012;19:360–75. DOI: 10.1111/j.1468-1331.2011.03501.x

10. Prise en charge des personnes atteintes de sclérose latérale amyotrophique. Recommandations HAS, conférence de consensus. Rev Neurol (Paris); 2006.

11. Burgos R, Bretón I, Cereda E, Desport JC, Dziewas R, Genton L, et al. ESPEN guideline clinical nutrition in neurology. Clin Nutr Edinb Scotl. 2018;37:354–96. DOI: 10.1016/j.clnu.2017.09.003

12. Czaplinski A, Yen AA, Simpson EP, Appel SH. Slower Disease Progression and Prolonged Survival in Contemporary Patients With Amyotrophic Lateral Sclerosis: Is the Natural History of Amyotrophic Lateral Sclerosis Changing? Arch Neurol. 2006;63:1139–43. DOI: 10.1001/archneur.63.8.1139

13. Chiò A, Mora G, Leone M, Mazzini L, Cocito D, Giordana MT, et al. Early symptom progression rate is related to ALS outcome: a prospective population-based study. Neurology. 2002;59:99–103. DOI: 10.1212/wnl.59.1.99

14. Forbes R, Colville S, Swingler R, for the Scottish Motor Neurone Disease Research Group. Frequency, timing and outcome of gastrostomy tubes for amyotrophic lateral sclerosis/motor neurone disease: A record linkage study from the Scottish Motor Neurone Disease Register. J Neurol. 2004;251:813–7. DOI: 10.1007/s00415-004-0429-9

15. Mitsumoto H, Davidson M, Moore D, Gad N, Brandis M, Ringel S, et al. Percutaneous endoscopic gastrostomy (PEG) in patients with ALS and bulbar dysfunction. Amyotroph Lateral Scler Other Motor Neuron Disord. 2003;4:177–85. DOI: 10.1080/14660820310011728

16. ProGas Study Group. Gastrostomy in patients with amyotrophic lateral sclerosis (ProGas): a prospective cohort study. Lancet Neurol. 2015;14:702–9. DOI: 10.1016/S1474-4422(15)00104-0

17. Chumlea WC, Roche AF, Steinbaugh ML. Estimating stature from knee height for persons 60 to 90 years of age. J Am Geriatr Soc. 1985 Feb;33(2):116–20. DOI: 10.1111/j.1532-5415.1985.tb02276.x

18. HAS - Synthèse des recommandations 2007. Stratégie de prise en charge en cas de dénutrition protéino-énergétique chez la personne âgée. [Internet]. Available from: https://www.has-sante.fr/portail/jcms/c_546549/fr/strategie-de-prise-en-charge-en-cas-de-denutrition-proteino-energetique-chez-la-personne-agee

19. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser. 1995;854:1–452.

20. Desport JC, Preux PM, Bouteloup-Demange C, Clavelou P, Beaufrère B, Bonnet C, et al. Validation of bioelectrical impedance analysis in patients with amyotrophic lateral sclerosis. Am J Clin Nutr. 2003;77:1179–85. DOI: 10.1093/ajcn/77.5.1179

21. Desport J-C, Marin B, Funalot B, Preux P-M, Couratier P. Phase angle is a prognostic factor for survival in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2008;9:273–8. DOI: 10.1080/17482960801925039

22. Kimura F, Fujimura C, Ishida S, Nakajima H, Furutama D, Uehara H, et al. Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS. Neurology. 2006;66:265–7. DOI: 10.1212/01.wnl.0000194316.91908.8a

23. Shefner JM. Strength Testing in Motor Neuron Diseases. Neurotherapeutics. 2017;14:154–60. DOI: 10.1007/s13311-016-0472-0

24. Jackson-Tarlton CS, Benstead TJ, Doucette S, CNDR INVESTIGATOR NETWORK. Correlating factors in the recommendation of feeding tubes in the nutritional management of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Front Degener. 2016;17:515–21. DOI: 10.1080/21678421.2016.1213851

25. Conde B, Martins N, Rodrigues I, Pimenta A, Winck J. Functional and Endoscopic Indicators for Percutaneous Endoscopic Gastrostomy (PEG) in Amyotrophic Lateral Sclerosis Patients. J Clin Med. 2018;7:352. DOI: 10.3390/jcm7100352

26. Marin B, Hamidou B, Couratier P, Nicol M, Delzor A, Raymondeau M, et al. Population-based epidemiology of amyotrophic lateral sclerosis (ALS) in an ageing Europe - the French register of ALS in Limousin (FRALim register). Eur J Neurol. 2014;21:1292–300. DOI: 10.1111/ene.12474

27. Desport J-C, Mabrouk T, Bouillet P, Perna A, Preux P-M, Couratier P. Complications and survival following radiologically and endoscopically-guided gastrostomy in patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2005;6:88–93. DOI: 10.1080/14660820410021258

28. Stavroulakis T, Walsh T, Shaw PJ, McDermott CJ, (on behalf of the Progas Study). Gastrostomy use in motor neurone disease (MND): A review, meta-analysis and survey of current practice. Amyotroph Lateral Scler Front Degener. 2013;14:96–104. DOI: 10.3109/17482968.2012.723722

29. DE PIPPO K, HOLAS M, REDING M. The Burke Dysphagia Screening Test: validation of its use in patients with stroke. Arch Phys Rehabil. 1994;75:1284–6. PMID: 7993165

30. DE PIPPO K, HOLAS M, REDING M. Validation of the 3-oz water swallow test for aspiration following stroke. Arch Neurol. 1992;49:1259–61. DOI: 10.1001/archneur.1992.00530360057018

31. Jésus P, Fayemendy P, Nicol M, Lautrette G, Sourisseau H, Preux P-M, et al. Hypermetabolism is a deleterious prognostic factor in patients with amyotrophic lateral sclerosis. Eur J Neurol. 2018;25:97–104. DOI: 10.1111/ene.13468

32. Mazzini L, Corrà T, Zaccala M, Mora G, Del Piano M, Galante M. Percutaneous endoscopic gastrostomy and enteral nutrition in amyotrophic lateral sclerosis. J Neurol. 1995;242:695–8. DOI: 10.1007/BF00866922

33. Desport JC, Preux PM, Truong C, Courat L, Vallat JM, Couratier P. Nutritional assessment and survival in ALS patients. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1:91–6. DOI: 10.1080/14660820050515386

34. Spataro R, Ficano L, Piccoli F, La Bella V. Percutaneous endoscopic gastrostomy in amyotrophic lateral sclerosis: Effect on survival. J Neurol Sci. 2011;304:44–8. DOI: 10.1016/j.jns.2011.02.016

35. Pena MJ, Ravasco P, Machado M, Pinto A, Pinto S, Rocha L, et al. What is the relevance of percutaneous endoscopic gastrostomy on the survival of patients with amyotrophic lateral sclerosis? Amyotroph Lateral Scler. 2012;13:550–4. DOI: 10.3109/17482968.2012.684215

36. Fasano A, Fini N, Ferraro D, Ferri L, Vinceti M, Errals, et al. Percutaneous endoscopic gastrostomy, body weight loss and survival in amyotrophic lateral sclerosis: a population-based registry study. Amyotroph Lateral Scler Front Degener. 2017;18:233–42. DOI: 10.1080/21678421.2016.1270325

37. Russ KB, Phillips MC, Mel Wilcox C, Peter S. Percutaneous Endoscopic Gastrostomy in Amyotrophic Lateral Sclerosis. Am J Med Sci. 2015;350:95–7. DOI: 10.1097/MAJ.0000000000000517

38. Burkhardt C, Neuwirth C, Sommacal A, Andersen PM, Weber M. Is survival improved by the use of NIV and PEG in amyotrophic lateral sclerosis (ALS)? A post-mortem study of 80 ALS patients. Zhou R, editor. PLoS One. 2017;12:1–12. DOI: 10.1371/journal.pone.0177555

39. Cui F, Sun L, Xiong J, Li J, Zhao Y, Huang X. Therapeutic effects of percutaneous endoscopic gastrostomy on survival in patients with amyotrophic lateral sclerosis: A meta-analysis. Green J, editor. PLoS One. 2018;13:e0192243. DOI: 10.1371/journal.pone.0192243

Appendix A**:** Characteristics of patients at indication, comparing patients who accepted or refused gastrostomy placement (n= 182):

Variables	INDICATION *(n= 182)*	GASTROSTOMY PLACEMENT		MD	p
		Yes *(n=116)*	***No*** *(n=66)*		
	n (%) or Median [IQR]	n (%) or Median [IQR]	n (%) or Median [IQR]		
Age at diagnosis (years)	66.8 [58.9-74.7]	67.0 [58.0-74.0]	67.0 [59.0-76.0]	0	0.785[b]
Sex				0	**0.010[a]**
Male	90 (49.5)	49 (42.2)	41 (62.1)		
Female	92 (50.5)	67 (57.8)	25 (37.9)		
Time to diagnosis (months)	8.4 [5.9-12.8]	8.1 [5.9-12.2]	9.3 [5.7-13.9]	0	0.371[b]
Onset				0	**0.001[a]**
Bulbar	83 (45.6)	64 (55.2)	19 (28.8)		
Spinal	99 (54.4)	52 (44.8)	47 (71.2)		
Airlie House criteria at indication				29	0.611[a]
Possible	13 (8.5)	10 (10.4)	3 (5.3)		
Laboratory-supported probable	17(11.1)	9 (9.4)	8 (14.0)		
Probable	64 (41.8)	40 (41.7)	24 (42.1)		
Definite	59 (38.6)	37 (38.5)	22 (38.6)		
ALSFRS-R (/48 points)	40.0 [36.0-43.2]	29.0 [24.0-37.0]	30.0 [24.0-36.0]	39	0.694[b]
ALSFRS-R slope (units/month)	-0.8 [-1.5- -0.5]	-2.2 [-3.6- -1.0]	-1.9 [-3.2- -0.9]	39	0.273[b]
MMT (/150 points)	139.0 [125.0-146.0]	120.0 [98.0-138.0]	117.0 [95.0-129.0]	44	0.226[b]
BFS (/39 points)	33.0 [27.0-39.0]	20.5 [16.0-27.5]	32.0 [27.0-36.0]	49	**0.000[b]**
Bulbar failures				37	**0.000[a]**
Yes	133 (91.8)	95 (99.0)	38 (77.6)		
No	12 (8.3)	1 (1.0)	11 (22.4)		
Swallowing disorders				12	**0.016 [a]**
Yes	162 (95.3)	108 (98.2)	54 (90.0)		
No	8 (4.7)	2 (1.8)	6 (10.0)		
FVC (% of theorical value)	88.0 [70.0-105.0]	71.0 [54.0-84.0]	69.0 [55.0-83.0]	89	0.720[b]
Weight (kg)	63.5 [56.5-72.7]	61.4 [54.9-69.3]	64.0 [55.5-71.3]	8	0.218[c]
BMI (kg/m²)	24.1 [22.0-26.2]	23.9 [21.3-25.8]	23.5 [20.9-25.6]	8	0.505[b]
Nutritional status				8	0.721[a]
Undernutrition	32 (18.4)	19 (17.4)	13 (20.0)		
Normal	107 (61.5)	68 (62.4)	39 (60.0)		
Overweight	23 (13.2)	13 (11.9)	10 (15.4)		
Obesity	12(6.9)	9 (8.3)	3 (4.6)		
Weight loss at diagnosis (%)	4.5 [0.0-11.1]	4.0 [0.0-11.25]	5.2 [1.3-9.8]	0	0.509[b]
Phase angle (°)	3.1 [2.5-3.8]	3.1 [2.4-3.5]	2.8 [2.4-3.3]	59	0.230[b]
Fat mass (kg)	20.1 [14.5-23.5]	20.8 [13.4-24.9]	19.7 [14.6-22.7]	67	0.401[b]
Fat mass (%)	30.2 [23.0-37.2]	32.6 [23.1-40.3]	29.9 [26.0-34.5]	67	0.127[b]
Fat free mass (kg)	42.9 [37.2-51.3]	40.0 [36.4-46.7]	46.4 [37.4-52.2]	67	**0.032[b]**
Fat free mass (%)	69.8 [62.8-77.0]	67.4 [59.7-76.9]	70.1 [65.5-74.0]	67	0.127[b]
Waist circumference (cm)	87.0 [80.0-95.0]	85.0 [77.0-93.0]	90.0 [81.0-97.0]	53	0.067[c]

ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised; BFS: Bulbar Functional Scale; BMI: Body Mass Index; FVC: Forced Vital Capacity; IQR: Interquartile range; MD: Missing data; MMT: Manual Muscle Test; n: number; p: probability

a: Chi² test; b: Mann-Whitney test; c: Student test; in bold: p<0.05

Appendix B: Methodological aspects and main results of studies assessing survival of ALS patients with gastrostomy

AUTHORS / YEARS	STUDY DESIGN	NUMBER OF SUBJECTS	RESULTS	METHODOLOGY
Mazzini /1995 (32)	Prospective	66 patients with swallowing disorders & weight loss > 5% 31 PEG / 35 refusal	Mean survival from symptom onset: - 38 ± 17 months: with gastrostomy - 30 ± 13 months: without gastrostomy; (p = 0.03)	Univariate survival analysis
Desport /2000 (33)	Retrospective (1996-1998)	- 30 PEG / 30 oral	No difference	Survival analysis
Chio / 2002 (13)	Prospective	- 52 PEG / 169 oral	aHR = 0.26 ; p = 0.0004	Cox model
Mitsumoto / 2003 (15)	Retrospective	-137 PEG / 187 oral	Mean survival: 47 vs 58 months ; p = 0.33	Adjustment on bulbar score
Forbes / 2004 (14)	Retrospective (1989-1998)	142 PEG / 1084 oral	Median survival from symptom onset: -2.08 years [1.44-2.99]: with gastrostomy -2.06 years [1.29-3.49]: without gastrostomy ; p = 0.52	Kaplan-Meier and Log rank test
Czaplinski / 2006 (12)	Retrospective (1984-2004)	175 PEG / 766 oral	HRa = 0.75 [IC95% 0.63-0.90] ; p= 0.003	Cox model
Spataro / 2011 (34)	Retrospective (2000-2007)	150 patients with swallowing disorders 76 PEG / 74 refusal	Median survival from symptom onset: - 38 months: with gastrostomy - 32 months: without gastrostomy (p = 0.05)	Kaplan-Meier and Log rank test
Pena / 2012 (35)	Retrospective (1995- 2011)	151 patients with PEG 106 bulbar onset / 45 spinal onset	Median survival after gastrostomy placement: - 7.9 months: bulbar onset - 7.1 months: spinal onset (p > 0.05) aHR = 1.41 [IC95% 0.8-2.4] ; p = 0.21	Kaplan-Meier and Log rank test Cox model
Fasano 2017 (36)	Retrospective (2009-2013)	193 patients with swallowing disorders 152 PEG / 41 refusal	Median survival from recommendations: - 6 months: with gastrostomy - 2 months: without gastrostomy (p = 0.008) HR = 1.72 [IC95% 1.15-2.57] ; p = 0.008	Kaplan-Meier and Log rank test Cox model (univariate)
Russ / 2017 (37)	Retrospective (2010-2013)	21 PEG	Median survival after gastrostomy placement: 327 days [180-687]	Kaplan-Meier
Burkhardt / 2017 (38)	Retrospective (2003-2015)	80 patients	HRa 0.24 [IC95% 0.09-0.62] ; p < 0.01	Cox model
Cui / 2018 (39)	Meta-analysis	10 studies: 996 patients	1 months: aOR = 1.59 [IC95% 0.93-2.71] ; p = 0.092 10 months: aOR = 1.25 [IC95% 0.72-2.17] ; p = 0.436 20 months: aOR = 1.97 [IC95% 1.21-3.21] ; p = 0.007 30 months: aOR = 1.28 [IC95% 0.77-2.11] ; p = 0.338	-Studies before 2005 -Retrospective -Sample < 100 patients -Mean age ≥ 60 years -Percentage of men ≥ 50%