



**HAL**  
open science

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

Marion Vergonjeanne, Philippe Fayemendy, Benoît Marin, Marie Penoty, Géraldine Lautrette, Huguette Sourisseau, Pierre-Marie Preux, Jean-Claude Desport, Philippe Couratier, Pierre Jésus

### ► To cite this version:

Marion Vergonjeanne, Philippe Fayemendy, Benoît Marin, Marie Penoty, Géraldine Lautrette, et al.. Predictive factors for gastrostomy at time of diagnosis and impact on survival in patients with amyotrophic lateral sclerosis. *Clinical Nutrition*, Elsevier, 2020, 39 (10), pp.3112-3118. 10.1016/j.clnu.2020.01.018 . hal-02489353

**HAL Id: hal-02489353**

**<https://hal-unilim.archives-ouvertes.fr/hal-02489353>**

Submitted on 17 Oct 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution-NonCommercial 4.0 International License

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

3 Marion Vergonjeanne<sup>a</sup>, Philippe Fayemendy<sup>b</sup>, Benoit Marin<sup>c</sup>, Marie Penoty<sup>d</sup>, Géraldine  
4 Lautrette<sup>e</sup>, Huguette Sourisseau<sup>f</sup>, Pierre-Marie Preux<sup>g</sup>, Jean-Claude Desport<sup>h</sup>, Philippe  
5 Couratier<sup>i</sup>, Pierre Jésus<sup>j</sup>

6

7 <sup>a</sup> INSERM U1094, Univ. Limoges, CHU Limoges, IRD, U1094, Tropical  
8 Neuroepidemiology, Institute of Epidemiology and Tropical Neurology, GEIST, Limoges,  
9 France. Electronic address: marion.vergonjeanne@yahoo.fr

10 <sup>b</sup> INSERM U1094, Univ. Limoges, CHU Limoges, IRD, U1094, Tropical  
11 Neuroepidemiology, Institute of Epidemiology and Tropical Neurology, GEIST, Limoges,  
12 France; CHU Limoges, Department of Nutrition, Limoges, France. Electronic address:  
13 Philippe.Fayemendy@chu-limoges.fr

14 <sup>c</sup> INSERM U1094, Univ. Limoges, CHU Limoges, IRD, U1094, Tropical  
15 Neuroepidemiology, Institute of Epidemiology and Tropical Neurology, GEIST, Limoges,  
16 France; Epidemiology, Biostatistics and Methodological research centre, University Hospital  
17 of Limoges. Electronic address: benoit.marin@unilim.fr

18 <sup>d</sup> INSERM U1094, Univ. Limoges, CHU Limoges, IRD, U1094, Tropical  
19 Neuroepidemiology, Institute of Epidemiology and Tropical Neurology, GEIST, Limoges,  
20 France; ALS center, Neurology department, University Hospital of Limoges, France.  
21 Electronic address: Marie.Penoty@chu-limoges.fr

22 <sup>e</sup> ALS center, Neurology department, University Hospital of Limoges, France. Electronic  
23 address: Geraldine.Lautrette@chu-limoges.fr

24 <sup>f</sup> CHU Limoges, Department of Nutrition, Limoges, France. Electronic address:  
25 Huguette.SOURISSEAU@chu-limoges.fr

26 <sup>g</sup> INSERM U1094, Univ. Limoges, CHU Limoges, IRD, U1094, Tropical  
27 Neuroepidemiology, Institute of Epidemiology and Tropical Neurology, GEIST, Limoges,  
28 France; Epidemiology, Biostatistics and Methodological research centre, University Hospital  
29 of Limoges. Electronic address: pierre-marie.preux@unilim.fr

30 <sup>h</sup> INSERM U1094, Univ. Limoges, CHU Limoges, IRD, U1094, Tropical  
31 Neuroepidemiology, Institute of Epidemiology and Tropical Neurology, GEIST, Limoges,  
32 France; CHU Limoges, Department of Nutrition, Limoges, France. Electronic address:  
33 nutrition@unilim.fr

34 <sup>i</sup> INSERM U1094, Univ. Limoges, CHU Limoges, IRD, U1094, Tropical  
35 Neuroepidemiology, Institute of Epidemiology and Tropical Neurology, GEIST, Limoges,  
36 France; ALS center, Neurology department, University Hospital of Limoges, France.  
37 Electronic address: philippe.couratier@unilim.fr

38 <sup>j</sup> INSERM U1094, Univ. Limoges, CHU Limoges, IRD, U1094, Tropical  
39 Neuroepidemiology, Institute of Epidemiology and Tropical Neurology, GEIST, Limoges,  
40 France; CHU Limoges, Department of Nutrition, Limoges, France. Electronic address:  
41 Pierre.Jesus@chu-limoges.fr

42

43 **Corresponding author:** Dr. Pierre Jésus, Nutrition Unit, University Hospital of Limoges, 2  
44 Avenue Martin Luther King, 87042 Limoges cedex. pierre.jesus@chu-limoges.fr Phone: + 33  
45 5 55 05 66 21 Fax: + 33 5 55 05 63 54

46

47 **Running head:** Survival in ALS patients with gastrostomy indication.

48

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

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

57 **ABSTRACT:**

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

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

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

69 **Results:** Two hundred and eighty-five patients were included. Among the 182 for whom  
70 gastrostomy was indicated, 63.7% accepted the placement. The median time was 7.3 months  
71 [IQR: 3.2 – 15.0] and 2.7 months [IQR: 0.9 – 5.8] respectively from diagnosis to indication  
72 and from indication to placement. Weight loss > 5% significantly increased the risk of death  
73 by 17% ( $p < 0.0001$ ). At time of diagnosis, bulbar onset, a loss of one point in the body mass  
74 index or on the bulbar functional scale were all positively associated with indication for  
75 gastrostomy (aOR = 10.0 [95%CI: 1.96-25.0];  $p = 0.002$ , aOR = 1.17 [95%CI: 1.02-1.36];  $p =$   
76  $0.025$  and aOR = 1.19 [95%CI: 1.06-1.32];  $p = 0.002$ , respectively). However, gastrostomy  
77 placement did not have any impact on survival (aHR = 1.25 [95%CI: 0.88-1.79];  $p = 0.22$ ).

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

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

83

84 **Introduction:**

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

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

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

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

105

## 106 **Materials and Methods**

### 107 Study design

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

### 120 Nutritional assessment:

121 During the follow-up, every three months, at each clinical consultation, current weight  
122 and usual weight (in kg, six months before the first symptoms) are prospectively collected.  
123 Patients are weighted in their underwear on an 0.1 kg electronic SECA scale (Vogel & Halke,  
124 Hamburg, Germany), in either a standing or a seated position for those who cannot stand up.  
125 Height (in m) is measured in the upright position with a 0.2 cm SECA gauge (Vogel & Halke,  
126 Hamburg, Germany), or with the Chumlea formula for patients over 60 years who could not  
127 stand up (17). Body mass index (BMI), in kg/m<sup>2</sup>, is calculated, which allowed to classify  
128 patients as follows: (i) undernutrition: BMI <18.5 for age <70 years and BMI <21 for age ≥70  
129 years; (ii) normal: 18.5≤BMI<25 for age <70 years and 21≤BMI<27 for age ≥70 years; (iii)  
130 overweight: 25≤BMI<30 for age <70 years and 27≤BMI<30 for age ≥70 years; (iv) obesity:



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

144 Neurological and respiratory assessments:

145       Functional decline is recorded on the Amyotrophic Lateral Sclerosis Functional Rating  
146 Scale revised version (ALSFRS-R) and the ALSFRS-R slope was calculated according to the  
147 formula:  $(48 - \text{ALSFRS-R at time of diagnosis}) / (\text{duration from onset to diagnosis})$  (22). The  
148 modified Norris bulbar score (39 points maximum) and Manual Muscular Testing (MMT)  
149 (150 points maximum) are also collected (10,23). The date of the first symptom and the site of  
150 onset are recorded. FVC expressed as percentage of theoretical value is measured at each visit  
151 every three months and the presence of non-invasive ventilation had been collected during the  
152 follow-up.

153 Statistical methods:

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

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

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

173 **Results:**

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

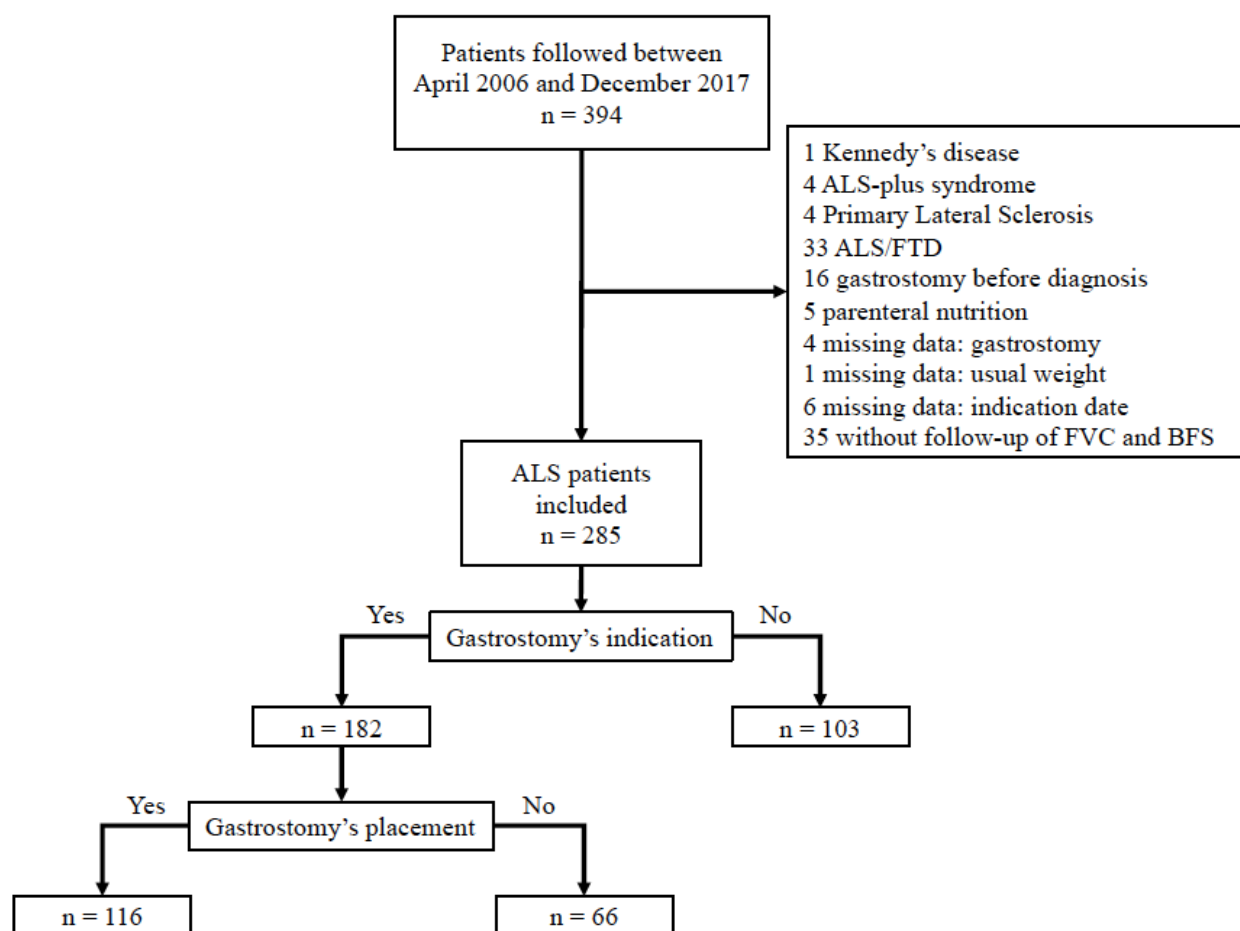


Figure 1: Flowchart of included ALS patients (n = 285)

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

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

178           During the follow-up, 117 (62.1%) had Non-Invasive Ventilation (NIV) and 182  
179 (63.9%) had indication for gastrostomy. Mean time from diagnosis to gastrostomy indication  
180 was 7.3 months [IQR: 3.2 – 15.0]. The characteristics of patients with and without  
181 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) n (%) or Median [IQR]	Yes (n=182) n (%) or Median [IQR]	No (n=103) n (%) or Median [IQR]		
<b>Age</b> (years)	66.0 [57.7-74.5]	66.8 [58.9-74.7]	64.6 [54.5-73.9]	0	0.139 <sup>b</sup>
<b>Sex</b>				0	<b>0.026<sup>a</sup></b>
Male	155 (54.4)	90 (49.5)	65 (63.1)		
Female	130 (45.6)	92 (50.5)	38 (36.9)		
<b>Time to diagnosis</b> (months)	9.3 [6.0-13.9]	8.4 [5.9-12.8]	10.9 [6.8-17.5]	0	<b>0.036<sup>b</sup></b>
<b>Type of onset</b>				0	<b>&lt;0.0001<sup>a</sup></b>
Bulbar	88 (30.9)	83 (45.6)	5 (4.9)		
Spinal	197 (69.1)	99 (54.4)	98 (95.1)		
<b>Airlie House criteria</b>				0	<b>0.007<sup>a</sup></b>
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)		
<b>ALSFRS-R</b> (/48 points)	40.8 [36.0-43.2]	40.0 [36.0-43.2]	41.0 [38.0-43.2]	6	0.218 <sup>b</sup>
<b>ALSFRS-R slope</b> (units/month)	-0.7 [-1.4- -0.4]	-0.8 [-1.5- -0.5]	-0.7 [-1.1- -0.4]	0	<b>0.008<sup>b</sup></b>
<b>MMT</b> (/150 points)	138.0 [125.0-145.0]	139.0 [125.0-146.0]	136.0 [128.0-143.0]	8	<b>0.037<sup>b</sup></b>
<b>BFS</b> (/39 points)	37.0 [31.0-39.0]	33.0 [27.0-39.0]	39.0 [38.0-39.0]	5	<b>&lt;0.0001<sup>b</sup></b>
<b>FVC</b> (% of theoretical value)	94.0 [73.0-109.0]	88.0 [70.0-105.0]	99.0 [83.5-111.5]	58	<b>0.012<sup>b</sup></b>
<b>Weight</b> (kg)	65.8 [58.6-75.2]	63.5 [56.5-72.7]	71.1 [63.4-79.2]	0	<b>&lt;0.0001<sup>c</sup></b>
<b>BMI</b> (kg/m <sup>2</sup> )	24.6 [22.3-27.6]	24.1 [22.0-26.2]	25.8 [23.4-28.0]	0	<b>&lt;0.0001<sup>b</sup></b>
<b>Nutritional status</b>				0	<b>0.002<sup>a</sup></b>
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)		
<b>Weight loss</b> (%)	3.8 [0.0-9.4]	4.5 [0.0-11.1]	2.1 [0.0-7.4]	0	<b>0.011<sup>b</sup></b>
<b>Phase angle</b> (°)	3.1 [2.6-3.9]	3.1 [2.5-3.8]	3.1 [2.6-4.3]	12	0.195 <sup>b</sup>
<b>Fat mass</b> (kg)	20.6 [15.5-25.0]	20.1 [14.5-23.5]	22.7 [17.6-26.7]	16	<b>0.006<sup>b</sup></b>
<b>Fat mass</b> (%)	30.3 [24.1-37.7]	30.2 [23.0-37.2]	30.6 [25.6-38.8]	16	0.516 <sup>b</sup>
<b>Fat free mass</b> (kg)	45.8 [38.0-52.7]	42.9 [37.2-51.3]	49.8 [39.8-55.4]	16	<b>0.002<sup>b</sup></b>
<b>Fat free mass</b> (%)	69.7 [62.3-75.9]	69.8 [62.8-77.0]	69.4 [61.2-74.4]	16	0.516 <sup>b</sup>
<b>Waist circumference</b> (cm)	90.0 [81.0-99.0]	87.0 [80.0-95.0]	94.0 [87.0-102.0]	6	<b>&lt;0.0001<sup>c</sup></b>

ALSFERS-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<sup>2</sup> test; b: Mann-Whitney test; c: Student test; in bold:  $p < 0.05$

182 After adjustment, the factors associated with a gastrostomy indication at time of  
183 diagnosis were bulbar onset (aOR = 10.00 [95%CI: 1.96 – 25.0]), loss of 1 point on the BFS  
184 (aOR: 1.19 [95%CI: 1.06-1.32]), weight loss of 1 kg (aOR = 1.03 [95%CI: 1.01 – 1.06]) and  
185 loss of 1 point of BMI (aOR = 1.17 [95%CI: 1.02-1.36]) (Table 2). During the follow up, the  
186 placement of NIV was also associated with the indication for gastrostomy (aOR = 4.58  
187 [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
<b>Age* (+1 year)</b>	1.01 [1.00-1.04]	0.13	0.98 [0.96-1.01]	0.170
<b>Sex</b>				
Male	1.00		1.00	
Female	1.75 [1.07-2.86]	<b>0.027</b>	1.23 [0.61-2.50]	0.547
<b>Non-invasive ventilation<sup>#</sup></b>				
No	1.00		1.00	
Yes	3.40 [2.05-5.65]	<b>0.0001</b>	<b>4.58</b> [2.36-8.88]	<b>0.0001</b>
<b>Time onset - diagnosis (+1 year)</b>	0.98 [0.97-1.00]	0.10	-	-
<b>Type of onset</b>				
Spinal	1.00		1.00	
Bulbar	16.67 [6.25-50]	<b>0.0001</b>	<b>10.00</b> [1.96-25.0]	<b>0.002</b>
<b>ALSFRS-R slope* (-1 point/month)</b>	1.47 [1.08-2.00]	<b>0.016</b>	-	-
<b>BFS* (-1 point)</b>	1.35 [1.23-1.47]	<b>0.0001</b>	<b>1.19</b> [1.06-1.32]	<b>0.002</b>
<b>Weight* (-1 kg)</b>	1.04 [1.02-1.06]	<b>0.0001</b>	<b>1.03</b> [1.01-1.06]	<b>0.037</b>
<b>BMI loss* (-1 kg/m<sup>2</sup>)</b>	1.25 [1.12-1.40]	<b>0.0001</b>	<b>1.17</b> [1.02-1.36]	<b>0.025</b>
<b>Fat mass* (-1 kg)</b>	1.03 [1.01-1.06]	<b>0.032</b>	-	-
<b>Phase angle* (-1°)</b>	1.23 [0.97-1.59]	0.098	-	-

ALSFERS-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:  $p < 0.05$

188 For the 285 patients with ALS, the median survival from diagnosis was 18.7 months [IQR:  
189 16.2 – 21.2] and the crude mortality rate by December 31<sup>st</sup> 2017 was 77.9%. Among the 182  
190 patients with indication for gastrostomy placement, 116 (63.7%) patients accepted the  
191 placement of the feeding tube. Characteristics of ALS patients at gastrostomy indication,  
192 comparing patients who declined or accepted gastrostomy placement, are presented in  
193 Appendix A. The mean time from indication to placement was 2.7 months [0.9 – 5.8]. The  
194 crude mortality rate was 8.6%, one month after gastrostomy placement. Nevertheless,  
195 multivariate survival analysis showed that gastrostomy placement during the follow-up had no  
196 significant impact on survival (Table 3). At time of diagnosis, each 5% of weight loss  
197 increased the risk of death by 17%. There was no interaction between gastrostomy placement  
198 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
<b>Time onset – diagnosis</b> (+6 months)	0.91	[0.84-0.99]	<b>0.024</b>			
<b>Time diagnosis - indication</b> (+6 months)	0.95	[0.88-1.02]	0.15			
<b>Age*</b> (+5 years)	1.10	[1.04-1.18]	<b>0.002</b>	<b>1.16</b>	[1.09-1.24]	<b>&lt;0.0001</b>
<b>MMT<sup>#</sup></b> (- 10 points)	1.15	[1.10-1.21]	<b>&lt;0.0001</b>			
<b>ALSFRS-R<sup>#</sup></b> (- 5 points)	1.40	[1.27-1.54]	<b>&lt;0.0001</b>	<b>1.43</b>	[1.26-1.57]	<b>&lt;0.0001</b>
<b>BFS<sup>#</sup></b> (- 5 points)	1.08	[0.99-1.16]	0.058			
<b>FVC<sup>#</sup></b> (- 10% of theoretical value)	1.05	[0.99-1.12]	0.01			
<b>Weight loss<sup>#</sup></b> (- 5%)	1.13	[1.05-1.21]	<b>0.0006</b>	<b>1.17</b>	[1.09-1.26]	<b>&lt;0.0001</b>
<b>Sex</b>			0.57			
Male	1.00					
Female	1.10	[0.80-1.52]				
<b>Type of onset</b>			0.09			
Spinal	1.00					
Bulbar	1.32	[0.95-1.82]				
<b>Airlie House criteria*</b>			<b>&lt;0.0001</b>			
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]				
<b>Gastrostomy<sup>#</sup></b>			<b>0.002</b>			0.216
No	1.00			1.00		
Yes	1.74	[1.23-2.45]		1.25	[0.88-1.79]	
<b>NIV<sup>#</sup></b>			<b>&lt;0.0001</b>			<b>0.03</b>
No	1.00			1.00		
Yes	2.33	[1.61-3.36]		<b>1.54</b>	[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:**

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

206           Jackson-Tarlton et al., have demonstrated that the presence of moderate swallowing  
207 troubles scoring 3 on the swallowing item of the ALSFRS-R (maximum 4 points) was  
208 associated with indication for percutaneous endoscopic gastrostomy (PEG) placement with an  
209 OR at 4.24 [95% CI 1.47-12.23]. When swallowing function was evaluated between 0 was 2,  
210 the OR dramatically increased at 52.23 [95% CI 19.12-142.69] (24). According to Conde et  
211 al., PEG could be performed following sensitive indicators like  $FVC \leq 74\%$ , Cough Peak  
212 Flow  $\leq 205$  l/min, ALSFRS-R  $< 29$  or bulbar sub-score of ALSFRS-R  $\leq 8$  (25). In their  
213 population, 75% of patients who accepted PEG had a bulbar onset. Similarly, in our study,  
214 55.2% of patients who accepted PEG had a bulbar onset.

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

223 (14,15). These contradictory results may be explained by the difficulty to compare the group  
224 of ALS patients accepting tube feeding with those who refuse it (Appendix B).

225         According to this methodological aspect, survival was assessed not only considering  
226 patients with or without gastrostomy, but taking into account patients who needed and then  
227 accepted or not the feeding tube placement. This study allowed to identify a 17% increase in  
228 the risk of death for each 5% of weight loss based on usual weight as previously reported  
229 (26). Moreover, in the ProGas study, patients with a weight loss greater than 10% between  
230 diagnosis and gastrostomy placement had a risk of death increased by 151% (aHR = 2.51; p =  
231 0.0011) compared with those who lost less than 10% of body weight. According to the  
232 European guidelines for ALS nutritional management, the aim of nutritional care is to  
233 stabilize the weight if BMI is between 25 and 35kg/m<sup>2</sup> and to improve nutritional status if  
234 BMI is under 25kg/m<sup>2</sup> (11). It remains essential to assess the nutritional status and to adapt  
235 nutritional care since time of diagnosis using oral nutritional supplements and texture  
236 adaptation in order to have a positive impact on functional evolution and survival. In this  
237 sense, the placement of gastrostomy could improve ALS patients' survival. Unfortunately, our  
238 study did not find any impact of gastrostomy on survival of probable ALS patients because  
239 the placement occurred too late as we observed in our study with a median delay of 10 months  
240 after diagnosis whereas the median survival was 17.5 months (26).

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

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

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

258 Our study has also some limitations : our ALS population was selected from the  
259 referral centre and not from the French register of ALS in Limousin (FRALim), which could  
260 have induced some selection bias (26). Another limit is the absence of use concerning the  
261 daily food intake data at diagnosis and during follow-up, the results of the DePippo test  
262 (29,30) and the value of resting energy expenditure. These parameters would have allowed to  
263 clarify the causes of early weight loss in our patients. Daily food intake data are difficult to  
264 obtain mainly at diagnosis. Furthermore, food surveys can be biased. The De Pippo test is  
265 performed at each nutritional examination. However, data are not systematically entered in  
266 the database or in medical records and therefore induce a high number of missing data at  
267 diagnosis (n=212) and at gastrostomy indication (n=260). Concerning the resting energy  
268 expenditure, also to limit missing data and the non-inclusion of patients we did not study this  
269 parameter. Moreover, a recent study has demonstrated that mean time until the feeding tube  
270 placement is not statistically different between patients with or without hypermetabolism (31).

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

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

275

276 **Conflicts of interest**

277 No conflicts are declared

278 **Acknowledgements:**

279 We thank Professor Sylvie Gautier for proofreading the manuscript.

280 **Author contributions**

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

284 **Funding:**

285 The present study was supported by a research grant from association ALAIR.

**REFERENCES:**

- 286 1. Swinnen B, Robberecht W. The phenotypic variability of amyotrophic lateral sclerosis.  
287 Nat Rev Neurol. 2014;10:661–70. DOI: 10.1038/nrneurol.2014.184
- 288 2. Desport JC, Preux PM, Truong TC, Vallat JM, Sautereau D, Couratier P. Nutritional  
289 status is a prognostic factor for survival in ALS patients. Neurology. 1999;53:1059–63.  
290 DOI: 10.1212/wnl.53.5.1059
- 291 3. Marin B, Desport JC, Kajeu P, Jesus P, Nicolaud B, Nicol M, et al. Alteration of  
292 nutritional status at diagnosis is a prognostic factor for survival of amyotrophic lateral  
293 sclerosis patients. J Neurol Neurosurg Psychiatry. 2011;82:628–34. DOI:  
294 10.1136/jnnp.2010.211474
- 295 4. Genton L, Viatte V, Janssens J-P, Héritier A-C, Pichard C. Nutritional state, energy  
296 intakes and energy expenditure of amyotrophic lateral sclerosis (ALS) patients. Clin  
297 Nutr. 2011;30:553–9. DOI: 10.1016/j.clnu.2011.06.004
- 298 5. Couratier P, Desport J-C, Antonini M-T, Mabrouk T, Perna A, Vincent F, et al. Prise en  
299 charge nutritionnelle et respiratoire des patients atteints de Sclérose Latérale  
300 Amyotrophique (SLA). Rev Neurol (Paris). 2004;160:243–50. DOI: 10.1016/S0035-  
301 3787(04)70898-X
- 302 6. Andersen PM, Borasio GD, Dengler R, Hardiman O, Kollewe K, Leigh PN, et al. Good  
303 practice in the management of amyotrophic lateral sclerosis: Clinical guidelines. An  
304 evidence-based review with good practice points. EALSC Working Group. Amyotroph  
305 Lateral Scler. 2007;8:195–213. DOI: 10.1080/17482960701262376
- 306 7. Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshe D, Johnston W, et al.  
307 Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis:  
308 Drug, nutritional, and respiratory therapies (an evidence-based review): Report of the  
309 Quality Standards Subcommittee of the American Academy of Neurology. Neurology.  
310 2009;73:1227–33. DOI: 10.1212/WNL.0b013e3181bc01a4
- 311 8. Greenwood DI. Nutrition management of amyotrophic lateral sclerosis. Nutr Clin Pract  
312 Off Publ Am Soc Parenter Enter Nutr. 2013;28:392–9. DOI:  
313 10.1177/0884533613476554

- 314 9. EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis:,  
315 Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, et al. EFNS guidelines  
316 on the clinical management of amyotrophic lateral sclerosis (MALS)--revised report of  
317 an EFNS task force. *Eur J Neurol.* 2012;19:360–75. DOI: 10.1111/j.1468-  
318 1331.2011.03501.x
- 319 10. Prise en charge des personnes atteintes de sclérose latérale amyotrophique.  
320 Recommandations HAS, conférence de consensus. *Rev Neurol (Paris)*; 2006.
- 321 11. Burgos R, Bretón I, Cereda E, Desport JC, Dziewas R, Genton L, et al. ESPEN guideline  
322 clinical nutrition in neurology. *Clin Nutr Edinb Scotl.* 2018;37:354–96. DOI:  
323 10.1016/j.clnu.2017.09.003
- 324 12. Czaplinski A, Yen AA, Simpson EP, Appel SH. Slower Disease Progression and  
325 Prolonged Survival in Contemporary Patients With Amyotrophic Lateral Sclerosis: Is  
326 the Natural History of Amyotrophic Lateral Sclerosis Changing? *Arch Neurol.*  
327 2006;63:1139–43. DOI: 10.1001/archneur.63.8.1139
- 328 13. Chiò A, Mora G, Leone M, Mazzini L, Cocito D, Giordana MT, et al. Early symptom  
329 progression rate is related to ALS outcome: a prospective population-based study.  
330 *Neurology.* 2002;59:99–103. DOI: 10.1212/wnl.59.1.99
- 331 14. Forbes R, Colville S, Swingler R, for the Scottish Motor Neurone Disease Research  
332 Group. Frequency, timing and outcome of gastrostomy tubes for amyotrophic lateral  
333 sclerosis/motor neurone disease: A record linkage study from the Scottish Motor  
334 Neurone Disease Register. *J Neurol.* 2004;251:813–7. DOI: 10.1007/s00415-004-0429-9
- 335 15. Mitsumoto H, Davidson M, Moore D, Gad N, Brandis M, Ringel S, et al. Percutaneous  
336 endoscopic gastrostomy (PEG) in patients with ALS and bulbar dysfunction. *Amyotroph*  
337 *Lateral Scler Other Motor Neuron Disord.* 2003;4:177–85. DOI:  
338 10.1080/14660820310011728
- 339 16. ProGas Study Group. Gastrostomy in patients with amyotrophic lateral sclerosis  
340 (ProGas): a prospective cohort study. *Lancet Neurol.* 2015;14:702–9. DOI:  
341 10.1016/S1474-4422(15)00104-0

- 342 17. Chumlea WC, Roche AF, Steinbaugh ML. Estimating stature from knee height for  
343 persons 60 to 90 years of age. *J Am Geriatr Soc.* 1985 Feb;33(2):116–20. DOI:  
344 10.1111/j.1532-5415.1985.tb02276.x
- 345 18. HAS - Synthèse des recommandations 2007. Stratégie de prise en charge en cas de  
346 dénutrition protéino-énergétique chez la personne âgée. [Internet]. Available from:  
347 [https://www.has-sante.fr/portail/jcms/c\\_546549/fr/strategie-de-prise-en-charge-en-cas-](https://www.has-sante.fr/portail/jcms/c_546549/fr/strategie-de-prise-en-charge-en-cas-)  
348 [de-denuitration-proteino-energetique-chez-la-personne-agee](https://www.has-sante.fr/portail/jcms/c_546549/fr/strategie-de-prise-en-charge-en-cas-de-denuitration-proteino-energetique-chez-la-personne-agee)
- 349 19. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert  
350 Committee. *World Health Organ Tech Rep Ser.* 1995;854:1–452.
- 351 20. Desport JC, Preux PM, Bouteloup-Demange C, Clavelou P, Beaufrère B, Bonnet C, et  
352 al. Validation of bioelectrical impedance analysis in patients with amyotrophic lateral  
353 sclerosis. *Am J Clin Nutr.* 2003;77:1179–85. DOI: 10.1093/ajcn/77.5.1179
- 354 21. Desport J-C, Marin B, Funalot B, Preux P-M, Couratier P. Phase angle is a prognostic  
355 factor for survival in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler.*  
356 2008;9:273–8. DOI: 10.1080/17482960801925039
- 357 22. Kimura F, Fujimura C, Ishida S, Nakajima H, Furutama D, Uehara H, et al. Progression  
358 rate of ALSFRS-R at time of diagnosis predicts survival time in ALS. *Neurology.*  
359 2006;66:265–7. DOI: 10.1212/01.wnl.0000194316.91908.8a
- 360 23. Shefner JM. Strength Testing in Motor Neuron Diseases. *Neurotherapeutics.*  
361 2017;14:154–60. DOI: 10.1007/s13311-016-0472-0
- 362 24. Jackson-Tarlton CS, Benstead TJ, Doucette S, CNDR INVESTIGATOR NETWORK.  
363 Correlating factors in the recommendation of feeding tubes in the nutritional  
364 management of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Front Degener.*  
365 2016;17:515–21. DOI: 10.1080/21678421.2016.1213851
- 366 25. Conde B, Martins N, Rodrigues I, Pimenta A, Winck J. Functional and Endoscopic  
367 Indicators for Percutaneous Endoscopic Gastrostomy (PEG) in Amyotrophic Lateral  
368 Sclerosis Patients. *J Clin Med.* 2018;7:352. DOI: 10.3390/jcm7100352

- 369 26. Marin B, Hamidou B, Couratier P, Nicol M, Delzor A, Raymondeau M, et al.  
370 Population-based epidemiology of amyotrophic lateral sclerosis (ALS) in an ageing  
371 Europe - the French register of ALS in Limousin (FRALim register). *Eur J Neurol*.  
372 2014;21:1292–300. DOI: 10.1111/ene.12474
- 373 27. Desport J-C, Mabrouk T, Bouillet P, Perna A, Preux P-M, Couratier P. Complications  
374 and survival following radiologically and endoscopically-guided gastrostomy in patients  
375 with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron*  
376 *Disord*. 2005;6:88–93. DOI: 10.1080/14660820410021258
- 377 28. Stavroulakis T, Walsh T, Shaw PJ, McDermott CJ, (on behalf of the Progas Study).  
378 Gastrostomy use in motor neurone disease (MND): A review, meta-analysis and survey  
379 of current practice. *Amyotroph Lateral Scler Front Degener*. 2013;14:96–104. DOI:  
380 10.3109/17482968.2012.723722
- 381 29. DE PIPPO K, HOLAS M, REDING M. The Burke Dysphagia Screening Test: validation  
382 of its use in patients with stroke. *Arch Phys Rehabil*. 1994;75:1284–6. PMID: 7993165
- 383 30. DE PIPPO K, HOLAS M, REDING M. Validation of the 3-oz water swallow test for  
384 aspiration following stroke. *Arch Neurol*. 1992;49:1259–61. DOI:  
385 10.1001/archneur.1992.00530360057018
- 386 31. Jésus P, Fayemendy P, Nicol M, Lautrette G, Sourisseau H, Preux P-M, et al.  
387 Hypermetabolism is a deleterious prognostic factor in patients with amyotrophic lateral  
388 sclerosis. *Eur J Neurol*. 2018;25:97–104. DOI: 10.1111/ene.13468
- 389 32. Mazzini L, Corrà T, Zaccala M, Mora G, Del Piano M, Galante M. Percutaneous  
390 endoscopic gastrostomy and enteral nutrition in amyotrophic lateral sclerosis. *J Neurol*.  
391 1995;242:695–8. DOI: 10.1007/BF00866922
- 392 33. Desport JC, Preux PM, Truong C, Courat L, Vallat JM, Couratier P. Nutritional  
393 assessment and survival in ALS patients. *Amyotroph Lateral Scler Other Motor Neuron*  
394 *Disord*. 2000;1:91–6. DOI: 10.1080/14660820050515386
- 395 34. Spataro R, Ficano L, Piccoli F, La Bella V. Percutaneous endoscopic gastrostomy in  
396 amyotrophic lateral sclerosis: Effect on survival. *J Neurol Sci*. 2011;304:44–8. DOI:  
397 10.1016/j.jns.2011.02.016



- 398 35. Pena MJ, Ravasco P, Machado M, Pinto A, Pinto S, Rocha L, et al. What is the  
399 relevance of percutaneous endoscopic gastrostomy on the survival of patients with  
400 amyotrophic lateral sclerosis? *Amyotroph Lateral Scler*. 2012;13:550–4. DOI:  
401 10.3109/17482968.2012.684215
- 402 36. Fasano A, Fini N, Ferraro D, Ferri L, Vinceti M, Errals, et al. Percutaneous endoscopic  
403 gastrostomy, body weight loss and survival in amyotrophic lateral sclerosis: a  
404 population-based registry study. *Amyotroph Lateral Scler Front Degener*. 2017;18:233–  
405 42. DOI: 10.1080/21678421.2016.1270325
- 406 37. Russ KB, Phillips MC, Mel Wilcox C, Peter S. Percutaneous Endoscopic Gastrostomy in  
407 Amyotrophic Lateral Sclerosis. *Am J Med Sci*. 2015;350:95–7. DOI:  
408 10.1097/MAJ.0000000000000517
- 409 38. Burkhardt C, Neuwirth C, Sommacal A, Andersen PM, Weber M. Is survival improved  
410 by the use of NIV and PEG in amyotrophic lateral sclerosis (ALS)? A post-mortem  
411 study of 80 ALS patients. Zhou R, editor. *PLoS One*. 2017;12:1–12. DOI:  
412 10.1371/journal.pone.0177555
- 413 39. Cui F, Sun L, Xiong J, Li J, Zhao Y, Huang X. Therapeutic effects of percutaneous  
414 endoscopic gastrostomy on survival in patients with amyotrophic lateral sclerosis: A  
415 meta-analysis. Green J, editor. *PLoS One*. 2018;13:e0192243. DOI:  
416 10.1371/journal.pone.0192243

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

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

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<sup>2</sup> 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
<b>Mazzini /1995</b> (32)	Prospective	66 patients with swallowing disorders & weight loss > 5% 31 PEG / 35 refusal	<u>Mean survival from symptom onset:</u> - 38 ± 17 months: with gastrostomy - 30 ± 13 months: without gastrostomy; (p = 0.03)	Univariate survival analysis
<b>Desport /2000</b> (33)	Retrospective (1996-1998)	- 30 PEG / 30 oral	No difference	Survival analysis
<b>Chio / 2002</b> (13)	Prospective	- 52 PEG / 169 oral	aHR = 0.26 ; p = 0.0004	Cox model
<b>Mitsumoto / 2003</b> (15)	Retrospective	-137 PEG / 187 oral	<u>Mean survival:</u> 47 vs 58 months ; p = 0.33	Adjustment on bulbar score
<b>Forbes / 2004</b> (14)	Retrospective (1989-1998)	142 PEG / 1084 oral	<u>Median survival from symptom onset:</u> -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
<b>Czaplinski / 2006</b> (12)	Retrospective (1984-2004)	175 PEG / 766 oral	HRa = 0.75 [IC95% 0.63-0.90] ; p= 0.003	Cox model
<b>Spataro / 2011</b> (34)	Retrospective (2000-2007)	150 patients with swallowing disorders 76 PEG / 74 refusal	<u>Median survival from symptom onset:</u> - 38 months: with gastrostomy - 32 months: without gastrostomy (p = 0.05)	Kaplan-Meier and Log rank test
<b>Pena / 2012</b> (35)	Retrospective (1995- 2011)	151 patients with PEG 106 bulbar onset / 45 spinal onset	<u>Median survival after gastrostomy placement:</u> - 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
<b>Fasano 2017</b> (36)	Retrospective (2009-2013)	193 patients with swallowing disorders 152 PEG / 41 refusal	<u>Median survival from recommendations:</u> - 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)
<b>Russ / 2017</b> (37)	Retrospective (2010-2013)	21 PEG	<u>Median survival after gastrostomy placement:</u> 327 days [180-687]	Kaplan-Meier
<b>Burkhardt / 2017</b> (38)	Retrospective (2003-2015)	80 patients	HRa 0.24 [IC95% 0.09-0.62] ; p < 0.01	Cox model
<b>Cui / 2018</b> (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%