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1 **Increased resting energy expenditure compared to predictive theoretical equations in**
2 **Amyotrophic Lateral Sclerosis.**

3

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26 **Short running head:** Increased resting energy expenditure in ALS

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33

34 **Highlights:**

35 - In ALS patients measured REE is higher than calculated REE.

36 - Increase of metabolic rate is present whatever the REE predictive equations used.

37 - HB 1919 formula is still relevant as a reference value to search a REE variation.

38 - Mifflin formula seems also interesting to screen patient with evolving risk.

39 - Threshold of REE variation of 20% is better than 10% to screen patient with evolving
40 risk.

41

42 **Abstract**

43 Introduction: About 50-60% of Amyotrophic Lateral Sclerosis (ALS) is characterized by an
44 increase of metabolic rate. Harris and Benedict's (HB) 1919 formula is the equation mainly
45 used to calculate REE (cREE) compared to measured REE (mREE) by indirect calorimetry
46 (IC), but others are also applied in current practice. The present study aimed i) to assess
47 mREE in ALS patients compared to 12 cREE formulas and ii) to study the relevant threshold
48 of REE variation to screen patients with the higher evolving risk.

49 Method: Nutritional assessments and body composition (by bioimpedance analysis) were
50 performed in ALS patients. mREE was measured by IC and cREE was calculated using HB
51 1919 and 1984, World Schofield, De Lorenzo, Johnstone, Mifflin, WHO/FAO, Owen,
52 Fleisch, Wang, Rosenbaum and Nelson formulas. Functional and Respiratory evolution and
53 survival by Log-rank test according to two thresholds of REE variation 10% and 20% were
54 studied.

55 Results: 315 ALS patients were included. Median mREE was 1503 kcal/24h (1290 – 1698)
56 and was higher than all predictive equations ($p < 0.0001$). Depending on the predictive
57 equation, REE variation over 10% and 20% was found in 35.2% to 76.3% and in 14.6% to
58 53.3% of ALS patients, respectively. Patients with REE variation over 20% with HB 1919
59 and HB 1984 had a lower survival. Moreover, with this same threshold with Mifflin formula
60 patients had a higher functional and respiratory evolution and a lower survival.

61 Conclusion: The increase of metabolic rate is present according to the different cREE
62 formulas used compared to IC. In clinical practice REE formulas, such as HB 1919, HB 1984
63 or Mifflin, can be used as a reference value compared to IC to screen ALS patients with REE
64 variation over 20% who have a higher evolving risk.

65

66

67 **Keywords:** Amyotrophic lateral sclerosis, metabolic rate, resting energy expenditure,
68 predictive equation, evolution, survival.

69

70 **Introduction**

71 Amyotrophic lateral sclerosis (ALS) is a rare and severe neurodegenerative disease with an
72 age at diagnosis of 65-70 years and a median survival of 25 to 30 months after diagnosis in
73 Europe [1]. Its incidence is stable at around 2/ 100 000 person years in Western populations
74 [1]. For 9-55% of patients according to the studies, malnutrition is present, which is an
75 independent factor for survival [2–4]. One cause of malnutrition is an abnormal increase of
76 resting energy expenditure (REE) [4–9]. The reference method to assess REE is to measure it
77 (mREE) by indirect calorimetry (IC) [6,7,10–13]. When this method is not available,
78 predictive formulas are used to derive theoretical REE (cREE) principally Harris and
79 Benedict 1919 (HB 1919) [6,7,10–14].

80 The increase of metabolic rate in ALS is defined by more than +10% of REE variation
81 between mREE and cREE [4–7,14]. Using HB 1919 for cREE, this REE variation over 10%
82 was found in 48.0% to 68.0% of ALS patients [4–7,14]. Funalot et al. reported that all of 11
83 patients with familial form with SOD1 mutation had an increase of metabolic rate [10]. In
84 ALS patients with this increase of metabolic rate, the level of REE variation was +10 to 20%
85 [4–7]. The REE variation during ALS is a prognostic factor for the survival in patients with a
86 REE variation over +20% [15,16]. However, Vaisman et al. found + 3.6% REE variation in
87 ALS patients, with no difference compared to healthy controls [12]. All these data were
88 derived using only HB 1919 equations [17]. Thus, authors are not in agreement about this
89 increase of metabolic rate in ALS and the validity of the HB 1919 formula. Assessment of
90 REE variation in ALS using REE formulas other than HB 1919 is therefore necessary. The
91 aim of our study was i) to assess the level of REE and REE variation in ALS patients, with 12
92 predictive formulas, commonly used in healthy patients (HB 1919, HB 1984, World Schofield
93 (WSchofield), De Lorenzo, Johnstone, Mifflin St. Jeor (Mifflin)) [18] and used in ALS
94 studies (HB 1919, world health organization / food and agriculture organization of the United

95 Nations (WHO/FAO), Owen, Fleisch, Wang, Rosenbaum, Mifflin and Nelson) [6,7,19–21]
96 and ii) to study the relevant threshold of REE variation to screen patients with the higher
97 evolving risk.

98

99 **Methods**

100 ALS patients were diagnosed according to Airlie House criteria (definite, probable, or
101 laboratory-supported probable and possible) [22], followed in the ALS expert center in
102 Limoges (France) and all treated with riluzole. IC was performed less than 12 months after
103 diagnosis. The respiratory quotient (RQ) during IC was between 0.7 and 0.87 [23]. The
104 general data were sex and date of IC. The data were collected prospectively and extracted
105 from the CleanWEBTM database of the Limoges ALS expert center. The databases were
106 validated by the French Commission Nationale de l'Informatique et des Libertés (CNIL;
107 reference: DP/DMS/DI074591, No. 1244525). ALS patients gave their informed consent for
108 the data collection.

109

110 The nutritional assessment of ALS patients was performed within four months after the
111 diagnosis in the Nutrition Unit of the University Hospital of Limoges. Patients were weighed
112 in underwear using a SECA[®] electronic balance recording to 0.1 kg (Vogel & Halke,
113 Hamburg, Germany) in an upright position or on a SECA[®] weighing chair if they could not
114 stand upright. Their height was measured using a SECA[®] gauge recording to 0.2 cm (Vogel &
115 Halke, Hamburg, Germany) in an upright position or using the Chumlea formulas for people
116 over 60 years old who could not be held vertically [24]. BMI was calculated as weight (kg) /
117 height x height (m²). Malnutrition was defined according to French criteria by a BMI < 18.5
118 for patients under 70 years, and a BMI < 21.0 for those over 70 [25]. Normal status was
119 defined as a BMI between 18.5 and 24.9 for patients under 70 and between 21.0 and 26.9 for
120 patients over 70. Overweight was defined as a BMI between 25.0 and 29.9 under 70 and
121 between 27.0 and 29.9 over 70. Obesity was defined as a BMI \geq 30. Body composition, fat
122 free mass (FFM in kg) and fat mass (FM in kg) were calculated by bioelectrical impedance
123 analysis (BIA) with the validated formula of Desport et al. for ALS patients (FFM = (0.436 *

124 $W) + (0.349 * \text{mean } H^2/Z50) - (0.695 * \text{mean triceps skinfold [TSF])} + 9.245$ with FFM in kg,
125 W in kg, H in cm, Z in Ohm, and TSF in mm) with the Analycor[®] device (Eugédia, Chambly,
126 France) [27]. TSF necessary for the formula of Desport et al. was obtained from the average
127 of three measurements on each side with a Harpenden caliper (Baty International, Burgess
128 Hill, UK) according to the usual modalities [26].

129 IC was performed during 30 min with the Quark RMR[®] with canopy (Cosmed, Rome, Italy)
130 for ALS patients after calibration of the instrument ($\pm 0.02\%$ on absolute concentration of
131 expired CO₂ and inspired O₂) [23]. IC was performed in the morning after 12 hours of fasting
132 at home without treatment, drink, tobacco or chewing gum during this period of fasting. IC
133 was realized in a supine position and at rest. The patient did not have physical activity before
134 the IC nor sleep during the exam, nor hyperventilate. During IC, the respiratory quotient (RQ)
135 between 0.7 and 0.87 were needed [28]. The REE was also calculated (cREE in kcal / 24h)
136 according to 12 predictive formulas (HB 1919, HB 1984, WSchofield, De Lorenzo,
137 Johnstone, Mifflin, WHO/FAO, Owen, Fleisch, Wang, Rosenbaum and Nelson) (Table 1)
138 [18,19,21]. Results in kJ (WSchofield, De Lorenzo, Johnstone and Nelson) were converted to
139 kcal by multiplying by 0.2388. The REE variation (in %) for each predictive formula used
140 was calculated according to the formula: $(\text{mREE [kcal / 24h]} - \text{cREE [kcal / 24h]}) / \text{cREE}$
141 $(\text{kcal / 24h}) * 100$. Increase of metabolic rate was defined by REE variation over 10% of the
142 theoretical value for each predictive formula used [6,7,10]. A major increase of metabolic rate
143 was defined by a REE variation over 20% of the theoretical value for each predictive formula
144 used [15,16].

145
146 The amyotrophic lateral sclerosis functional rating scale (ALSFERS) (on 40 points before
147 2009) and ALSFRS-revised (ALSFRS-R on 48 points after 2009) were collected. To
148 homogenize the results, ALSFRS was converted into a score on 48 points [29]. ALSFRS-R

149 slope (in points/month) from diagnosis to the last assessment was calculated according to the
150 formula: (ALSFRS-R score at the last assessment – ALSFRS-R score at diagnosis) / (time
151 from diagnosis to the last assessment [month]). Forced vital capacity (FVC, % of the
152 theoretical value), was collected using a Hans Rudolph® pneumotachograph, integrated into a
153 body plethysmography system 1085 (CPF Medical Graphics, St Paul, Minnesota, USA). FVC
154 slope (in %/month) from diagnosis to the last assessment was also calculated according to the
155 formula: (FVC at the last assessment – FVC at diagnosis) / (time from diagnosis to the last
156 assessment [month]).

157

158 Statistical analysis was performed using GraphPad Prism 6.0 (GraphPad Software Inc, La
159 Jolla, CA, USA). Quantitative variables were expressed with the median (interquartile range
160 [IQR]). The qualitative variables were expressed in number and percentage. Normality was
161 studied using the Shapiro-Wilk test. Comparisons of quantitative variables were made using
162 non-parametric Mann-Whitney test. Comparisons of the qualitative variables were made
163 using the Chi2. Comparative analyses were conducted, mREE and cREE with HB 1919 was
164 compared to all cREE with other formulas, REE variation and percentage of patients with
165 REE variation over 10% and 20% with HB 1919 versus other formulas. FVC slope and
166 ALSFRS-R slope were compared between patients with or without REE variation over 10%
167 and over 20% according to each REE formula used. For survival analysis, the event was the
168 date of death or of tracheostomy. Univariate survival analysis between patients with or
169 without REE variation over 10% and over 20% (according to each REE formula used), was
170 performed using the Log-rank test. The threshold of significance for all statistical analyses
171 was $p < 0.05$. We complied with the STROBE statement to be in agreement for observational
172 - cross sectional studies [30].

173

174 **Results**

175 The nutritional characteristics of ALS patients are presented in Table 2.

176 From November 1996 to November 2014, 405 ALS patients had IC, 90 were excluded
177 (flowchart: Figure 1). The 315 patients included had a median age at IC of 66.6 years (56.9–
178 4.1) with a sex ratio of 1.0. ALS patients. Median BMI was 24.2 kg / m² (22.0 – 27.6). There
179 was missing data on BIA measurement which could not be realized for 28 patients.

180 Figure 2 shows mREE, REE variations and percentages of patients with REE variation over
181 10%.

182 mREE was 1503 kcal /24h (1290-1698), higher than cREE with the formulas ($p < 0.0001$
183 whatever the equation used). Increase of metabolic rate with REE variation over 10% was
184 found in 35.2% to 76.3% of cases (Table 3). These percentages were lower for WSchofield,
185 WHO/FAO, Owen and Fleisch versus HB 1919 ($p = 0.03$, $p < 0.0001$, $p < 0.0001$, and $p =$
186 0.007 , respectively) and higher for Johnstone, Mifflin, Wang and Nelson versus HB 1919 ($p =$
187 0.03 , $p < 0.0001$, $p = 0.003$ and $p < 0.0001$, respectively). Nelson equations provided the
188 highest REE variation compared to HB 1919. A REE variation over 20% was found in 14.6%
189 to 53.3% of patients (Table 3).

190 Patients with the same metabolic status as HB 1919 using the other predictive formulas is
191 presented in figure 3. Concerning the patient with a REE variation under 10% more than 80%
192 of patients kept the same metabolic status with HB1984, WSchofield, De Lorenzo,
193 WHO/FAO, Owen, Fleisch and Rosenbaum formulas with respect to HB 1919. Concerning
194 the patient with a REE variation over 20% more than 80% of patients kept the same metabolic
195 status with HB1984, De Lorenzo, Johnstone, Mifflin, and Nelson formulas with respect to HB
196 1919.

197

198 The respiratory and functional evolution and the survival of patients with or without REE

199 variation over 10% and 20% are presented in Table 4 and 5. With a threshold of REE
200 variation of 10%, only with HB 1919 formula respiratory evolution was worst in patients over
201 10% (Table 4). No other pejorative evolution was found in these patients according to the
202 different formulas studied. With a threshold of REE variation of 20%, using HB 1919, HB
203 1984 and Mifflin formulas patients over 20% had a lower survival compared to the other
204 patients ($p = 0.01$, $p = 0.02$ and $p = 0.003$, respectively) (Table 5). Moreover, with the Mifflin
205 formula, patients over 20% had a more severe respiratory and functional evolution ($p = 0.02$
206 and $p = 0.03$, respectively).
207

208 **Discussion**

209 This study assessed the increase of metabolic rate in ALS patients with 12 equations to
210 evaluate cREE compared to mREE by IC. The results strongly suggest that the increase of
211 metabolic rate is a reality in ALS patients. REE variation was in accordance with the main
212 previous studies [6,7,11,13–16]. REE variation over 10% was very prominent, with a
213 prevalence of 55.2% with HB 1919 reference equation and this phenomenon was confirmed
214 with all the formulas used (35.2% to 76.3% of cases). A major REE variation over 20% was
215 found in 14.6% to 53.3% of patients in our study according to the predictive formulas used.
216 Indeed, this increase of metabolic rate during ALS is a prognostic factor for the functional
217 status and the survival, mainly in patients with a REE variation over +20% assessed with HB
218 1919 formula [15,16]. We found that a threshold of +20% for the REE variation especially
219 with HB 1919, HB 1984 and Mifflin formulas seemed more interesting to screen patients with
220 a higher evolving risk (functional and respiratory evolution and survival). As with HB 1919,
221 the increase of metabolic rate with HB 1984 was also a prognostic factor for survival over
222 20% of REE variation. Indeed, classification of patients according to REE variation with HB
223 1984 was close to HB1919 in our study. Nevertheless, there were differences according to
224 other formulas used versus HB 1919. Indeed, Mifflin equations yielded one the highest REE
225 variation compared to IC and to HB 1919. Our results could suggest that Mifflin is less
226 appropriate than other formulas to be used to calculate cREE in ALS patients. However, with
227 this formula as a reference, we found a more severe respiratory and functional evolution and a
228 lower survival in patients with REE variation over 20%. Indeed, 93.1% of patients kept this
229 same metabolic status (REE variation over 20%) with Mifflin according to HB 1919. With
230 Nelson formula which use body composition to predict REE we found the highest REE
231 variation compared to IC. This is in relation with a lower REE prediction with this formula as
232 in the study of Ioannides et al. although they used another method of body composition

233 measurement (plethysmography) [21]. But the variation of REE with Nelson formula
234 compared to IC did not seem interesting for the evolving risk of ALS patients. The finding
235 was the same with the other formulas which used body composition (Johnstone, Wang and
236 Rosenbaum), although body composition was assessed in our study by BIA with a validated
237 formula for ALS patients [27]. Indeed, the decrease of predicted REE with formula using
238 body composition could be related with this decrease of FFM in ALS. These formulas
239 including body composition were created in healthy people and with different methods of
240 body composition measurement (Dual X-ray absorptiometry, double labelled water...) which
241 could bias the results of prediction of REE. Moreover, the FFM decrease during the ALS but
242 the mREE by IC and the REE variation is stable during the disease as found by Bouteloup et
243 al. [7]. It suggests other mechanisms causing an increase of the metabolic rate during this
244 disease. Concerning the presence of this modification of metabolic rate in ALS patient, based
245 on studies using HB 1919 formula, increase of metabolic rate was not associated with
246 neurological form (bubar form, ALSFRS-R), riluzole treatment, tobacco, fasciculation,
247 respiratory insufficiency, or the familial form which could explain this increase in energy
248 metabolism [14,15]. Further studies are needed to investigate the causes of this metabolic
249 change in ALS and which may involve several neurological mechanisms (alteration of central
250 nervous system, neuro-inflammation, nerve hyperexcitability or re-innervation) [31–34].
251 Cortical hyperexcitability could be related to this metabolic dysfunction with an increase of
252 glucose metabolism which is the main energy substrate in neuron. Indeed, an increase of
253 glucose metabolism was found in brain of ALS patients and could lead to an increase of
254 metabolic rate in these patients [35,36]. Globally, the REE predictive formulas should not be
255 used to calculate the energy needs of ALS patients but only used as a reference to calculate
256 and assess the level of REE variation compared to IC. Indeed, predictive formulas would
257 allow to assess REE for the healthy condition of the patient and IC would allowed to assess

258 REE for the pathological condition (ALS) of the patient. IC is thus, a very useful tool for the
259 measurement of REE in ALS, but is still not available.

260 Our study presents several limitations. First, we did not measure REE during the follow up of
261 the patients to assess its evolution according to body composition evolution and the evolution
262 of REE variation according to the different formulas used. We did not use a control
263 population of healthy people. Indeed, the study of Vaisman et al. did not find difference of
264 REE variation between healthy control and ALS patient [12]. In addition, they found a higher
265 mREE in control than in ALS patients. However, there was a notable bias in this study
266 because FFM was significantly higher in the control group, suggesting that after
267 normalization for FFM, ALS patients could have a higher metabolic level than the controls.
268 However, the strength of our work is the study of metabolic rate of ALS patients with a
269 reference method (IC) compared to several (n=12) different predictive REE formulas.
270 Moreover, we studied a large ALS patients' cohort with functional, respiratory and survival
271 analysis according to their metabolic rate.

272

273

274 **Conclusion**

275 In ALS mREE by IC is higher than cREE whatever the equation used. A major REE variation
276 over 20% between mREE and cREE is found in 14.6% to 53.3% of patients according to the
277 formulas used. In our study with this threshold of 20%, the HB 1919, HB 1984 and Mifflin
278 formulas seem the more pertinent formula as a reference compared to IC to screen ALS
279 patient with a higher evolving risk. Using HB 1919 and HB 1919 formula as a reference,
280 patients with a REE variation over 20% had a lower survival. However, with Mifflin as a
281 reference, a more severe respiratory and functional evolution and a lower survival were found
282 in patients with REE variation over 20%. Our Study confirm the importance to assess the
283 metabolic rate in ALS with IC and relevant predictive formula as HB 1919, HB 1984 and
284 Mifflin formulas.

285

286

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Figure 1: Flowchart of ALS patients included in the study.

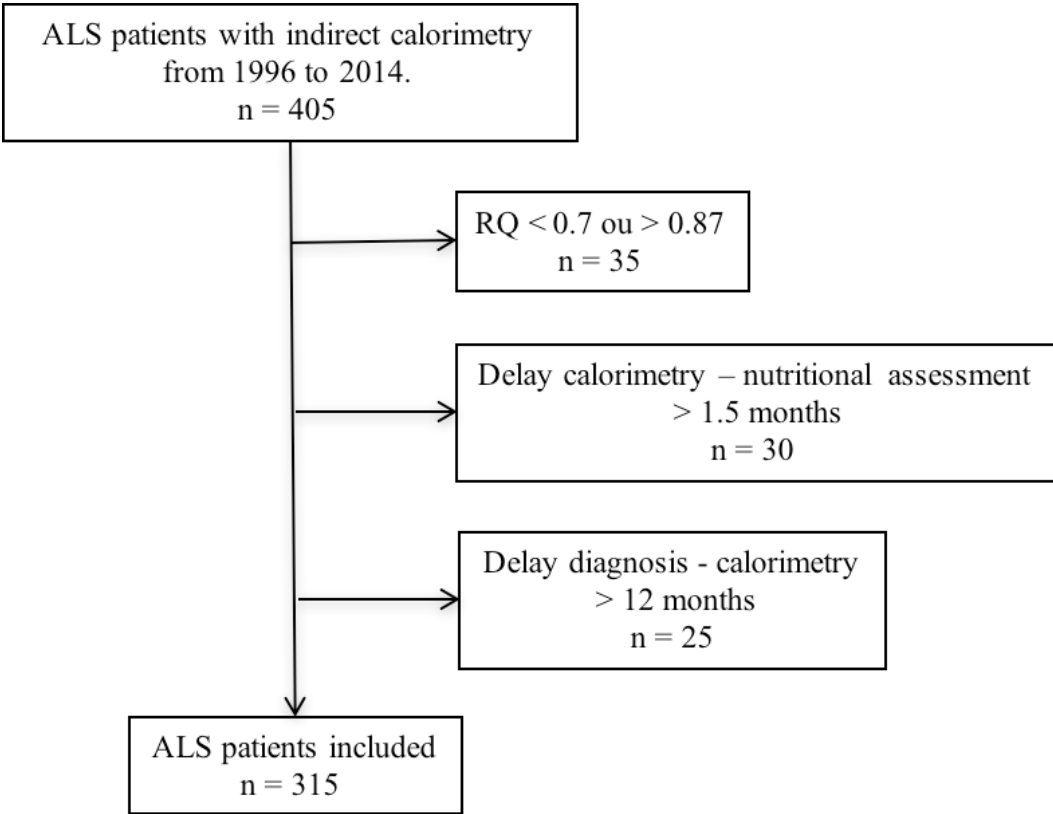
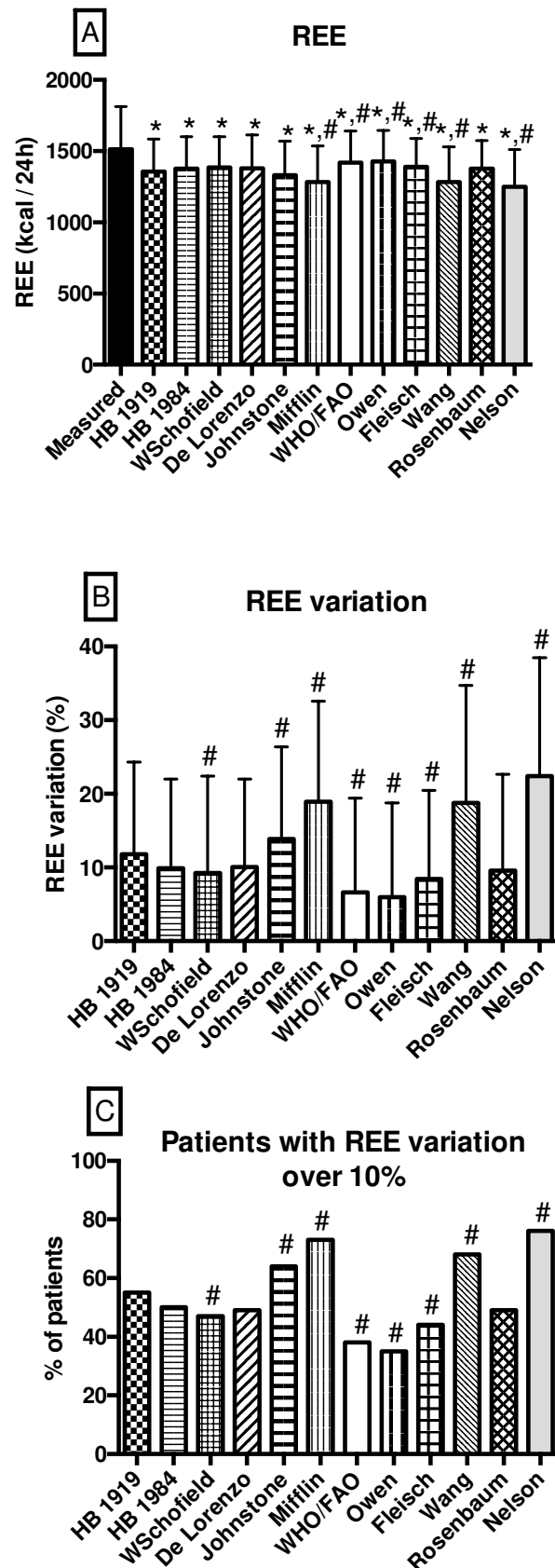


Figure 2: Resting energy expenditure (REE), REE variation and percentage of patients with REE variation over 10% in ALS patients (n=315) according to the 12 predictive formulas used.

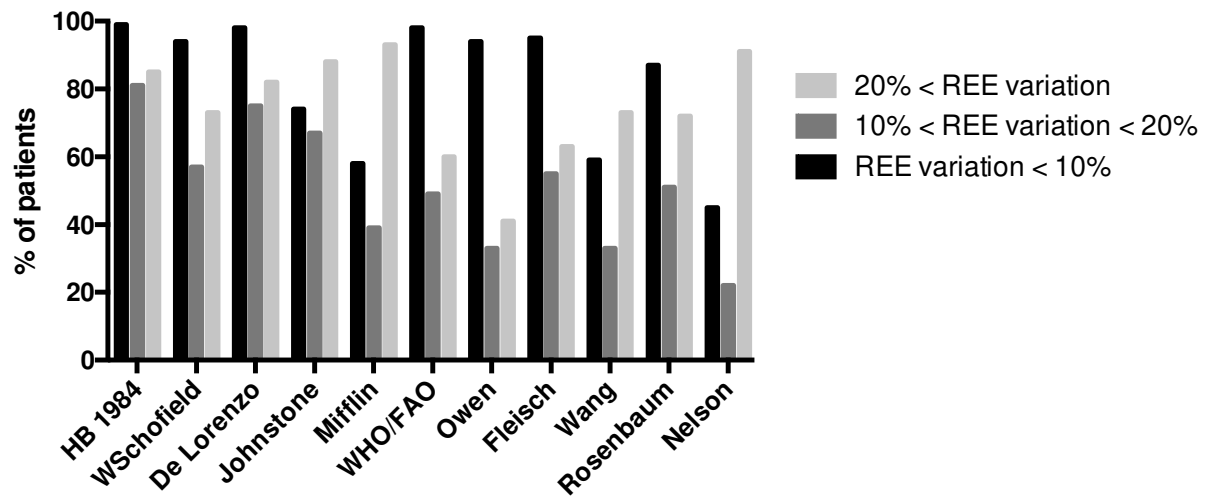


ALS: amyotrophic lateral sclerosis; HB: Harris & Benedict; Mifflin: Mifflin St. Jeor; REE: resting energy expenditure; cREE: calculated resting energy expenditure; mREE: measured resting energy expenditure; WHO/FAO: World health organization / food and agriculture organization of the United Nations, WSchofield: World Schofield.

*: mREE vs. cREE, $p < 0.05$

: HB 1919 vs. other formulas, $p < 0.05$

Figure 3: Patients with the same metabolic status as Harris and Benedict 1919 using the other predictive formulas.



HB: Harris & Benedict; Mifflin: Mifflin St. Jeor; REE: resting energy expenditure; WHO/FAO: World health organization / food and agriculture organization of the United Nations, WSchofield: World Schofield.

Table 1: Resting energy expenditure formulas used.

Harris & Benedict 1919	- Male: $(\text{Weight (kg)} * 13.7516) + (\text{Height (cm)} * 5.0033) - (\text{Age (years)} * 6.755) + 66.473$ - Female: $(\text{Weight (kg)} * 9.5634) + (\text{Height (cm)} * 1.8496) - (\text{Age (years)} * 4.6756) + 655.0955$
Harris & Benedict 1984	- Male: $(\text{Weight (kg)} * 13.397) + (\text{Height (cm)} * 4.799) - (\text{Age (years)} * 5.677) + 88.362$ - Female: $(\text{Weight (kg)} * 9.247) + (\text{Height (cm)} * 3.098) - (\text{Age (years)} * 4.33) + 477.593$
World Schofield	- Male of 18 - 30 years: $(0.063 * \text{Weight (kg)}) + 2.896$ - Male of 30 - 60 years: $(0.048 * \text{Weight (kg)}) + 3.653$ - Male > 60 years: $(0.049 * \text{Weight (kg)}) + 2.459$ - Female of 18 - 30 years: $(0.062 * \text{Weight (kg)}) + 2.036$ - Female of 30 - 60 years: $(0.034 * \text{Weight (kg)}) + 3.538$ - Female > 60 years: $(0.038 * \text{Weight (kg)}) + 2.755$
De Lorenzo	- Male: $(53.284 * \text{Weight (kg)}) + (20.957 * \text{Height (cm)}) - (23.859 * \text{Age (years)}) + 487$ - Female: $(46.322 * \text{Weight (kg)}) + (15.744 * \text{Height (cm)}) - (16.66 * \text{Age (years)}) + 944$
Johnstone	$(90.2 * \text{FFM (kg)}) + (31.6 * \text{FM (kg)}) - (12.2 * \text{Age (years)}) + 1613$
Mifflin St. Jeor	- Male: $(9.99 * \text{Weight (kg)}) + (6.2 * \text{Height (cm)}) - (4.92 * \text{Age (years)}) + 5$ - Female: $(9.99 * \text{Weight (kg)}) + (6.2 * \text{Height (cm)}) - (4.92 * \text{Age (years)}) - 161$

WHO/FAO	<ul style="list-style-type: none"> - Male of 18 - 30 years: $(15.4 * \text{Weight (kg)}) - (27 * \text{Height (cm)}) + 717$ - Male of 31 - 60 years: $(11.3 * \text{Weight (kg)}) + (16 * \text{Height (cm)}) + 901$ - Male of > 60 years: $(8.8 * \text{Weight (kg)}) + (1128 * \text{Height (cm)}) - 1071$ - Female of 18 - 30 years: $(13.3 * \text{Weight (kg)}) + (334 * \text{Height (cm)}) + 35$ - Female of 31 - 60 years: $(8.7 * \text{Weight (kg)}) - (25 * \text{Height (cm)}) + 865$ - Female of > 60 years: $(9.2 * \text{Weight (kg)}) + (637 * \text{Height (cm)}) - 302$
Owen	<ul style="list-style-type: none"> - Male: $879 + 10.2 * \text{Weight (kg)}$ - Female: $795 + 7.18 * \text{Weight (kg)}$
Fleisch	<ul style="list-style-type: none"> - Male: $24 * \text{BSA} * (38 - 0.073 * (\text{Age (years)} - 20))$ - Female: $24 * \text{BSA} * (35.5 - 0.064 * (\text{Age (years)} - 20))$
Wang	$24.6 * \text{FFM (kg)} + 175$
Rosenbaum	$(17.2 * \text{FFM (kg)}) + (10.5 * \text{FM (kg)}) + 375$
Nelson	$(108 * \text{FFM (kg)}) + (16.9 * \text{FM (kg)})$

BSA: body surface area = $0.007184 * (\text{Height (cm)}^{0.725}) * (\text{Weight (kg)}^{0.425})$; FFM: fat-free mass; FM: fat mass; WHO/FAO: world health organization / food and agriculture organization of the United Nations.

Table 2: Characteristics of ALS patients (n = 315).

	Median (IQR)	Missing data
	n (%)	
Age (years)	66.6 (56.9 – 74.1)	0
Men (%)	161 (51.1)	0
Weight (kg)	65.0 (57.3 – 74.7)	0
Height (cm)	163.0 (155.0 – 171.0)	0
BMI (kg / m ²)	24.2 (22.0 – 27.6)	0
Nutritional status		0
- Malnutrition	30 (9.5)	
- Normal	168 (53.3)	
- Overweight	73 (23.2)	
- Obesity	44 (14.0)	

FFM (kg)	44.4 (36.9 – 51.9)	28
FM (kg)	20.7 (15.2 – 25.4)	28
ALSFRS-R (points)	40 (35 – 43)	24
FVC (%)	90.0 (69.0 – 106.0)	76

ALS: amyotrophic lateral sclerosis; ALSFRS-R: amyotrophic lateral sclerosis functional rating scale-revised; BMI: body mass index; FFM: free fat mass; FM: fat mass; FVC: forced vital capacity; IQR: interquartile range; n: number.

Table 3: Patient with increase of metabolic rate according to the predictive formula used and compared to Harris & Benedict 1919.

	Total (10% < REE variation) n (%)	10% < REE variation ≤ 20% n (%)	20% < REE variation n (%)
HB 1919	174 (55.2)	101 (32.1)	73 (23.1)
HB 1984	157 (49.8)	94 (29.8)	63 (20.0)
WSchofield	147 (46.7) [#]	85 (27.0)	62 (19.7)
De Lorenzo	155 (49.2)	92 (29.2)	63 (20.0)
Johnstone	184 (64.1) [#]	101 (35.2)	83 (28.9)
Mifflin	229 (72.7) [#]	78 (24.8) [#]	151 (47.9) [#]
WHO/FAO	121 (38.4) [#]	74 (23.5) [#]	47 (14.9) [#]
Owen	111 (35.2) [#]	65 (20.6) [#]	46 (14.6) [#]

Fleisch	140 (44.4) [#]	89 (28.2)	51 (16.2) [#]
Wang	194 (67.6) [#]	71 (24.7) [#]	123 (42.9) [#]
Rosenbaum	141 (49.1)	76 (26.5)	65 (22.6)
Nelson	219 (76.3) [#]	66 (23.0) [#]	153 (53.3) [#]

HB: Harris & Benedict; MD: missing data; Mifflin: Mifflin St. Jeor; n: number; REE: resting energy expenditure; WHO/FAO: world health organization / food and agriculture organization of the United Nations; WSchofield: World Schofield.

[#]: p < 0.05 compared to HB 1919

Table 4: Respiratory and functional evolution and survival according to a threshold of REE variation of 10% with the different predictive formula used.

	FVC slope (%/month)			ALSFRS-R slope (points/month)			Survival	
	(n = 171)			(n = 264)			(n = 315)	
	REE variation ≤10%	REE variation >10%	p	REE variation ≤10%	REE variation >10%	p	REE variation >10% vs. ≤10%	p
	Median (IQR)	Median (IQR)		Median (IQR)	Median (IQR)		HR (95%CI)	
HB 1919	-2.2 (-4.2 – -1.1)	-3.2 (-6.2 – -1.5)	0.03	-1.1 (-1.9 – -0.6)	-1.3 (-2.0 – -0.6)	0.61	1.13 (0.89 – 1.43)	0.31
HB 1984	-2.3 (-4.3 – -1.1)	-3.1 (-6.2 – -1.5)	0.11	-1.2 (-2.0 – -0.6)	-1.2 (-2.0 – -0.6)	0.97	1.11 (0.88 – 1.40)	0.40
WSchofield	-2.5 (-4.7 – -1.1)	-2.7 (-6.2 – -1.5)	0.20	-1.2 (-2.1 – -0.7)	-1.2 (-1.9 – -0.5)	0.39	1.04 (0.81 – 1.31)	0.77
De Lorenzo	-2.4 (-4.5 – -1.1)	-3.0 (-6.1 – -1.4)	0.23	-1.2 (-2.0 – -0.6)	-1.2 (-2.0 – -0.6)	1.00	1.16 (0.92 – 1.47)	0.20
Johnstone	-2.3 (-4.2 – -0.8)	-3.0 (-5.8 – -1.4)	0.12	-1.2 (-2.0 – -0.6)	-1.3 (-2.0 – -0.6)	0.91	1.06 (0.82 – 1.36)	0.68
Mifflin	-2.3 (-4.2 – -1.0)	-3.0 (-6.1 – -1.2)	0.09	-1.1 (-1.9 – -0.6)	-1.2 (-2.0 – -0.6)	0.67	1.29 (1.00 – 1.65)	0.06

WHO/FAO	-2.7 (-5.1 – -1.1)	-2.7 (-6.1 – -1.7)	0.30	-1.2 (-2.1 – -0.6)	-1.3 (-1.9 – -0.6)	0.98	1.03 (0.81 – 1.31)	0.84
Owen	-2.5 (-5.5 – -1.1)	-3.1 (-5.6 – -1.4)	0.52	-1.1 (-2.0 – -0.6)	-1.3 (-1.9 – -0.6)	0.88	0.87 (0.68 – 1.10)	0.25
Fleisch	-2.7 (-5.3 – -1.1)	-2.7 (-5.8 – -1.5)	0.45	-1.2 (-2.0 – -0.6)	-1.2 (-1.9 – -0.6)	0.81	1.01 (0.80 – 1.23)	0.94
Wang	-2.7 (-6.5 – -1.0)	-2.6 (-5.2 – -1.3)	0.90	-1.4 (-2.1 – -0.7)	-1.1 (-1.9 – -0.6)	0.11	0.81 (0.61 – 1.05)	0.11
Rosenbaum	-2.8 (-5.3 – -1.1)	-2.5 (-5.3 – -1.2)	0.94	-1.3 (-2.0 – -0.7)	-1.2 (-1.9 – -0.6)	0.35	0.76 (0.60 – 0.97)	0.03
Nelson	-2.3 (-4.6 – -0.9)	-2.8 (-5.4 – -1.3)	0.38	-1.4 (-2.1 – -0.7)	-1.2 (-2.0 – -0.6)	0.40	0.82 (0.60 – 1.10)	0.17

ALSFRS-R: amyotrophic lateral sclerosis functional rating scale-revised; CI: confidence interval; FVC: forced vital capacity; HB: Harris & Benedict; HR: hazard ratio; IQR: interquartile range; Mifflin: Mifflin St. Jeor; REE: resting energy expenditure; WHO/FAO: world health organization / food and agriculture organization of the United Nations; WSchofield: World Schofield

In bold: $p < 0.05$

Table 5: Respiratory and functional evolution and survival according to a threshold of REE variation of 20% with the different predictive formula used.

	FVC slope (%/month)			ALSFRS-R slope (points/month)			Survival	
	(n = 171)			(n = 264)			(n = 315)	
	REE variation ≤20%	REE variation >20%	p	REE variation ≤20%	REE variation >20%	p	REE variation >20% vs. ≤20%	p
	Median (IQR)	Median (IQR)		Median (IQR)	Median (IQR)		HR (95%CI)	
HB 1919	-2.7 (-5.3 – -1.1)	-2.7 (-6.1 – -1.4)	0.40	-1.1 (-2.0 – -0.6)	-1.4 (-2.8 – -0.7)	0.28	1.42 (1.10 – 1.99)	0.01
HB 1984	-2.7 (-5.2 – -1.1)	-2.7 (-6.2 – -1.3)	0.40	-1.1 (-1.9 – -0.6)	-1.5 (-2.3 – -0.7)	0.10	1.38 (1.06 – 1.92)	0.02
WSchofield	-2.7 (-5.3 – -1.1)	-2.6 (-6.4 – -1.3)	0.61	-1.2 (-1.9 – -0.6)	-1.4 (-2.2 – -0.7)	0.22	1.27 (0.95 – 1.76)	0.10
De Lorenzo	-2.7 (-5.2 – -1.2)	-2.7 (-5.2 – -1.2)	1.00	-1.1 (-1.9 – -0.6)	-1.5 (-2.4 – -0.8)	0.047	1.30 (0.98 – 1.81)	0.07
Johnstone	-2.6 (-5.0 – -1.1)	-2.7 (-5.7 – -1.4)	0.48	-1.2 (-1.9 – -0.7)	-1.4 (-2.0 – -0.6)	0.78	1.02 (0.78 – 1.32)	0.90
Mifflin	-2.3 (-4.4 – -1.1)	-3.5 (-6.5 – -1.5)	0.03	-1.0 (-1.7 – -0.6)	-1.4 (-2.2 – -0.6)	0.02	1.42 (1.14 – 1.83)	0.003

WHO/FAO	-2.7 (-5.5 – -1.2)	-2.5 (-5.7 – -1.0)	0.97	-1.1 (-1.9 – -0.6)	-1.5 (-2.4 – -0.6)	0.17	1.13 (0.83 – 1.57)	0.44
Owen	-2.6 (-5.5 – -1.1)	-3.2 (-6.0 – -1.5)	0.56	-1.1 (-2.0 – -0.6)	-1.4 (-2.1 – -0.9)	0.07	0.91 (0.66 – 1.25)	0.56
Fleisch	-2.7 (-5.5 – -1.2)	-2.5 (-6.0 – -1.1)	0.93	-1.1 (-1.9 – -0.6)	-1.4 (-2.3 – -0.8)	0.11	1.14 (0.82 – 1.59)	0.42
Wang	-2.3 (-4.5 – -1.1)	-3.2 (-5.8 – -1.4)	0.24	-1.1 (-2.0 – -0.6)	-1.3 (-2.0 – -0.6)	0.95	0.91 (0.71 – 1.17)	0.45
Rosenbaum	-2.6 (-5.2 – -1.1)	-2.7 (-6.1 – -1.2)	0.57	-1.2 (-2.0 – -0.6)	-1.4 (-2.0 – -0.7)	0.30	0.96 (0.73 – 1.28)	0.80
Nelson	-2.5 (-6.5 – -1.1)	-2.7 (-5.1 – -1.2)	0.99	-1.3 (-2.1 – -0.7)	-1.2 (-1.9 – -0.6)	0.15	0.91 (0.71 – 1.16)	0.45

ALSFRS-R: amyotrophic lateral sclerosis functional rating scale-revised; CI: confidence interval; FVC: forced vital capacity; HB: Harris & Benedict; HR: hazard ratio; IQR: interquartile range; Mifflin: Mifflin St. Jeor; REE: resting energy expenditure; WHO/FAO: world health organization / food and agriculture organization of the United Nations; WSchofield: World Schofield.

In bold: $p < 0.05$