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# Rates of progression of weight and forced vital capacity as relevant measurement to adapt Amyotrophic Lateral Sclerosis management for patient Result of a French multicentre cohort survey

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ABSTRACT

*Objectives:* To compare survival, to describe the progression of anthropometry, pulmonary capacity and functioning in ALS (Amyotrophic Lateral Sclerosis) and to identify the most relevant variables to adapt ALS management for patients.
*Methods:* A cohort study was performed in French ALS centres between January 2003 and July 2005. Eligible patients were treated by Riluzole and had a slow vital capacity (SVC) or a forced vital capacity (FVC) at least equal to 60%. Demographic, medical and ALS characteristics were registered. Manual Muscular Testing (MMT) and ALS Functional Rating Scale (ALSFRS) were performed. Kaplan Meier method was used to analyse survival. ALS progression was measured by the percentage weight, FVC, SVC, MMT and ALSFRS loss and was analysed as longitudinal data using mixed model.
*Results:* Three hundred and eighty three patients were included. The median survival since ALS diagnosis was 2.34 years (95%CI 2.10–2.65). Mixed model analyses revealed a more significant worsening progression of weight and FVC loss for bulbar onset. The drop of ALSFRS and SVC is similar whatever the ALS forms.
*Conclusions:* Rates of progression of weight and FVC should be regularly watched over to support neurologists to adapt ALS management for patients.



## 1. Introduction

The Amyotrophic Lateral Sclerosis (ALS) belongs to the group of motor neuron diseases (MND). It is a fatal pathology resulting from lesions of peripheral and central motor neurons. Diagnosis of ALS is sure, probable, possible or suspected according to the El Escorial criteria [1,2]. Incidence of ALS is ranged from 1.5 to 2.5 for 100,000 inhabitants per year. Ninety per cents of ALS cases are sporadic forms. The median survival is ranged from 12 to 23 months since the diagnosis. The onset site of the disease, bulbar or spinal, defines different forms [3]. Patients have a progressive impairment of their physical, swallowing and pulmonary capacities, which prevent them to perform activities of daily living, to eat and to breathe normally. Cognitive disorders are observed in 50% of ALS cases and a common pathogenic mechanism between ALS and frontotemporal lobar dementia has been identified recently [4].

Several studies have already explored nutritional status, pulmonary capacity and patients' functioning and the impact on survival but Chio et al. underlines that only few studies have assessed the progression rate of such characteristics [5]. Consequently, further information concerning the entire course of the disease is needed.

The main goals of our survey were to compare survival and to describe the long term course of ALS through the evolution of anthropometry, pulmonary capacity and functioning in a large ALS population by conducting a multicentre study. The last aim is to identify the most relevant variables that should be watch over regularly to support neurologists to adapt ALS management for patients.

## 2. Method

### 2.1. Study design

The study was funded by the French ministry of Health from the national research program in hospitals. A multicentre longitudinal cohort, based on a quarterly follow up during thirty months, was performed in neurology wards of sixteen French university hospitals, fifteen of which were expert centres (among the eighteen French ALS expert centres). Eligible patients had a diagnosis of definite or probable ALS which dated from 6 months or less, were treated by Riluzole and had a forced vital capacity (FVC) or a slow vital capacity (SVC) measure at least equal to 60% of the predicted value [6,7]. Moreover, patients agreed to participate, read and spoke French fluently and

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were 18 years old or more. Patients were not eligible if they had a family history of ALS, a medical history of monoclonal gammapathies, cognitive disorders or obstructive or restrictive chronic lung diseases and a treatment for heart failures or cancers at the time of the study. Inclusion took place between January 2003 and July 2005.

### 2.2. Data collection

The study was supported by the ethics committee of the University Hospital of Clermont-Ferrand. Data registration was made in accordance with the respect of the French rules of privacy protection [8].

### 2.3. Inclusion process

Inclusion process began with the selection of eligible patients. Then, registration of demographic data (birth date, sex), characteristics of ALS (onset of symptoms, diagnosis, El Escorial criteria, form) and medical history of patients was performed. Weight before the diagnosis of ALS was noted, weight and height were measured and body mass index (BMI) was calculated. Neurologists performed manual muscular testing (MMT) for upper limbs, lower limbs and neck and filled in the ALS Functional Rating Scale (ALSFRS). Then, patients filled in both a generic and a specific health related quality of life questionnaire: the MOS-SF36 and the ALS Assessment Questionnaire (ALSAQ40 and ALSAQ5). The psychiatric issue was assessed using the Mental Health Inventory in 5 items (MHI5) of the MOS-SF36. Quality of life questionnaires were completed by an item that precised if patients needed help to fill in. At the end, an appointment for the quarterly follow up was scheduled.

### 2.4. Quarterly follow up

Measures were performed by a neurologist and were classified into five classes to allow a clarified analysis: anthropometry (weight, BMI), pulmonary capacity (FVC, SVC), functioning (MMT, ALSFRS), quality of life (MOS-SF36, ALSAQ40, ALSAQ5) and psychiatric issue (MHI5). Neurologist noted if he had proposed the gastrostomy placement or not and if a ventilation support, Non-Invasive Positive Pressure Ventilation (NIPPV) or invasive ventilation (tracheostomy with artificial ventilation) support, was performed.

### 2.5. Patients' evaluations

FVC and SVC measurements were expressed in percentage of the predicted value. MMT assesses the degree of muscular weakness by the clinical evaluation of each muscular group for three categories: upper limbs (thumb adductors and flexors, wrist extensors and flexors, elbow extensors and flexors, shoulder abductors), lower limbs (toes flexors, ankle dorsiflexors, plantar flexors, knee extensors and flexors, hip flexors and abductors), and neck (neck flexors and extensors). According to the Medical Research Council work [9] each muscle was classified from 0 for no contraction to 1 for flicker or trace contraction, 2 for active movement with gravity eliminated, 3 for active movement against gravity, 4 for active movement against gravity and resistance and 5 for normal power. ALSFRS explores the performance of activities of daily living with 10 items: speech, salivation, swallowing, handwriting, meal for patients with gastrostomy or not, dressing and hygiene, turning in bed and adjusting bedclothes, walking, climbing stairs and breathing [10–12]. Each item is quoted from 0 (unable to perform the task) to 4 (normal function) so the global score goes from 0 (worst possible health state) to 40 (best possible health state).

### 2.6. Statistical analysis

A descriptive analysis was performed; percentages and means with their standard deviation (SD) were calculated for qualitative variables and quantitative variables respectively. Bivariate associations between ALS forms and explanatory variables were calculated with Chi-square test for qualitative variables and analysis of variance for quantitative variables. Survival analysis was performed for the whole population and for each ALS forms using the Kaplan Meier method, considering death and then both death and gastrostomy placement as events. Survival curves were compared with the log rank test. Because ten patients had a diagnosis of mixed ALS spinal form (impairment of both the lower and the upper limbs), the closest survival curve for them among upper limbs, lower limbs and bulbar was checked. As these 10 patients have their own characteristics, they were not included in one of the three main groups.

To compare ALS forms' evolution the percentage of loss for weight, pulmonary capacity and functioning were studied as longitudinal data using mixed model. Weight before the diagnosis was chosen as reference to calculate percentage of weight loss. SVC, FVC and ALSFRS performed at the inclusion were selected as reference to calculate percentage of loss for pulmonary capacity and functioning. Time and ALS forms were introduced as fixed effect. When a patient death took place during the follow-up, last measurements performed were kept to perform the mixed model analysis for the remaining months. However, using mixed model involves the selection of an appropriate covariance model in order to draw accurate conclusions. This covariance model is a model that adequately accounts for within subject correlation but does not require the estimation of an excessive number of covariance parameters. To choose the appropriate covariance model, the correlation structure by plotting changes in covariance and correlation among residuals on the same subject over lag between times of observation was checked. The Akaike Information Criterion and the Bayesian Information Criterion has also been used to improve our analysis strategy. The heterogeneous first-order autoregressive and Toeplitz were the two structures selected. The results of mixed models are presented as least square means (LSMeans) values.

Some patient had missing data on weight, pulmonary capacity and functioning variables. Assuming unobserved measurements were missing at random, we used mixed model in order to obtain unbiased estimates of change in variables over time. Using likelihood based mixed models is appropriate because information from patients with complete data is used to implicitly impute the missing values [13].

A meaningful threshold of 5% was chosen for all the statistical analyses which were performed on SAS software v9.3.

## 3. Results

### 3.1. Population

Of the 382 patients included, 170 were women (44.50%) and 212 were men (55.50%) – sex ratio 1.25. At the time of diagnosis, patients were 60.7 ± 12.39 years old. Diagnosis of ALS was definite and probable (according to El Escorial criteria) for 60.89% and 39.11% of cases respectively. The time delay from onset to diagnosis was equal to 9.59 months ± 8.06. Bulbar, upper limbs and lower limbs forms were diagnosed in 23.30% (89), 39.79 % (152) and 33.51% (128) of cases respectively (Table 1). Three patients had a diagnosis of ALS spinal form without any precision about the limbs impaired so they were not included in the analysis. The bivariate analysis revealed that age at inclusion, time spent between onset of symptoms and ALS diagnosis, NIPPV and time spent between ALS diagnosis and NIPPV were not associated to ALS forms. On the other hand, sex is statistically associated with ALS forms with fewer men having bulbar forms. Tube feeding placement is associated with bulbar form without any difference shown between ALS forms for the time spent between ALS diagnosis and tube-feeding placement (Table 2).