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A Predictive Model for Prognosis in Motor Neuron Disease

Mirian Conceicao Moura[1*], **Luiz Augusto Casulari**[2] **and Maria Rita Carvalho Garbi Novaes**[3]

[1]*Department of Neurology, Hospital Regional da Asa Norte, State Secretariat of Health of the Federal District, DF, Brazil*

[2]*Department of Endocrinology, University Hospital of Brasília, DF, Brazil*

[3]*School of Health Sciences, University of Brasilia, DF, Brazil*

[*]**Corresponding author:** Mirian Conceicao Moura, Neurologist, Hospital Regional da Asa Norte, State Secretariat of Health of the Federal District, DF, Brazil, Tel: (061) 3905-4680 E-mail: mcmoura0812@gmail.com

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Abstract

Objectives: There have been attempts to establish biomarkers for motor neuron disease, without success. The study aim to seek possible markers to be used in the clinical routine evaluation, to optimize timing for palliative interventions.

Methods: A cohort study evaluated clinical, respiratory and neurophysiological variables every 3-4 months across 20 months in 101 patients with motor neuron disease using riluzole. Primary endpoint was death or tracheostomy. The most significant parameters in cox regression analysis created a predictive model.

Results: There were 58 men and 43 women with a mean age of 57.2 ± 11.7 years. 77 patients (76.2%) had spinal onset and 24 (23.8%) had bulbar onset. The mean survival time was 43.5 ± 5.7 months (CI 95% 32.3-54.8). The variables related to worse prognosis were: age > 65 years (HR=2.50, CI 95% (1.23–5.08); involvement of a second site in less than six months (HR=2.02, CI 95% (1.04 – 3.94); supine Forced Vital Capacity <63% (HR=2.78, CI 95% 1.03–7.48), neck weakness (HR=2.28, CI 95% (1.03–5.05) and presence of pyramidal syndrome (HR= 2.36, CI 95% (1.05–5.33).

Conclusion: It was created a five-factors set that predicts evolution to death or tracheostomy within one year.

Keywords: Motor neuron disease; Amyotrophic lateral sclerosis; Prognosis; Decision making; Palliative; Biomarkers

Introduction

Motor Neuron Disease (MND) is a rare neurodegenerative disease characterized by progressive loss of upper motor neurons in the brain and lower motor neurons in the brain stem and spinal cord, resulting in generalized weakness and muscle atrophy. Although the pathogenesis and course of the disease are heterogeneous, the disorder is inexorably progressive, and up to 70% of patients die within 3 years from symptom onset [1]. Most forms of MND are sporadic, and the incidence in Brazil and South America ranges between 0.89-2.3 per 100,000 person-years, according to age adjustment [2].

There are few treatment options to reduce disease progression and most of measures are palliative. Although riluzole provides a survival benefit of 3 months in MND, non-pharmacological interventions including ventilation and gastrostomy can improve both survival and quality of life [1]. Decision making about end of life in the late stages generally includes nutritional and respiratory support, gastrostomy insertion, non-invasive ventilation (NIV), and invasive mechanical ventilation [1,3]. However, these practices are often delayed or triggered in a crisis by the occurrence of life-threatening complications [3].

The variability in the clinical features of MND complicates efforts to measure disease progression and frequently it is difficult to determine time to interventions. In most studies, endpoints have relied on death, tracheostomy or the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) [4]; however, quality of life scales, the occurrence of death, non-invasive ventilation usage time, and tracheostomy usage are endpoints that are now considered to be linear, inaccurate and subject to bias [5].

By improving prognostic determination, individual clinical care can be planned, including discussions about inserting a gastrostomy tube and use of noninvasive ventilation. Moreover, in public health systems, prognosis statement is also valuable to give insights into health care policy to assess the comparative effectiveness of different systems of care that are helping to formulate services and develop policies.

Prognostic biomarkers also could have a meaningful effect on the conduct of clinical trials, allowing the determination of subgroup analysis. Biomarker subgroup analyses in clinical trials have the potential to permit the stratification of clinical response results [5].

In recent years, there have been attempts to establish biomarkers for MND, without success. This study aims to create a predictive model by combining simple possible markers to be used in the routine evaluation of patients to improve timing to palliative measures.

Materials and Methods

A descriptive prospective cohort study was performed on prognostic factors in 101 patients diagnosed with ALS according to El Escorial [6] and Awaji-Shima Criteria] at the Neuromuscular Disease Reference Center of Federal District (CRDN), a public

multidisciplinary team, which mandatorily receives all local patients with suspicious and confirmed ALS to undergo riluzole use.

The inclusion criteria were a) diagnosis of motor neuron disease done by a neurologist that eliminated other similar diseases; b) age over 18 years; c) a written informed consent that was signed by patients; d) a forced vital capacity (FVC) greater than or equal to 50%, except in progressive bulbar palsy; and d) El Escorial ALS diagnostic criteria that were either definite, probable and possible.

Patients with progressive bulbar palsy and a FVC below 50% that had facial weakness were submitted for nocturnal oximetry and were included when the procedure was discovered to be normal.

The exclusion criteria were a) other forms of disease that affect the anterior horn of the spinal cord; b) nerve conduction studies showing motor nerve block; c) respiratory failure defined by oxyhemoglobin saturation levels lower than or equal to 90% and/or less than or equal to a PaO_2 of 60 mmHg.

The patients were admitted to the CRDN from March 2014 to September 2015, and the evaluations were performed every three months across a 20-month time. Primary endpoint was death or tracheostomy. The following variables were evaluated: age, gender, race/color for heterodetermination, body mass index (BMI) [7,8], time of onset of symptoms, and time and direction of the first spread of motor deficits. The functional scale was as follows: ALSFRS [4] with a maximum score of 40; the Compound Muscular Action Potential (CMAP) area in the right median and ulnar nerves [9]; The same investigator graded bilateral shoulder abduction, elbow flexion and extension, wrist flexion and extension, and thumb and fifth finger abduction (range 0–5). The MRC sum score was calculated by summing all 14 MRC grades (maximum 70) according to the Medical Research Council (MRC) [10]; flexor cervical muscle weakness defined as a MRC score ≤ 3; FVC in the supine position; pulse oximetry in the supine position; predominance of upper motor neuron signs; smoking; family history; frontotemporal dementia, defined as a history of cognitive and behavioral deficits according to the Lund and Manchester Group criteria [11-13]; and frontotemporal atrophy in neuroimaging.

The protocol for CMAP (Compound Muscle Action Potential) amplitude, Ideal Case Motor Unit Count (ICMUC) and Motor Unit Number Estimation Index (MUNIX) measurements follows the model postulated by Nandedkar et al. [14]. A self-adhesive disposal surface ground and two disc recording electrodes with 15 mm diameters were used. Measurements were performed using a commercially available Keypoint-Classic-electromyograph, and MUNIX was performed in the right Adbutor Pollicis Brevis (APB) and Abdutor Digitti Minimus (ADM).

It was also used a delta CMAP with the summation of ulnaris and medianus nerve CMAP negative peak amplitudes, performing the subtraction between the first and second measurement [9].

Disease onset was regarded as the time from symptom onset to the endpoint (death or tracheostomy) expressed in months.

The BMI was calculated as weight (kg)/height 2 (m^2).

Data were recorded in Microsoft Office Excel 2010 charts and analyzed using Statistical Package for Social Sciences (SPSS) version 19.0. and SAS 9.3. Categorical variables were analyzed using the chi-square test and quantitative variables, with the Student t-test, with a significance level set at $p<0.05$.

All related variables were subjected to multivariate analysis. Initially, univariate Cox regression analyzes were used for clinical variables partner with respect to survival time. Variables with $p<0.25$ in the univariate analysis were selected for inclusion in the multivariate Cox regression analysis. The variables age, time of progression to second member and FVC values were categorized per quartile distribution. The final multivariate regression model was built by the successive exclusion of the variable from the initial multivariate model, using the likelihood ratio test to determine the importance of each variable excluded.

The internal validation was performed calculating the sensitivity and specificity of individual variables and the final model by the standard means and Receiver Operating Characteristic (ROC) Curve. ROC curve analysis was based on binary outcome. The level of significance was set at 0.05.

The internal validation was performed calculating the sensitivity and specificity of significant individual variables and the final model by the standard means and receiver operating characteristic (ROC) curve.

Approval was obtained from the Research Ethics Committee under number 525 241 FEPECS Protocol/2014 requiring signed informed consent.

Results

Between March 2014 and December 2015, 101 patients visiting CRDN were consecutively enrolled and none of them withdrew consent. The mean follow-up time (FUT) was 8.55 5.84 (CI 95% 7.4-9.7) months. Follow-up was successfully performed on all patients and FUT range was 3-20 months. There were no missing data because the multidisciplinary team also visits patients that undergo home care.

There were 43 women (42.6%) and 58 men (57.4%), with the proportion of men to women at 1: 1.3. The age range was 25-80 years, the mean age was 57.2 ± 11.7 years, and the median age was 58 years. In women, the age at onset of symptoms was significantly higher compared to men at 60.5 ± 10.8 years and 54.8 ± 11.8 years, respectively, (p=0.015).

A total of 84 patients (83.2%) had definite or probable ALS, per El Escorial Criteria. In 77 patients (76.2%) that were composed of 48 men and 29 women, the disease had spinal onset with the predominance of one leg as the initial symptom site (41.6%). Twenty-four patients (23.8%) that consisted of 14 women (58.3%, p=0.07) had bulbar onset. The signs of involvement of upper motor neurons were present in 70 patients (69.3%) and 31 patients (30.7%) had lack of pyramidal signs and confirmed diagnosis with laboratory support.

Only two patients (2%) exhibited the flail arm variant, and five patients (5%) had symptoms of frontotemporal dementia. Twelve patients (11.9%) had a positive family history for the disease. In relation to race, 81 (80.2%) patients were Caucasian, 12 (11.9%) were Mestizos, 7 (6.9%) were Black and 1 (1%) was Asian.

Table 1 shows the baseline parameters and its variation per gender. The average time from onset of symptoms to diagnosis (diagnosis delay time) was 25 ± 5.6 months (CI 95% 23.9 - 46.1) with a range of 4 to 500 months.

Body mass index range was 15.9 to 39.0 Kg/m^2 and the average BMI at admission was 26.75 ± 7.6 Kg/m^2. In four to six months, 34 patients had weight loss and the average BMI was 24.80 2.01 Kg/m^2, with no significance for survival time (p=0.96).

By the end of the 20-month study, 44 patients (43.6%) had reached endpoint. Thirty patients (29.7%) died, two patients died from stroke, and 28 died from respiratory distress and/or pneumonia. At the same time, 18 patients (17.8%) had received a gastrostomy tube and 27 (26.7%) had received non-invasive ventilation. The mean survival time was 43.5 5.7 months (CI 95% 32.3-54.8).

Parameter	Men(n=58)	SD	Women(n=43)	SD	p
Follow-up time	9.72	5.86	6.98	5.5	0.019
BMI	24.89	3.62	25.37	4.45	0.551
Neck strenght (MRC)	4.55	0.65	4.67	4.97	0.853
Age (years)	54.83	11.79	54.83	10.78	0.015
Onset of symptoms (months)	27.59	68.01	21.51	35.05	0.594
Time to second site (months)	10.6	19.86	8.42	6.37	0.489
ALSFRS slope	5.47	7.41	4.47	7.75	0.519
initial ALSFRS	28.07	7.49	24.98	7.4	0.042
MRC slope	3.49	5.52	3.62	4.47	0.902
initial MRC	31.79	6.64	30.09	6.46	0.201
Supine FVC	69.02	22.66	58.63	24.54	0.031
Sat O_2	96.16	2.52	95.79	2.25	0.454
CMAP medianus amplitude	2.64	2.84	2.46	2.7	0.765
CMAP ulnaris amplitude	2.92	2.81	2.97	2.51	0.935
Survival	47.31	68.73	38.49	35.78	0.445
Caucasian (%)	39 (48.1)	-	42 (51.9)	-	0.002
Familial	6 (50)	-	6 (50)	-	0.76
El Escorial (Definite + Probable)	48 (47.6)	-	36 (36.3)	-	0.62
Crossed progression	17 (43.5)	-	22 (56.4)	-	0.41
Ipsilateral progression	22 (44)	-	28 (56)	-	-
Bulbar progression	3 (27.2)	-	8 (72.8)	-	-

*ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; BMI: Body Mass Index; FVC: Forced Vital Capacity; CMAP: Compound Muscle Action Potential; sat: Saturation; MRC: Medical Research Council; SD: Standard Deviation; amp: Amplitude.

Table 1: Baseline characteristics of the patients with motor neuron disease (n=101) in Federal District of Brazil from 2014-2015.

One patient with 500 months' survival was considered outlier and excluded from multivariate Cox regression. When analyzing the unadjusted hazard ratio (Table 2 and supplementary Table 1), the following variables with p<0.25 were included in the multivariate analysis: neck weakness, age, gender, site of onset, time of onset (months), time to second member, ALSFRS slope, ALSFRS at admission, MRC score, MRC slope, supine FVC, and signs of upper motor neuron (UMN) dysfunction. The multivariate Cox regression model showed that age, time to second member, supine FVC and signs of UMN dysfunction were the only significant risk factors affecting patient survival time. However, also the variables neck weakness and admission ALSFRS-R 24 showed significance in bivariate analysis.

The risk of death among patients older than 65 years was 2.5 times (HR = 2.50, p= 0.0111) that of patients less than 65 years of age. Otherwise, the risk of death among patients with involvement of a second member in less than 6 months was about two times higher than the risk among patients with involvement of a second member in a time greater than or equal to 6 months (HR=2.02, p=0.0390).

The risk of death among patients with a supine FVC that was less than or equal to 50% was about four times (HR=3.80, p=0.0137) that of the patients with a supine FVC that was greater than 82%. The risk of death among patients with a supine FVC between 50 and 63% was about three times more (HR=2.78, p=0.0437) than the risk among patients with a supine FVC greater than 82%. Patients with a supine FVC between 63 and 82% did not present significant differences in the risk of death (HR=1.14, p=0.8195) compared to patients with a supine FVC greater than 82%.

The risk of death among patients with concurrence of upper motor neuron dysfunction was about two times higher (HR=2.36, p=0.0387). The relative risk of death among patients with neck flexor weakness was 2.28 (CI 95% 1.03–5.05, p=0.04).

Prognostic Factor	Hazard Ratio (CI 95%)			
	Crude	p	Adjusted a	p
Neck weakness	-	0.0414	-	-
No	1	-	-	-
Yes	2.28 (1.03 – 5.05)	0.0414	-	-
Age (Years)		0.0032		0.0111
≤ 65	1	-	1	-
> 65	2.75 (1.40 – 5.40)	0.0032	2.50 (1.23 – 5.08)	0.0111
Second Member	-	0.1483		0.039
< 6 meses	1.60 (0.85 – 3.01)	0.1483	2.02 (1.04 – 3.94)	0.039
≥ 6 meses	1	-	1	-
Admission ALSFRS	-	0.0035	-	-
≤ 24	2.57 (1.36 – 4.85)	0.0035	-	-
> 24	1	-	-	-
Supine FVC		0.0079		0.0186
≤ 50	4.85 (1.78 – 13.22)	0.002	3.80 (1.31 – 11.00)	0.0137
50.1 – 62.9	3.39 (1.30 – 8.84)	0.0125	2.78 (1.03 – 7.48)	0.0433
63 – 82	1.69 (0.57 – 5.06)	0.3457	1.14 (0.36 – 3.63)	0.8195
> 82	1	-	1	-
UMN		0.0453	-	0.0387
No	1	-	1	-
Yes	2.14 (1.02 – 4.52)	-	2.36 (1.05 – 5.33)	0.0387
*ALSFRS: Amyotrophic Lateral Sclerosis Functional Rating Scale; FVC: Forced Vital Capacity, UMN: Upper Motor Neuron.				

Table 2: Significant prognostic factors in a cohort of patients with motor neuron disease (n=101). Crude and adjusted hazard ratio for death or tracheostomy in a Cox Regression model. Period: 2014-2015. Federal District, Brazil.

To create the final model, the authors used FVC<63%, instead of 50% and did not use ALSFRS-R score below 24, because these factors are widely recognized as related to worse prognosis in ALS and do not need to be validated in a predictive model [1,4,12-14].

The parameters included in the predictive model were: age above 65 years, supine FVC below 63%, progression to second member within in less than six months, associated pyramidal syndrome and neck flexors weakness.

The analysis of sensibility and specificity of the five significant variables is shown in Table 3 and Figure 1, where the final model accuracy obtained by a Receiver Operating Characteristic (ROC) curve is 74%, considered satisfactory.

Parameter	ROC Area	SD*	95% Confidence Interval	
Age > 65 years	0.6	0.05	0.5	0.69
Second site < 6 months	0.57	0.05	0.46	0.67
Supine FVC < 63%	0.66	0.05	0.56	0.76
Signs of upper motor neuron	0.58	0.04	0.49	0.68

Neck weakness	0.54	0.04	0.46	0.62
*SD: Standard Deviation; FVC: Forced Vital Capacity				

Table 3: Internal validation of prediction model according to each parameter considered in Cox Regression. Cohort of patients with motor neuron disease. 2014-2015, (n=101), in Federal District, Brazil.

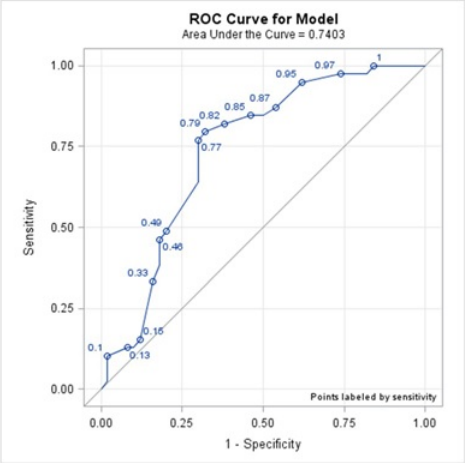

Figure 1: Receiver Operating Characteristic (ROC) Curve for model created with significant variables of Cox Regression. Cohort of patients with motor neuron disease.

Discussion

MND may represent a spectrum of diseases with diverse causes and etiologies; thus, it is difficult to identify a single biomarker to monitor disease progression and the time to adopt necessary invasive measures [3].

The authors identified five independent prognostic factors that can be easily observed through routine clinical evaluation and that are powerful enough to predict the outcome of MND patients who may be within a year of respiratory failure. The combination of these factors resulted in a model that was internally validated, demonstrating an acceptable 74% of accuracy in ROC curve.

The accuracy of this set of variables is satisfactory, although the study needs better validation with other populations in a wider and prospective study cohort, evolving more than a single center. Other limitations of the study are the number of participants and considering death or tracheostomy as the endpoint. Moreover, with death or tracheostomy considered the gold standard in the analysis of study accuracy, studies are subject to bias because often some patients refuse the necessary procedures that prolong survival.

This study was preceded by a retrospective population-based study that analyzed prognostic factors in 218 patients over 10 years and used Cox regression [13] to identify three independent factors related to reducing survival: bulbar onset, age above 75 years and BMI below 25 Kg/m^2.

Recent studies reported that the survival rate decreased linearly with the increase in age [13,14]. Here, the authors show that a patient age above 65 years old is an independent factor for endpoint [15-17].

Although pyramidal syndrome is part of MND diagnosis, it was observed that almost 30% of patients had no signs of pyramidal syndrome, moreover the occurrence of associated signs of upper motor neuron increased the risk of death by two times. There is controversy in current studies: a recent study about clinical biomarkers correlated reduced survival time with a lower motor neuron score [18], whereas others [19] reported a worse prognosis with the presence of a pyramidal syndrome.

Another important prognostic factor was cervical weakness, with a relative survival risk of 128%. Other studies [20,21] agree that cervical weakness is a factor associated with poor prognosis and lower survival.

The risk of death among patients with involvement of a second site or member in less than six months was about two times higher than later, but not in relation to the site of progression. The results of Turner et al. [22] reinforce the hypothesis that the period of progression to another site is more important for disease prognosis than the anatomical distribution, but some authors related lower survival when bulbar manifestations were present in the first year of disease [19,23] and better survival when the onset site is in the lower limbs [22,23] or of the bibrachial variant [24].

This study shows that the risk of death is about three times more among patients with supine FVC values below 63%. FVC has been used as an index of respiratory failure in most MND trials [25,26] and most studies correlate values below 50% to 60% of the standardized value with poor prognosis. The FVC value may not fall until severe muscle weakness develops because patients with bulbar involvement might not be able to correctly perform the spirometry test [27,28]. However, supine FVC [28] and Sniff nasal inspiratory pressure (SNIP), which is known to predict hypoventilation and hypercapnia [27], are important predictors of respiratory failure in MND patients.

No correlation was observed in this study between survival period and diagnostic delay times; however, the diagnostic delay times were longer herein (averages of 27.59 ± 8.9 months among men and 21.51 ± 5.3 months among women) compared with other studies, wherein the average delay was below 15 months [29-32].

The present study did not identify the ALSFRS as a potential marker of MND prognosis. The disability score for this functional scale has been used to measure the course of the disease and to assess the efficacy of candidate treatments in clinical trials [4]. Recently, there are efforts to establish other functional scales, to improve evaluation of MND progression [33,34].

About the neurophysiological parameters, although they have been cited as potential biomarkers to predict MND prognosis in clinical trials [5], this study failed to correlate these variables with patient survival. Maybe because the CMAP amplitude and area reflect loss of

motor units and muscle fiber innervation, but the reinnervation process can maintain CMAP normality [35-38].

The current study did not identify low BMI and nutritional status as an independent prognostic factor, but with the adoption of multidisciplinary care, the nutritional status of the patients was significantly better than it was in previous studies [13,39-43].

Conclusion

The study identified five biomarkers useful in a predictive model for worse prognosis in MND, which are: age >65 years (HR=2.50 CI 95% 1.23–1.08), involvement of second site in <six months (HR=2.02 CI 95% 1.04–3.94), supine FVC<63% (HR=2.78 CI 95% 1.03–7.48), neck weakness (HR=2.28 CI 95% 1.03–5.05) and associated pyramidal syndrome (HR=2.36 CI 95% 1.05–5.33). The authors propose a model with 74% of accuracy that can easily be used in clinical practice, although it needs external validation in larger and different populations.

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