2024 46th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) | 979-8-3503-7149-9/24/$31.00 ©2024 IEEE | DOI: 10.1109/EMBC53108.2024.10782485

Predicting Amyotrophic Lateral Sclerosis Progression: an EMG-based Survival Analysis

1st Irene Rechichi
Politecnico di Torino
Turin, Italy
irene.rechichi@polito.it

2nd Gianluca Amprimo
Politecnico di Torino
Turin, Italy
gianluca.amprimo@polito.it

3rd Alessandro Cicolin
University of Turin
Turin, Italy
alessandro.cicolin@unito.it

4th Gabriella Olmo
Politecnico di Torino
Turin, Italy
gabriella.olmo@polito.it

***Abstract*—Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease, ultimately leading to muscle inefficiency and death. A vast majority of people with ALS also suffer from sleep disorders. Previous studies highlighted the presence of REM Sleep Without Atonia (RSWA) in an ALS cohort, and suggested its strong correlation with the disease severity. This study investigates the ability of electromyography (EMG) parameters recorded during Rapid-eye Movement (REM) sleep to predict disease progress and outcome rapidity in ALS. Survival models trained on a cohort of 45 ALS patients undergoing a longitudinal study, revealed a promising predictive power for the proposed EMG-derived metrics (c-index $\geq$ 0.65) and encouraging goodness of fit (through c-index and χ^2). These results suggest the possibility of employing the trained model in follow-up procedures, based on non-invasive, lightweight EMG metrics, which would significantly ease disease monitoring and help personalized symptomatic care.**

***Index Terms*—Amyotrophic Lateral Sclerosis, Sleep, RSWA, Survival Analysis, Health Informatics, EMG**

I. Introduction

Amyotrophic lateral sclerosis (ALS) is a chronic neurodegenerative disorder characterized by the progressive degeneration of motor neurons. This process results in muscle weakness and paralysis [1], and related dysarthria and dysphagia, significantly affecting diaphragmatic fatigue and ultimately leading to respiratory failure [2], also accounted as the main cause of death [3]. Therefore, not only ALS presents with a complex clinical scenario, but also with great challenges in predicting disease progression and optimizing patient care. Indeed, at present there is no established curative therapy, and clinical care aims primarily at palliative or symptomatic treatment, while the median survival time is of approximately 2 to 5 years from symptom onset [1]. In addition to motor dysfunction, ALS is often associated with various non-motor symptoms, including sleep disturbances [4]. Among sleep disorders, the most frequent are sleep disordered breathing and sleep fragmentation; many studies also identified the presence of RSWA in ALS patients, with or without association to REM Sleep Behavior Disorder (RBD) [5]. RSWA, which is also associated to other neurodegenerative diseases, is a parasomnia that presents with sustained, abnormal muscle activity during REM sleep. Previous studies highlighted the potential correlation between RSWA and disease severity in ALS [6], [7], based on the qualitative and quantitative analysis of the EMG activity from polysomnography (PSG) recordings. However, PSG is often regarded as invasive, as it relies on cumbersome instrumentation and needs to be performed in outpatient clinic, which limits the possibilities of non-invasive follow-up for ALS patients. This highlights the need for lightweight metrics for continuous monitoring, to improve patient care and allow for minimally-invasive follow-up protocols in high-risk patients. This study aims to investigate the ability of EMG parameters recorded during REM sleep as predictors of disease progression and survival outcomes in ALS patients. Specifically, it exploits survival analysis to explore the association between EMG-derived metrics and disease progression, as well as the ability of these variables to actually predict survival time. To the best of the Authors' knowledge, this is the first study that tackles ALS disease modeling and prediction through the use of simple, quantitative, muscular metrics. In [8], survival models were trained on a cohort of ALS subjects, by stratification on their ALS Functional Ratings Scale, or Age; whereas [9] presented a survival analysis on a cohort of ALS subjects, based on their Apnea-Hypopnea index.

II. Materials

A. Subjects and Protocol

This longitudinal retrospective study was envisaged with domain experts, and included 58 subjects diagnosed with ALS, who underwent PSG at the outpatient Sleep Clinic of the Regional Center for Sleep Medicine in Turin, Italy. The subjects were undergoing melatonin treatment and were evaluated for RSWA symptomatology at the time of enrollment (T0). Follow-up time was after 6-months (T1), 12-months (T2), and 18 months (T3), though only one subject reached this time point. After inspection, 13 subjects were excluded from the analysis due to technical issues during the PSG recordings. The final dataset comprised 45 subjects (15 females), out of which only 9 reached the end of the study (due to death or invasive ventilation, thus unable to follow-up). The primary end-point of the study was, therefore, death or inability to follow-up due to critical health conditions. At the time of the enrollment, nearly half of the subjects tested positive for RSWA (RSWA+); Table I summarizes the demographic data of the cohort under study. As said, at the time of censor, 36 patients reached the primary endpoint (death or inability to follow-up). The study also included 35, age-matched controls

Authorized licensed use limited to: Universita Studi di Torino - Dipartimento Di Informatica. Downloaded on June 03,2025 at 11:03:32 UTC from IEEE Xplore. Restrictions apply.

TABLE I
SUMMARY OF THE DEMOGRAPHIC CHARACTERISTICS OF THE COHORT.

	Sample	**Age** (years)	**RAI**
General	45 (15 females)	65.51 $\pm$ 9.34	0.62 $\pm$ 0.34
RSWA+	25 (9 females)	65.36 $\pm$ 9.77	0.40 $\pm$ 0.30
RSWA−	20 (6 females)	65.70p $\pm$ 8.77	0.90 $\pm$ 0.04

that underwent PSG and were employed to build the healthy reference model, described in detail in Section III. Data collection was carried out in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the A.O.U. Città della Salute e della Scienza di Torino (Approval Number: 00384/2020); written informed consent for longitudinal study was obtained.

III. METHODS

A. Data Processing and Feature Extraction

This feasibility study aimed at testing the capability of modeling disease progress in ALS through muscular parameters in REM sleep. Indeed, only the EMG recorded at the mylohyoid muscle (submental) was taken into account for the subsequent analysis. This choice is dictated by the aim of providing a predictive model based on EMG parameters captured through a simplified approach with respect to PSG, less invasive and complex, in the perspective of long-term follow up. PSG recordings were manually scored by an expert sleep technologist following standard criteria [10]; EMG pre-processing and feature extraction were carried out in MATLAB® R2022a.

First, according to standard diagnostic criteria, and to quantitatively characterise EMG during REM sleep, the REM Atonia Index (RAI) was computed [11]. This continuous metric accounts for the percentage of 1-s mini-epochs during REM sleep with amplitude $\leq$1 μV, and ranges between 0 and 1, with 0 representing total loss of physiological REM atonia. Second, following the method first presented in [12], the EMG segments in REM were processed in order to extract the Dissociation Index (DI); namely, a distance-based, continuous metric correlated to the degree of sleep impairment. The index is mapped to the range (0, 1), where 1 represents total dissimilarity with respect to an healthy model.

As described in [12], to compute the DI, each subject is mapped into vector spaces, and represented by an array of EMG features; then, the distance between each subject and a *reference array*, which represents the healthy model, is computed. The healthy model, the same of [12], was constructed using the data of the 36 recruited healthy controls. The array of features encompasses quantitative EMG metrics, both in the time and frequency domains. The EMG features employed for this computation are displayed in Table II, along with their description and reference. For the sake of consistency with the RAI computation, the features were extracted on 1-s mini-epochs; finally, for each parameter, various statistics were computed (median, 25^{th} and 75^{th} percentiles, interquartile range (IQR), kurtosis, skewness, maximum and minimum of the distribution), which made up the final feature array.

TABLE II
FEATURES EMPLOYED IN THE COMPUTATION OF THE DISSOCIATION INDEX, ALONG WITH THE DOMAIN.

Domain	**Feature (Name and description)**	**Reference**
Time	Amplitude metrics: mean, standard deviation, skewness, kurtosis, range, maximum and minimum value	various
	Hjorth Parameters: activity, mobility	[12]
	Percentiles (25^{th}, 75^{th}, 95^{th})	various
Frequency	Power Spectral Density: numerical and statistical measures (mean and median frequencies, total power)	various
	Spectral Edge Frequencies (i.e., spectral percentiles): SEF25, SEF95	$\diamond$ [12]
	Average power of the whole signal band	various

B. Survival Analysis for Disease Modeling

As introduced earlier, various survival models were trained to model disease progress and tackle survival prediction. All processing was carried out in Python language. The final dataset relied on five variables (or features): Age, Sex, Follow-up Time, RAI_{T0} and DI_{T0} (T0: time of study enrollment), this latter derived from various EMG metrics (cf. Section III-A).

First, a univariate survival function was fit, through a Kaplan-Meier approach [13], to represent the general probability of survival in this cohort. Second, given the presence of various co-variates in the dataset (Age, Sex, Follow-up Time, RAI, DI), a multivariate survival analysis (Cox' Proportional Hazards model [14]) was carried out in order to assess the risk prediction capability (i.e. predictive power) of each employed variable. Feature importance was assessed by means of the Harrell's concordance index (c-index) [15].

Finally, as previous studies highlighted the possible correlation between the presence of RSWA and the clinical severity of the disease [6], a stratified survival analysis was carried out in the dataset, according to the presence or absence of RSWA. Subjects were divided into two groups, according to their RAI score. A value of RAI of 0.8 was chosen as cut-off, as previously recommended in [11]; for the sake of clarity, subjects presenting with values above 0.8 did not show any sign of altered REM atonia (RSWA-), and *vice versa*. A Kaplan-Meier estimator was trained on these strata. Finally, given the age homogeneity in the dataset, stratification according to age could not be performed; instead, a second stratified analysis according to sex was carried out, and a Kaplan-Meier model was fit on the two resulting groups. Prediction performance of all fitted models was evaluated through the log-rank test, and χ^2 and p-values were obtained.

C. Predictive ALS Modeling

To assess the feasibility of modeling the evolution in time of ALS, and explore its potential application in prospective follow-up scenarios, a Cox' Proportional Hazards model was trained on the available dataset, following a multivariate approach, as in Subsection IV-A. The model performance was

Authorized licensed use limited to: Universita Studi di Torino - Dipartimento Di Informatica. Downloaded on June 03,2025 at 11:03:32 UTC from IEEE Xplore. Restrictions apply.

estimated through the c-index. Synthetic subjects data (in the form of variables) were generated in order to cover the whole symptoms spectrum (i.e., early/late onset ALS, presence or absence of RSWA). Finally, synthetic data were given as input to the trained model and predictive survival curves were fitted on a time-scale of 365 days, to simulate a prospective follow-up scenario.

IV. Results

A. Overall Survival and Feature Importance

The general Kaplan-Meier model showed a median survival time to the primary end-point (i.e., death or inability to follow-up) of nearly above 6 months after study enrollment. As described earlier, given the presence of multiple variables for prediction, a Cox' Proportional Hazards model was fit to the extracted variables and the c-index was obtained in order to evaluate their predictive power. This performance metric serves as a descriptor of the association between the predictor variable and the survival time; Table III displays the estimated c-index in the training dataset. As appreciable, DI_{T0} is the best variable, with a c-index of almost 0.7, suggestive of good predictive power. Age is the second-best predictor according to the c-index (though with a non-significant p-value); the RAI_{T0}, which is computed from the EMG signal amplitude during the REM stage, features a value of nearly 0.6, underlying a reasonable, though not strong, predictive power of this feature.

B. Stratified Analysis

The paragraphs below report the results of the two stratified survival analyses, with strata formed according to the RSWA and Sex predictors.

1) RSWA: According to the selected cut-off for RSWA (RAI=0.8), two groups were identified. Namely, the subjects with RSWA at the time of the enrollment (RSWA+, 25 subjects) and those who had no loss of REM atonia (RSWA-, 20 subjects). Kaplan-Meier models were applied to these two groups; the resulting survival curves are shown in Figure 1. As appreciable, the two groups show a similar evolution, with a steep, descending trend. From a preliminary visual inspection, the RSWA- group appears to have an initial more rapid evolution, which eventually falls into a plateau in the later stages of the disease. Statistical comparison of the two groups was tested through log-rank test; the test yielded a χ^2=1.817 (p-value=0.5). This result confirms the similarity found during visual inspection of the survival curves, and suggests that a stratification according to RSWA is not informative in this cohort.

TABLE III
HARRELL'S CONCORDANCE INDEX FOR EACH TESTED PREDICTOR.

Feature	c-index	p-value
DI_{T0}	0.693	0.021*
Age	0.622	0.437
RAI_{T0}	0.572	0.045*
Sex	0.557	0.032*

*: $p < .05$

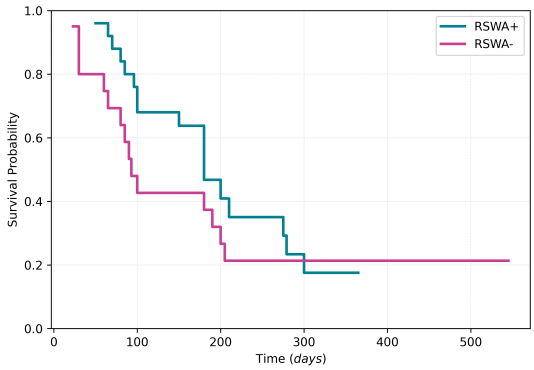

Fig. 1. Estimated survival curves for the stratified analysis according to the RSWA co-variate, in the time between study entrollment and primary endpoint.

2) Sex: A Kaplan-Meier model was fitted on training data, following this second stratification; subjects were divided into two groups, though in the presence of class imbalance (30 males vs 15 females). The survival probability according to this stratification is shown in Figure 2; from a visual inspection, the male subgroup appears to follow a more rapid degeneration. The log-rank test on this stratification yielded a χ^2 of 3.768 (p-value 0.035), indicative of strong statistical significance, confirming the clinical implications of the disease [8].

C. Prediction of the Disease Progress

Eventually, the Cox' Hazards Ratio model trained on the whole dataset with a multivariate approach (cf. Section IV-A) was employed to carry out predictions on synthetic data, in order to assess the feasibility of a lightweight, EMG-based prediction model. The multivariate analysis yielded a c-index of 0.734, indicating favorable prediction performance of the employed variables. Synthetic data (as feature arrays), purposely generated to represent various subjects with different starting conditions, were then given as input to the trained

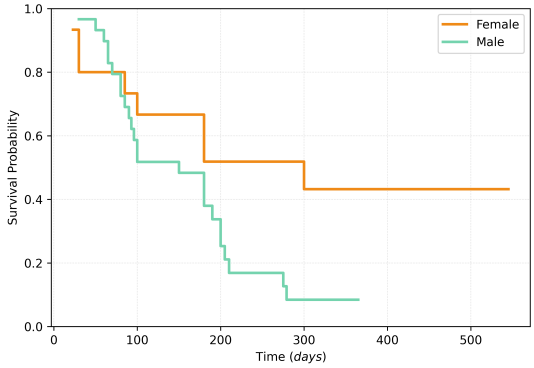

Fig. 2. Estimated survival curves for the stratified analysis according to the Sex co-variate. in the time between study entrollment and primary endpoint.

Authorized licensed use limited to: Universita Studi di Torino - Dipartimento Di Informatica. Downloaded on June 03,2025 at 11:03:32 UTC from IEEE Xplore. Restrictions apply.

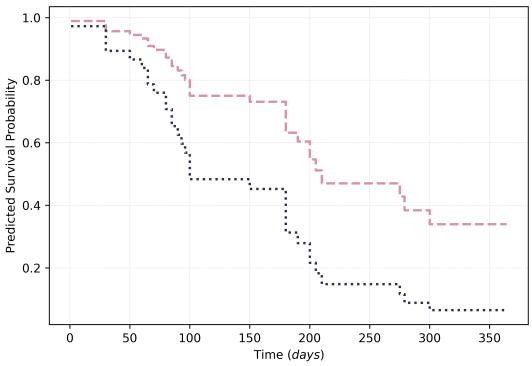

Fig. 3. Predicted survival probability on synthetic subjects data. Dotted line: older patient, RSWA+. Dashed line: patient with young onset, RSWA–.

model, and survival functions for the new subjects were obtained. As previously said, this analysis highlights a use case of application of the trained predictive models. For the sake of brevity, Figure 3 shows the predicted survival curves for two relevant synthetic patients: one young subject with early onset ALS and no RSWA at the time of enrollment, and a second one older in age, with moderate RSWA at the time of enrollment. The two curves estimate the progression rapidity of the disease, and may serve as predictors of the expected median survival time, or may find their application as a support tool in follow-up assessments, to mitigate the burden of diagnostic tests for patients at risk.

V. Conclusions and Future Work

This study explored the feasibility of predicting ALS progression by leveraging EMG metrics which could be extracted through the use of lightweight, minimally-invasive sensors, with respect to traditional PSG. Indeed, previous studies highlighted the correlation of RSWA with the clinical severity of the disease, suggesting its role as risk factor for a more rapid progression; however, its traditional assessment method (i.e., PSG) remains a highly invasive exam, making follow-up assessments challenging for ALS subjects. The variables employed in the analysis showed good predictive power, with the DI, a distance-based metric retrieved from various EMG features, yielding a c-index of 0.7. Furthermore the trained Cox' Hazards Ratio model featured an overall encouraging goodness of fit (c-index=0.73). To the best of the Authors' knowledge, this is the first study that carries out survival analysis on ALS based on muscular parameters during REM sleep, as most studies only performed quantitative, statistical comparisons on different covariates, including RAI, between ALS subjects and age-matched controls [6], [7]. For this reason, a direct comparison with other studies cannot be performed; however, the obtained statistics are in line with previous studies [8], [9], though on different cohorts, with qualitative co-variates. Finally, predictive modeling of ALS progression was proposed, and tested on synthetic data; the resulting survival curves highlight their potential in prospective, clinical follow-up protocols, thus encouraging personalised care and reducing diagnostic intrusiveness in high-risk patients cohorts. Future developments will address the limitations of this study. First, a larger number of subjects will be enrolled, to improve the model reliability and the robustness of the prediction. Second, a larger cohort will necessarily call for a more detailed stratification – e.g., according to the type of onset (bulbar, truncal, spinal), the age of onset, the functional scale or the presence of non-invasive ventilation. This would help in creating a descriptive progression model for neurodegenerative diseases on short time-scales, as well as expanding the generalization of such findings to other neurodegenerative disorders with slower progression rates.

Acknowledgment

This work was partially supported by the NextGeneration EU under the Italian NRRP, Telecommunications of the Future (PE00000001, RESTART). The Authors thank the personnel of the Molinette Hospital (Turin, Italy) for the fruitful cooperation, and A.A. *the stargazer* for the useful insights.

References

[1] P. Masrori and P. Van Damme, "Amyotrophic lateral sclerosis: a clinical review," *European journal of neurology*, vol. 27, no. 10, pp. 1918–1929, 2020.
[2] O. Hardiman, "Management of respiratory symptoms in als," *Journal of neurology*, vol. 258, no. 3, pp. 359–365, 2011.
[3] A. Chiò *et al.*, "Amyotrophic lateral sclerosis care in italy: a nationwide study in neurological centers," *Journal of the neurological sciences*, vol. 191, no. 1-2, pp. 145–150, 2001.
[4] M. Boentert, "Sleep disturbances in patients with amyotrophic lateral sclerosis: current perspectives," *Nature and science of sleep*, pp. 97–111, 2019.
[5] D. Lucia *et al.*, "Disorders of sleep and wakefulness in amyotrophic lateral sclerosis (als): a systematic review," *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, vol. 22, no. 3-4, pp. 161–169, 2021.
[6] M. Puligheddu *et al.*, "Isolated rapid eye movement sleep without atonia in amyotrophic lateral sclerosis," *Sleep Medicine*, vol. 26, pp. 16–22, 2016.
[7] D. Lo Coco *et al.*, "Rem sleep behavior disorder and periodic leg movements during sleep in als," *Acta neurologica Scandinavica*, vol. 135, no. 2, pp. 219–224, 2017.
[8] A.-L. Kjældgaard, K. Pilely, *et al.*, "Prediction of survival in amyotrophic lateral sclerosis: a nationwide, danish cohort study," *BMC neurology*, vol. 21, no. 1, pp. 1–8, 2021.
[9] V. Quaranta *et al.*, "The prognostic role of obstructive sleep apnea at the onset of amyotrophic lateral sclerosis," *Neurodegenerative Diseases*, vol. 17, no. 1, pp. 14–21, 2016.
[10] R. B. Berry, R. Brooks, C. Gamaldo, S. M. Harding, R. M. Lloyd, S. F. Quan, M. T. Troester, and B. V. Vaughn, "Aasm scoring manual updates for 2017 (version 2.4)," 2017.
[11] R. Ferri *et al.*, "Improved computation of the atonia index in normal controls and patients with rem sleep behavior disorder," *Sleep medicine*, vol. 11, no. 9, pp. 947–949, 2010.
[12] I. Rechichi *et al.*, "Assessing rem sleep behaviour disorder: From machine learning classification to the definition of a continuous dissociation index," *International Journal of Environmental Research and Public Health*, vol. 19, no. 1, p. 248, 2021.
[13] W. N. Dudley, R. Wickham, and N. Coombs, "An introduction to survival statistics: Kaplan-meier analysis," *Journal of the advanced practitioner in oncology*, vol. 7, no. 1, p. 91, 2016.
[14] B. Efron, "The efficiency of cox's likelihood function for censored data," *Journal of the American statistical Association*, vol. 72, no. 359, pp. 557–565, 1977.
[15] F. E. Harrell Jr, K. L. Lee, and D. B. Mark, "Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors," *Statistics in medicine*, vol. 15, no. 4, pp. 361–387, 1996.

Authorized licensed use limited to: Universita Studi di Torino - Dipartimento Di Informatica. Downloaded on June 03,2025 at 11:03:32 UTC from IEEE Xplore. Restrictions apply.