Predicting Non-Invasive Ventilation in ALS Patients using Time Windows

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ABSTRACT

Amyotrophic Lateral Sclerosis (ALS) is the most common neurodegenerative disorder of young adults. ALS patients usually present a rapidly progressive motor weakness caused by motor neuron demise. Death occurs in a few years, mainly due to respiratory failure. Therefore, adequate prediction of respiratory insufficiency has great importance in ALS management. We propose a prognostic model based on time windows, where a set of initial evaluations is used to predict the probability that an ALS patient will require non-invasive ventilation (NIV) k days after the last observation. Data includes clinical features, functional impairment scores and different respiratory measures. Our experimental results suggest a good performance, achieving an area under the receiver operating characteristics curve (AUC) of 84.64%, 75.86% and 77.06% for, respectively, the windows of 90, 180 and 365 days, using a Bayesian classifier, which can provide a risk measure associated to respiratory failure.

Categories and Subject Descriptors

H.2.8 [**Database applications**]: Data Mining; H.3.3 [**Information Search and Retrieval**]: File organization; J.3 [**Computer Applications**]: Life and Medical Sciences

General Terms

Experimentation, Performance, Verification

Keywords

Amyotrophic Lateral Sclerosis, Data Mining, Prognostic prediction, Time windows

1. INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a devastating motor neuron disease usually associated to a rapidly progressive functional impairment, due to denervation of limb, bulbar, axial and respiratory muscles [11]. Given that respiratory insufficiency (RI) accounts for the majority of deaths in ALS [11], better predictive factors for hypoventilation are crucial to preserve quality of life (QoL) and prolong survival [18], by timely adaptation to non-invasive ventilation (NIV) [2, 5].

Many biological and clinical problems have been tackled using data mining, from cancer and cardiovascular diseases [3], to neurodegenerative diseases, such as Alzheimer's Disease and Parkinson's Disease [17]. Regarding ALS, examples in the literature are almost entirely based on population-based approaches, resorting to statistical analyses, as Kaplan-Meier survival tables and multivariable Cox proportional hazard regression models [8] pursuing the identification of prognostic factors. These include respiratory measures, such as the forced vital capacity (FVC) and the maximal inspiratory and expiratory pressures (MIP/MEP) [4, 12], onset age and site of disease onset (bulbar vs. spinal onset), disease duration until the diagnosis [14, 16], gender [16], and the ALS Functional Rating Scale (ALSFRS-R) score [12, 14]. ALSFRS-R translates functional impairment and incorporates a respiratory subscore, which yields prognostic value by itself [12]. Recently, diaphragmatic motor responses by phrenic nerve stimulation were also identified as an independent prognostic factor for hypoventilation and survival in ALS [15].

In this work, we propose a new supervised patient-driven learning strategy based on time windows to address an important clinical question: "Given the patient's initial condition, will he/she need NIV after a given period of time?". To achieve this goal, we developed an innovative prognostic model able to evaluate the patient's initial set of data and, according to it, infer whether the patient will require NIV, or not, within a determined time window. Five hundred and seventeen ALS patients have been followed in our ALS Clinic in the last 10 years. Demographic characteristics, respiratory function tests, functional scores and neurophysiological data were recorded.

Given the original dataset, we trained the predictive models using 75% of the patients (training set), to find the best preprocessing techniques and classifiers' parameters, accord-

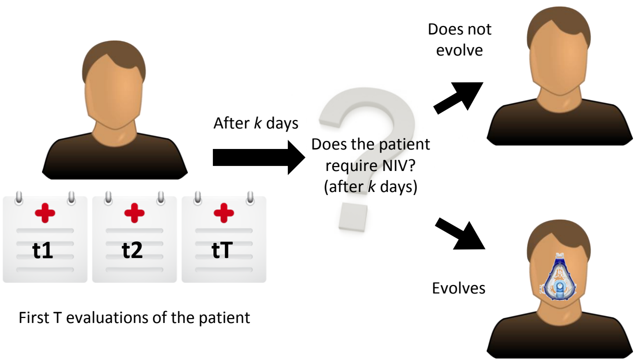

Figure 1: Problem formulation.

ing to metrics such as the area under the receiver operating characteristics (ROC) curve (AUC), sensitivity and specificity. We used state-of-the-art classifiers, available in Weka [10]. The models were tested using the remaining 25% of patients achieving AUC values of 84.64%, 75.86% and 77.06% for, respectively, the windows of 90, 180 and 365 days, using a Bayesian classifier.

We present and discuss the methods comprising the workflow, from the preprocessing techniques and creation of learning examples, to the analysis and comparison of the predictive power of using a number of time points (patient's history), instead of using only the last known condition for the patient. We also study the use of temporal dynamics, as well as specific models for two progression groups. We present and discuss the results for the different models and finally draw the main conclusions and outline future work.

2. METHODS

In this work an important clinical question is addressed, as illustrated in Figure 1: "Given an initial set of patient evaluations, can we predict whether that patient will require NIV k days after the last observation?". Patients were adapted to NIV if required following international guidelines [2].

We propose a supervised learning strategy using data from the patient's first evaluations to predict whether the patient will require NIV within the considered time window of k days. If this happens, it is considered that the patient evolved, and thus the corresponding *Evolution* label is used as the class to train and test our predictive models. The workflow is presented in Figure 2. We start by preprocessing the original data, grouping together the exams that belong to the same evaluation, labeling the instances (patients) according to the mentioned *Evolution* class (considering the time window of k days), and choosing how many time points are to be included in the models and how the temporal information is used. Furthermore, two subgroups of patients were considered: slow and fast progressors, taking into consideration their ALSFRS temporal evolution. Afterwards, the training set (75% of the patients) is used to build the predictive models, optionally applying techniques such as feature selection (FS) and oversampling (SMOTE [6]). Resorting to 5 x 10-fold cross validation (CV), the best parameters for each model are chosen. Finally, final models are applied to the test set (remaining 25% of original instances), evaluating the predictive power. In the following subsections, the individual steps are presented and discussed.

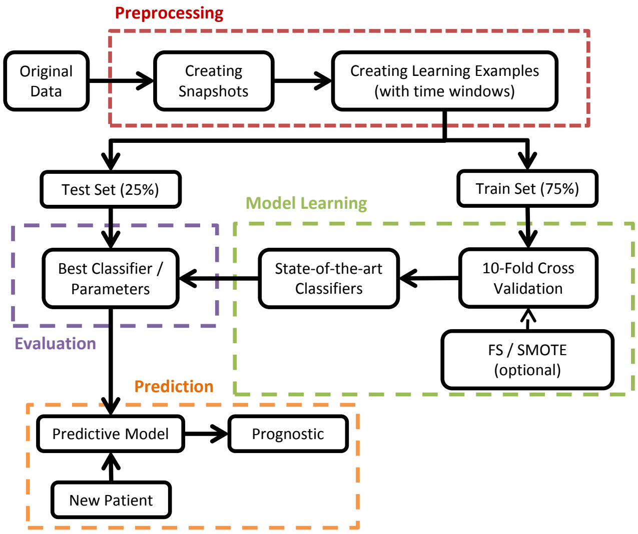

Figure 2: Workflow of the proposed strategy for ALS prognostic prediction.

2.1 Data Preprocessing

In this section, the preprocessing stage is discussed, including the creation of snapshots and the learning examples based on time windows, together with other techniques such as FS and SMOTE, used to improve predictive power.

2.1.1 *Creating Snapshots*

The data used in this work consists of both static (demographic data) and temporal information (different clinical evaluations). Originally, the data were organized in a file per type, such as demographic, respiratory, functional, muscle analysis, and other exams. Since a patient is not able to perform all prescribed exams in a single day, rather than a few weeks or months, it was necessary to consider the temporal organization of the different exams, grouping them in a single evaluation, or snapshot, representing the patient's condition at the time. The followed strategy to achieve this goal was proposed in previous work [1], where bottom-up hierarchical clustering was used to group the temporally-related exams, taking into account constraints, namely not allowing two evaluations of the same exam to belong to the same snapshot, and keeping class coherence. The latter was introduced to prevent changes of the NIV status within a given evaluation, resulting in more consistent snapshots [1]. If such changes occur, a new snapshot (with new exams) begins. The result of creating snapshots from the original data is illustrated in Figure 3.

2.1.2 *Creating Learning Examples*

Evolution Class.

After transforming the data into snapshots, and since our goal is to predict the evolution of the NIV status, learning examples with the corresponding class label were built. Figure 4 shows the *Evolution* (E) class and how the labels are computed from the changes in the NIV status within the specified time window of k days: $E = 1$, if the patient needs external ventilation (NIV) within a time window of k days, or $E = 0$, if the respiratory condition does not change in that interval. This approach is relevant for the clinical practice,

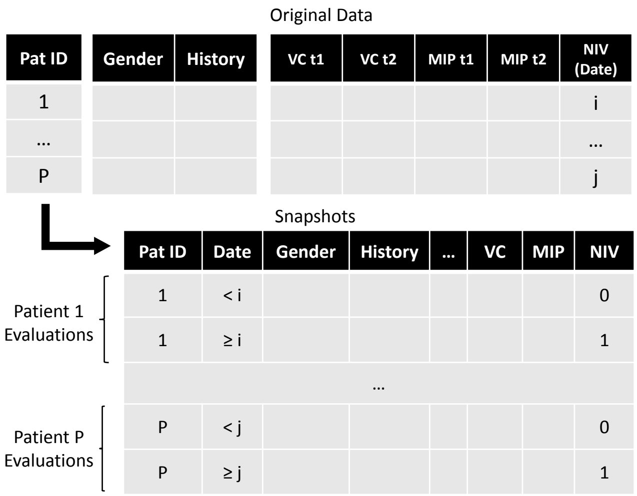

Figure 3: Transformation of original data into snapshots, grouping batches of exams together. Vital capacity (VC) and maximum inspiratory pressure (MIP) are examples of respiratory measures; NIV is non-invasive ventilation.

allowing clinicians to identify higher risk patients in what concerns the development of hypoventilation. We decided to use k values of 90, 180 and 365 days, taking into account that appointments are typically separated by three months, as recommended elsewhere [2]. Analyzing Figure 4 in more detail, we notice the relabeling of the first snapshot for both patients 1 and P, where the latter evolves to require NIV within the window of k days after i. We focus only on NIV status evolution, and thus the snapshots where the patient already requires NIV at the beginning of the time window are discarded (patient 2 in Figure 4). Moreover, a snapshot is discarded if we do not have information regarding the NIV status after k days from the snapshot time, since we could not safely label it as evolving, or not. For instance, the last information available for patient 3 in Figure 4 allows a gap between j and $i + k$ days where we do not know if the NIV status changed. As the time window increases, the probability of evolving to require NIV increases, and more snapshots are discarded due to the aforementioned reasons.

T First Snapshots.

In previous work [1] we used the computed snapshots as instances to achieve NIV diagnosis, discarding any temporal relations. In this work, each patient is an instance, comprised of its initial set of snapshots, to predict NIV prognosis within a time window. As a first analysis, we assessed the predictive power of using only a few of the initial snapshots (2 or 3 time points (TP)), and compared it with the one obtained when using only the last of those snapshots (second or third). These numbers were chosen in order to guarantee that we have more than 100 patients with such temporal data, given that many patients were not followed for a longer time frame, or did not survived. Hence, according to the number of snapshots chosen to be used, and considering the discarded snapshots as previously explained, Table 1 shows the class distribution for the different time windows and number of considered time points, where we see that as the time window increases, the total number of patients

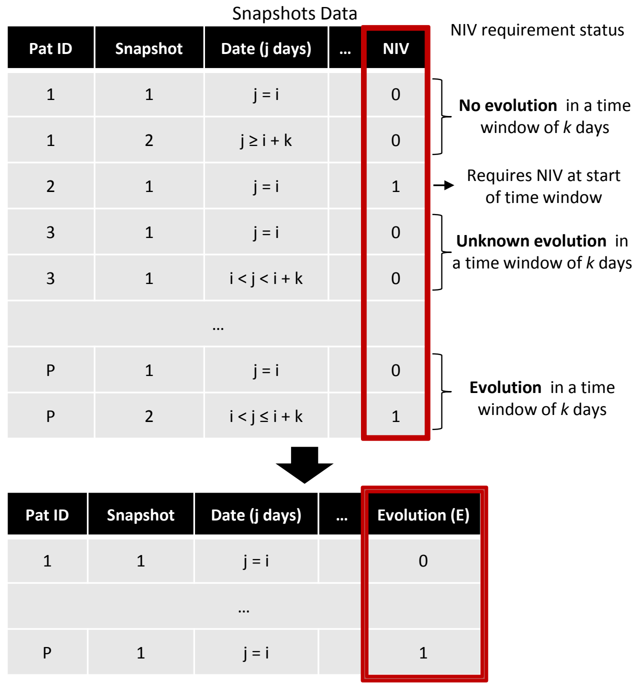

Figure 4: Creating the Evolution class label, given the changes of the NIV status in a given time window of k days after i.

available decreases, while the proportion of evolving patients increases, in general. Figure 5 shows the final format of the input files regarding the T time points considered, with a patient per row and temporal evaluations distributed along the columns.

k	#TP	Patients	Evolution (E)	No Evolution (¬E)
90	2	285	51 (17.89%)	234 (82.11%)
	3	211	40 (18.96%)	171 (81.04%)
180	2	223	42 (18.83%)	181 (81.17%)
	3	202	71 (35.15%)	131 (64.85%)
365	2	181	104 (57.46%)	77 (42.54%)
	3	133	25 (18.80%)	108 (81.20%)

Table 1: Class distribution for time windows of 90, 180 and 365 days. # TP is number of time points.

Temporal Dynamic Patterns.

In the initial set of snapshots, as shown in Figure 5, each feature's temporal evaluations are treated independently. This may lead to the loss of significant temporal information, which could improve the predictive power of the models. Thus, one way to consider the temporal dynamics of the attributes is to build new variables representing the temporal pattern, as shown in Figure 6. These variables can be provided as new features or used in combination with the previous features, to assess if the performance improves.

Progression Groups.

Although some patients present a very slow progression, the mean survival from symptom onset ranges from 2 to 5 years [7]. In order to explore distinct disease progression rates, two groups of patients were considered: slow and fast progressors. This was performed by computing the median numerical slope of the ALSFRS total scores, as in (1), for all training patients.

$$\text{Slope} = \frac{\text{ALSFRS Score}_{tT} - \text{ALSFRS Score}_{t1}}{T}, \qquad (1)$$

where T is the number of snapshots of a given patient.

Since in this computation we used all the available time points for each patient, this analysis is a preliminary attempt to assess if specific models for different progression groups can be used to improve prognosis, even though in clinical practice it is very difficult to infer the rate of progression after just the first set of appointments.

ID	Att1 t1	Att2 t1	...	Att1 tT	Att2 tT	Evolution
1						1
2						0
...			...			
P						1

Figure 5: Example of an input file comprising two attributes, along T time points, for P patients.

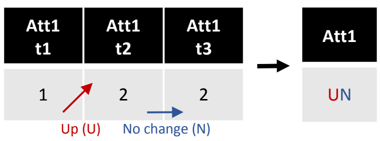

Figure 6: Transforming sequential evaluations into a pattern representing temporal dynamics.

2.2 Classification

The preprocessing step yields a different dataset according to the chosen time window. In this work we study three different values: 90, 180 and 365 days. These preprocessed data are given as input to different classifiers, available in Weka [10], including k-Nearest Neighbor (kNN) with `IBK` implementation, Naïve Bayes (NB), Decision Tree (DT) with `J48` algorithm as well as Random Forest (RF), Support Vector Machines (SVM) using `SMO` implementation with polynomial (SVM P) and Gaussian (SVM G) kernels, and Logistic Regression (LR) using the SimpleLogistic implementation. To build the predictive models, we trained the classifiers with 75% of the patients using stratified 5 x 10-fold CV [13] as well as a grid search to find the best set of parameters for each classifier (not shown due to space constraints).

Furthermore, we evaluated how FS and SMOTE impacted the performance of the predicted models. For the first, we used a wrapper approach available in Weka, where we chose NB as the underlying classifier. We applied FS on the training set to select the relevant features and use them later in the test set. Nonetheless, the oversampling, SMOTE [6] in Weka, is applied to each CV train fold, interpolating known samples of the minority class with synthetic ones, thus rendering the training set more balanced (or even reversing the unbalance). We chose to use SMOTE values of 100, 200, 300, 400 and 500%, where a 100% value means that the minority class instances are doubled. Note that these techniques (FS and SMOTE) can be used simultaneously.

3. RESULTS AND DISCUSSION

We present and discuss the results of the stratified 5 x 10-fold CV [13] scheme using the training set (75% of the original patients), to assess the best learning examples and classifier parameters. We present the AUC, sensitivity and specificity, as it is current practice, although other metrics were also obtained, as computed from the confusion matrix. Afterwards, we show the results of applying the best prognostic models obtained for the different time windows to the test set (25% of the initial dataset).

3.1 Training Set

Tables 3, 4 and 5 show, respectively, the results of AUC, sensitivity and specificity obtained with the training set under stratified 5 x 10-fold CV, for the different time windows, number of time points (TP) and type of learning examples.

When analyzing the utility of using the first 2 or 3 TP, or snapshots, and comparing with resorting only to the 2^{nd} or 3^{rd} ones (Orig vs. Last in Table 3), we found that, for the windows of 180 and 365 days, the AUC was significantly better when we used 3 TP (vs. 3^{rd}) and 2 TP (vs. 2^{nd}), respectively, with a $p \leq 0.036$ assessed with a Wilcoxon Signed-Ranks Test [9]. However, we found that using only the 2^{nd} snapshot for the 180 days window returned generally, although not significantly ($p = 0.123$), better AUC values across the different classifiers, with the exception of LR, comparing to 2 TP. Although there are no statistical significant differences of AUC for the window of 90 days under this comparison (Orig vs. Last), we can see that the best performing classifiers, such as NB and RF, seem to benefit, even if marginally, from using more snapshots. In terms of sensitivity (Table 4), the results are poor, and we can see that, in general, for windows of 90 and 180 days, sensitivity increases when only the last snapshot is considered, while the contrary happens for most classifiers for 365 days. The opposite behavior is seen for specificity (Table 5).

Regarding the combination of patterns to represent temporal dynamics with the original variables (Orig vs. Dyn in Table 3), we found that it only significantly improved the AUC for the window of 365 days using 3 TP ($p = 0.017$), whereas it significantly decreased the AUC for the windows of 90 days using 2 TP, and 180 days (both 2 and 3 TP) ($p \leq 0.05$). We note, however, that for the windows of 180 and 365 days using 3 TP, the best results for including dynamic temporal patterns were obtained when FS was applied, resulting in a very reduced set of features, including both original attributes, at a given time point, and the computed dynamic temporal patterns. The selected features are shown in Table 2. This is especially relevant for the window of 365 days (3 TP model), given it outperformed the original set of features using only four features, including the carbon dioxide pressure (PCO2) and phrenic nerve amplitude (PhrenMeanAmpl) at time point 2, the ALSFRS score at time point 3, and the dynamic temporal pattern representing the variations of the vital capacity (VC) measure.

This supports the importance of taking the temporal re-

Window	#TP	Selected Features
180	3	MIP_{t1} $ALSFRS_{Dyn}$ R_{Dyn}
365	3	$PCO2_{t2}$ $PhrenMeanAmpl_{t2}$ $ALSFRS_{t3}$ VC_{Dyn}

Table 2: Selected features for windows of 180 and 365 days using 3 TP and including dynamic temporal patterns: maximum inspiratory pressure (MIP), ALS Functional Rating Scale (ALSFRS) and respiratory subscore (R), carbon dioxide pressure (PCO2), phrenic nerver mean amplitude (PhrenMeanAmpl) and vital capacity (VC). tT is the time point T and Dyn is the dynamic temporal pattern.

lationships between evaluations of the same variable into account. This is, however, a first attempt, requiring further analysis and improvements. In fact, with exception of few classifiers, especially for 365 days, we can observe that, in general, both the sensitivity and specificity (Tables 4 and 5) decrease when temporal dynamic patterns are included.

Considering the separation into slow and fast progressors, and in order to conclude that there is a real benefit in using specific predictive models, we should observe a statistical significant improvement for both groups, when compared to the original learning examples. Nevertheless, we couldn't find such significance, although, in general, we can see marginal improvements for both groups for the window of 90 days using 3 TP (and at least for one group using 2 TP). Regarding sensitivity and specificity, there is a great variability, where in some cases, the "slow" group presents an increased sensitivity and decreased specificity while the "fast" group shows a decreased sensitivity and increased specificity, or vice-versa. The strategy to correctly classify new patients into slow or fast progressors is a different and interesting problem, which we wish to address in future work. However, this shows the potential of creating specific models for subgroups of patients to improve prognosis.

Taking into consideration the analysis using the 2 TP or 3 TP model, we concluded that there are no significant differences across the three time windows. Nonetheless, studying each individually we found that, for the window of 90 days, the 2 TP model significantly outperformed 3 TP ($p < 0.001$) across all classifiers and different learning examples. Significant differences can also be observed for the 365 days window, although in this case the AUC is increased for the 3 TP model ($p < 0.001$), suggesting that, when predicting an event in a longer time window, it may be better to use more initial snapshots.

In order to compare the performance of the different classifiers, we applied the Friedman test (as suggested in [9]) in IBM SPSS Statistics 22, concluding that there are statistical significant differences between the AUC values. We analyzed the pairs comparison, with significance values corrected for multiple testing and found that kNN, NB and RF performed significantly better than DT, LR and both SVMs (polynomial and Gaussian kernels) ($p \leq 0.014$). Moreover, we verified that the top performing classifier, according to the mean test rank, was NB. Although this analysis is based on AUC values, NB presents other advantages: it is virtually non-parametric, and returns a numerical confidence on the result, which can be used by the clinician as a risk measure. For these reasons, we proceed to the test set with only NB.

3.2 Test Set

After choosing the best classification models based on a stratified 5 x 10-fold CV using the training set, we proceeded to study their performance on the test set (remaining 25% of patients). As usual, we use all the available training instances to train the final models used in the test phase. These results allow us to know what to expect in terms of predictive power when dealing with new, unknown, patients' data. Table 6 shows the results of AUC, sensitivity and specificity obtained for the test set, with the chosen classifier NB. We note that we dismissed the progression groups from this analysis. Although the groups are promising in terms of improving prognosis, we first must solve the problem of classifying new patients according to their progression, using only the initial time points, which we leave for future work.

Comparing the results of AUC in Table 6 with Table 3, we did not find any significant differences across all time windows and learning examples. In fact, for the 90 days window we observe that the test results are always within or above the confidence interval (mean$\pm$standard deviation) obtained for the train set. The same does not happen for the other two time windows, especially for the 2 TP model, where we see that the test results are under the confidence interval. This might be a result of overfitting the models when the variables are in lower number, as it is the case in the 2 TP model.

Another interesting result is the fact that, exception made to the 2^{nd} TP model for 180 and 365 days, the test results when using only the last snapshot are better than the train results. In fact, some of the conclusions we drew for the training set are now reverted, such as for the 180 days window, where now using only the last snapshot yields better AUC for the 3 TP model and worse for the 2 TP model. This justifies the use of an independent test set, to validate, or refute, previous conclusions. Nonetheless, we believe that these models can be very useful in the clinical practice, especially when using Bayesian classifiers such as NB, which can return confidence values in the prognosis.

4. CONCLUSIONS

In this work we propose a new patient-driven approach for predicting RI in ALS, based on time windows and using different types of learning examples. The key question addressed is whether we can predict if a patient will evolve to require NIV k days after an initial set of evaluations. Although we use the same data used in previous work [1] and the same strategy to build the patients' snapshots, we are not interested in the simple NIV diagnosis, but on the prognosis of the evolution of NIV status. Furthermore, while in [1] each patient's snapshot was used as a model instance, in this work each patient represents an instance, to grasp more of the underlying temporal relationships between variable evaluations. Different types of learning examples and time windows were used (90, 180 and 365 days), in an attempt to investigate whether there are any improvements when using a set of initial snapshots versus using the last one; or introducing temporal dynamics of variables in the form of patterns. Furthermore, we made a first attempt at developing specific models for two progression groups. In the last case, even though the results show some promise, the initial classification into slow and fast progressors is still critical, and should be achieved with only the initial snapshots.

We performed a stratified 5 x 10-fold CV using the training set, to choose the best classifier models and assess the impact of the different learning examples. Finally, we applied the best models to the test set, and obtained AUC values of 84.64%, 75.86% and 77.06% for, respectively, the windows of 90, 180 and 365 days using NB classifier models. The results did not allow us to clearly conclude whether the use of the last snapshot yields consistently better or worse results than using a set of snapshots. However, when comparing the use of 2 or 3 snapshots, the general conclusion is that, if available, more time points should be considered. Regarding the introduction of temporal dynamics, our initial approach of patterns did not return significant improvements. However, we plan to use other strategies to explore the temporal nature of data, namely Dynamic Bayesian Networks.

The proposed approach, based on time windows, shows promise in ALS prognostic prediction, and is especially relevant given that the overall disease progression is very fast, usually leading to RI in just a few years. Thus, the possibility of earlier intervention, translating into improvements of the patients' QoL, and even healthcare effectiveness, rises as a crucial aspect of this type of patient-driven analysis.

Acknowledgments

This work was supported by national funds through Fundação para a Ciência e a Tecnologia (FCT), under projects PEst-OE/EEI/LA0021/2013 and DataStorm (EXCL/EEI-ESS/0257/2012), and a doctoral grant SFRH/BD/82042/2011 to AVC.

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Table 3: AUC values obtained using the train set (stratified 5 x 10-fold CV). TP is time points; Orig is the original data; Last is the last snapshot; Dyn is the inclusion of temporal dynamic patterns; Slow and Fast are the two progression groups. SMOTE is oversampling of the minority class; FS is feature selection.

			AUC						
			DT	kNN	SVM P	SVM G	NB	RF	LR
90d	2 TP	Orig + SMOTE(200%)	61.07 ± 5.34	70.14 ± 1.59	66.39 ± 2.59	65.08 ± 1.77	**72.42 ± 1.22**	**73.19 ± 1.77**	66.92 ± 4.36
		Last + SMOTE(400%)	65.65 ± 2.94	72.67 ± 3.65	66.16 ± 1.84	66.19 ± 0.87	**71.37 ± 1.67**	**73.35 ± 0.48**	65.52 ± 2.75
		Dyn + SMOTE(200%)	58.10 ± 1.96	67.24 ± 1.20	63.19 ± 1.80	62.63 ± 2.57	70.39 ± 1.70	70.94 ± 4.39	61.24 ± 2.37
		Slow + SMOTE(200%)	**63.97 ± 3.59**	**73.01 ± 3.77**	65.25 ± 1.45	**66.23 ± 2.51**	**74.40 ± 3.15**	**74.47 ± 4.01**	63.24 ± 4.19
		Fast + SMOTE(200%)	59.29 ± 9.08	**75.81 ± 1.78**	**69.03 ± 3.28**	**68.80 ± 2.00**	**76.32 ± 1.27**	**75.24 ± 1.88**	**76.06 ± 4.03**
	3 TP	Orig + SMOTE(400%)	57.21 ± 3.02	68.32 ± 2.39	56.33 ± 1.91	60.61 ± 2.94	**65.11 ± 1.62**	**68.23 ± 4.34**	59.40 ± 4.76
		Last + SMOTE(100%)	60.96 ± 4.35	59.31 ± 2.12	51.18 ± 1.74	51.05 ± 1.85	**61.40 ± 1.74**	**54.30 ± 3.07**	59.46 ± 5.88
		Dyn + SMOTE(400%)	57.37 ± 4.97	65.78 ± 3.49	57.49 ± 2.07	56.39 ± 2.16	60.36 ± 2.18	66.20 ± 5.53	59.52 ± 4.18
		Slow + SMOTE(500%)	49.94 ± 6.71	**80.18 ± 3.43**	**59.28 ± 5.01**	**65.41 ± 5.49**	**72.90 ± 1.95**	**74.78 ± 2.93**	**74.28 ± 1.94**
		Fast + SMOTE(100%)	**64.67 ± 5.22**	**74.32 ± 2.64**	**66.40 ± 2.13**	**63.01 ± 2.41**	**69.84 ± 0.95**	**73.63 ± 1.81**	**68.64 ± 3.15**
180d	2 TP	Orig + SMOTE(300%)	67.44 ± 5.52	**74.94 ± 2.69**	65.75 ± 3.79	65.28 ± 3.02	**74.12 ± 2.00**	**73.81 ± 3.87**	69.36 ± 3.95
		Last + SMOTE(500%)	**72.15 ± 3.85**	**76.62 ± 4.59**	**70.13 ± 1.67**	**72.25 ± 3.97**	**77.84 ± 1.58**	**76.13 ± 1.79**	63.26 ± 4.13
		Dyn + SMOTE(300%)	66.92 ± 3.90	72.51 ± 2.52	64.47 ± 1.34	63.32 ± 3.53	70.30 ± 1.54	73.48 ± 1.24	70.80 ± 4.45
		Slow + SMOTE(400%)	66.37 ± 6.23	74.08 ± 0.53	69.72 ± 0.95	70.29 ± 2.42	73.00 ± 0.84	71.85 ± 3.26	68.28 ± 5.12
		Fast + SMOTE(200%)	56.14 ± 7.82	82.46 ± 1.88	60.08 ± 4.56	58.89 ± 6.37	80.16 ± 2.50	74.84 ± 3.82	72.76 ± 4.25
	3 TP	Orig + SMOTE(200%)	68.30 ± 3.68	**72.54 ± 2.84**	70.75 ± 1.73	70.66 ± 3.26	**71.26 ± 1.22**	**75.05 ± 1.22**	**73.68 ± 3.82**
		Last + SMOTE(400%)	62.36 ± 1.92	72.63 ± 1.29	66.05 ± 0.49	65.47 ± 1.04	70.27 ± 1.50	68.93 ± 3.10	73.72 ± 2.74
		Dyn + FS	68.16 ± 1.76	69.98 ± 1.43	62.96 ± 0.85	63.80 ± 0.37	68.48 ± 2.05	66.67 ± 1.41	66.74 ± 2.35
		Slow + SMOTE(300%)	64.95 ± 5.29	74.12 ± 1.61	67.75 ± 2.90	68.19 ± 2.72	**75.31 ± 0.86**	72.92 ± 4.03	65.72 ± 3.39
		Fast + SMOTE(100%)	73.20 ± 2.68	68.03 ± 1.57	68.24 ± 5.61	68.88 ± 5.57	**74.39 ± 1.47**	70.77 ± 2.97	71.70 ± 2.80
365d	2 TP	Orig + SMOTE(300%)	61.50 ± 8.85	69.03 ± 1.74	**70.14 ± 3.60**	69.10 ± 2.60	**71.32 ± 2.02**	**69.80 ± 2.20**	46.64 ± 5.18
		Last + SMOTE(500%)	53.86 ± 3.42	61.47 ± 2.89	65.90 ± 2.08	64.90 ± 0.83	65.16 ± 3.67	62.03 ± 3.41	49.20 ± 6.00
		Dyn + SMOTE(400%)	61.03 ± 3.50	70.84 ± 2.27	65.29 ± 2.69	65.52 ± 2.13	71.10 ± 2.24	68.75 ± 5.89	51.32 ± 5.02
		Slow + SMOTE(200%)	58.43 ± 7.85	65.50 ± 3.95	61.89 ± 2.92	60.09 ± 2.63	66.64 ± 3.13	63.25 ± 3.66	40.38 ± 6.10
		Fast + SMOTE(200%)	56.88 ± 8.29	60.97 ± 5.75	56.96 ± 5.12	57.33 ± 4.58	59.63 ± 5.15	56.45 ± 4.92	45.04 ± 6.45
	3 TP	Orig + SMOTE(200%)	**74.87 ± 2.93**	69.27 ± 1.41	70.97 ± 2.65	69.33 ± 1.94	**75.35 ± 1.64**	68.66 ± 2.09	66.72 ± 3.75
		Last + SMOTE(200%)	72.99 ± 4.46	72.07 ± 1.42	66.47 ± 1.73	67.11 ± 2.03	72.60 ± 1.47	70.01 ± 2.58	65.84 ± 3.48
		Dyn + FS	73.60 ± 1.43	**77.74 ± 1.75**	**76.71 ± 1.60**	**77.73 ± 1.77**	**79.16 ± 1.71**	**78.83 ± 2.11**	**68.64 ± 1.98**
		Slow + SMOTE(400%)	58.26 ± 9.63	73.57 ± 4.32	64.52 ± 3.67	64.71 ± 5.56	73.98 ± 4.62	71.00 ± 7.88	68.44 ± 8.12
		Fast + SMOTE(300%)	58.47 ± 3.80	61.66 ± 3.80	63.33 ± 6.59	62.39 ± 6.85	71.33 ± 4.05	60.28 ± 4.31	64.02 ± 5.29

Table 4: Sensitivity values obtained using the train set (stratified 5 x 10-fold CV). TP is time points; Orig is the original data; Last is the last snapshot; Dyn is the inclusion of temporal dynamic patterns; Slow and Fast are the two progression groups. SMOTE is oversampling of the minority class; FS is feature selection.

			Sensitivity						
			DT	kNN	SVM P	SVM G	NB	RF	LR
90d	2 TP	Orig + SMOTE(200%)	36.57 ± 4.70	29.71 ± 3.26	42.29 ± 4.70	39.43 ± 3.13	40.57 ± 2.39	29.14 ± 3.73	40.00 ± 5.36
		Last + SMOTE(400%)	39.43 ± 3.13	44.57 ± 3.83	41.71 ± 5.57	44.57 ± 4.33	41.14 ± 5.19	38.86 ± 6.26	37.14 ± 10.49
		Dyn + SMOTE(200%)	28.57 ± 2.86	26.86 ± 5.93	39.43 ± 6.19	32.57 ± 7.72	34.29 ± 2.86	26.29 ± 8.18	32.00 ± 6.16
		Slow + SMOTE(200%)	42.35 ± 2.63	37.65 ± 3.22	44.71 ± 3.22	45.88 ± 2.63	37.65 ± 7.89	29.41 ± 11.77	37.64 ± 11.47
		Fast + SMOTE(200%)	37.65 ± 8.92	36.47 ± 4.92	43.53 ± 5.26	41.18 ± 4.16	41.18 ± 0.00	35.29 ± 0.00	45.88 ± 6.41
	3 TP	Orig + SMOTE(400%)	32.14 ± 11.01	27.86 ± 11.68	30.00 ± 5.42	40.71 ± 4.07	16.43 ± 4.07	22.14 ± 4.66	28.58 ± 10.10
		Last + SMOTE(100%)	20.00 ± 4.07	20.00 ± 3.19	7.86 ± 12.47	11.43 ± 11.95	32.86 ± 2.99	17.14 ± 8.89	25.70 ± 5.87
		Dyn + SMOTE(400%)	34.29 ± 11.46	35.00 ± 5.87	27.14 ± 5.98	24.29 ± 5.30	8.57 ± 1.96	21.43 ± 5.65	26.42 ± 5.99
		Slow + SMOTE(500%)	24.00 ± 8.94	44.00 ± 15.17	26.00 ± 8.94	72.00 ± 13.04	6.00 ± 5.48	20.00 ± 7.07	32.00 ± 8.37
		Fast + SMOTE(100%)	36.47 ± 4.92	18.82 ± 4.92	43.53 ± 3.22	36.47 ± 4.92	28.24 ± 9.67	11.77 ± 0.00	34.12 ± 8.75
180d	2 TP	Orig + SMOTE(300%)	47.74 ± 7.70	41.94 ± 7.90	43.87 ± 6.69	45.16 ± 6.04	36.13 ± 5.77	38.71 ± 8.22	46.46 ± 10.35
		Last + SMOTE(500%)	54.84 ± 7.57	66.45 ± 8.72	56.13 ± 3.68	63.23 ± 8.41	43.23 ± 3.68	49.68 ± 5.86	43.20 ± 4.90
		Dyn + SMOTE(300%)	49.68 ± 6.29	34.84 ± 6.99	43.23 ± 5.86	38.71 ± 5.10	31.61 ± 2.70	37.42 ± 7.77	48.38 ± 6.44
		Slow + SMOTE(400%)	54.78 ± 7.90	66.96 ± 13.95	64.35 ± 1.94	55.65 ± 3.64	42.61 ± 7.78	53.91 ± 7.28	46.08 ± 6.59
		Fast + SMOTE(200%)	33.33 ± 16.67	6.67 ± 9.13	23.33 ± 9.13	20.00 ± 13.94	13.33 ± 7.45	3.33 ± 7.45	16.68 ± 11.77
	3 TP	Orig + SMOTE(200%)	67.08 ± 7.13	41.67 ± 3.61	60.42 ± 2.95	59.17 ± 5.63	46.25 ± 3.09	51.25 ± 4.06	60.44 ± 5.71
		Last + SMOTE(400%)	55.00 ± 5.63	62.08 ± 3.42	58.33 ± 3.90	60.83 ± 9.36	45.83 ± 5.71	53.33 ± 4.56	65.44 ± 2.39
		Dyn + FS	37.50 ± 2.55	17.08 ± 3.09	43.33 ± 3.42	44.17 ± 2.72	48.75 ± 1.86	39.17 ± 3.42	35.86 ± 4.74
		Slow + SMOTE(300%)	52.50 ± 10.04	59.17 ± 5.43	53.33 ± 6.85	53.33 ± 5.43	52.50 ± 2.28	53.33 ± 4.56	53.34 ± 6.19
		Fast + SMOTE(100%)	79.11 ± 2.53	60.44 ± 1.86	78.22 ± 3.65	76.89 ± 7.47	74.67 ± 2.98	77.78 ± 2.72	52.16 ± 4.35
365d	2 TP	Orig + SMOTE(300%)	46.00 ± 10.84	48.00 ± 6.71	57.00 ± 7.58	53.00 ± 4.47	49.00 ± 7.42	48.00 ± 5.70	20.00 ± 0.00
		Last + SMOTE(500%)	37.00 ± 7.58	48.00 ± 6.71	57.00 ± 4.47	55.00 ± 9.35	40.00 ± 7.91	41.00 ± 10.84	22.00 ± 5.70
		Dyn + SMOTE(400%)	49.00 ± 7.42	62.00 ± 5.70	44.00 ± 6.52	42.00 ± 5.70	25.00 ± 5.00	49.00 ± 12.45	29.00 ± 6.52
		Slow + SMOTE(200%)	37.78 ± 14.91	31.11 ± 4.97	35.56 ± 4.97	28.89 ± 6.09	37.78 ± 6.09	31.11 ± 9.30	19.98 ± 4.96
		Fast + SMOTE(200%)	29.09 ± 7.61	34.55 ± 9.96	34.55 ± 7.61	30.91 ± 8.13	38.18 ± 4.07	30.91 ± 8.13	23.66 ± 10.38
	3 TP	Orig + SMOTE(200%)	65.64 ± 2.78	28.46 ± 4.10	70.51 ± 3.39	68.46 ± 3.22	76.15 ± 3.46	61.28 ± 1.07	61.54 ± 8.39
		Last + SMOTE(200%)	56.92 ± 4.85	39.74 ± 3.95	64.36 ± 3.56	56.67 ± 12.67	64.87 ± 2.33	62.82 ± 2.03	63.58 ± 3.07
		Dyn + FS	66.41 ± 4.48	70.00 ± 7.34	78.72 ± 1.72	78.72 ± 1.72	75.90 ± 2.47	77.18 ± 3.32	74.36 ± 3.51
		Slow + SMOTE(400%)	79.23 ± 8.86	83.85 ± 11.35	80.77 ± 8.16	77.70 ± 5.02	73.08 ± 6.08	68.46 ± 11.35	63.86 ± 6.44
		Fast + SMOTE(300%)	38.95 ± 6.00	72.63 ± 4.40	60.00 ± 16.89	52.63 ± 15.35	36.84 ± 7.44	35.79 ± 11.41	71.36 ± 4.30

Table 5: Specificity values obtained using the train set (stratified 5 x 10-fold CV). TP is time points; Orig is the original data; Last is the last snapshot; Dyn is the inclusion of temporal dynamic patterns; Slow and Fast are the two progression groups. SMOTE is oversampling of the minority class; FS is feature selection.

			Specificity						
			DT	kNN	SVM P	SVM G	NB	RF	LR
90d	2 TP	Orig + SMOTE(200%)	88.17 ± 2.39	93.54 ± 1.86	90.49 ± 3.10	90.73 ± 2.71	90.00 ± 1.81	94.02 ± 1.17	82.22 ± 2.68
		Last + SMOTE (400%)	87.56 ± 0.93	83.42 ± 1.90	90.61 ± 2.22	87.81 ± 3.61	90.00 ± 0.33	88.66 ± 1.11	82.22 ± 4.80
		Dyn+ SMOTE(200%)	87.32 ± 1.32	92.93 ± 1.11	86.95 ± 4.77	92.68 ± 2.62	90.24 ± 1.56	92.81 ± 3.15	84.88 ± 3.00
		Slow + SMOTE(200%)	86.32 ± 2.73	87.63 ± 3.03	85.79 ± 2.85	86.58 ± 4.78	87.63 ± 1.77	90.79 ± 2.08	78.68 ± 2.87
		Fast + SMOTE(200%)	84.76 ± 1.96	94.05 ± 1.68	94.52 ± 2.74	96.43 ± 1.46	94.52 ± 1.81	94.29 ± 1.55	87.14 ± 2.86
	3 TP	Orig + SMOTE(400%)	81.17 ± 3.15	88.50 ± 2.97	82.67 ± 5.25	80.50 ± 6.36	92.83 ± 2.09	90.67 ± 2.31	81.02 ± 3.18
		Last + SMOTE(100%)	79.17 ± 3.63	77.83 ± 4.02	94.50 ± 9.05	90.67 ± 8.96	73.33 ± 1.56	79.00 ± 2.85	84.82 ± 1.36
		Dyn + SMOTE(400%)	78.83 ± 4.15	84.00 ± 3.51	87.83 ± 3.15	88.50 ± 1.49	95.83 ± 1.56	91.50 ± 2.08	85.82 ± 4.08
		Slow + SMOTE(500%)	81.96 ± 7.12	85.10 ± 2.63	92.55 ± 2.56	58.82 ± 17.97	92.94 ± 2.24	90.98 ± 3.56	86.28 ± 3.66
		Fast + SMOTE(100%)	88.06 ± 5.68	89.25 ± 1.25	89.25 ± 2.45	89.55 ± 3.50	81.79 ± 2.67	89.55 ± 2.79	83.30 ± 3.73
180d	2 TP	Orig + SMOTE(300%)	86.51 ± 2.02	88.73 ± 0.36	87.62 ± 2.78	85.40 ± 2.78	89.21 ± 1.33	89.05 ± 1.53	80.96 ± 1.65
		Last + SMOTE(500%)	83.33 ± 3.22	80.95 ± 4.09	84.13 ± 3.02	81.27 ± 5.57	88.73 ± 0.66	86.03 ± 1.33	78.74 ± 2.94
		Dyn + SMOTE(300%)	83.81 ± 2.78	84.76 ± 1.81	85.71 ± 6.17	87.94 ± 3.86	90.64 ± 2.54	89.37 ± 1.65	83.48 ± 2.81
		Slow + SMOTE(400%)	76.07 ± 4.72	77.71 ± 4.72	75.08 ± 0.73	84.92 ± 2.69	85.90 ± 1.87	81.31 ± 2.98	75.10 ± 3.55
		Fast + SMOTE(200%)	90.16 ± 2.61	94.60 ± 1.81	96.83 ± 0.00	97.78 ± 1.42	94.29 ± 1.42	97.46 ± 2.88	92.29 ± 3.49
	3 TP	Orig + SMOTE(200%)	69.03 ± 4.26	82.80 ± 3.14	81.08 ± 1.80	82.15 ± 1.63	83.01 ± 1.40	80.00 ± 2.70	74.84 ± 4.08
		Last + SMOTE(400%)	63.66 ± 3.52	67.10 ± 5.41	73.76 ± 4.14	70.11 ± 8.65	79.36 ± 4.52	69.46 ± 3.00	73.10 ± 3.23
		Dyn + FS	87.74 ± 1.23	88.60 ± 2.59	82.58 ± 4.65	83.44 ± 2.70	87.74 ± 1.23	78.07 ± 2.59	84.30 ± 2.49
		Slow + SMOTE(300%)	71.30 ± 5.63	72.17 ± 5.83	82.17 ± 2.38	83.04 ± 3.57	82.17 ± 2.38	76.96 ± 6.07	68.26 ± 4.48
		Fast + SMOTE(100%)	66.09 ± 8.36	65.22 ± 6.15	58.26 ± 10.47	60.87 ± 13.40	61.74 ± 7.78	50.44 ± 12.14	79.12 ± 7.30
365d	2 TP	Orig + SMOTE(300%)	86.30 ± 1.68	83.01 ± 2.84	83.29 ± 1.79	85.21 ± 3.55	86.85 ± 3.95	84.38 ± 3.95	74.80 ± 4.72
		Last + SMOTE(500%)	73.15 ± 5.53	69.04 ± 4.40	74.80 ± 7.03	74.80 ± 8.53	84.11 ± 3.70	78.08 ± 4.84	73.16 ± 2.67
		Dyn + SMOTE(400%)	85.75 ± 1.23	73.15 ± 2.49	86.58 ± 3.12	89.04 ± 1.68	92.88 ± 1.79	84.11 ± 3.95	76.70 ± 1.71
		Slow + SMOTE(200%)	86.67 ± 5.56	90.77 ± 2.29	88.21 ± 3.89	91.28 ± 1.40	87.18 ± 2.56	85.64 ± 6.18	75.90 ± 7.60
		Fast + SMOTE(200%)	81.25 ± 4.42	87.50 ± 5.85	79.38 ± 3.56	83.75 ± 5.14	81.25 ± 3.13	76.88 ± 5.23	73.76 ± 7.20
	3 TP	Orig + SMOTE(200%)	83.67 ± 3.23	92.65 ± 5.51	71.43 ± 5.20	70.20 ± 6.71	54.69 ± 0.91	64.90 ± 6.36	61.20 ± 5.95
		Last + SMOTE(200%)	80.82 ± 5.88	87.35 ± 3.35	68.57 ± 5.12	77.55 ± 11.55	65.31 ± 3.82	65.31 ± 3.82	59.18 ± 6.45
		Dyn + FS	77.96 ± 3.03	77.96 ± 4.65	74.69 ± 2.74	76.74 ± 3.71	75.92 ± 3.03	75.51 ± 3.82	48.16 ± 5.52
		Slow + SMOTE(400%)	38.62 ± 5.12	38.62 ± 11.28	48.28 ± 7.32	51.72 ± 8.09	58.62 ± 6.45	54.48 ± 7.48	64.14 ± 7.17
		Fast + SMOTE(300%)	74.90 ± 3.77	44.71 ± 7.52	66.67 ± 9.20	72.16 ± 5.44	83.92 ± 2.56	76.08 ± 2.15	42.08 ± 12.90

Table 6: Results obtained using the test set and Naïve Bayes (NB) classifier. TP is time points; Orig is the original data; Last is the last snapshot; Dyn is the inclusion of temporal dynamic patterns. SMOTE is oversampling of the minority class; FS is feature selection.

			NB		
			AUC	Sensitivity	Specificity
90d	2 TP	Orig + SMOTE(200%)	71.61	43.75	85.71
		Last + SMOTE(400%)	75.71	43.75	90.00
		Dyn + SMOTE(200%)	70.80	31.25	87.14
	3 TP	Orig + SMOTE(400%)	65.44	50.00	78.43
		Last + SMOTE(100%)	84.64	66.67	82.35
		Dyn + SMOTE(400%)	66.34	58.33	76.47
180d	2 TP	Orig + SMOTE(300%)	63.31	27.27	83.64
		Last + SMOTE(500%)	55.70	27.27	81.82
		Dyn + SMOTE(300%)	60.50	36.36	85.46
	3 TP	Orig + SMOTE(200%)	74.49	65.22	78.95
		Last + SMOTE(400%)	75.86	73.91	65.79
		Dyn + FS	60.30	34.78	84.21
365d	2 TP	Orig + SMOTE(300%)	52.57	20.00	62.86
		Last + SMOTE(500%)	54.86	0.00	74.29
		Dyn + SMOTE(400%)	58.29	40.00	71.43
	3 TP	Orig + SMOTE(200%)	63.12	61.54	57.14
		Last + SMOTE(200%)	77.06	69.23	60.71
		Dyn + FS	64.35	50.00	67.86