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Predicting progression of Alzheimer's disease using new survival analysis approach

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ABSTRACT

It is critical to determine the risk of Alzheimer's disease (AD) in people with mild cognitive impairment (MCI) to begin treatment early. Its development is affected by many things, but how each effect and how the disease worsens is unclear. Nevertheless, an in-depth examination of these factors may provide a reasonable estimate of how long it will take for patients at various stages of the disease to develop Alzheimer's. Alzheimer's disease neuroimaging initiative (ADNI) database had 900 people with 63 features from magnetic resonance imaging (MRI), genetic, cognitive, demographic, and cerebrospinal fluid data. These characteristics are used to track AD progression. A hybrid approach for dynamic prediction in clinical survival analysis has been developed to track progression to AD. The method uses a random forest cox regression approach to figure out how long it will take for MCI to turn into AD. In order to evaluate the result concordance index is used. The concordance index measures the rank correlation between predicted risk scores and observed time points. The concordance index was statistically considerably higher in the suggested work than in previous approaches with a score of 95.3%, which is higher than others.

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1. INTRODUCTION

Understanding and predicting the progression of Alzheimer's disease (AD) is a crucial aspect of managing and providing care for individuals affected by this debilitating condition. AD is a progressive neurodegenerative disorder that primarily affects memory, cognition, and behavior [1]. As the global population continues to age, the prevalence of AD is expected to rise, highlighting the urgent need for accurate prediction models that can assist in early detection, treatment planning, and personalized care [2].

In recent years, advancements in medical research and technology have paved the way for the development of sophisticated predictive models that aim to forecast the progression of AD in patients. These models utilize a combination of clinical data, neuroimaging techniques, genetic information, and cognitive assessments to identify patterns, biomarkers, and risk factors associated with disease progression [2], [3]. One powerful approach that has gained traction in recent years is the use of survival analysis techniques to model and forecast disease progression in Alzheimer's patients. Survival analysis, also known as time-to-event analysis, provides a framework for analyzing and predicting the time until an event of interest occurs, such as disease progres-

sion, in the presence of censored data. In the context of AD, survival analysis offers a unique perspective by considering the time from diagnosis to specific milestones or endpoints, such as the onset of severe cognitive impairment, institutionalization, or mortality. By incorporating various factors such as demographic characteristics, genetic markers, biomarkers, and clinical data [4], [5], survival analysis models can provide valuable insights into the factors that influence disease progression and estimate individualized risk profiles.

This article explores the application of survival analysis techniques in predicting the progression of AD. We will delve into the fundamental concepts and statistical methods behind survival analysis, including the Kaplan-Meier estimator, Cox proportional hazards model, and parametric survival models [6], [7]. The proposed approach uses the random forest cox regression method to investigate the effect of several variables on the time it takes for AD to progress. We will also discuss how these models can be adapted and extended to address the unique challenges and complexities associated with AD, such as the presence of competing risks and the incorporation of time-varying covariates.

The objective of predicting the progression of AD using survival analysis is to develop robust and accurate models that can estimate the time until patient suffers severe cognitive decline, institutionalization. By leveraging survival analysis techniques, the aim is to identify prognostic factors, risk profiles, and predictive markers that can aid in early detection, treatment planning, and personalized care for individuals with AD. As composed to other machine learning methods [8]-[10], which divide subjects into two groups, such as stable or progressive MCI. The specific objectives of predicting the progression of AD using survival analysis include: i). Time-to-event estimation: developing survival analysis models that can estimate the time until specific disease-related events occur. It will provides valuable insights into the progression patterns of AD and allow for the estimation of event probabilities and survival outcomes. ii). Identification of prognostic factors: identifying and quantifying the influence of various factors on the progression of AD. It will helps clinicians and caregivers identify high-risk individuals and tailor interventions accordingly. iii). Individualized risk assessment: developing personalized prediction models that consider a patient's unique characteristics and incorporate relevant risk factors. It allows treatment plans, clinical monitoring, and support services tailored based on a patient's specific risk profile. iv). Evaluation of treatment effectiveness: utilizing survival analysis techniques to evaluate the effectiveness of therapeutic interventions and treatment modalities. By analyzing the time until specific disease-related events occur in treatment groups, researchers can assess the impact of interventions on disease progression and inform clinical decision-making. v). Validation and external replication: conducting rigorous validation studies to assess the generalizability and reproducibility of predictive models. Validating the models using independent datasets helps establish their reliability and ensures their applicability in diverse clinical settings.

By achieving these objectives, the prediction of AD progression proposed approach can provide valuable insights into disease trajectory, aid in personalized care planning, improve treatment outcomes, and contribute to the development of targeted interventions. Ultimately, this research aims to enhance the quality of life for individuals with AD and their caregivers.

2. RELATED WORK

2.1. Predictions based on magnetic resonance imaging (MRI) only

Mart´ı-Juan *et al.* [11] performed an approach focused on vertical image data. MCI and CN were predicted as AD by Bashira and Rams framework [12]. He developed a 2D convolutional neural network (CNN) model using 3-channel 2D patches to predict the number of voxels belonging to the hippocampus using only MRI scans [13]. The objective of this approach [14] is to use a multivariate support vector machine (SVM) to determine reliable MRI markers for AD. Farooq and Rady [15] reviewed an unsupervised clustering algorithm for the early detection of AD. This work compares k-means and k-medoids using MRI images' voxel-based morphometry (VBM) function. Valsala and Kariputtaiah [16] detect the presence of AD from MRI and positron emission tomography (PET) through neuro imaging to perform fusion process with more detailed information.

2.2. Prediction based on multiple feature

Shikalgar and Sonavane [17] proposed a method to use a SVM to select the optimal subset of overlapping features based on a least-squares loss function and within-class multimodal data. Bi *et al.* [18] represent the relationship between brain regions and genes. Zawawi *et al.* [19] suggest methodology that can predict next stage of AD progression using neural network model. Qiu *et al.* [20] explain how MRI data improves

the diagnostic accuracy of the mini-mental state examination (MMSE) and logical memory (LM) tests. An easy-to-use web page has been introduced to assist clinicians. Researchers in uploading Alzheimer's tests and obtaining statistics on the occurrence or presence of AD as a result of abnormal tests for one or more biomarkers [21], [22]. While, [23], [24] suggested reducing the high-dimensional by feature selection techniques based on a swarm's algorithm to predict MCI to AD progression.

3. METHODS

3.1. Study participants

We used data from 1,737 patients who were followed for 18 months as part of the Alzheimer's disease neuroimaging initiative (ADNI) to train and test our prediction method. It includes 24 distinct neurological exams along with matching MRIs. There were seven picture files and twenty-four tests in each patient profile. The time evolution of all variables was characterized by patient trajectories at 3-month intervals. The next subsection provides a detailed description of the data processing procedures. The data utilized are the topic criteria listed in Table 1: 1. neuropsychological evaluation; and 2. brain imaging technique (MRI only).

Table 1. The research criteria that were employed in this study

	Subject	Range
1	Age	55-90
2	Educational level	Primary to graduate
3	Color	All colors
4	Ethnicities	All ethnicities

3.2. Data preprocessing

Preprocessing data is an essential step in data analysis and machine learning workflows. It involves transforming raw data into a format that is suitable for further analysis or modeling. The goal of preprocessing is to clean, normalize, and organize the data, making it easier to work with and ensuring the quality and reliability of the results obtained.

The first step in preprocessing data is data cleaning, which involves handling missing values, outliers, and noisy data. Missing values can be filled using techniques like mean imputation or interpolation. Outliers, which are extreme values that deviate significantly from the rest of the data, can be detected and either removed or corrected [25], [26]. Once the data is cleaned, the next step is data normalization, where features are transformed to have a consistent scale. Of the nine classes, the idea of AD survival time prediction is only demonstrated in two AD and MCI.

Data was gathered utilizing assessment data, and included information from neurological tests, time, and imaging MRI. Imputation inside the cross-validation cycle was carried out using the prediction matrix constructed on the training set. In order to improve the accuracy and efficiency of later operations, these preprocessing stages make sure the data is prepared for analysis or modeling. One category, three ordinals, and the remaining six features (which are numbers because the image has been turned to numbers) made up the ADNI data set after data preparation. To the normalization procedure, all continuous features are used. Features that were eliminated had more than 60% of their values missing.

3.3. Method selection

When it comes to survival analysis, the Cox proportional hazards regression model is a popular and widely used technique to analyze the relationship between covariates and survival time [27]-[29]. However, in some cases, the Cox regression model may encounter limitations, such as assumptions of proportional hazards or non-linear relationships between predictors and the hazard function. In such situations, incorporating machine learning methods like random forest with Cox regression (RF-CoxReg) can offer a promising alternative.

Random forest is a versatile ensemble learning method that combines multiple decision trees to make predictions. It has gained popularity due to its ability to handle complex interactions, non-linear relationships, and high-dimensional datasets [30]-[32]. When combined with the Cox regression model, random forest can provide several advantages in survival analysis: i). Variable selection: the variable importance measures produced by random forest can guide the selection of covariates to include in the Cox regression model, improving

the model's predictive accuracy and interpretability. ii). Handling non-linear relationships: by incorporating random forest as a feature selection step or as a predictor in the Cox regression model, the combined approach can handle complex relationships and provide more accurate survival predictions. iii). Model performance: random forest can enhance the predictive performance of the Cox regression model by reducing bias and overfitting. The ensemble nature of random forest helps to mitigate the impact of outliers and noisy predictors, leading to more robust and reliable survival predictions. iv). Handling missing data: by using random forest to impute missing values before applying the Cox regression model, potential biases due to missingness can be reduced, resulting in more accurate and reliable survival analyses. v). Interaction detection: random forest can identify interactions between predictors, which can be included as additional terms in the Cox regression model. A hybrid approach of RF-CoxReg; it investigates the influence of different variables on the occurrence and progression of AD. It properly calibrated and validated using a cross-validation technique. Figure 1 illustrates the proposed approach pipeline. Each phases depends on others. The steps is summarized by the different parties within the proposed framework pipeline. RF-CoxReg takes the data there are three different types of data (MRI, neurological test and baseline diagnosis). Then, the data moves into three different phases until the prediction phase (output phase). The original data contains 68 attributes, while after this step, there is nine. The final step predict the time patient needs to progress from mid cognitive impariment to Alzheimer.

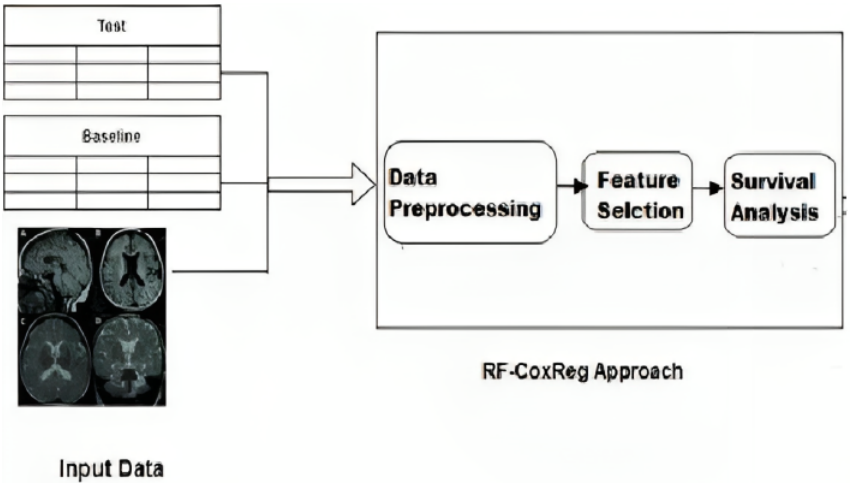

Figure 1. RF-CoxReg pipeline

3.4. Method evaluation

Evaluating the performance of RF-CoxReg model requires a comprehensive assessment to ensure its reliability and suitability for survival analysis. It is essential to assess the predictive accuracy of the model by comparing its predictions to the actual survival outcomes. Concordance index (C-index) [33], [34] is used to evaluate the discriminatory power of the model. Then, the stability and robustness of the model is evaluated. This is achieved by performing cross-validation, which assess the model's performance on different subsets of the data. These techniques help estimate the model's generalization and identify potential issues like overfitting or instability.

Interpretability is another crucial aspect of model evaluation. While random forest offers excellent predictive performance, it may lack interpretability due to its ensemble nature. In contrast, Cox regression provides interpretable hazard ratios, which can aid in understanding the relationship between predictors and survival outcomes. Therefore, it is important to consider the trade-off between predictive accuracy and interpretability when evaluating the combined model.

A comprehensive evaluation ensures that the model is reliable, well-suited for survival analysis, and provides meaningful insights for decision-making in the targeted domain. The performance of RF-CoxReg in terms of discrimination and calibration is assessed. Discrimination refers to the capacity to appropriately differentiate between two types of outcomes. Individuals with events had higher predicted abilities than subjects

who did not join events when using an approach with good discrimination ability [6]. The concordance index (CI), which is the generalization of the ROC curve in the survival complete data, is the most commonly used survival approach evaluation metric. CI is classified into two types based on whether or not the data is linked.

In real-world scenarios, both samples (δi=1 and δj=1) in the sample pair may exhibit progression, and the observed survival times are equal, $T_i = X_i = X_j = T_j$. In this instance, the approach has perfect predictive ability when the survival probabilities or survival times predicted by it are likewise equal to $Y_i = Y_j$. Nevertheless, this type of sample pair cannot improve CI for the original CI definition if ties between survival times are not taken into account. Ishwaran developed a better CI calculation technique for the tied survival data [35] to address this issue. As per their definition, the more negative the prediction result, if it is based on survival time or survival probability, and the more positive the prediction result, if it is based on the hazard function, the worse the prediction result. (1)-(4) is a detailed explanation of how to calculate CI. First define the comparable sample pair:

$$npi_{ij}(X_i, \delta_i, X_j, \delta_j) = max(I(X_i \geqslant X_j)\delta_j, I(X_i \leqslant X_j)\delta_i) \tag{1}$$

in the second step, calculate the complete concordance (CC):

$$CC = \sum_{ij} I(sign(Y_i, Y_j) = csign(X_i, X_j) \mid npi_{ij} \tag{2}$$

where,

$$sign(Y_i, Y_j) = I(Y_i \geqslant Y_j) - I(Y_i \leqslant Y_j)$$
$$csign(X_i, \delta_i, X_j, \delta_j) = I(X_i \geqslant X_j)\delta_j - I(X_i \leqslant X_j)\delta_i$$

then, derive the partial concordance (PC):

$$PC = \sum_{ij} I(Y_i = Y_j \mid npi_{ij} = 1, X_i \neq X_j) \tag{3}$$
$$+I(Y_i \neq Y_j \mid npi_{ij} = 1, X_i = X_j, \delta_i = \delta_j = 1) + I(Y_i \geq Y_j \mid npi_{ij} = 1, X_i = X_j, \delta_i = 1, \delta_j = 0)$$

finally, CI can be calculated as:

$$CI = \frac{Concordance}{Permissible} = \frac{CC + 0.5 * PC}{\sum_{i,j} npi_{ij}(X_i, \delta_i, X_j, \delta_j)} \tag{4}$$

where Yi and Xi stand for the expected and observed survival times, respectively, and δj is the sample i's survival status (0 indicates censoring, 1 indicates event). The paired t-test is used by the null hypothesis to determine whether the means of the two sets of values are equal. Two non-overlapping sets of projected probabilities-positive outcomes and unfavorable events-would result from perfect discrimination. Calibration is the extent to which the expected probability matches the observed events numerically.

4. RESULTS AND DISCUSSION

In this work, "survival" refers to the patient's transition from MCI to AD. These terms suggest that the survival function's shape is not taken into account in the estimation. Using proportional hazard techniques, Table 2 calculates the estimated survivor function for AD patients. A semi-parametric technique created by Cox [36] is referred to as Cox regression, Cox, and Cox proportional hazards regression. No assumptions are made regarding the event time distribution while using the RF-CoxReg method. It does make the assumption that a number of parameters affect the hazard function. Hazard function h(t) expresses the hazard function, which is the risk of advancement at time t. It can be calculated in the manner shown (5):

$$h(t) = h_0(t) * exp(b_1x_1 + b_2x_2 + ... + b_px_p) \tag{5}$$

where: t represents the survival time, h(t) is the hazard function determined by a set of p covariates $(x_1, x_2, ..., x_p)$. The impact (or effect size) of covariates is measured by the coefficients $(b_1, b_2, ..., b_p)$. The baseline hazard is denoted by the term h_0. When all of the x_i are equal to zero (the quantity exp(0) equals 1), it corresponds to the hazard's value. We are reminded that the hazard may change over time by the t in h(t).

On one degree of freedom, the chi-square statistics value is 415, and the p-value is 2e-16, which is not statistically significant. The log-rank test for survival difference yields a p-value of p = 2e-16, indicating a significant difference in survival between year groups. This test aims to determine whether the difference between the observed and predicted data was due to chance or if there was a relationship between the variables being studied.

Table 2. Patients' proportional hazards approach

	Initial examination	After 48 months
n.risk	1800	67
n.event	239	27
Survival	86%	16%
Standard error	0.8%	1.8%
Means value	-0.852 and 0.883	-0.126 and 0.200
Concordance index	95%	5%

The time for progression referred to as "survival time," is studied and modeled in survival analysis. Table 3 shows the effect of each feature on the survival analysis. Coefficient: measure the impact of covariates (log hazard ratio), exp (coefficient): hazard ratio; calculate the covariate size, se (coefficient): standard error it computes the wald statistic (z = coef/ se (coef)), which is the ratio of each regression coefficient to its standard error, Pr($|z|$): The probability of statistics explains the significance of each feature, DX_ bl for CN (first diagnosis for normal patients), DX_ bl for LMCI (first diagnosis for late mild cognitive impairment patients), and CDRSB are highly significant values (their values affect the survival results). This empathise on the effect of first diagnosis for two extremely different scenarios, with the importance of making an interview with the patient and an appropriate informant or caregiver to detect stage and assess progression of AD. Then there is the FAQ, which has a lower priority. The hazard ratios' confidence intervals: in the summary, the hazard ratio (exp (coef)) has upper- and lower-95 percent confidence intervals and Inf: innate immune response.

Table 3. Cox proportional-hazards regression approach summary

	Coef	Exp (coef)	Se (coef)	z	Pr($|z|$)	Lower 0.95	Upper 0.95
DXbl (CN)	6.605e+00	7.390e+02	1.101e+00	5.998	2.00e-09	85.3637	6397.9988
DXb (lEMCI)	-8.691e+00	1.681e-04	1.332e+03	-0.007	0.995	0.0000	Inf
DXbl (LMCI)	6.155e+00	4.712e+02	1.006e+00	6.117	9.54e-10	65.5666	3386.7562
CDRSB	-3.263e-01	7.216e-01	5.222e-02	-6.249	4.14e-10	0.6514	0.7994
ADAS11	-5.029e-03	9.950e-01	2.323e-02	-0.217	0.829	0.9507	1.0413
ADAS13	-6.066e-03	9.940e-01	1.820e-02	-0.333	0.739	0.9591	1.0300
RAVLT immediate	3.398e-03	1.003e+00	6.243e-03	0.544	0.586	0.9912	1.0158
RAVLT learning	-2.788e-03	9.972e-01	2.105e-02	-0.132	0.895	0.9569	1.0392
RAVLT forgetting	2.370e-02	1.024e+00	1.903e-02	1.246	0.213	0.9865	1.0629
FAQ	-2.420e-02	9.761e-01	1.207e-02	-2.005	0.045	0.9533	0.9995
Hippocampus	-3.840e-05	1.000e+00	3.995e-05	-0.961	0.336	0.9999	1.0000
Yearsbl	5.213e+03	Inf	1.709e+04	0.305	0.760	0.0000	Inf
Monthbl	-4.359e+02	4.716e-190	1.427e+03	-0.305	0.760	0.0000	Inf

The likelihood-ratio test, the wald test, and score log-rank statistics are the tests used for the overall performance of the RF-CoxReg approach. They will get comparable outcomes if N is large enough. The likelihood ratio test performs better with the small sample sizes commonly used. Can be observed in Table 1 concordance = 998 (se = 0.001; p = 2e-16, likelihood ratio test = 2727 on 13 df; wald test = 5 on 13 observations, p = 2e-16; test score (log-rank) = 1419 on 13 DF, p = 2e-16.

When evaluating the approach's performance, it is better to combine multiple features to get better performance. The c-index is a metric to evaluate the predictions made by the approach. It is defined as the proportion of concordant pairs divided by the total number of possible evaluation pairs [37]. A value below 0.5 indicates poor approach performance. A value of 0.5 means that the approach is no better at predicting an outcome than random chance. Finally, values over 0.7 indicate good performance.

$$C - index = \frac{N.ConcordantPair}{N.ConcordantPair + N.DiscordantPair} \quad (6)$$

Table 4 illustrates the c-index value comparison between the proposed work and others. It shows that our work got a C-index that it is higher than others. RF-CoxReg outperform other models by 95%.

Table 4. Approach performance using c-index

Proposed approach	Khajehpiri *et al.* [7]	Mirabnahrazam *et al.* [38]
0.953	0.845	0.831

The Kaplan-Meier survival curve defines the probability of surviving for a given time while considering the time in many small intervals. There are three assumptions used in this analysis. Firstly, patients who are censored at any time have the same survival prospects as those who continue to be followed. Secondly, the survival probabilities are the same for subjects recruited early and late in the study. Thirdly, the event happens at the time specified. The Kaplan-Meier method involves computing the probabilities of the occurrence of an event at a certain point in time. These successive probabilities are multiplied to get the final estimate. The survival that follows an AD diagnosis are shown in Table 5. Every six months, the patients get reexaminations. The risk of patient conversion decreased after two years. The approach started with 1,800 cases; in the end, 67 patients did not convert to AD.

Table 5. Approach interpretation

Time	n.risk	n.event	Survival	Std.err	Lower 95% CI	Upper 95% CI
0	1800	239	0.867	0.0080	0.852	0.883
6	1314	212	0.727	0.0111	0.706	0.749
12	910	167	0.594	0.0130	0.569	0.620
18	576	123	0.467	0.0144	0.440	0.496
24	409	79	0.377	0.0148	0.349	0.407
36	181	53	0.266	0.0165	0.236	0.301
48	67	27	0.159	0.0188	0.126	0.200

5. CONCLUSION

We proposed a method to improve MCI prediction for AD diagnosis by adding feature sets using random forest. To proceed, we propose a survival analysis strategy using feature selection techniques. Survival analysis techniques are particularly useful in medical and health research for early detection of various diseases. Unlike existing approaches, the patient's life situation can be predicted without classifying the current diagnostic status. Compared to other works, the work performs better; it can predict the progression of MCI to AD with a 95% prediction accuracy. Nevertheless, prior studies have connected a number of the attributes selected in our method to AD, proving the effectiveness of the model. In order for the model to be significantly detected, increase the number of AD and MCI instances.

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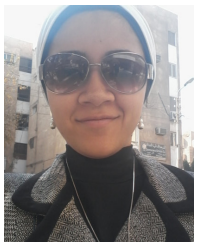

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