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RESEARCH ARTICLE

Time-to-event prediction using survival analysis methods for Alzheimer's disease progression

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Abstract

Introduction: Many research studies have well investigated Alzheimer's disease (AD) detection and progression. However, the continuous-time survival prediction of AD is not yet fully explored to support medical practitioners with predictive analytics. In this study, we develop a survival analysis approach to examine interactions between patients' inherent temporal and medical patterns and predict the probability of the AD next stage progression during a time period. The likelihood of reaching the following AD stage is unique to a patient, helping the medical practitioner analyze the patient's condition and provide personalized treatment recommendations ahead of time.

Methodologies: We simulate the disease progression based on patient profiles using non-linear survival methods—non-linear Cox proportional hazard model (Cox-PH) and neural multi-task logistic regression (N-MTLR). In addition, we evaluate the concordance index (C-index) and Integrated Brier Score (IBS) to describe the evolution to the next stage of AD. For personalized forecasting of disease, we also developed deep neural network models using the dataset provided by the National Alzheimer's Coordinating Center with their multiple-visit details between 2005 and 2017.

Results: The experiment results show that our N-MTLR based survival models outperform the CoxPH models, the best of which gives Concordance-Index of 0.79 and IBS of 0.09. We obtained 50 critical features out of 92 by applying recursive feature elimination and random forest techniques on the clinical data; the top ones include normal cognition and behavior, criteria for dementia, community affairs, etc. Our study demonstrates that selecting critical features can improve the effectiveness of probabilities at each time interval.

Conclusions: The proposed deep learning-based survival method and model can be used by medical practitioners to predict the patients' AD shift efficiently and recommend personalized treatment to mitigate or postpone the effects of AD. More generally, our proposed survival analysis approach for predicting disease stage shift can be used for other progressive diseases such as cancer, Huntington's disease, and scleroderma, just to mention a few, using the corresponding clinical data.

1 | INTRODUCTION

Alzheimer's disease (AD) is an irreversible, progressive disorder that causes health problems with thinking, behavior, and memory. In the United States, there are > 5 million cases.[1] Patients with AD may show different symptoms, progress at different rates through disease stages, and respond differently toward therapy provided by health professionals. The approach of understanding disease treatment and prevention, considering the patient's individuality, is the primary goal of precision medicine.[2]

The majority of the applications leveraging machine learning and statistical inference techniques use historical datasets from patients' records to examine the disease progression and provide reliable predictive models to deal with patient heterogeneity, that is, natural response variation between patients toward the same disease.[3,4]

Data collected from clinical studies present numerous challenges to building effective and reliable machine learning and deep learning models to predict the probability of progression to the next stage of AD. These challenges include, but are not limited to, handling heterogeneous data with multiple types and levels, having imbalanced data or a relatively smaller number of observations, and many missing observations caused by human or measurement errors.[5] From a medical perspective, the main challenge is to build predictive models that are reliable and explainable with high-quality data to support medical care decisions.

From preventive medicine clinical practice, the ability to accurately predict the next stage of progression of AD for a patient over a given period could help physicians make more informed clinical decisions on treatment strategies.[6] Several studies have extended traditional Cox proportional hazards models with machine learning approaches for time-to-event prediction in breast cancer,[7] heart disease,[8] and tuberculosis.[9] However, few to no similar research using survival analysis has been conducted on AD clinical data. With any clinical trial patient data, there are several challenges to overcome, including:

- Aggregating, cleaning, and transforming clinical trial data is manual and laden with completeness, quality, and inconsistency issues.
- Heterogeneity between patients' medical records, that is, different patients with the same disease may respond differently and progress at different rates.
- Limited data points of patients with an adequate number of visits resulting in low confidence in the model and increase in the chance of Type II errors.
- Change in AD progression might be seen in some patient visits, it does not imply that the patient has developed the progression level during the time around that visit. It could be possible that the patient did not visit the clinic despite having (or having a higher level of)

dementia and found out about it in the subsequent visits. These scenarios make it challenging to accurately determine the survival time for a patient.

This article develops survival analysis models to examine interactions between a patient's temporal and medical inherent patterns and predict the probability of AD's next stage progression during a time period. Our proposed survival models aim at estimating the probability of moving to the next stage of progression over a given period. We also propose a survival analysis workflow to explore and preprocess the dataset to handle patients' heterogeneity and their multifactorial progression, that is, AD stage shift.

The benefits of our contributions can be summarized as follows:

- Personalized treatment (determine effective treatment) based on the patient's history.
- Better decision-making support.
- Model interpretability.
  - Selecting important features.
  - Evaluation metrics: C-index and IBS.
  - Neural networks interpretation.
- Generalized deep learning-based survival analysis.

The paper is organized as follows: In Section 2, we provide all the related works that have been conducted in this domain. In Section 3, we showcase our implementation approach. In Section 4, we present our results, and Section 5 concludes the paper.

2 | RELATED WORKS

A range of disease progression models has been developed for AD treatment and forecasting in the last two decades. Many AD risk prediction models have used predefined sociodemographics, physical activity, health risk factors, and cognitive profiles.[10–12] Wang et al.[13] presented a study on predicting AD progression in the patient's next visit to the hospital modeled using the National Alzheimer's Coordinating Center (NACC) patient dataset, containing 5432 patients studied between 2005 and 2017. The predictive model is based on the long short-term memory (LSTM) networks and captured 99.06% accuracy with the temporal component. Park et al.[14] predicted AD future incidence using random forest, support vector machines, and logistic regression on health data obtained from the Korean National Health Insurance Service containing 4894 unique clinical features. Additionally, they extracted critical clinical features. Ito et al.[15] studied the effect of covariates such as age, apolipoprotein E ε4 genotype, sex, family history of AD, and years of education on AD

progression based on the longitudinal ADAS-Cog (Alzheimer's Disease Assessment Scale-Cognitive subscale) scores from 817 patients. The disease progression rate in patients with mild to moderate AD was estimated at ≈5.5 points/year based on their study. While these studies use various machine learning approaches to predict AD's progression, they fail to provide concrete insights about the duration to reach the next stage. That is the motivation for our work.

Medical researchers use survival models to determine the importance of prognostic factors in outcomes like death or predicting the next stage of cancer and then advise patients about their treatment options. Kaplan-Meier[16] and Cox proportional hazard models (CoxPH) [17] are the two traditional approaches used in patient survival analysis. CoxPH determines the risk score for each of the patient's covariates and then calculate the overall risk by their linear combination. Many studies have conducted experiments to compute the survivability of progressive disease patients. For example, Huh et al.[18] conducted a survival analysis on National Health Insurance Service Senior Cohort database (2002 to 2013) comparing the survival of subjects in AD and non-AD groups using the CoxPH model. The results showed that the overall mortality risk is higher in the AD group. Abadi et al.[19] implemented the CoxPH regression model and stratified Cox model based on the proportional hazard assumption[20] using a breast cancer dataset. They concluded that for patients with Stage I and Stage II breast cancer, radiotherapy and chemotherapy have the highest hazard, whereas for patients with Stage III and IV breast cancer, the surgery produces the most heightened hazard. Adamu et al.[21] estimated the survival time of cancer using the Kaplan-Meier method. Ahmad et al.[8] used the CoxPH model to evaluate heart disease's death rate and estimate the significant contributing features.

Katzman et al.[22] used deep neural learning to improve the traditional CoxPH models. They developed the DeepSurv model, a CoxPH neural network for modeling interactions between patients' covariates and treatment effectiveness. The efficiency of their survival model is evaluated using a concordance index (C-index) introduced by Harrell et al.[23] and the Integrated Brier Score (IBS).[24] The DeepSurv model also showed that a deep neural network could surpass classical Cox models in terms of the C-index studied on various datasets, including Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) and Worcester Heart Attack Study (WHAS). Fotso[25] examined WHAS and Weibull survival time dataset, where their proposed Neural Multi-Task Logistic Regression (N-MTLR) model outperforms the traditional CoxPH model by providing a higher concordance index.

The application of these models provided new insights into the estimated time of survival and survivability prediction. However, these models failed to provide the distribution of survivability over time. There is limited to no work done in evaluating the AD stage shift of patients and survival time estimation while considering the risk factors and survivability.

HIGHLIGHTS

- Develop an end-to-end framework to predict the stage-shift duration of Alzheimer's disease patients.
- Use deep learning-based non-linear survival models using patients' historical records.
- The model performance is significantly enhanced using advanced feature selection methods.
- Medical practitioners can leverage our approach to formulate a personalized recommendation to patients.

RESEARCH IN CONTEXT

1. **Systematic Review:** The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. There have been limited to no studies conducted for time-to-event (stage-shift duration) prediction on Alzheimer's disease clinical data.

2. **Interpretation:** Our approach produced individual patient trajectories for the next stage-shift duration along with the risk involved in terms of probability.

3. **Future Directions:** Our proposed methodology considers the patients to be similar, which can be enhanced in future work by identifying similarities among patients and clustering them together. Additionally, a more complex model can be built using state-of-the-art deep learning architecture to achieve increased precision in predicting stage-shift duration.

3 | METHODOLOGY

We leverage survival modeling techniques to build a survival analysis approach to examine interactions between a patient's inherent temporal and medical patterns and predict the probability of progression to the next AD stage during a time period. We define the event of interest as the "patient's progression into the next stage of AD." The approach aims to determine the probability of a patient progressing into the next AD progression stage after any given period T.

Our end-to-end survival analysis approach combines survivability of progressive disease (estimated time of survival) and risk factors while shifting to the next stage. Our approach provides insights into preventive medicine and medical-grade decision supports and comprises of data analytics workflow and deep learning-based survival model. Figure 1 shows an end-to-end data analytic approach, including various steps such as data collection and analysis, data preprocessing, missing value imputation, and independent features scaled to speed up the
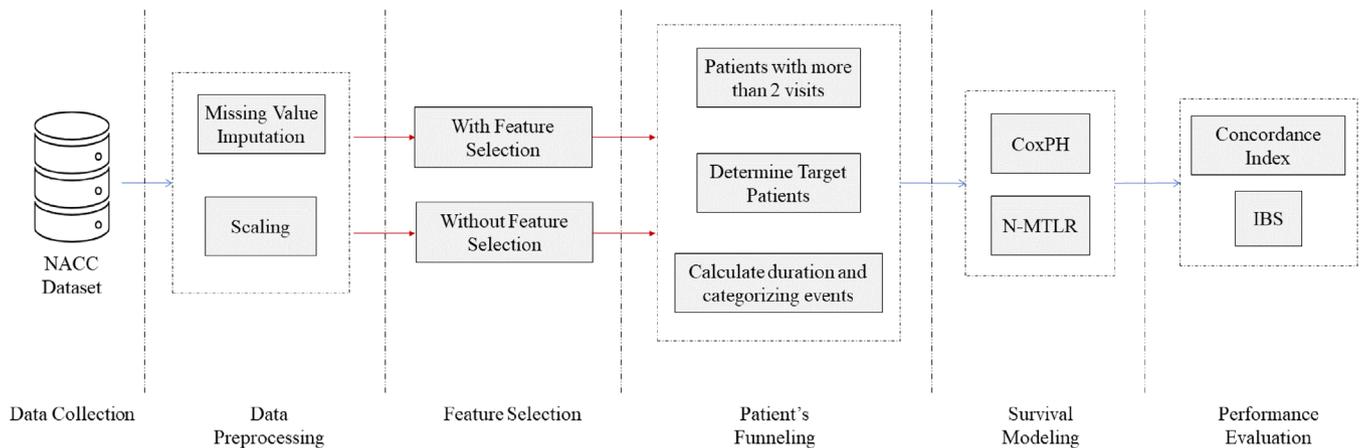
FIGURE 1 Overview of the end-to-end survival analysis workflow. CoxPH, Cox proportional hazard; IBS, Integrated Brier Score; NACC, National Alzheimer's Coordinating Center; N-MTLR, neural multi-task logistic regression

algorithmic calculations. Further, we used random forest and recursive feature selection to obtain the essential features, and patient funneling to acquire the target patients. The target patients are the subjects of our study, and we built various survival models, including non-linear CoxPH and N-MTLR, to compare and discover the probability of progression to next AD stage.

3.1 | Data collection and preprocessing

The dataset is provided by the NACC and includes 123,417 records of > 36,000 patients with their multiple-visit details between 2005 and 2017 with a total of 92 features in the dataset. Features are divided into several categories, such as: subject demographics, co-participant demographics, medications, subject's health history, physical parameters, Parkinson's Disease Rating, Neuropsychiatric Questionnaire. To build the predictive models, we consider 71 categorical features and eight continuous features. Thirteen variables in the dataset were the raw columns for which the derived logical columns were already present. For example, with age as one of the variables, we also had birth month, birth year, etc. The collected data underwent several data preprocessing steps, including missing value imputation and feature selection. The missing values (Figure 5) were imputed with the mean for continuous data columns and mode for categorical data columns. The relevant features are selected using feature importance score (Figure 6).

3.2 | Patient funnel

For the survival analysis, we considered the patients with more than two visits to the study center. Therefore, ≈50% of the unique patients are in the scope of 36,327 unique patients. The selection of these patients was carried out to make the missing value imputation logical. It also helped remove outliers that could be present due to the lower

TABLE 1 Alzheimer's disease (AD) progression stage for patients with more than two visits

Stages	Patients
1_AD (0)	8444
2_AD (0.5)	6609
3_AD (1)	2465
4_AD (2)	600
5_AD (3)	222

number of visits of the patients. Figure 2 shows the number of visits per unique patient.

For the patients with more than two visits, the number of patients with initial stages of AD disease is shown in Table 1.

Examining the AD dataset, we observe 1521 patients who have shown a downfall in the AD stage from the initial visit. For example, a patient in Stage 2 on initial visit to the study center who on the subsequent visit decreased a stage instead of an increase are not considered in the scope of our study. Additionally, a few patients were initially in Stage 2, but the stage went down after one or many visits. And for a few patients, the health conditions went bad, and their disease's stage got deteriorated than the initial visit. Such patients are considered in the study to build our survival and disease progression models.

We introduce the "duration" feature, which is calculated based on the difference between the initial visit and the most recent visit, having the maximum stage shift compared to the patient's initial stage. For example, if a patient's initial visit was reported with Stage 1_AD on April 23, 2007, then the patient had other subsequent visits with stages either less than or equal to the initial stage and has a visit on April 23, 2010 that shows that the patient has Stage 3_AD (more significant than the initial visit), the duration would be 3 years or 36 months. After the April 23, 2010 visit, if the patient visits again and shows a decrease in stage, that is, less than three, the duration would still be considered 36
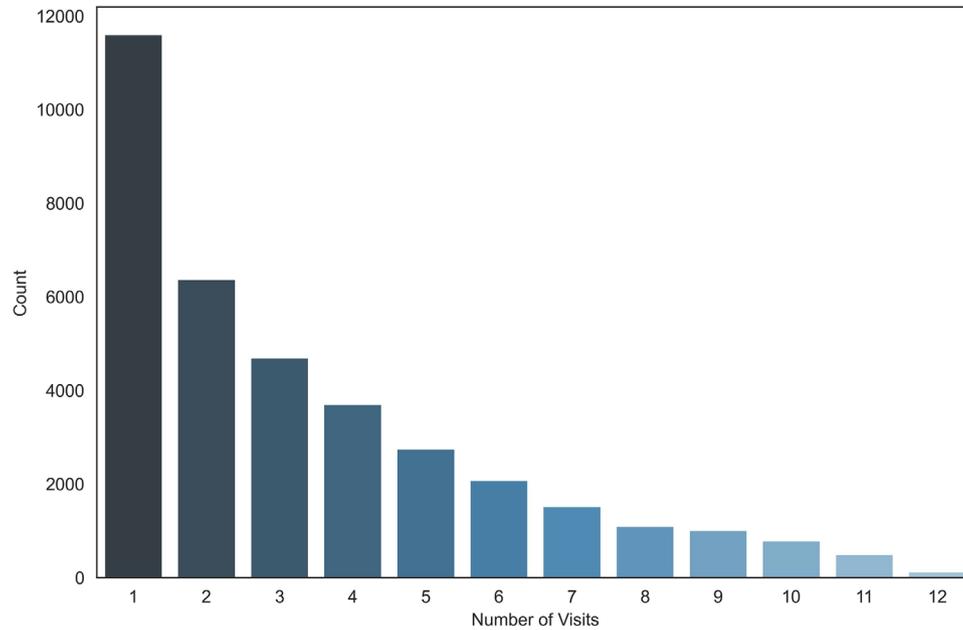
FIGURE 2 Visit counts per patient

TABLE 2 Patient count based on event

Event indicator	# Unique patients	Flag
Right-censored	8571	0
Event	8248	1

TABLE 3 Event indicator

x_1	x_2	…	x_n	Duration (month)	Event indicator (Boolean)
2	4	…	4	40	1
⋮	⋮	⋮	⋮	⋮	⋮
1	3	…	2	80	0

months until the most recent maximum stage shift, which was on April 23, 2010.

All patients who show the same stage throughout their visits are considered right-censored; otherwise, the visits are considered events. For the analysis, the features that the data shows during the most recent visit with maximum stage shift (in case of events) or during the most recent visit (in case of censored) are considered for analysis. After filtering and data transformation, we have 16,819 unique patients, with the event indicator shown in Table 2.

Hence, 92% of patients with more than two visits are considered for survival analysis. The input data to the model is in the schema, Table 3, where x_i, $i \in \{1, 2, \ldots, n\}$ represents the n features of the patients, the duration is the duration in months, and the event flag is to represent the event indicator.

3.3 | Modeling and evaluation

We built multiple models using both neural CoxPH and N-MTLR with different hyper-parameters. Their results and performance are then evaluated. The C-index and IBS to compare these models are also discussed and interpreted.

The dataset is, respectively, divided into training, validation, and test sets with the distribution of 64%, 16%, and 20%. We distinguish two scenarios. In the first scenario, the dataset contains the full set of features (79 features), whereas the second scenario is limited to the top 50 features based on their importance. The models and their parameters are provided in Table 4. The model name follows the convention: *{Model Type}_{Number of Hidden Layers}_{Number of Features Used}*.

Because right-censored data are present in the dataset, the performance metrics used in standard machine learning must be adapted to the survival analysis models. Therefore, we will be using two traditional evaluation criteria, namely, C-index and IBS. The concordance index or C-index is a generalization of the area under the receiver operating characteristic (ROC) curve (AUC) that can take censored data into account.[24] For example, patient i is given a risk score by our survival risk model η_i. If our risk model is correct, there will be higher risk scores for shorter time-to-next-stage patients. Abridging to two patients this intuition: the patient with the higher risk score will have a shorter time-to-disease.[27]

The top eight results of the model after hyperparameter tuning and considering the top 50 features based on the feature importance are presented in Table 5.

Based on Table 5, we observe that the CoxPH_4_50 and NMTLR_4_50 models give the best result. This is when the top 50 features are considered with multiple hidden layers and hyperparameter tuning. However, the difference between the other models is

TABLE 4 Model hyper-parameters

Parameters	CoxPH				N-MTLR			
	CoxPH_1_79	CoxPH_1_50	CoxPH_4_79	CoxPH_4_50	NMTLR_1_79	NMTLR_1_50	NMTLR_4_79	NMTLR_4_50
Hidden layers	One layer		Four layers		One layer		Four layers	
Neurons in each layer	[32]		[64,128,64,64]		[26][32]		[64,128,64,64]	
Activation function	ReLU in hidden layer(s)							
Loss function	CoxPH loss				N-MTLR loss			
Optimizer	Adaptive moments estimation optimizer							
Epochs	100 with early stopping							
Dropout in each layer	10%		[20%, 20%, 20%, 20%]		10%		[20%, 20%, 20%, 20%]	
Learning rate	Calculated using *One Cycle Policy*[26] method							
Batch size	64							

Abbreviations: CoxPH, Cox proportional hazard; N-MTLR, Neural multi-task logistic regression

TABLE 5 Performance metrics of (a) Cox proportional hazard models (CoxPH) models (b) neural multi-task logistic regression (NMTLR) models

Model	C-index	IBS score	Model	C-index	IBS score
CoxPH_1_79	0.7647	0.3131	NMTLR_1_79	0.7781	0.1066
CoxPH_1_50	0.7757	0.1008	NMTLR_1_50	0.7762	0.1021
CoxPH_4_79	0.7751	0.3079	NMTLR_4_79	0.7821	0.1086
CoxPH_4_50	0.7843	0.1001	NMTLR_4_50	0.7985	0.0952
(a)			(b)		

Abbbreviations: IBS, Integrated Brier Score.

not significant. We infer that N-MTLR performs better than CoxPH because during the model training phase, it came out to be ≈25% more efficient than CoxPH, in terms of time taken on the same machine and it overcomes the following key limitations of the CoxPH.

• CoxPH relies on the proportional hazard assumption, which specifies that the hazard function of two individuals must be constant over time.
• The exact formula of the model that can handle ties is not computationally efficient. It is often rewritten using approximations, such as Efron's or Breslow's approximations, to fit the model in a reasonable time.
• The fact that the hazard function's time component remains unspecified makes the CoxPH model ill-suited for actual survival function predictions.
• N-MTLR seems much more robust than CoxPH as IBS scores are consistent.

Figures 3 and 4 show the training and validation loss and the prediction of the first 10 patients in the test set. The prediction on the first 10 patients shows that their average time to progress into the next stage lies between 120 and 140 months. However, a couple of patients whose survival probability stays close to 100% implies that they are highly unlikely to move into the next stage of AD based on their baseline patient data.

4 | RESULTS

The work presented in this paper will play a crucial role in helping the medical practitioner to recommend the patient's specific treatment based on their historical data. We simulated the disease progression based on patient profiles using non-linear survival methods and evaluated using C-index and IBR. Before modeling, we conducted feature analysis and selection based on two techniques–random forest classifier and recursive feature elimination. While modeling, we created multiple models with and without considering the top features. Additionally, hyperparameter optimization was ensured to control the learning process for the best result.

Our proposed model, NMTLR_4_50, can predict the probability of a patient moving into the next stage with a concordance index of 0.79. This model considers the top 50 features; it produces a more interpretable model with a reduced computational cost. Additionally, it helps eliminate the highly correlated features or the features with limited to no information. Features such as normal cognition and behavior, criteria for dementia, community affairs, etc., were given
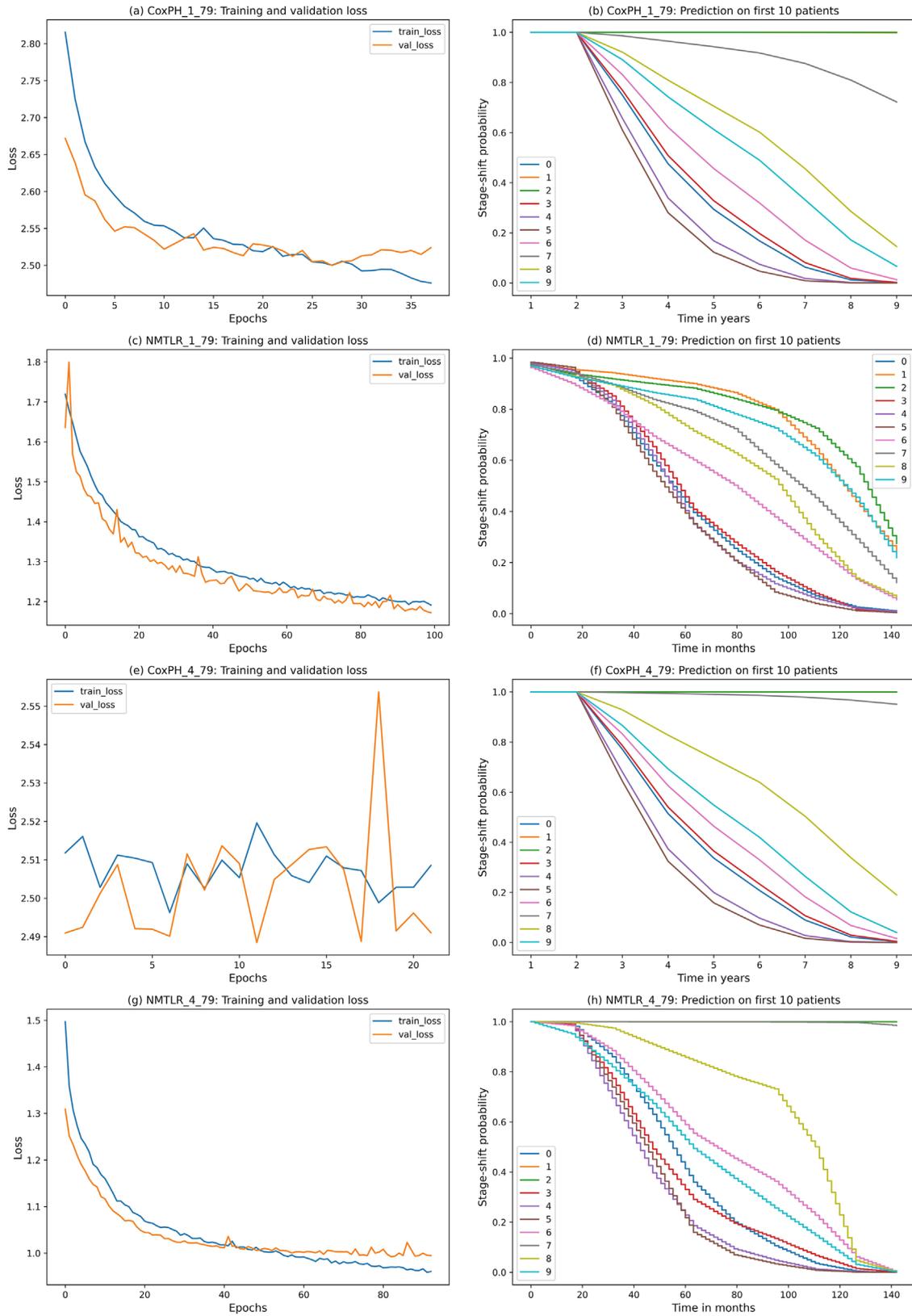
FIGURE 3 Model evaluation and performance on first 10 patients using all features. CoxPH, Cox proportional hazard; NMTLR, neural multi-task logistic regression
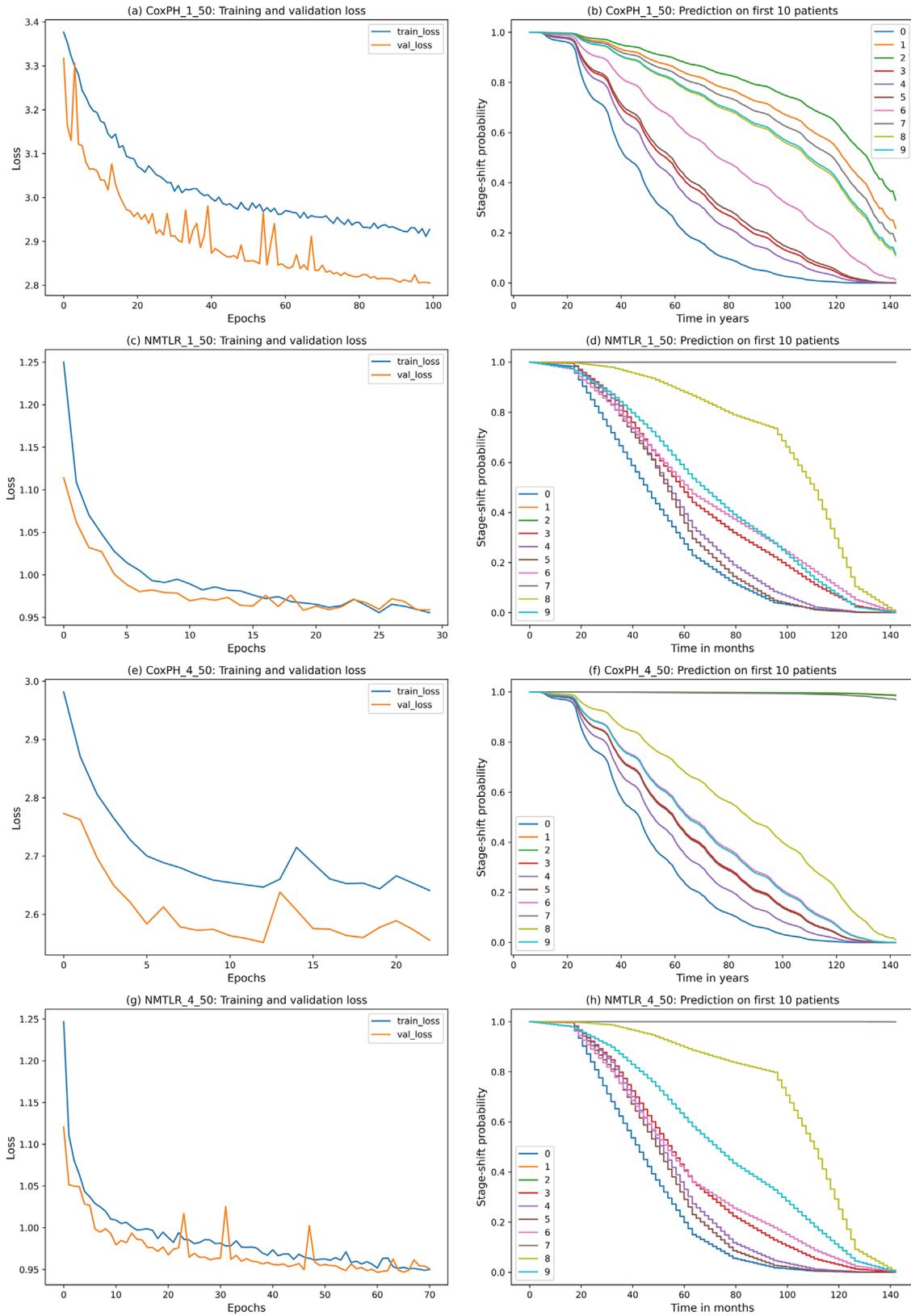
FIGURE 4 Model evaluation and performance on first 10 patients using top 50 features. CoxPH, Cox proportional hazard; NMTLR, neural multi-task logistic regression
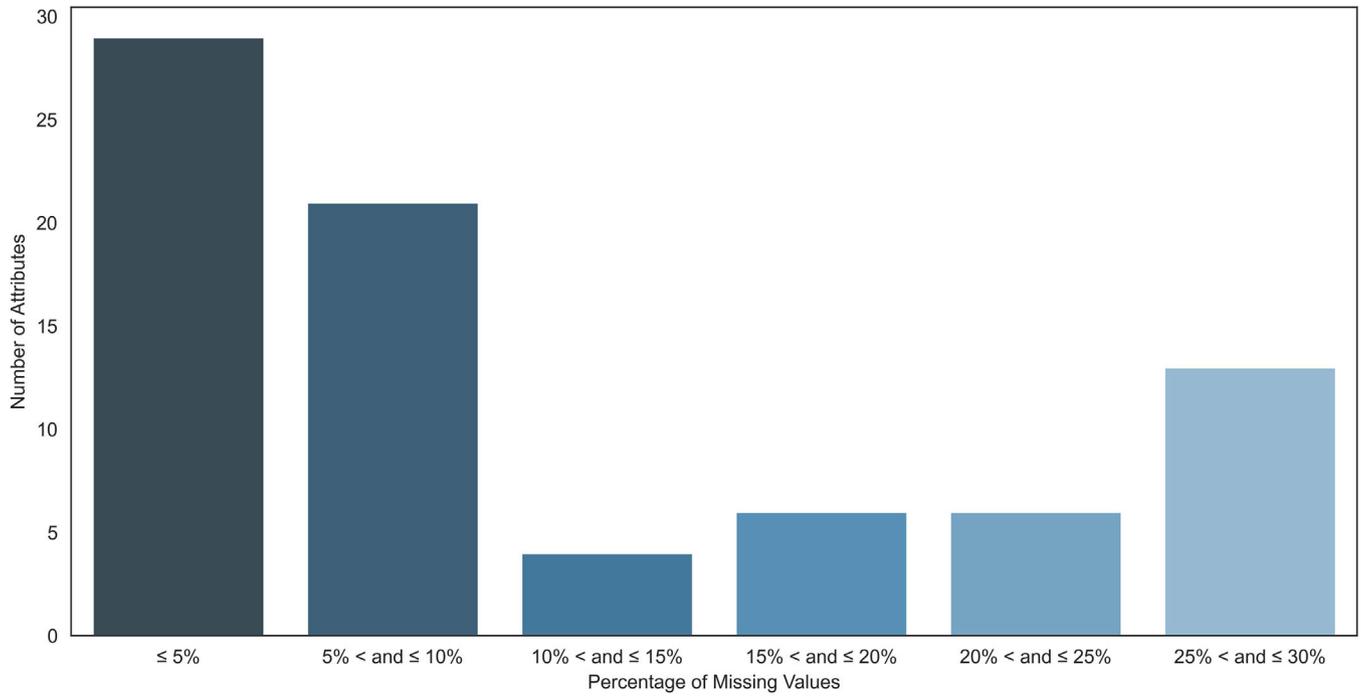
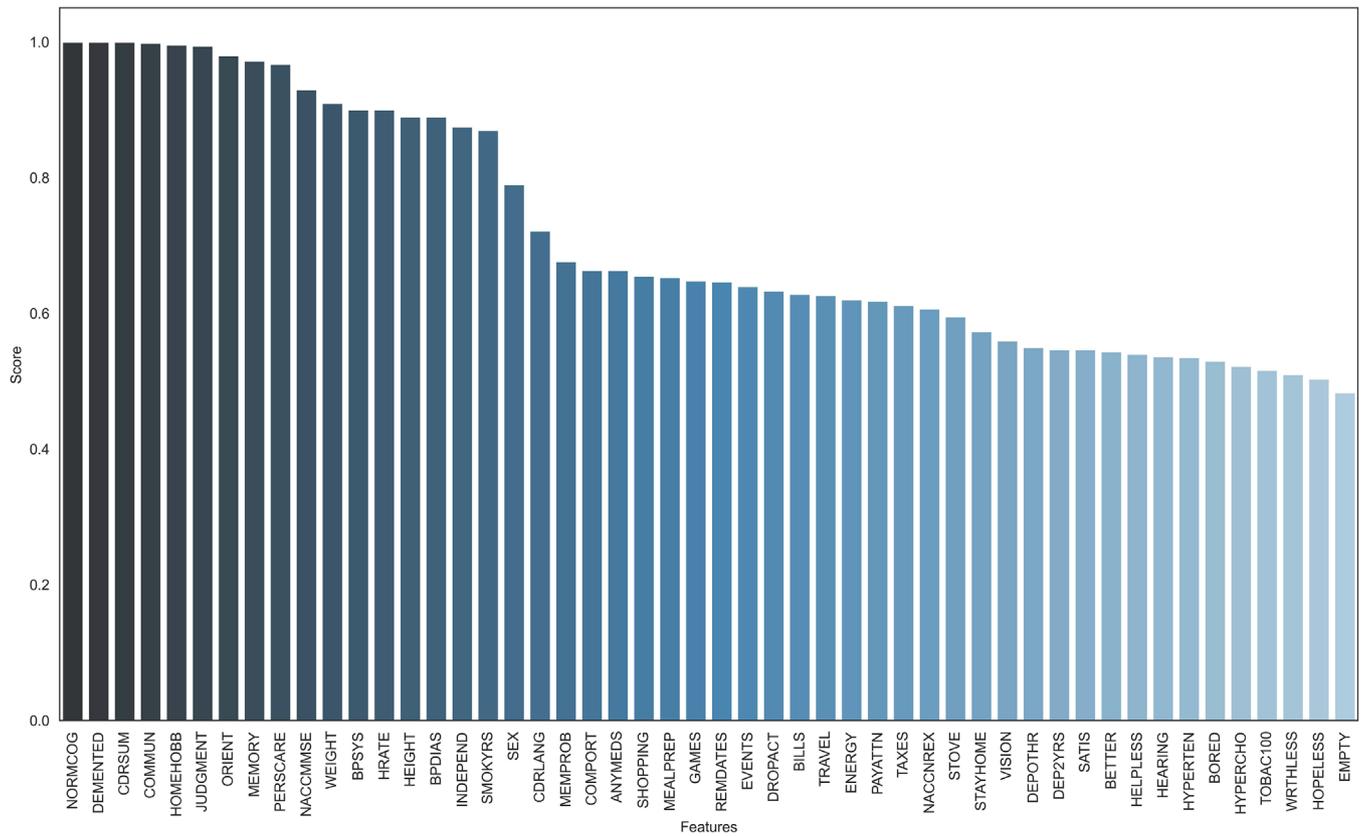**FIGURE 5** Missing data distribution

FIGURE 6 Top 50 features

higher weight during the feature selection phase. Many practitioners logically consider these features to detect the AD stage during the trial visits by the patients.

Overall, our model would benefit the medical community, especially the practitioner working closely with AD patients. Practitioners can also extend the model to other progressive diseases such as cancer, Huntington's disease, and scleroderma. One of the critical reasons suspected of AD clinical trials' repeated failure is the inability to recognize AD patients at early stages. As a part of a successful trial, our model will help forecast the duration of the next AD shift, which the medical practitioners will use to provide personalized treatments to delay AD's effect. The AD trajectory over time for patients incorporated the heterogeneity among patients. As AD is classified as a chronic disease, the risk involved with patients present in higher stages remains higher.

5 | CONCLUSION

The ability of our deep learning-based survival and disease progression models to leverage short-term data to obtain long-term probabilistic trajectories for predicting the shift in AD stage over time would be critical in creating a significant impact on the medical research community. The model will be useful for many tasks in precision medicine and clinical trial patient disease inference. The medical researcher and practitioner can use the model to simulate different scenarios and can recommend a better estimate to the patients in terms of check-ups, financial concerns, and so on, and provide the required medication to reduce the calculated risk.

We have assumed all the patients to be similar in our approach; hence, in future work, the models can be enhanced by clustering similar patients to provide personalized prediction results more precisely. In addition, a more complex model can be built using state-of-the-art deep neural network architecture.

INFORMED CONSENT
The dataset is provided by the NACC (National Alzheimer's Coordinating Center). NACC has obtained written informed consent from all participants and co-participants while collecting the data. The detailed description of the dataset is available on the NACC website.

CONFLICTS OF INTEREST
The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

AUTHOR CONTRIBUTIONS
Rahul Sharma and Harsh Anand: investigation, data duration, visualization, methodology, software, validation, original draft preparation, writing and editing. Youakim Badr: conceptualization, methodology, supervision, resources, draft validation, reviewing, and editing. Robin G. Qiu: conceptualization, methodology, validation, reviewing.

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SUPPORTING INFORMATION

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