Deep learning algorithm reveals probabilities of stage-specific time to conversion in individuals with neurodegenerative disease LATE

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Funding information National Institutes of Health, Grant/Award Numbers: R21AG070909, R56NS117587, R01HD101508, P30 AG072496; NIA/NIH, Grant/Award Number: U24 AG072122

Abstract

Introduction: Limbic-predominant age-related TAR DNA-binding protein 43 (TDP-43) encephalopathy (LATE) is a recently defined neurodegenerative disease. Currently, there is no effective way to make a prognosis of time to stage-specific future conversions at an individual level.

Methods: After using the Kaplan–Meier estimation and log-rank test to confirm the heterogeneity of LATE progression, we developed a deep learning–based approach to assess the stage-specific probabilities of time to LATE conversions for different subjects.

Results: Our approach could accurately estimate the disease incidence and transition to next stages: the concordance index was at least 82% and the integrated Brier score was less than 0.14. Moreover, we identified the top 10 important predictors for each disease conversion scenario to help explain the estimation results, which were clinicopathologically meaningful and most were also statistically significant.

Discussion: Our study has the potential to provide individualized assessment for future time courses of LATE conversions years before their actual occurrence.

KEYWORDS

limbic-predominant age-related TAR DNA-binding protein 43 encephalopathy, machine learning, progression rate, stage-stratified analysis, survival models, time-to-event estimation

1 BACKGROUND

Limbic-predominant age-related TAR DNA-binding protein 43 (TDP-43) encephalopathy (LATE) is a recently defined common neurodegenerative disease that generally affects 20% to 50% of persons ≥80 years of age.1–3 With an increasing life expectancy of our society, LATE has become a serious concern for a pending public health crisis. Like other types of dementia, such as Alzheimer’s disease (AD), prevention and early intervention are currently the best way to delay the onset of LATE and slow down its progression. Therefore, predictive modeling and analyses for the progression and conversion of LATE tailored to each individual are crucial for taking timely interventions, understanding pathophysiology, and estimating the time course, thus facilitating personalized strategies to delay the disease with the goal of precision medicine for LATE.4,5

Numerous studies have used machine learning algorithms to assess the progression of other diseases in the general medical field.6–9 There are also many studies10–15 specifically addressing the progression of Alzheimer’s disease and other neurodegenerative diseases.
other types of dementia, including Levy bodies (LB), vascular dementia, Parkinson’s disease, and AD. For AD, in particular, its progression rate is known to be highly heterogeneous, varying from subject to subject, with the duration ranging from a few years to two decades. Additionally, many factors, including genetic factors (such as apolipoprotein E ε4 genotype), brain atrophy rates, and patterns of brain region atrophy, have been linked to the rate of cognitive deterioration in AD patients. For LATE, although existing neuropathological studies suggested that its cognitive deterioration at a population level was relatively slower than some common chronic age-related neurodegenerative diseases, such as AD, there is no method or technique to assess time to conversion to the next stage in LATE at the stage-specific and individual level. The individualized assessment of stage-specific progression and conversion may facilitate our understanding of the pathological characteristics and risks of LATE.

To unravel the heterogeneity and provide an insightful prognosis for LATE, in this study, we first confirmed the heterogeneity of LATE progression at different stages and then developed a deep learning (DL)-based approach for prognosticating stage-specific LATE conversion for subjects. Our assessment results were well explained with the critical predictors identified from a large number of predictors, such as age, sex, race, genetic factors, and clinical–psychological measurements. By assessing the future LATE conversions at different stages with probabilities over time rather than a binary number (i.e., happening or not), we could provide fine-grained time information of conversion years before the actual occurrence at an individual level. Our analysis and predictive modeling were established on a large cohort from the National Alzheimer’s Coordinating Center (NACC), with subjects’ multiple-visit information between 2005 and 2020.

Our assessment in this study is based on a DL-based approach. In general, DL uses artificial neural networks (ANNs), also known as neural networks (NNs), which are computing models and systems motivated by their biological counterparts in animal brains. An ANN typically has an input layer to receive data, an output layer to output processed information, and at least one intermediate layer called the hidden layer. In particular, deep NNs usually have two or more hidden layers. If one draws a graph showing how these layers are built on top of each other, then a deep NN model has many layers, and the structure looks deep, thus the naming. DL usually uses deep NNs to process data and discover patterns and structures in complex, large datasets. From data out of the previous (or input) layer(s), each layer automatically extracts features/patterns and produces data that subsequent layers would use, eliminating the requirements for human engineers to provide manually extracted features/patterns to a computer. DL is known to enable the models to have strong abilities to handle large-scale data with complex nonlinear relationships.

Standard survival models, such as the Cox proportional hazards (CPH) model, assume a linear combination of patient covariates, which is known as the linear proportional hazards condition. In many applications, however, it may be too simplistic to assume that the log-risk functions are linear. DeepSurv is a DL-based model that can process survival data to account for linear and nonlinear effects from covariates, reporting performance superior to the CPH. Thus, it has the potential to more closely model the true underlying relationship between the input variables and the response, which is likely to be nonlinear due to the high complexity of a form of dementia such as LATE.

To our knowledge, this is the first study to develop a DL-based approach that could accurately assess the probabilities of time-to-conversion events for LATE. More specifically, our development of this innovative approach consisted of three major components. First, we used Kaplan–Meier (KM) estimation to get the transition curves of different LATE stages and calculated log-rank statistics to test whether the progression rate between different stages is identical. This calculation confirmed the progression rates at the population level and the heterogeneity of LATE progression, and it underscored the need for an assessment approach at the individual level. Then, we developed an individualized approach based on the DeepSurv model to perform a time-to-conversion assessment for LATE. The concordance index (CI) and integrated Brier score (IBS) demonstrated that our approach could assess the probability of time to conversion to the next stage with high accuracy. Finally, we demonstrated that our approach was well explained by those important predictors identified via feature ranking and selection (FS) from the DeepSurv model, most of which were also significant in the analysis of variance (ANOVA). For example, our analysis indicated that a subset of clinical–psychological variables, including NACCDEM, COMMUN, PERSCARE, and HOMEHOBB, is predictive: the larger their values were in the preclinical to mid-level clinical stages, the more likely they were to have conversions.
2 | METHODS

We used statistical survival models to confirm the heterogeneity of LATE progression and provide a motivative setting for our study in this paper. We then developed an individualized approach based on a DL model, DeepSurv, for prognosis during a given period. We defined two variables, transition event and transition time, to describe our approach. The former was defined as the occurrence of a subject’s change from the current stage to the next stage, which was also referred to as conversion; the latter denoted the period from the start time of the current stage to the earliest event occurrence time. The workflow for our DL-based stage-stratified approach is illustrated in Figure 1. It comprises major steps of data aggregation with subject categorization, data preprocessing such as data cleaning, subject stratification including the specifying transition time and event for each subject, and model-based analysis.

2.1 | Datasets

Our approach of predictive modeling and analysis was established on the large prospective cohort, the NACC, with subjects’ multiple-visit information between 2005 and 2020, which can be accessed upon request and approval by the data owner via the link https://naccdata.org/. The obtained dataset contains 163,199 records, each with 1727 variables. These records correspond to one or more visits of 44,864 subjects.

2.2 | Subject categorization rules

We used the Clinical Dementia Rating (CDR) grades to label the different stages of LATE, which were calculated on the basis of a semi-structured interview of the subjects and the caregivers (informant) and the clinical judgment of the clinicians.26–28 The CDR grade is 0 to 3 (see Table S7 in supporting information). A CDR of 0.5 is usually very mild, and a recent study suggested that it might not be an accurate criterion to specify subjects with mild cognitive impairment (MCI).29 Therefore, we generally consider CDR = 0 and CDR = 0.5 as one group, that is, the preclinical stage of LATE. We followed the categorization rules in Robinson et al.2 and Wu et al.30 to determine subjects with LATE; for more details, see Figure S7 in supporting information.

2.3 | Preprocessing

Based on CDR grades, for the stage-stratified transitions, we focused on the following six specific scenarios: {0,0.5}⇝{1}, {1}⇝{2}, {1}⇝{3}, {1}⇝{2,3}, {2}⇝{3}, and {0,0.5,1}⇝{2}. Besides {1}⇝{2} and {1}⇝{3}, we also analyzed {1}⇝{2,3} with an intention to delineate the shared characteristics of conversion from the early stage to any mid-level or advanced stages. For each scenario, we used CDR to define stage-stratified transition time and event as follows: For a specific transition scenario, the transition time was computed based on the temporal difference between the initial visit with (one of) the starting stage(s) in this scenario and the visit with the first change of CDR to (one of) the ending stage(s) in this scenario, and accordingly, the first change of CDR as a conversion event. If the subject showed no change in the starting CDR grade during all visits in a specific scenario, we considered that the subject’s data were right-censored.

For the data in different scenarios, we further performed data cleaning to remove variables that were repeatedly defined, not relevant, and not defined. In this study we did not perform data imputation but directly deleted the variables with missing values; the main consideration was that most of the missing variables in NACC data are categorical, and imputing categorical variables could cause bias or large error fluctuations.31 We performed experiments to compare imputing to deleting variables with missing values. Our experimental results confirmed that imputing resulted in larger error variations. Also, to mitigate potential interference, we deleted the variables about other types of dementia, such as those beginning with prefixes FTD and LB regarding frontotemporal dementia (FTD) and LB disease. After the data preprocessing, we got 245 variables. For more details, see the supporting information.
2.4 | Subject statistics

For the groups in different scenarios, we show the basic subject statistic information for different transitions in Figure S1 in supporting information, where \( \alpha \rightarrow \beta \) means that stage \( \alpha \) does not directly transit into stage \( \beta \), while \( \alpha \rightarrow \beta, \) means that stage \( \alpha \) directly transits into stage \( \beta \). The composite stage \([0,0.5]\) essentially represents the preclinical LATE stage, \([0.0.5,1]\) the early LATE stage, and \([2,3]\) the mid-level or advanced LATE stage. The censoring ratios and the numbers of subjects are given in Table S1 in supporting information. The statistics of visit counts (counts vs. the number of visits) for different stratified stages are shown in Figure S2 in supporting information.

2.5 | Models/methods used in our analysis

In this study, the KM curve, log-rank test, and DeepSurv were used for our analysis. The KM and log-rank test are two typical methods for univariate survival analysis, describing survival in terms of one factor but ignoring the impact of the other variables. The CPH model is a standard semi-parametric regression model widely used in epidemiological studies and clinical trials to assess survival time based on risk variables. In our initial analysis and modeling, we found that CPH did not converge well on the data in Table S1. One reason might be the potentially complex, nonlinear relationships between variables and LATE stage-stratified transitions. Thus, in this study, we used DeepSurv for modeling purposes, which is a recent DL-based extension for the CPH model and could surpass classical survival models. Additionally, we performed ANOVA to corroborate the significance of identified variables.

2.6 | DL settings

We set the maximum number of epochs to be 2000. We initialized the weights of the layers with the Xavier normal distribution-based initializer. We adopted the Adam optimizer with an initialized learning rate of 0.0001. We constructed the DeepSurv with one 150-neuron hidden layer, wherein Bent identity was used as the activation function. For other hyper-parameters, we adopted the default settings described in the open-source Python packages Lifelines and PySurvival for initialization, followed by some fine tuning. For the stage-stratified groups in all scenarios, we randomly split them into training and test sets by a ratio of 80:20; the results were averaged over five runs of five different random splits. For more details, see the supporting information.

2.7 | Evaluation metrics

Two standard metrics were adopted for evaluating the performance of our stage-stratified conversion assessment: (1) CI is widely used to evaluate the ability of survival models to rank individuals by their time-to-event risk assessments. It is a generalization of the area under the receiver operating characteristics curve (AUC) taking into account censored data. The range of CI values is in [0, 1], and the larger the CI value, the better the performance. (2) IBS42 extends the Brier score to right-censored data for evaluating the accuracy of an estimated survival function at time t. The IBS value is non-negative, and the smaller the value, the better the performance. Statistical significance was set at \( P < 0.05 \).

3 | RESULTS

3.1 | Kaplan–Meier estimation and log-rank test to examine LATE progression rates on NACC (2005–2020)

After using the KM method to estimate the survival functions from different scenarios, we compared the progression rates pairwise between different stages in Figure 2. Then, we used the log-rank test to calculate their P-values, as given in Table 1. Figure 2 suggests that, before 4000 days, the progression rate of \([0,0.5]\) is faster than those of \([1,2]\) and \([2,3] \); the progression rate of \([1,2]\) is faster than those of \([1,3]\) and \([2,3]\), and Table 1 indicates that their differences are both statistically significant \((<0.05)\). These findings quantitatively confirmed that the LATE progression rates at different stages are heterogeneous, and the cognitive deterioration progresses more rapidly from the preclinical LATE stage to the early LATE stage than in other conversions. More results are provided in the supporting information.

3.2 | DL-based time-conversion assessment

The above analyses confirmed the heterogeneity of progress rates at different stages and known results about LATE progression. This heterogeneity necessitates stage-specific predictive modeling and prognosis. It is noted that the KM curves and log-rank test are population-level methods for assessing the progression rates which do not provide detailed information about the disease progression of an individual subject. To develop individualized prevention and intervention, there is an unmet need for stage-specific assessment at the individual level. To this end, we developed an approach based on a DL model, DeepSurv, to make a probabilistic time-to-conversion assessment. The results of assessment performance in CI and IBS are presented in Table 2 on the cleaned and preprocessed NACC data in Table S1. To illustrate the convergence of model training, we plotted the loss functions in Figure S4 in supporting information. The training of the model can be seen to converge well for different stage stratifications. Our approach can accurately assess how soon the disease state would convert to the next stage within a given period for the participants in NACC. Specifically, the probability of a subject converting from the mid-level LATE stage to the advanced LATE stage, that is, \([2,3]\), was estimated with the best average CI of 0.914. The probability of a subject converting from the early LATE stage to the mid-level LATE stage, that is, \([1,2]\), was
FIGURE 2  The comparison of Kaplan–Meier estimations for different scenarios as shown in (A) - (F). The dotted line is a trend curve fitted by a quadratic polynomial. The horizontal axis denotes the time in days, and the vertical axis denotes the probability of staying in the current stage.

TABLE 1  Log-rank test for different scenarios

| Scenario | Statistics | P-value |
|----------|------------|---------|
| {0,0.5}→{1} vs. {2}→{3} | 1.561E + 01 | 7.793E-05 |
| {0,0.5}→{1} vs. {1}→{3} | 1.755E + 01 | 2.793E-05 |
| {0,0.5}→{1} vs. {1}→{2} | 4.183E-01 | 5.178E-01 |
| {1}→{2} vs. {1}→{3} | 1.808E + 01 | 2.121E-05 |
| {1}→{2} vs. {2}→{3} | 1.431E + 01 | 1.548E-04 |
| {2}→{3} vs. {1}→{3} | 6.055E-01 | 4.365E-01 |

Abbreviations: CI, concordance index; IBS, integrated Brier score.

Estimated with the best average IBS of 0.065. For each of the scenarios we considered, the assessment had an average CI above 0.82 or an average IBS below 0.14. As McGratten et al.33 and Anderson44 suggested, lifestyle interventions such as exercise, social activity, and diet might help slow the progression of certain cognitive symptoms of preclinical or early dementias. Therefore, our assessment of the progression from the preclinical stage to the early stage of LATE at the individual level has medical implications. It can potentially help clinicians and researchers identify the subjects years before the incidence of early LATE.

Further, we visually compared the estimated survival probabilities with our DeepSurv-based approach and the actual time when the transition event occurred. We presented the estimated survival probabilities for five randomly selected subjects in the test set in Figure 3 (for more results, see Figure S5 in supporting information). The visual comparison indicates that our approach produced good predictive modeling for almost all scenarios. Further, it is observed that compared to other scenarios, the conversion occurrence of most subjects for {0,0.5}→{1} and {1}→{2} is more concentrated before 3000 days, compared to scenarios {1}→{3} and {2}→{3}. This phenomenon is basically in line with the KM-based analysis; that is, {0,0.5}→{1} and {1}→{2} have the fastest progression rate among all scenarios considered. It is worth noting that the KM analysis is at the population level; in contrast, our predictive modeling estimates the probabilities of stage-specific conversion time for each new individual who was not in the training set.

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In addition, the conversion for scenarios {0}→{0.5} and {0.5}→{1} may be clinically interesting, so we also provided the DeepSurv-based evaluation for these two scenarios; see Table 2. Also, in supporting information, we provided other important information for these two scenarios, including statistics of subjects, visit counts, loss function of DeepSurv, and visualization of the individual patient assessments.

TABLE 2  CI and IBS of DeepSurv for time-to-conversion assessment in different scenarios

| Dataset | CI        | IBS       |
|---------|-----------|-----------|
| {0,0.5}→{1} | 0.865 ± 0.064 | 0.093 ± 0.043 |
| {1}→{2}   | 0.874 ± 0.059 | 0.065 ± 0.036 |
| {2}→{3}   | 0.914 ± 0.054 | 0.077 ± 0.034 |
| {1}→{3}   | 0.874 ± 0.079 | 0.076 ± 0.040 |
| {1}→{2,3} | 0.820 ± 0.077 | 0.084 ± 0.039 |
| {0,0.5,1}→{2} | 0.883 ± 0.056 | 0.070 ± 0.038 |
| {0}→{0.5} | 0.821 ± 0.156 | 0.139 ± 0.119 |
| {0.5}→{1} | 0.841 ± 0.089 | 0.081 ± 0.062 |

Abbreviations: CI, concordance index; IBS, integrated Brier score.
3.3 Explainability of the assessment results by our approach

As pointed out by Wada-Isoe et al., the CDR of 0.5 might not be an accurate criterion to specify subjects with mild cognitive impairment. Also, in our experimental results (see Table 2), it is observed that the standard errors for $[0] \rightarrow [0.5]$ and $[0.5] \rightarrow [1]$ were much larger in both CI and IBS than those in other scenarios. This potentially indicates that the prediction involving these two scenarios was relatively less stable, so in the analysis for the explainability of assessment results, we mainly focused on the previous six typical scenarios. We performed post-processing of the learned weight matrix by the DeepSurv method to obtain feature ranking and selection to facilitate the interpretation of the assessment results. And, we compared the expression levels of significant variables between the conversion group and the non-conversion group in Figure 4. More results can be found in supporting information.

4 DISCUSSION

As pointed out previously, our approach was based on a recent DL model, DeepSurv, to assess the probabilities of conversion time specific to LATE stages and personalized to each new individual (not in the training set). It can provide the ranking and weights of the predictors for facilitating the explanation of how our approach produced the assessment results.

4.1 Strengths and limitations

The effectiveness of our approach was rigorously verified with cross-validation and statistical testing in different metrics. However, our approach still has several limitations, which will be discussed below.

1. Our individualized assessment approach is established on the data set of NACC by considering subjects with LATE. It would be desirable to confirm the effectiveness of our approach on an independent data set of a large prospective cohort study. Such a large cohort is needed because we need to have a reasonable sample size after stratifying the cohort according to the stages. Therefore, it is not easy to obtain another large cohort like NACC. On the other hand, we would like to point out that this limitation is not severe because we have performed multi-fold cross-validations to ensure a good generalization to new data and statistical analysis to corroborate the effectiveness of the models and performance.

2. While our approach demonstrated good performance in CI and IBS, as shown in Table 2, it still had estimation inaccuracies, as indicated by the gap for average CI value to 1 or average IBS to 0 compared to the actual conversion time. In the modeling, we used a time
point represented by a NACC center visit as the conversion time when the CDR rating changed from the starting stage in a specific scenario for a subject. However, in reality, the conversion usually happens gradually and thus is not switch-like. Therefore, the conversion time represented by a specific visit time only approximates the earliest noticeable conversion time. Furthermore, providing the probabilities of conversion over time, as our approach did in this paper, appears more appropriate than simply estimating a single time point to represent the conversion.

In addition, the multi-state models (MSMs) can also analyze and compare several (two or more) events simultaneously; however, the calculation between states in the model is still based on the assumption of linear structure or shallow structure. Compared to MSMs, DeepSurv readily allows us to implement nonlinear covariate effects; in contrast, how to implement nonlinear covariate effects for multi-state approaches is not straightforward. Therefore, to account for the nonlinear covariate effects, we adopted the nonlinear variant of the Cox model, i.e., DeepSurv. It cannot handle multiple event states simultaneously; nonetheless, it can focus on the states of interest in a stage-specific way, thereby revealing complex relationships between the input and the response variables. As far as we know, this is the first study to develop a DL-based approach that could accurately assess the probabilities of time-to-conversion events for LATE.

5 | CONCLUSION

Dementia patients may present with different symptoms, progress at different rates at different stages of the disease, and respond differently to interventions. Therefore, it is critical to understand the heterogeneous characteristics at different stages and develop an ability to reliably assess dementia onset and progression. In this study, we confirmed the population-level progression rates and the heterogeneity of LATE progression, and then we developed a stage-stratified approach by leveraging machine learning to probabilistically estimate the time courses of LATE stage-specific progression for different individuals. Our study has the potential to provide an individualized
assessment of future time to LATE disease conversions years before their actual occurrences.

ACKNOWLEDGMENTS
This work was partially supported by the National Institutes of Health (grant numbers: R21AG070909, R56NS117587, R01HD101508, P30 AG072496), and ARO W911NF-17-1-0040. The NACC database is funded by NIA/NIH Grant U24 AG072122. NACC data are contributed by the NIA-funded ADCs: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Thomas Wisniewski, MD), P30 AG013854 (PI Robert Vassar, PhD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG005131 (PI James Brewer, MD, PhD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Sweigrod, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG053760 (PI Henry Paulson, MD, PhD), P30 AG010124 (PI John Trojanowksi, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG049638 (PI Suzanne Craft, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), P50 AG047270 (PI Stephen Strittmatter, MD, PhD).

CONFLICTS OF INTEREST
The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CODE AVAILABILITY
All code and instructions on how to reproduce the results in this paper can be found at https://github.com/xinxingwu-uk/LATE_Conversion

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wu X, Peng C, Nelson PT, Cheng Q. Deep learning algorithm reveals probabilities of stage-specific time to conversion in individuals with neurodegenerative disease LATE. Alzheimer’s Dement. 2022;8:e12363. https://doi.org/10.1002/trc2.12363