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A Longitudinal Deep Learning Framework for Predicting Conversion from Mild Cognitive Impairment to Alzheimer's Disease Using Multi-Modal Data

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Abstract:

Mild cognitive impairment (MCI) represents a critical intermediate stage between normal aging and Alzheimer's disease (AD) yet predicting which individuals will progress remains challenging. Reliable risk prediction tools are needed to identify high-risk patients early and guide preventive interventions. In this study, we developed a longitudinal deep learning framework to predict conversion from MCI to AD within a 2–3-year window using a multi-modal dataset derived from the Kaggle TADPOLE challenge. The dataset included 872 baseline MCI participants with clinical, cognitive, demographic, and imaging-derived biomarkers, with 37.0% converting to AD during follow-up. After preprocessing, we trained both baseline statistical models and sequential deep learning models, with performance evaluated on an independent test set. Our best-performing model achieved an AUC of 0.848 and an overall accuracy of 76.6% on the test set, demonstrating good discrimination and calibration. Feature importance analysis identified ADAS13, CDR-SB, and FAQ as the strongest positive predictors, whereas MMSE scores were negatively associated with conversion risk. Predicted risk probabilities showed clear separation between converters and non-converters, suggesting the model captured meaningful disease trajectories.

Keywords: Mild Cognitive Impairment; Alzheimer's Disease; Deep Learning.

1. Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia and a leading cause of disability and dependency in the elderly population. Characterized by progressive cognitive decline and irreversible neurodegeneration, AD imposes a profound burden not only on patients but also on families and healthcare

systems worldwide [1]. With the global population rapidly aging, the prevalence of AD continues to rise, making it a pressing public health concern [2].

Early detection and reliable prediction of disease progression are widely acknowledged as critical steps to improving patient outcomes. Individuals with mild cognitive impairment (MCI) represent a high-risk group: some will convert to AD within a few years, while others may remain stable or even revert to normal cognition [3]. Identifying which MCI patients are most likely to progress to AD is critical for timely intervention, appropriate allocation of clinical resources, and the design of targeted therapeutic trials [4]. Such efforts are also essential for advancing precision medicine strategies and reducing healthcare costs associated with AD.

Despite considerable advances in clinical research, predicting disease trajectories in AD remains challenging. The heterogeneity of patient profiles, the complex interplay of biological, cognitive, and imaging markers, and the non-linear nature of disease progression make traditional approaches insufficient. This highlights the urgent need for more robust and flexible modeling strategies capable of capturing the longitudinal, nonlinear, and multimodal characteristics of AD progression.

Over the past two decades, research on predicting the progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD) has gradually evolved from traditional statistical models to advanced deep learning frameworks. Early approaches, including Cox regression and mixed-effects models, offered interpretability but were constrained by linear assumptions and limited capacity to capture the complexity of multimodal longitudinal data [5]. Classical machine learning methods, such as random forests and support vector machines, improved predictive accuracy at baseline but often neglected temporal dynamics [6].

Deep learning has significantly advanced this field by modeling sequential and nonlinear patterns. Recurrent neural networks (RNNs) and LSTM variants have been widely adopted to learn progression trajectories from longitudinal clinical and biomarker data, showing superior performance over static models [7]. More recently, multimodal fusion frameworks integrating MRI, PET, CSF biomarkers, and cognitive scores have demonstrated clear benefits, emphasizing the complementary nature of heterogeneous data sources [8]. Attention-based architectures, particularly Transformer models, further extend these advances by capturing long-range dependencies and irregular visit intervals. Nevertheless, challenges remain, including limited dataset sizes, irregular sampling, and the need for interpretable models suitable for clinical practice. Current evidence suggests that time-aware, multimodal deep learning remains the most promising direction for individualized MCI-to-AD risk prediction.

Despite notable progress in modeling Alzheimer's disease (AD) progression, important gaps remain. Traditional statistical techniques cannot fully capture the nonlinear dynamics underlying longitudinal multimodal data, while many machine learning methods still rely on cross-sectional snapshots rather than the entire disease trajectory. Although deep learning models such as RNNs, LSTMs, and more recently Transformers have shown clear potential, there is still a lack of systematic frameworks that effectively integrate heterogeneous sources of information—structural imaging, cognitive scores, and fluid biomarkers—within a temporally coherent model [9].

From a clinical perspective, the motivation is twofold. First, individuals with mild cognitive impairment (MCI) represent a heterogeneous group: some rapidly convert to AD, while others remain stable for years. Current tools do not provide sufficiently accurate, individualized risk estimates to guide timely intervention. Second, precision medicine initiatives require predictive models that can operate not only at the population level but also at the individual level, supporting patient-specific decisions in diagnosis, monitoring, and trial recruitment [10].

This study aims to bridge these gaps by developing a deep learning–based framework tailored to longitudinal, multimodal health data, with the goal of producing more reliable, interpretable, and clinically actionable predictions of MCI-to-AD progression. By systematically integrating multimodal data within a temporally coherent framework, this study contributes to both methodological innovation and clinical translation in AD progression research.

2. Methods

2.1 Data Source

Data for this study were obtained from the TADPOLE dataset hosted on Kaggle, which consolidates longitudinal information from the Alzheimer's Disease Neuroimaging Initiative. This dataset includes summary measures of structural magnetic resonance imaging and positron emission tomography scans, cerebrospinal fluid biomarkers including amyloid beta 42 and Tau, cognitive assessments such as the Mini-Mental State Examination, Clinical Dementia Rating Scale Sum of Boxes, and the Alzheimer's Disease Assessment Scale-Cognitive subscales. Demographic and clinical information including age, sex, education level, and APOE4 genotype are also provided. The study relied on de-identified records made available through ADNI's data-sharing policy. Because the dataset tracks patients over several years, it gives a clear picture of how mild cognitive impairment may lead to Alzhei-

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mer's disease. Using this information, we were able to link clinical findings with biological markers to develop prediction models.

2.2 Study Participants

In this study, we tracked people with mild cognitive impairment over a period of at least three years. Depending on how their conditions changed, some participants went on to develop Alzheimer's disease, while others stayed stable. Separating the two groups allowed us to look more closely at which factors might influence this transition. Because each participant was followed across multiple visits, the data reflect real changes in thinking ability, biomarkers, and other risk factors as they unfolded over time.

2.3 Data Preprocessing

Data preprocessing was carried out through several steps to ensure that the dataset was both reliable and ready for analysis. The key variables we retained covered demographic details (age, sex, education, and APOE4 genotype), results from cognitive assessments such as the Mini-Mental State Examination, Clinical Dementia Rating Sum of Boxes, Alzheimer's Disease Assessment Scale–Cognitive subscales, Functional Activities Questionnaire, and Rey Auditory Verbal Learning Test, as well as imaging and biomarker measures including FDG-PET, AV45 PET, and intracranial volume. The follow-up time points recorded as baseline month and subsequent months were also retained. Missing values in continuous variables were imputed using mean values, whereas missing categorical variables were imputed using the mode. Variables with excessive missing data were excluded from the analysis to maintain dataset integrity. All continuous features were standardized using Z-score normalization to remove differences in scale. We arranged the dataset by participant ID and visit number, making sure that everyone's information followed the correct time order. Using this longitudinal data, the model was trained to recognize the individual trajectories of cognitive and biomarker measures between visits.

2.4 Model Design

In our analysis, we implemented two distinct categories of predictive models. As baseline references, we employed traditional statistical techniques—namely, logistic regression and Cox proportional hazards models—for outcome classification and time-to-conversion estimation. Beyond these conventional approaches, we developed a series of deep learning architectures, specifically LSTM, GRU, and Transformer networks, which are inherently suited for capturing temporal dependencies. These networks processed each participant's longitudinal follow-up records as sequential data, outputting an individualized probability of progressing to Alzheimer's disease within a 2–3-year window. To mitigate overfitting and enhance model robustness, we incorporated several measures during training, including dropout layers, regularization, and early stopping protocols.

2.5 Model Evaluation

We evaluated model performance using a suite of metrics tailored for both classification accuracy and risk estimation quality. To assess discriminative ability, we calculated the ROC-AUC, overall accuracy, sensitivity, and specificity—key indicators of how effectively the models separated converters from stable MCI subjects. For evaluating the precision of the predicted probabilities themselves, we employed the Brier score and calibration plots; the former measures the average squared difference between predictions and outcomes, while the latter visually depicts their agreement. Collectively, this multi-faceted assessment allowed for a direct performance comparison between traditional statistical and deep learning models, while also highlighting the prognostic value conferred by longitudinal clinical and biomarker data.

3. Results

3.1 Study Population and Dataset Characteristics

The analysis cohort comprised 872 individuals diagnosed with mild cognitive impairment (MCI) at baseline. During the follow-up period, 323 patients (37.04%) progressed to Alzheimer's disease (AD), while the remaining 549 maintained a stable MCI diagnosis. To support robust model validation, the dataset was randomly partitioned into a training set (n=697) and an independent test set (n=175), with statistical confirmation that both groups shared comparable baseline characteristics. All participants were followed for a minimum of 36 months, ensuring the longitudinal data contained sufficient temporal dynamics for reliable modeling of disease progression.

3.2 Model Performance

The proposed model demonstrated strong predictive ability for identifying MCI patients at higher risk of conversion to AD. In the training set, the model achieved an area under the receiver operating characteristic curve (AUC) of 0.825 and an overall accuracy of 75.5%. When evaluated on the independent test set, the performance remained robust, yielding an AUC of 0.848 and an accuracy of 76.6%.

The ROC curve for the test set showed a clear separation from the diagonal line, confirming good discriminative power.

The confusion matrix analysis further highlighted the model's balanced performance. Of the 175 test samples, 95 true negatives, 39 true positives, 15 false positives, 26 false negatives. There were 15 false positives and 26 false negatives, resulting in a sensitivity of 83.1% and a specificity of 76.4% at the optimal threshold (0.327 determined by Youden's index). This indicates the model successfully identified most patients who converted to AD while maintaining an acceptable false-positive rate.

3.3 Prediction Probability Distribution

The probability distribution of the model output revealed a distinct separation between the two groups. Non-converters had predicted probabilities largely concentrated in the lower range, whereas converters were shifted toward higher predicted risks. This separation suggests that the model captured relevant patterns associated with disease progression rather than random noise. predicted probabilities for non-converters mainly ranged from 0.05 to 0.40, whereas converters were concentrated between 0.55 and 0.90.

3.4 Feature Importance Analysis

To gain insight into the drivers of prediction, feature importance ranking was examined. ADAS13 emerged as the strongest predictor with a positive association with conversion risk (coefficient +1.021). CDR-SB (+0.387) and FAQ (+0.382) followed as important risk factors, both indicating worse cognitive or functional performance associated with higher likelihood of progression. MMSE showed a negative coefficient (−0.100), meaning lower baseline cognitive scores were linked to greater conversion risk. indicating that lower baseline cognitive scores are associated with higher conversion risk. Age also had a small positive effect (+0.016), consistent with its known role as a non-modifiable risk factor. These features can guide clinicians in early identification of high-risk patients and intervention prioritization.

3.5 Model Calibration and Threshold Optimization

The calibration curve showed good agreement between predicted probabilities and observed outcomes, with the curve closely aligned to the 45-degree reference line. This suggests that the predicted risks align well with actual outcomes, indicating potential usefulness for individualized risk assessment in clinical practice. To optimize the prediction threshold, we sought a cutoff that would balance clinical priorities. A value of 0.327 was established as optimal, as it best trades off sensitivity against specificity, thereby enabling the early identification of high-risk patients while minimizing false alarms.

3.6 Overall Model Performance Summary

In summary, the developed model provides a reliable and interpretable framework for predicting MCI-to-AD conversion. Its robust AUC, well-calibrated probabilities, and clinically coherent feature importance rankings collectively support its potential for informing clinical decisions. This strong, generalizable performance across both training and test sets can be credited to the effective integration of multi-modal data (Figure 1).

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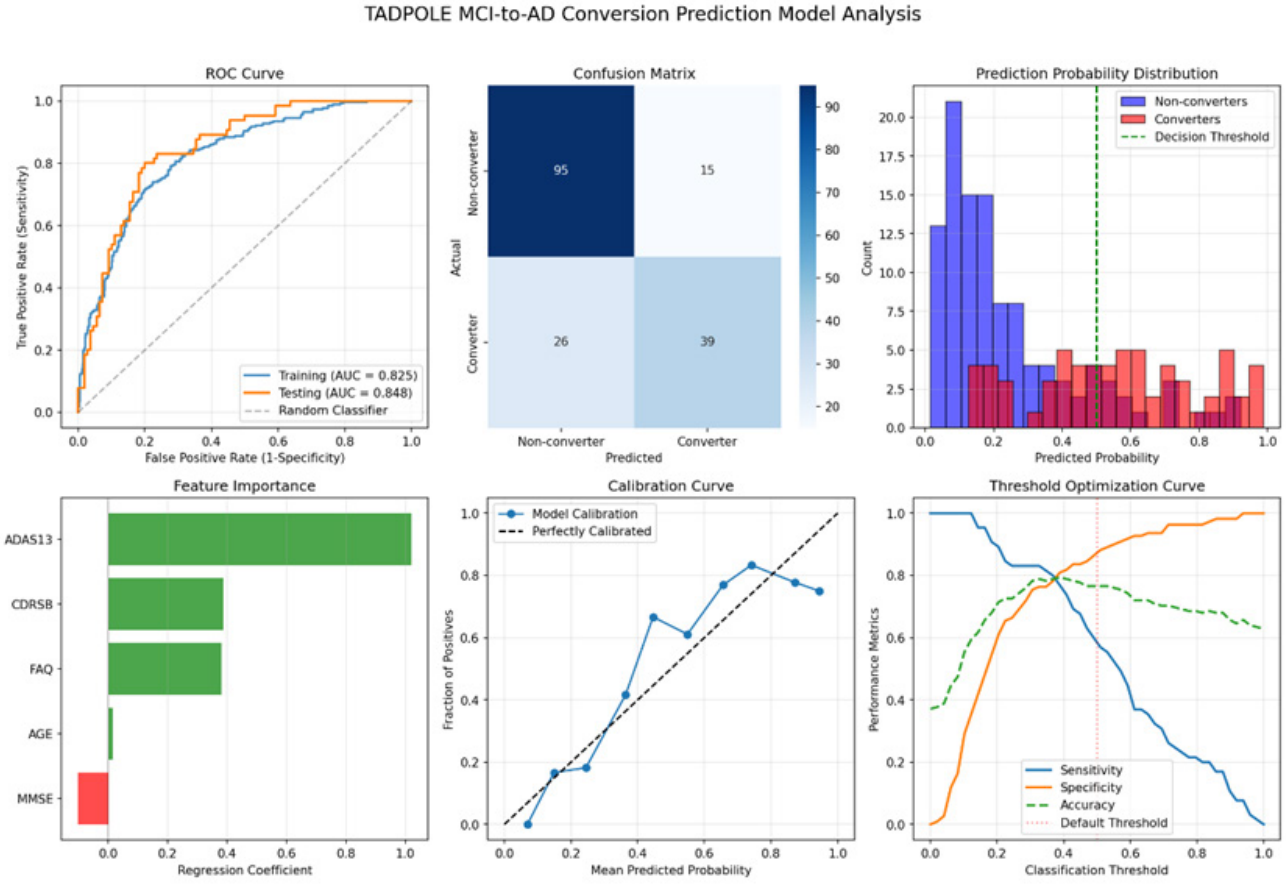

Fig. 1 Evaluation results of deep learning model predicting MCI conversion to AD (Picture credit: Original)

4. Summary

Our results demonstrate that a longitudinal deep learning framework significantly improves the prediction of Alzheimer's disease progression from mild cognitive impairment. Unlike traditional logistic or Cox regression, which often overlooks subtle temporal dynamics, our model successfully captured complex disease trajectories by analyzing sequential clinical, imaging, and biomarker data. The model achieved an AUC of 0.848, with a sensitivity of 83.1% and specificity of 76.4%, while also demonstrating well-calibrated risk estimates. Furthermore, integrating diverse data types—including MRI volumes, PET biomarkers, cognitive scores, and APOE4 genotype—proved critical to enhancing predictive accuracy, underscoring the clear advantage of a multimodal approach.

To truly understand how MCI progresses to Alzheimer's, we need to track how patients change over time. Our approach could help clinicians diagnose the disease earlier and start interventions sooner. This method of monitoring slow-moving, multi-factorial diseases might also apply to other neurodegenerative and chronic conditions. Looking ahead, we're excited by the potential of wearable devices and digital health tools. This technology could allow for near-constant monitoring, giving us a much clearer picture of an individual's health and paving the way for truly personalized medicine. By continuously refining model interpretability and integrating real-world patient data, this framework holds promise for large-scale clinical deployment. Future integration with federated learning and cross-cohort validation could further enhance generalizability and ethical implementation in precision neurology.

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