Studying MCI to AD Conversion Radiomics-Based Survival Indexes by Machine Learning

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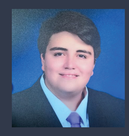
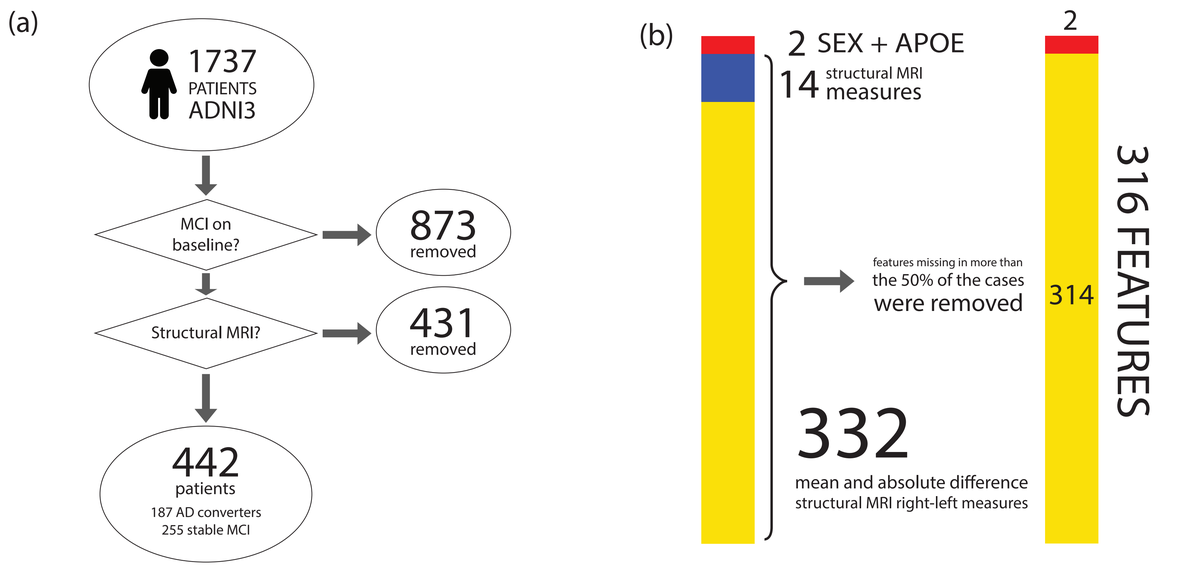
Abstract. Structural MRI provides information regarding the presence of early-stage Alzheimer Disease (AD) and several MRI findings are associated with the rate of conversion from mild cognitive impairment (MCI) to AD. However, the extent of the multivariate relationship between structural MRI findings and the rate of MCI to AD conversion has not been fully studied. The objective of this work was the exploration of different machine learning strategies (LASSO, BSWiMS, BeSS, and feature filters) to build MRI-based multivariate survival models to study MRI association with MCI to clinical AD conversion. 346 MRI-related features, where the location-paired left and right measurements were described by mean and absolute difference, of 442 ADNI subjects were used to construct cross-validated Cox multivariate survival models. The multivariate Cox model with the best concordance index (c-index) was built with BSWiMS features (c-index 0.64 95% CI: 0.61-0.67). Finally, we report an eight MRI-feature model that described risk factors for early MCI to AD conversion. We presented survival models that were able to separate the stable MCI subjects from those that converted to AD



- According to Alzheimer's Disease International, 60% to 70% of 50 million cases of dementia are Alzheimer disease (AD) [1].
- Between 2000 and 2015 the number of deaths caused by the disease has increased by 123% [2].
- **The objective of this work was the evaluation of seven different machine learning strategies to build MRI-based survival models of the rate of conversion between mild cognitive impairment (MCI) to full AD.**

PARTICIPANTS AND DATA CONDITIONING



- All the participants of the TADPOLE challenge.
- 1737 individuals from the ADNI3 database.
- 873 patients that were either normal or already had suffered the conversion of MCI to AD at the baseline
- 431 MCI subjects who did not have structural MRI information.
- 442 people with MCI status and MRI at the baseline

- MCI stable subjects, the difference in days between the baseline observation and the last follow-up date was calculated
- Subject MCI to AD, the baseline date and the date of change.
- 332 MRI-characteristics left and right are described, by the mean and absolute differences.
- The remaining empty values on structural MRI measures were imputed by the nearest neighbor strategy.

RESULTS

- BSWiMS (Model 1) chose on all the times, mean of volume of amygdala and entorhinal and mean cortical thickness average of bankssts
- CoxNet (Model 2) selected APOE4, mean cortical thickness AVG of Bankssts and the mean volume (CP) of entorhinal on all iterations
- Model 2 was the model with **the best mean on the c-index values** on the wrappers section
- BeSS (Model 3) selected APOE4, mean cortical thickness standard deviation of bankssts and mean volume (cortical parcellation) of entorhinal
- Filter methods used the same features extracted by the last three methods to build Cox Models
- Univariate Cox`selected 54 elements on all iterations, some of them were: APOE4, mean cortical thickness AVG of Parahippocampal, cortical thickness AVG and volume (CP) of Pars Opercularis.
- Cox Model built with BSWiMS is the model with the best c-index on Risk and Follow-up times. Model 4 showed a risk c-index of 0.74{0.71-0.76} and a log rank test pvalue of 8.10e-15. Figure 3.
- Analysis of the set of selected features across methods and holdout repetitions indicated that 10 features were common on 50% of the sets
- A refit process was carried out with these ten features. After this, we computed the hazard ratios (HR) with their corresponding 95% confidence intervals (CI). Figure 4 shows the heatmap representation of the features and shows information about HR.

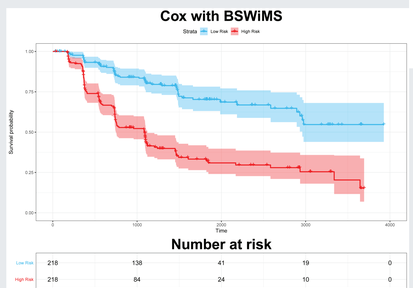


Fig. 3. Kaplan Meier Curves of Multivariate Cox model built with the features found with BSWiMS method (Model 7). Risk c-index of 0.74{0.71-0.76}.

Method	c-index Risk {95% CI}	c-index Follow-up {95% CI}	LogRank pvalue	ACC{95% CI}	AUC{95% CI}	Feature size ; Jaccard Index
Wrappers						
BSWiMS	0.60 {0.57-0.62}	0.81 {0.79-0.83}	1.58e-14	0.67{0.63-0.72}	0.73{0.68-0.78}	12.75 ; 0.34
Coxnet	0.61 {0.58-0.64}	0.84 {0.82-0.86}	3.33e-16	0.68{0.64-0.72}	0.73{0.68-0.78}	24.40 ; 0.31
BeSS	0.60 {0.57-0.63}	0.63 {0.60-0.66}	1.99e-10	0.62{0.58-0.67}	0.68{0.63-0.73}	52.85 ; 0.21
Filters						
Cox.BSWiMS	0.74{0.71-0.76}	0.74{0.71-0.76}	8.10e-15	0.67{0.63-0.72}	0.73{0.68-0.77}	12.75 ; 0.34
Cox.CoxNet	0.72{0.69-0.74}	0.72{0.69-0.74}	3.73e-13	0.67{0.62-0.72}	0.72{0.68-0.77}	24.40 ; 0.31
Cox.BeSS	0.63{0.60-0.66}	0.63{0.60-0.66}	1.99e-10	0.62{0.58-0.67}	0.68{0.63-0.73}	52.85 ; 0.21
Cox.UniCox	0.67{0.64-0.70}	0.67{0.64-0.70}	6.39e-11	0.63{0.58-0.67}	0.67{0.62-0.72}	101.30 ; 0.67

TABLE 1.. Survival and Classification stats for every model. For each model the concordance Index (c-index) for Risk and Follow-up Times were calculated on the test results. The Log Rank Test was computed by the identified low/high risk patients.

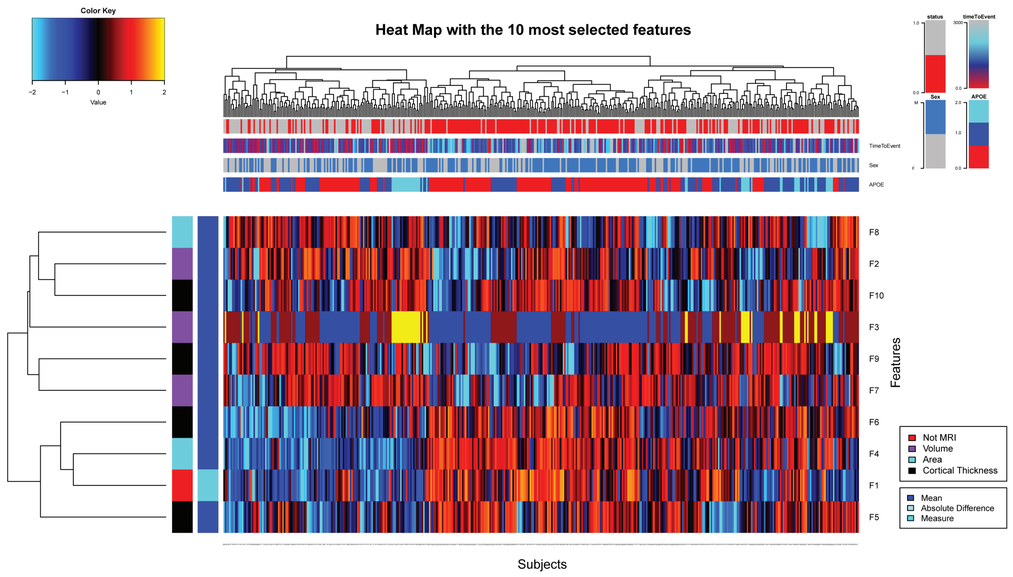


FIG 4.. A heat map representation of the features associated with MCI to AD conversion. The figure shows the ten features selected by all the 4 methods at least in the half of the iterations (horizontal axis) and subjects on the vertical axis. **(F1)** Mean volume (CP) of entorhinal HR=0.63(0.50, 0.80), **(F2)** mean cortical thickness SD of Bankssts HR=1.60(1.20, 2.12), **(F3)** APOE4 HR=1.74(1.40, 2.17), **(F4)** mean volume (WMP) of amygdala HR=0.88(0.69, 1.13), **(F5)** mean cortical thickness AVG of Bankssts HR=0.76(0.60, 0.97), **(F6)** mean volume (CP) of inferior temporal HR=0.79(0.62, 1.00), **(F7)** absolute difference cortical thickness AVG of middle temporal HR=1.38(1.07, 1.78), **(F8)** absolute difference of cortical thickness AVG of pars opercularis HR=1.46(1.09, 1.94), **(F9)** absolute difference cortical thickness AVG of inferior parietal HR=1.33(1.04, 1.70), **(F10)** mean cortical thickness SD of Rostral middle frontal HR=0.64(0.50, 0.81)

DISCUSION

- Many of the characteristics that have been selected in our study have been already presented as risk factors associated with MCI to AD conversion [3]–[5].
- The reduction of mean volume (CP) of entorhinal as a factor increases the risk of conversion validating what was presented in previous studies [4]-[5]
- The atrophy of mean volume (WMP) of the amygdala is related to APOE and therefore with the highest risk
- Mean cortical thickness of AVG and SD of Bankssts suggest the lack of homogeneity as risky, which differs in the observations presented in other studies [7] where asymmetry is mentioned as a risk factor
- In the same study [7] they observe but do not discuss the asymmetry of other structures; in our case, we find again that the increase in the asymmetry in the absolute size of the cortical thickness of the temporal and cortical thickness of pars opercularis increases the risk of conversion
- Finally, the atrophy in the mean volume of inferior temporal increases the risk of conversion, as mentioned in previous studies [8].
- All the models shown an acceptable accuracy compared to recent classification studies [9], this considering that our work also gives information about the hazard of every selected feature.
- Our analysis was carried out only with the patients belonging to ADNI cohort, which if there are changes in the group of people to be evaluated, which may affect the results shown.

CONCLUSION

We presented a comprehensive analysis of survival models that were able to separate the stable MCI subjects from those that converted to AD, indicating that machine learning approaches are very useful in discovering and analyzing the MRI features that are associated with the conversion of MCI subjects to AD.

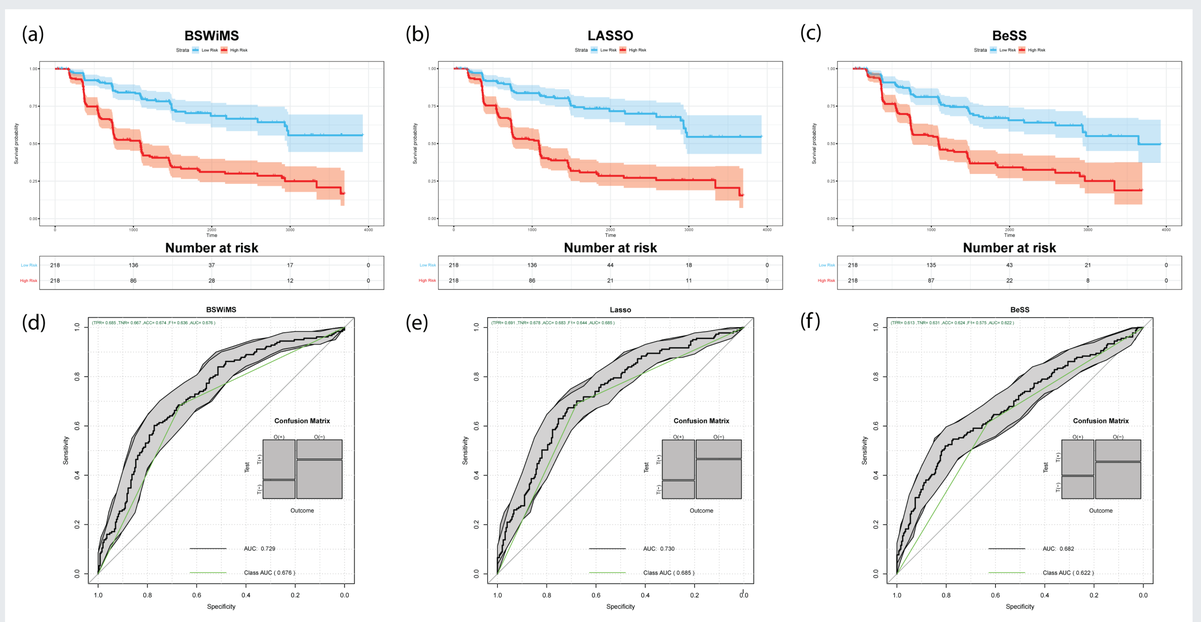


Fig. 5. Kaplan Meier (KM) and ROC curves for wrappers/embedded section. CoxNet showed the best accuracy on the classification and the best c-index on Risk and Follow-up times. (a) Model 1 BSWiMS KM (b) CoxNex KM (c) BeSS KM (d) BSWiMS ROC (e) CoxNet ROC (f) BeSS ROC.

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