Prediction of MCI to AD Risk of Conversion Survival Models: qMRI vs CSF Measures and Cognitive Assessments

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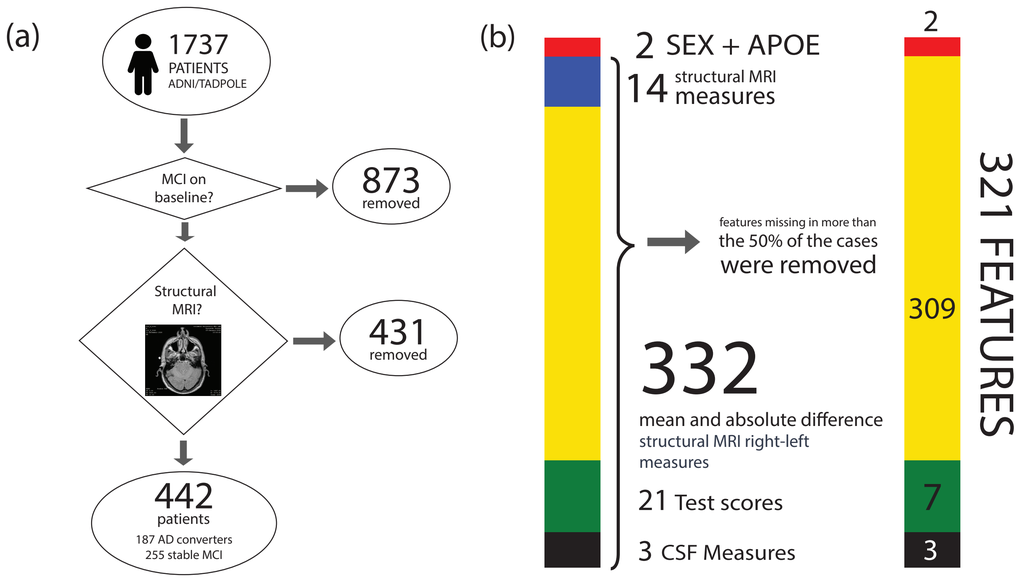
GOBIERNO DE LA REPÚBLICA DEL ECUADOR

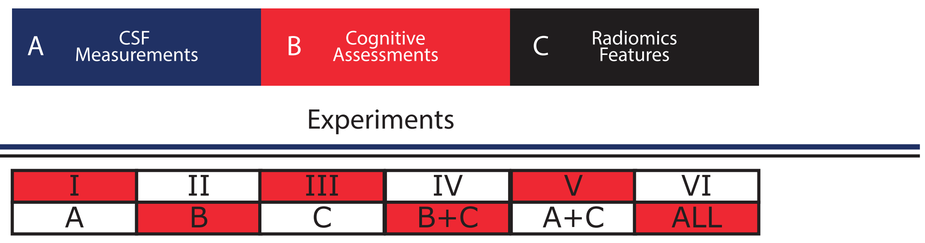
- According to Alzheimer's Disease International, 60% to 70% of 50 million cases of dementia are Alzheimer disease (AD) [1].
- Cerebrospinalfluid (CSF) biomarkers are iused to support difference between AD from non-Alzheimer's disease dementia [13].
- Cognitive Assessments are the startingpoint for brain screening on AD [18,19]
- **The main goal of this paper is the application of a unified approach to cross-validate Cox regression models for the exploration of survival-based analyses of different group of measures and the role of qMRI biomarkers to correctly predict the risk and rate of MCI to AD conversion against CSF Measures and Cog-assessments.**

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

Groups of features - Experiments



- **Experiment I** used CSF measures**. Experiment II** studied Cog-assessments scores**. Experiment III** explored Radiomics features. **Experiment IV** merged Cog-Assessments scores with Radiomics. **Experiment V** merge Radiomics information with CSF Measures**. Experiment VI** used all three features.

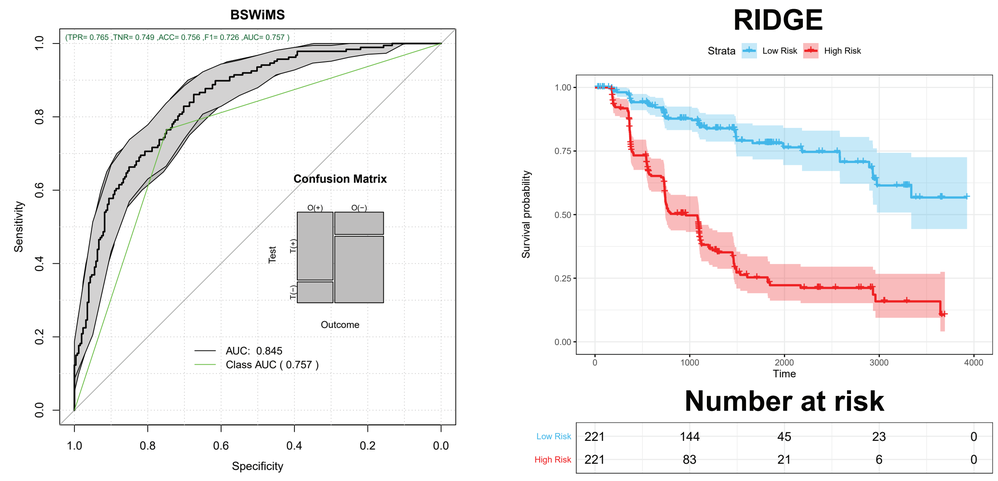
RESULTS

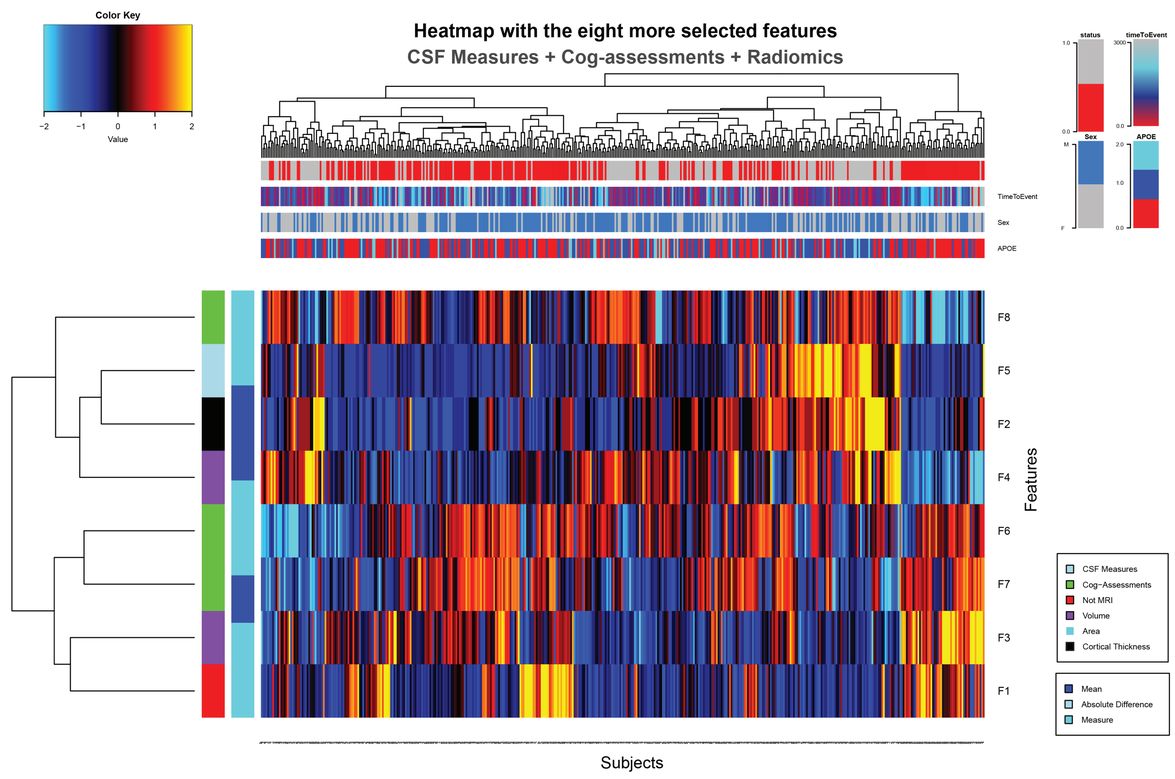
- **Experiment I:** SPDAS the best on ACC selected 3 features and the best on c-index FU was RIDGE with 0.76.
- **Experiment II:** LASSO reported the best c-index FU .69(0.66,0.72).ACC= 0.76, AUC= 0.81, SEN= 0.76, SPE= 0.76.
- **Experiment III:** The best performance on c-index FU is RIDGE and on c-index Risks is BSWiMS as a filter with 0.74(0.72-0.77)
- **Experiment VI:** LASSO found a better performance over c-index Risks with 0.66(0.63,0.69). ACC= 0.75, AUC=0.84,.

		Conversion Accuracy				Concordance Conversion Time			
		I	II	III	VI	I	II	III	VI
BSWiMS	Wrapper	0.67 (0.62,0.71)	0.74 (0.7,0.78)	0.66 (0.62,0.71)	0.76** (0.71,0.8)	0.75 (0.72,0.78)	0.68 (0.65,0.71)	0.81 (0.79,0.83)	0.69 (0.66,0.72)
	Filter	0.67 (0.62,0.71)	0.76 (0.72,0.8)	0.67 (0.62,0.71)	0.76** (0.71,0.8)	0.75 (0.72,0.77)	0.66 (0.63,0.69)	0.74 (0.72,0.77)	0.63 (0.59,0.66)
LASSO	Wrapper	0.67 (0.62,0.71)	0.76 (0.72,0.8)	0.68 (0.64,0.72)	0.75 (0.71,0.79)	0.74 (0.71,0.77)	0.69 (0.66,0.72)	0.84 (0.83,0.86)	0.77 (0.75,0.79)
	Filter	0.67 (0.62,0.71)	0.76 (0.72,0.8)	0.69 (0.64,0.73)	0.76 (0.72,0.8)	0.73 (0.7,0.76)	0.67 (0.63,0.7)	0.72 (0.7,0.75)	0.63 (0.6,0.66)
RIDGE	Wrapper	0.66 (0.61,0.7)	0.75 (0.71,0.79)	0.68 (0.63,0.72)	0.71 (0.66,0.75)	0.76 (0.74,0.79)	0.69 (0.66,0.72)	0.92 (0.91,0.93)	0.91 (0.89,0.92)
GSPDAS	Wrapper	0.67 (0.62,0.71)	0.76 (0.72,0.8)	0.64 (0.6,0.69)	0.74 (0.69,0.78)	0.75 (0.72,0.78)	0.66 (0.63,0.69)	0.63 (0.6,0.66)	0.59 (0.55,0.62)
	Filter	0.67 (0.62,0.71)	0.76 (0.72,0.8)	0.64 (0.6,0.69)	0.74 (0.69,0.78)	0.75 (0.72,0.78)	0.66 (0.63,0.69)	0.63 (0.6,0.66)	0.59 (0.56,0.62)
SPDAS	Wrapper	0.67 (0.62,0.71)	0.76* (0.72,0.8)	0.68 (0.64,0.73)	0.76 (0.72,0.8)	0.73 (0.7,0.76)	0.66 (0.63,0.69)	0.74 (0.71,0.77)	0.63 (0.6,0.67)
SPDAS.BIC	Wrapper	0.69 (0.64,0.73)	0.76 (0.72,0.8)	0.67 (0.63,0.72)	0.74 (0.69,0.78)	0.72 (0.69,0.74)	0.67 (0.64,0.7)	0.69 (0.66,0.72)	0.61 (0.58,0.64)
Unicox	Filter	0.67 (0.62,0.71)	0.76 (0.71,0.8)	0.63 (0.58,0.68)	0.7 (0.65,0.74)	0.73 (0.7,0.76)	0.66 (0.63,0.69)	0.67 (0.65,0.7)	0.61 (0.58,0.64)

Main classification (Accuracy ACC) and survival stats (c-index FT) for all the models on Experiments I, II,III, and VI. Red color on each column indicates the best stat on that specific experiment. Tiebreakers were performed by the AUC value and 95%CI, *AUC=0.81(0.77,0.85), **AUC=0.84(0.81,0.88).

KM for BSWiMS model and ROC Curve for RIDGE of Experiment VI (CSF Measures + Cog-assessments + Radiomics). (Left) BSWiMS Model [ACC=0.76(0.71,0.8) c-index FT=0.69(0.66,0.72) c-index Risks = 0.65(0.63,0.68)] (Rigth) RIDGE Model [ACC=0.71(0.66,0.75) c-index FT=0.91(0.89,0.92) c-index Risks = 0.63(0.61,0.66)].

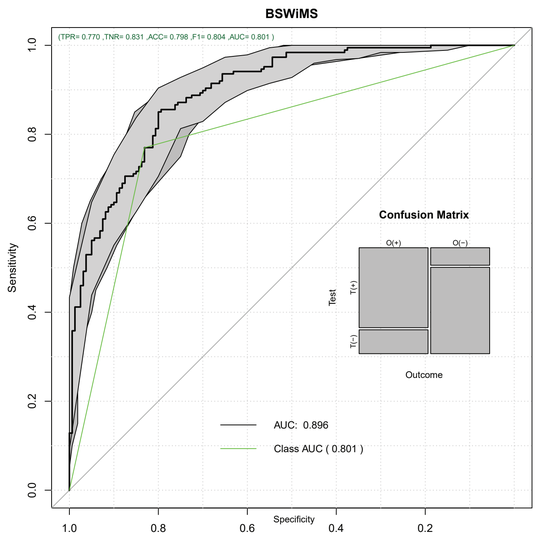




A heat map representation of the features associated with MCI to AD conversion. The figure shows the 8 features selected by all the 6 methods in at least in the half of the iterations (horizontal axis) and subjects on the vertical axis. (F1) Aβ_{1-42}, (F2) CDSRB, (F3) RAVLT immediate, (F4) ADAS13, (F5) FAQ, (F6) Mean volume CP Inferior Temporal, (F7) Mean volume CP Entorhinal, (F8) Mean cortical thickness SD Bankssts.

DISCUSSION AND CONCLUSION

- This RHOCV strategy allowed the evaluation of the effect of the training set on feature selection, and, at the same time, permitted a training-set unbiased evaluation of the test performance.
- We conducted a post hoc experiment which analyzed test prediction on MCI stable subjects whose last visit was greater than 3 years (52 no-event subjects did not meet the criteria). Figure 4 with the model build with BSWiMS in the Experiment VI. We clearly see that Cox based conversion risk prediction had a similar performance (ROC ACU= 0.896) to previous works [9].
- The detailed analysis of features selected in the Experiment VI indicated that only eight features out of 322, were selected at least 50% of the time. Almost all of these eight features have already been reported as potential biomarkers associated with MCI to AD conversion [5–7, 13.]
- The combination of the set of features on Experiments IV, V & VI results in some better performances over all the stats but with non-significative statistically differences between them. In the context of follow-uptimes, the best method over these three experiments was RIDGE. Results on the experiments were: ExperimentIV c-index FT = 0.92(0.91,0.93), Experiment V c-index FT = 0.93(0.91,0.94), and Experiment VI c-index FT= 0.91(0.89,0.92). **Therefore, adding information about CSF Measures or Cog-assessments to the model of Radiomics features do not add significative information.**



BSWiMS ROC with 347 patients who suffered the conversion or have a censored event in more than 3 years.

CONCLUSION

Radiomics biomarkers in the form of quantitative MRI assessments were an important source of features inthe prediction of MCI to AD conversion time in models that only contained ApoE4, Cognitive Assessments, and qMRI. Adding CSF biomarkers did not improve the accuracy nor the concordance of multi-source Survival Models.

[1] Alzheimer's Association, "2018 Alzheimer's disease facts and figures, "Alzheimer's & Dementia14, 367–429(mar 2018)
[5] Westman, E., Muehlboeck, J.-S., and Simmons, A., "Combining MRI and CSF measures for classification of Alzheimer's disease and prediction of mild cognitive impairment conversion.," NeuroImage 62, 229–38(Aug 2012)
[6] Popp, J., Wolfsgruber, S., Heuser, I., Peters, O., Hull, M., Schroder, J., Moller, H. J., Lewczuk, P., Schneider, A., Jahn, H., Luckhaus, C., Perneczky, R., Frolich, L., Wagner, M., Maier, W., Wiltfang, J., Kornhuber,J., and Jessen, F., "Cerebrospinal fluid cortisol and clinical ...", 601–607 (Feb 2015).
[7] Raghavan, N., Samtani, M. N., Farnum, M., Yang, E., Novak, G., Grundman, M., Narayan, V., andDibernardo, A., "The ADAS-Cog revisited: Novel composite scales based on ADAS-Cog to improve efficiency in MCI and early AD trials," Alzheimer's and Dementia 9(Feb 2013)
[9] Martínez-Torteya, A., Trevino, V., and Tamez-Pena, J. G., "Improved Diagnostic Multimodal Biomarkers for Alzheimer's Disease and Mild Cognitive Impairment," BioMed Research International 2015, 1–11 (jan2015)
[13] Paterson, R. W., Slattery, et al.,"Cerebrospinal fluid in the differential diagnosis of Alzheimer's disease: Clinical utility of an extended panel of biomarkers in a specialist cognitive clinic," Alzheimer's Research and Therapy10(Mar 2018).
[18] Cullen, B., O'Neill, B., Evans, J. J., Coen, R. F., and Lawlor, B. A., "A review of screening tests for cognitive impairment," (2007).
[19] Kirsebom, B.-E., Espenes, R., Waterloo, K., Hessen, E., Johnsen, S. H., Brathen, G., Aarsland, D., and Fladby, T., "Screening for Alzheimer's Disease: Cognitive Impairment in Self-Referred and Memory Clinic-Referred Patients.," Journal of Alzheimer's disease: JAD60(4), 1621–1631 (2017).

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TADPOLE