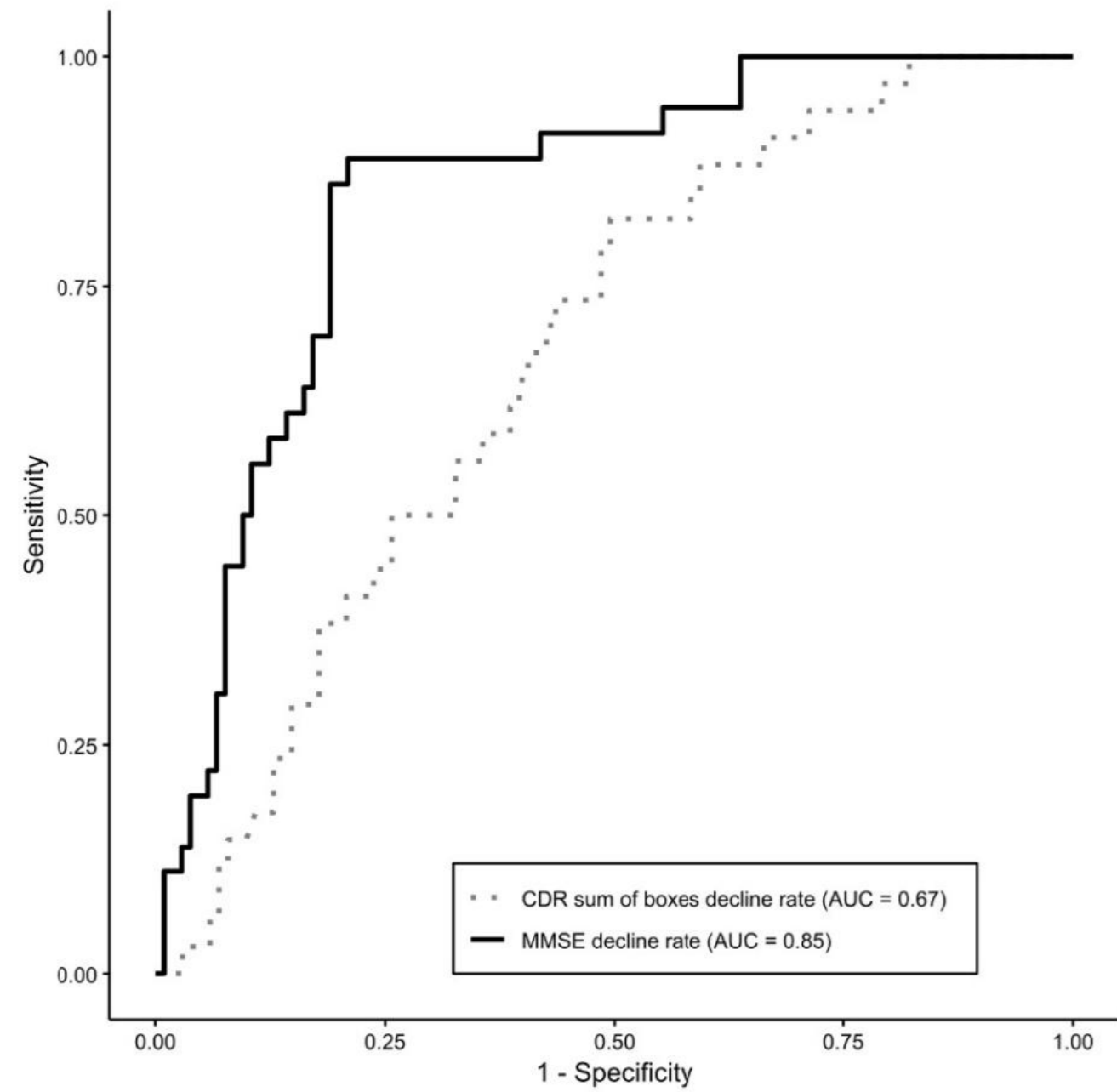


Early Alzheimer's Disease Prognosis Using Baseline And Minimally Invasive Data

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AIM: predicting individual decline using minimally invasive variables from baseline diagnosis

INTRODUCTION AND METHODS	RESULTS	CONCLUSION																																																									
Cohort: Patients with prodromal AD followed longitudinally for 2 years (n = 142). Statistical analysis: - Development of penalized predictive models: Elastic Net / Lasso / Ridge logistic regression with Leave-One-Out Cross-Validation (LOOCV). - Identifying independent predictors: stepwise selection-weighted logistic regression (AIC) to quantify Ors. Baseline Variables: Demographics, ApoE genotype, plasma biomarkers (Aβ42, Aβ40, t-Tau, p-Tau181, p-Tau217, NfL, GFAP), neuropsychological tests (MMSE, CDR, RBANS, FAQ, ADCS-ADL, GDS). Outcome Definition: Fast decliners were defined as patients in the lowest quartile (≤ 25th percentile) of the MMSE or upper quartile of the CDR-SB decline slope. Limitations: Small sample size; lack of external validation; possible selection bias; class imbalance mitigated by weights.	MMSE Classification: Significant biomarkers: p-Tau181, Aβ42/Aβ40, GFAP, p-Tau217, NfL (all p<0.05); ↑ levels in the rapid decline group. CDR-SB Classification: Significant biomarkers: NfL, GFAP, p-Tau217 (p<0.05); Aβ42/Aβ40 and p-Tau181 did not reach significance. Correlation with MMSE Slope: p-Tau217, p-Tau181, and GFAP are inversely correlated with decline; Aβ42/Aβ40 and RBANS are directly correlated (protective effect). MMSE vs. CDR-SB Agreement: Overall agreement 85.1%; kappa = 0.60 (95% CI: 0.44–0.76), moderate-to-substantial agreement. <table><tr><th>Metrics</th><th>MMSE model</th><th>CDR-SB model</th></tr><tr><td>AUC</td><td>0.847 (IC: 0.78-0.92)</td><td>0.672 (IC: 0.58-0.77)</td></tr><tr><td>Sensitivity</td><td>86.1% (70.5-95.3%)</td><td>67.7% (49.5-69.1%)</td></tr><tr><td>Specificity</td><td>81.0% (72.1-88.0%)</td><td>59.4% (49.2-69.1%)</td></tr><tr><td>PPV</td><td>60.8% (50.6-70.1%)</td><td>35.9% (28.7-43.9%)</td></tr><tr><td>NPV</td><td>94.4% (88.2-97.5%)</td><td>84.5% (76.6-90.1%)</td></tr><tr><td>Accuracy</td><td>82.3% (75.0-88.2%)</td><td>61.5% (52.7-69.7%)</td></tr></table> Optimal parameters: MMSE: α=0.9 (Elastic Net), λ=0.0078 CDR-SB: α=0 (Ridge), λ=0.9817	Metrics	MMSE model	CDR-SB model	AUC	0.847 (IC: 0.78-0.92)	0.672 (IC: 0.58-0.77)	Sensitivity	86.1% (70.5-95.3%)	67.7% (49.5-69.1%)	Specificity	81.0% (72.1-88.0%)	59.4% (49.2-69.1%)	PPV	60.8% (50.6-70.1%)	35.9% (28.7-43.9%)	NPV	94.4% (88.2-97.5%)	84.5% (76.6-90.1%)	Accuracy	82.3% (75.0-88.2%)	61.5% (52.7-69.7%)	Figure 1. Curve ROC MMSE model vs, DCR.SB model.  <table><tr><th>Baseline Variable</th><th>OR</th><th>value</th></tr><tr><td>High Education Level (vs. Basic)</td><td>11.15</td><td>p=0.002**</td></tr><tr><td>Medium Education Level (vs. Basic)</td><td>5.15</td><td>p=0.032*</td></tr><tr><td>Plasma p-Tau217</td><td>3.27</td><td>0.037</td></tr><tr><td>Plasma GFAP</td><td>Associated</td><td>0.037</td></tr><tr><td>Baseline Total RBANS</td><td>0,79</td><td>p<0.001***</td></tr></table> Table 2 Independent Predictors of Rapid Cognitive Decline (MMSE model). <table><tr><th>Baseline Variable</th><th>OR</th><th>value</th></tr><tr><td>GFAP</td><td>1.01</td><td>p=0.009*</td></tr><tr><td>p-Tau217</td><td>3.05</td><td>p=0.092</td></tr><tr><td>Masc sex</td><td>2.31</td><td>p=0.111</td></tr><tr><td>MMSE</td><td>0.78</td><td>p<0.001***</td></tr><tr><td>High Education Level (vs. Basic)</td><td>3.070</td><td>p=0.053</td></tr></table> Table 3 Independent Predictors of Rapid Cognitive Decline (CDR-SB model).	Baseline Variable	OR	value	High Education Level (vs. Basic)	11.15	p=0.002**	Medium Education Level (vs. Basic)	5.15	p=0.032*	Plasma p-Tau217	3.27	0.037	Plasma GFAP	Associated	0.037	Baseline Total RBANS	0,79	p<0.001***	Baseline Variable	OR	value	GFAP	1.01	p=0.009*	p-Tau217	3.05	p=0.092	Masc sex	2.31	p=0.111	MMSE	0.78	p<0.001***	High Education Level (vs. Basic)	3.070	p=0.053
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A combination of plasma biomarkers (p-Tau217, GFAP), neuropsychological tests (RBANS, MMSE), and educational level predicts rapid cognitive decline with an AUC of 0.847, sensitivity of 86%, and NPV of 94.4%.

P-Tau217 (OR~3.3) and GFAP as independent risk biomarkers.

Greater cognitive reserve (OR=11.15 for university students) is associated with a more accelerated decline. Perhaps more advanced underlying brain pathology previously compensated.

MMSE captures early progression better than CDR-SB (AUC 0.847 vs 0.672).

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