DAY 5
ABSTRACT 1

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Individualised prognostic models using plasma biomarkers for clinical progression to Alzheimer's disease dementia in non-demented elderly

Abstract:

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Background:

Blood-based biomarkers can provide a low-invasive and accessible way to identify neurodegenerative diseases before the clinical onset of dementia. We aimed to construct prognostic models for personalized risk of developing Alzheimer's disease (AD) dementia in a memory clinic population of individuals with either subjective cognitive decline (SCD) or mild cognitive impairment (MCI), using plasma phosphorylated-tau-181 (pTau181), amyloid beta 1-42/1-40 (Aβ42/40), glial fibrillary acidic protein (GFAP) and/or neurofilament light (NfL).

Method:

From the Amsterdam Dementia Cohort and SCIENCe project we included 303 individuals with SCD (age 61±9 years, n=126(42%) female, MMSE 28±1) and 250 with MCI (age 65±7 years, n=89(36%) female, MMSE 27±2), who had annual follow-up visits for re-evaluation of diagnosis (average follow-up duration: 2.7±1.7 years.) Our outcome measure was progression to AD dementia. Plasma biomarkers were measured at baseline using SiMoa. Concentrations were then Z-transformed for the statistical analysis and split into tertiles for risk chart visualisation. We evaluated adding the biomarkers individually, or as a panel, to a basic prognostic model including age, sex and baseline diagnosis. We selected a final model by its discrimination (Harrell's C-index, a value above 0.7 indicates a good model) and accuracy (Brier score, a value below 0.2 indicates a good model) and used it to calculate 5-year risk scores for progression to AD dementia.

Result:

During follow-up, 86 individuals developed AD dementia (8 with SCD, 78 with MCI at baseline, average time to progression: 2.8±1.7 years). Adding any of the biomarkers to the basic model improved the model discrimination (Table 1). The prognostic model with all four plasma biomarkers had the best discrimination and accuracy, followed by the model with GFAP only, and the model with pTau181 only (Table 1). Using the model with all four biomarkers, 5-year individual progression risks to AD dementia varied from 1.9% (lowest tertiles for GFAP, pTau181 and NfL, highest tertile for Aβ42/40 ratio) to 40.6% (highest tertiles for GFAP, pTau181 and NfL, lowest tertile for Aβ42/40 ratio) (Figure 1).
Conclusion: Plasma biomarkers, particularly plasma GFAP, can be utilized to provide prognostic risk information about progression to AD dementia for individuals presenting at a memory clinic.

Conclusion:

Plasma biomarkers, particularly plasma GFAP, can be utilized to provide prognostic risk information about progression to AD dementia for individuals presenting at a memory clinic.

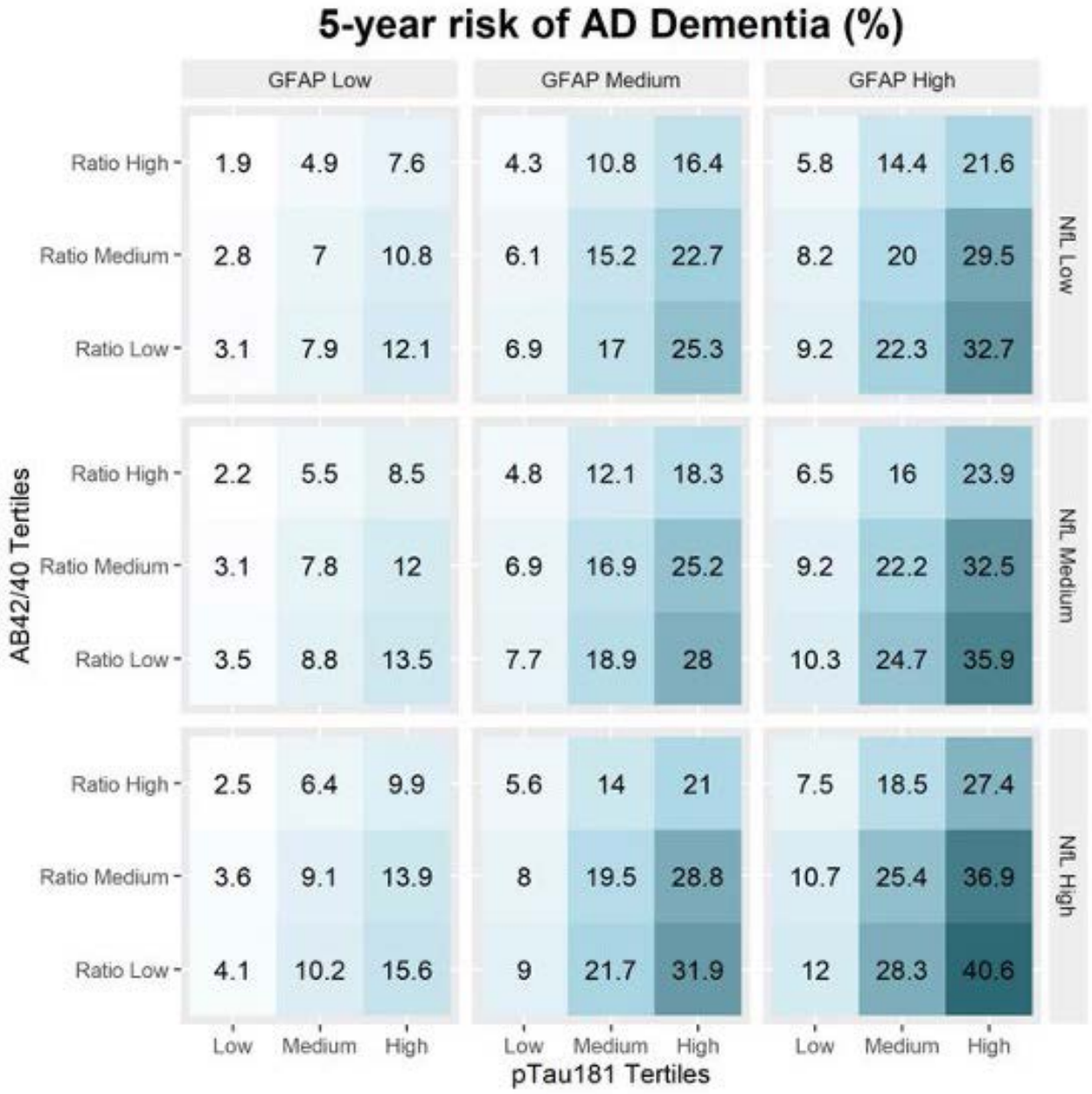

Figure 1: Risk charts to visualize risk of progression to AD dementia within 5 years. The prognostic model used to calculate the risk probabilities included age, sex, baseline diagnosis and all four plasma biomarkers measured at baseline. Plasma biomarker values were natural log-transformed, standardized as Z scores for analysis and split into tertiles for visualization. The risk probabilities presented are averaged over age, sex and baseline diagnosis. pTau181= phosphorylated-tau-181. $A\beta_{42/40}$ = Amyloid $\beta_{42/40}$. GFAP = glial fibrillary acidic protein. NfL = neurofilament light.

Model	Model description	C-index (95% CI)	1-year Brier score	3-year Brier score	5-year Brier score
1	Age, Sex, Baseline Diagnosis	0.763 (0.70 – 0.820)	0.0144	0.105	0.151
2	Age, Sex, Baseline Diagnosis, NfL	0.794 (0.734 – 0.854)	0.0143	0.102	0.152
3	Age, Sex, Baseline Diagnosis, Aβ42/40	0.796 (0.767 – 0.824)	0.0144	0.103	0.159
4	Age, Sex, Baseline Diagnosis, GFAP	0.839 (0.811 – 0.867)	0.0137	0.101	0.130
5	Age, Sex, Baseline Diagnosis, pTau181	0.817 (0.786 – 0.845)	0.0142	0.101	0.142
6	Age, Sex, Baseline Diagnosis, all four markers	0.849 (0.804 – 0.895)	0.0138	0.0983	0.134

Table 1: Evaluation of different cox regression prognostic models for AD dementia risk. Harrell's C-index is used to assess prognostic discrimination and ranges from 0 to 1, with a score of 0.5 indicating risk score predictions are no better than a random prediction, and a score of 1 indicating perfect model prediction. A score higher than 0.7 indicates a good model. Internal fivefold cross-validation of the models yielded cross-validated C-indexes with 95% confidence intervals. The brier score is used to assess the accuracy of probabilistic predictions at a given time, and ranges from 0 to 1, with a score closer to 0 indicating greater accuracy, and a score below 0.2 indicating a good model. Biomarker values were natural log-transformed and standardized as Z scores. pTau181= phosphorylated-tau-181. $A\beta_{42/40}$ = Amyloid $\beta_{42/40}$. GFAP = glial fibrillary acidic protein. NfL = neurofilament light.