

A Plasma Proteomic Signature For Stratifying Dementia Risk In Patients With Cardiometabolic Diseases

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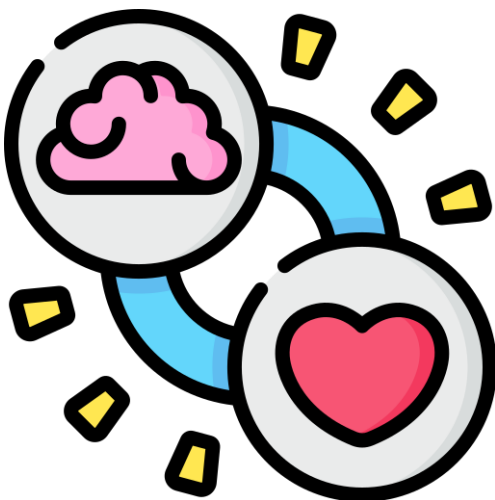


KEY TAKE-AWAY

Plasma proteomics substantially improved prediction and risk stratification of incident dementia beyond conventional clinical variables in patients with cardiometabolic diseases.

INTRODUCTION

- Patients with cardiometabolic diseases (CMDs) have elevated long-term dementia risk.
- Existing cardiovascular and dementia risk models rely mainly on conventional clinical variables and show limited discrimination in high-risk CMD populations.
- Plasma proteomics may capture residual vascular, metabolic, and neurodegenerative risk not reflected by routine clinical factors.
- **Aim:** evaluate whether plasma proteomics improves prediction of incident dementia in CMDs and major subgroups.



METHODS

Study workflow



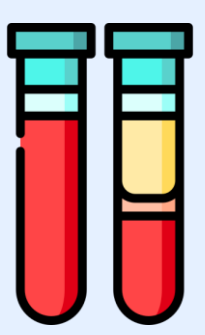
Study population

45,023 dementia-free adults Primary CMD cohort n=5,275



CMD subgroups

T2D n=2,499; Stroke n=808; CHD n=2,703



Predictors

2,916 plasma proteins + 170 baseline clinical features.



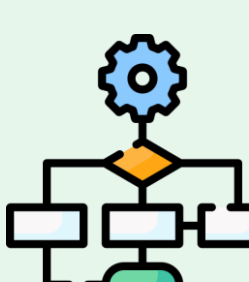
Outcome

Incident dementia from linked health records (331 events).



Analysis & modeling

Proteome-wide association Stability selection; Clinical-only, Protein-only, and Multimodal models.



Model evaluation

AUC, calibration, NRI, IDI, and decision curve analysis.

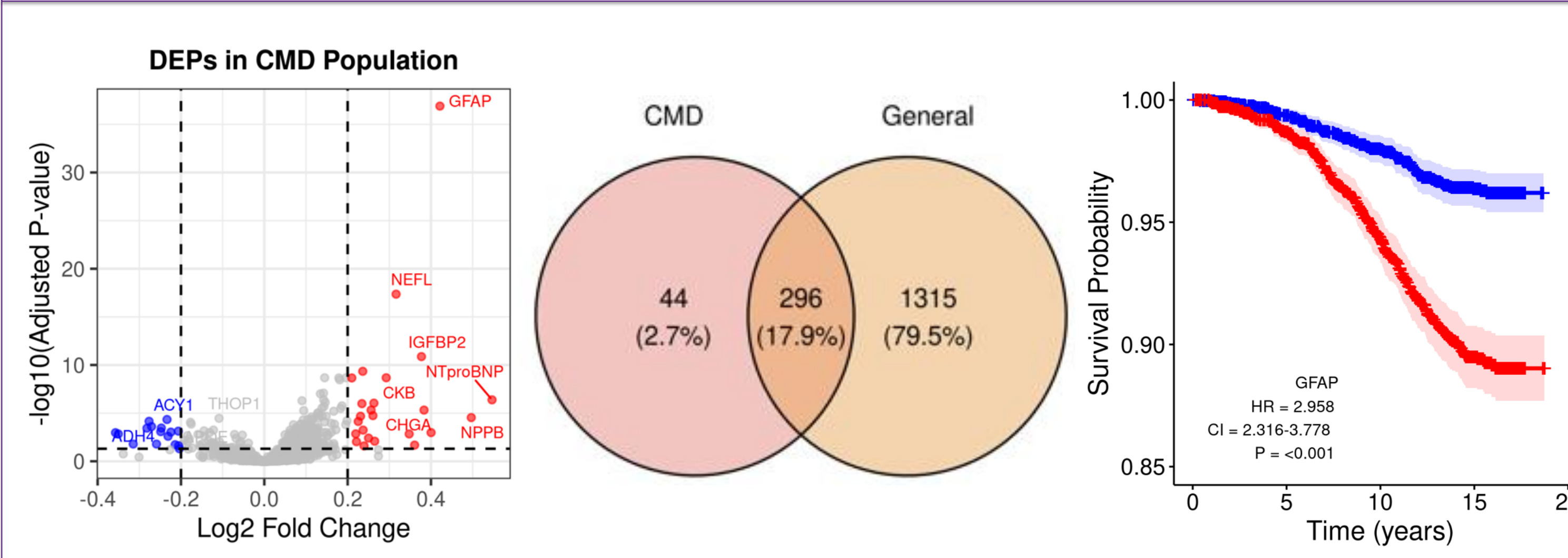
Training set
70%

Test set
30%

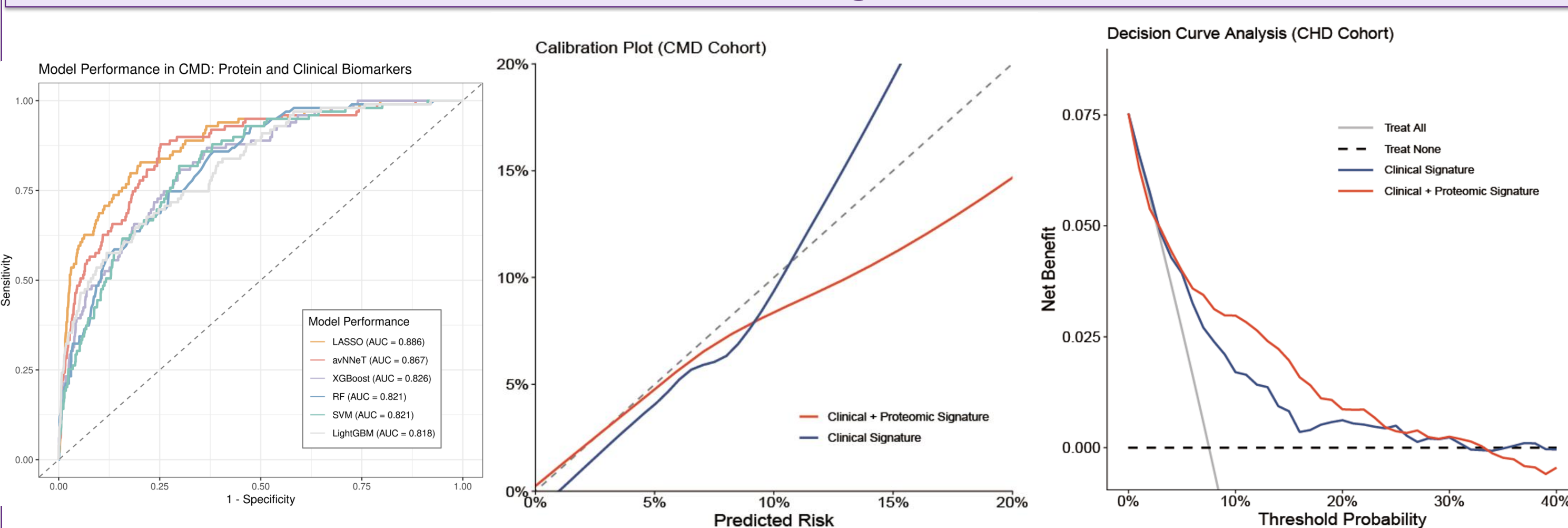
RESULTS

- Over median 14.8 years, 331 CMD participants developed dementia.
- Proteome-wide analyses identified dementia-associated proteins, including GFAP and NEFL; stability selection retained 82 clinical features and 137 proteins.
- In CMDs, the multimodal model outperformed the clinical-only model: AUC 0.886 (95% CI 0.851–0.920) vs 0.813 (0.771–0.855).
- Adding proteomics improved reclassification and discrimination: NRI 1.098 (0.925–1.272), IDI 0.186 (0.144–0.228).
- Similar gains were observed in T2D, stroke, and CHD subgroups.
- Protein-based risk stratification identified a clearly higher cumulative incidence in the high-risk group (log-rank $P < 0.001$).

Proteome-Wide Association & Survival Analysis

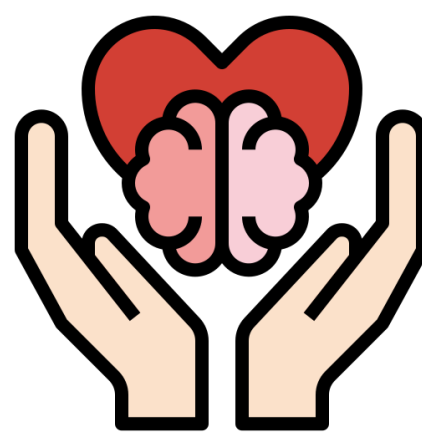


Prediction Modeling & Evaluation



CONCLUSIONS

- Plasma proteomics improved dementia prediction beyond conventional clinical variables in adults with CMDs.
- Proteomic information enhanced discrimination, reclassification, and potential clinical utility across CMD subgroups.
- Blood-based proteomic profiling may support precision cognitive risk stratification and targeted follow-up in high-risk cardiometabolic populations.
- External validation and implementation studies are warranted.



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