Plasma-based biomarkers for Alzheimer's (AD), Vascular (VD) and Inflammatory (ID) Diseases

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Introduction

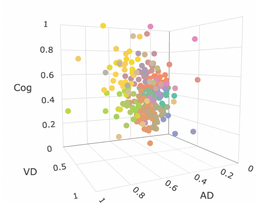
Dementia frequently involves overlapping pathological processes, particularly Alzheimer's disease (AD) and vascular disease (VD).

Standard measures (e.g., CSF pTau/Aβ42 for AD Koncz and Sachdev (2018) and MRI-based peak width of skeletonized mean diffusivity for VD) can be invasive or costly.

The Triple Dichotomy Approach Rosenberg et al. (2019) recognizes the interplay of AD, VD, and cognitive status, reflecting the complexity of these coexisting pathologies.

We are investigating whether plasma-based biomarkers could approximate AD and VD measures, potentially reducing clinical burden while maintaining accuracy.

We also test how these plasma markers relate to the albumin index, an indicator of blood–brain barrier integrity Iadecola (2013).



Research Questions

1. AD Axis: To what extent can plasma biomarkers approximate the AD pathology measure derived from CSF (pTau_181 / Aβ42)?
2. VD Axis: Can plasma biomarkers serve as a reliable surrogate for MRI-based vascular disease measures (PSMD)?
3. Inflammation Axis: How well do plasma biomarkers explain variability in the albumin index (a potential marker of blood–brain barrier integrity)?

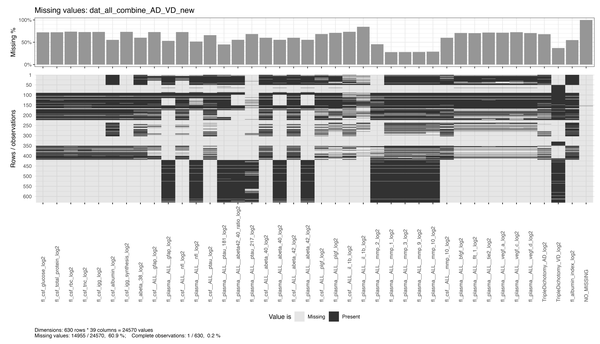
Methods

- **Data & Participants**: Baseline data (plasma, CSF, MRI) from ~630 individuals across four studies (VCI, MarkVCID1/2, ADRC) were extracted from a REDCap database. Only earliest measurements were used.
- **Outcomes**:
  - **AD Axis**: Measured as $\log_2\left(\frac{\text{pTau}_{181}}{\text{A}\beta_{42}}\right)$, capturing CSF-based AD pathology.
  - **VD Axis**: Derived from MRI-based PSMD (peak width of skeletonized mean diffusivity), reported as $\log_2(\text{PSMD})$.
  - **Inflammation Axis**: Modeled as $\log_2\left(\frac{\text{CSF Albumin}}{\text{Serum Albumin}}\right)$, a potential marker of blood–brain barrier integrity.
- **Plasma Biomarkers**: We evaluated several **response variables** as ground truths:
- **CSF pTau 181** : Twisted tau protein tangles disrupt neurons, causing neurodegeneration.
- **CSF Aβ42** : Sticky amyloid beta protein plaques form outside neurons, disrupting brain function.
- **MRI PSMD** : PSMD measures white matter injury, indicating small vessel disease, cognitive impairments.
- **Albumin Index**: Reflects blood-brain barrier dysfunction, resulting in inflammation.

From an extensive panel of plasma biomarkers, we focused primarily on the following categories:

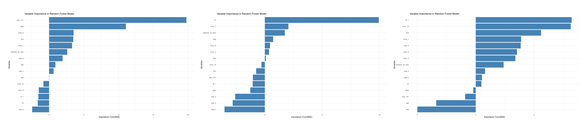
- **AD Factors (p-Tau 181, p-Tau 217, Aβ40/42)** These are hallmark Alzheimer's disease proteins and peptides associated with tau hyperphosphorylation (p-Tau) and amyloid plaque formation (Aβ).
- **Angiogenic Factors(VEGF-A, VEGF-C, VEGF-D, TIE2, Flt-1, bFGF)** These proteins and receptors regulate the formation and growth of blood vessels, impacting processes like wound healing, tumor growth, and vascular health in the brain.
- **Cytokines (TNF-α, IL-8, IL-6, IL-4, IL-2, IL-13, IL-12p70, IL-10, IFN-α)** These are signaling molecules that mediate immune responses and inflammation, coordinating how the body reacts to injury or infection.
- **MMPs (MMP-1, MMP-9, MMP-3, MMP-2, MMP-10)** These enzymes break down extracellular matrix components, playing a key role in tissue remodeling, inflammation, and potentially the disruption of the blood-brain barrier.
- **Others(Serum IgG, PlGF, NfL, Neuro GFAP)** This category includes general immunoglobulins (IgG), additional angiogenic proteins (PlGF), and markers of neurodegeneration or astrocyte activity (NfL, GFAP).

Some biomarkers were excluded from specific analyses due to **insufficient data** or **excessive missingness**. Details on these exclusions can be found below:



- **Statistical Approach**:

1. **Random Forest**: Measured variable importance (%IncMSE) and confirmed top predictors. Reduced models were refit to validate predictive power.



2.**Initial Model Setup**
- For each outcome (AD axis, VD axis, and Inflammation index), a main-effects linear model was fitted including all candidate plasma markers. - Potential second-order interactions were also considered.

3. **Stepwise Model Selection**
   - A stepwise procedure (using AIC or BIC) identified the final, more parsimonious model.
   - Model assumptions were checked:
     - **Normality of residuals** via Q–Q plots or a Shapiro–Wilk test.
     - **Even distribution of residuals** using a residuals-vs.-fitted plot.
4. **Model Evaluation**
   -R^2 was reported to indicate how well the model explained the data. -Interaction terms remained only if they improved model fit and were meaningful in context.

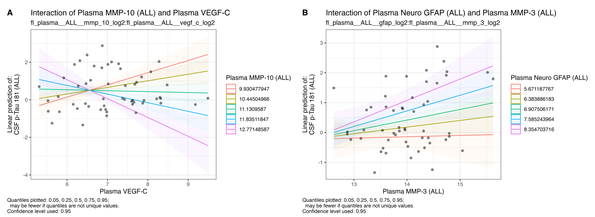
AD

Results of Multiple Regression with Two-Way Interactions for AD axis (Alzheimer disease)
Coefficient Estimates, Standard Errors, t-Values, and p-Values

Term	Estimate	Std. Error	t-Value	p-Value	Significance
(Intercept)	-55.5205	33.5059	-1.657	0.106713	NA
gfap	-1.0980	2.4209	-0.454	0.653025	NA
ptau_181	5.8705	1.8581	3.159	0.003311	**
mmp_3	-1.3740	1.1888	-1.156	0.255812	NA
mmp_10	2.9542	2.4451	1.208	0.235314	NA
bfgf	-2.0540	0.6068	-3.385	0.001810	**
flt_1	3.0063	2.6668	1.127	0.267512	NA
tie2	-4.1498	2.3281	-1.782	0.083601	.
vegf_a	5.3707	1.4730	3.646	0.000981	***
vegf_c	8.4112	2.4329	3.457	0.001485	**
mmp_10:vegf_c	-0.5822	0.1404	-4.147	0.000212	***
mmp_10:tie2	0.4326	0.2077	2.083	0.044888	*
gfap:vegf_a	-0.4682	0.1441	-3.249	0.002610	**
vegf_a:vegf_c	-0.4319	0.1064	-4.059	0.000274	***
bfgf:vegf_a	0.2976	0.0899	3.310	0.002217	**
mmp_10:flt_1	-0.6064	0.1939	-3.128	0.003603	**
ptau_181:vegf_c	-0.7692	0.2691	-2.858	0.007222	**
flt_1:vegf_c	0.5520	0.2695	2.049	0.048285	*
gfap:mmp_3	0.2502	0.1652	1.514	0.139168	NA
gfap:vegf_c	0.1728	0.1498	1.154	0.256654	NA

Model Summary for AD axis (Alzheimer disease)
Residual Error, R-Squared, F-Statistic, and p-Value

Statistic	Value
Residual standard error	0.4861 on 34 degrees of freedom
Multiple R-squared	0.8502
Adjusted R-squared	0.7664
F-statistic / p-value	10.15 on 19 and 34 DF, p = 4.921e-09



Examples of conditional relationship (interactions)

VD

Results of Multiple Regression with Two-Way Interactions for VD axis (vascular disease)
Coefficient Estimates, Standard Errors, t-Values, and p-Values

Term	Estimate	Std. Error	t-Value	p-Value	Significance
(Intercept)	-11.6115	9.4948	-1.223	0.23713	NA
nfl	0.6546	0.1588	4.122	0.00064	***
abeta42_40	-3.9830	2.4599	-1.619	0.12280	NA
plgf	5.1706	2.5191	2.053	0.05495	.
mmp_9	-0.3377	0.1929	-1.750	0.09706	.
abeta42_40:plgf	1.2545	0.6463	1.941	0.06806	.

Model Summary for VD axis (vascular disease)
Residual Error, R-Squared, F-Statistic, and p-Value

Statistic	Value
Residual standard error	0.5623 on 18 degrees of freedom
Multiple R-squared	0.6144
Adjusted R-squared	0.5073
F-statistic / p-value	5.737 on 5 and 18 DF, p = 0.002453

ID

Results of Multiple Regression with Two-Way Interactions for ID axis (Inflammation)
Coefficient Estimates, Standard Errors, t-Values, and p-Values

Term	Estimate	Std. Error	t-Value	p-Value	Significance
(Intercept)	46.6510	18.0752	2.581	0.0126030	*
flt_1	-5.4706	1.9445	-2.813	0.0068240	**
mmp_10	-4.7606	1.3410	-3.550	0.0008070	***
vegf_d	-7.3613	1.8513	-3.976	0.0002100	***
mmp_3	3.6625	0.8472	4.323	0.0000666	***
abeta42_40	-3.4850	3.0421	-1.146	0.2570220	NA
flt_1:vegf_d	0.6080	0.2074	2.932	0.0049370	**
mmp_10:abeta42_40	-0.5914	0.1581	-3.739	0.0004480	***
mmp_3:abeta42_40	0.9049	0.2103	4.303	0.0000713	***
mmp_10:vegf_d	0.2466	0.1247	1.978	0.0530130	.
vegf_d:abeta42_40	-0.2773	0.2000	-1.387	0.1712410	NA

Model Summary for VD axis (vascular disease)
Residual Error, R-Squared, F-Statistic, and p-Value

Statistic	Value
Residual standard error	0.4108 on 54 degrees of freedom (565 obs. deleted)
Multiple R-squared	0.4431
Adjusted R-squared	0.34
F-statistic / p-value	4.297 on 10 and 54 DF, p = 0.0001997

Discussion

- **Summary**: Our results show that plasma biomarkers can explain a substantial portion of the variance in neuropathological outcomes:
  - **AD pathology** was best captured ($R^2 \sim 0.85$).
  - **Vascular** models also performed reasonably well ($R^2 \sim 0.61$), though limited by sample size.
  - **Inflammation** showed moderate explanatory power ($R^2 \sim 0.44$).
- **Clinical Relevance**: A reliable plasma-based test could reduce the need for CSF lumbar punctures and expensive MRI scans, accelerating dementia diagnostics and research.
- **Limitations**: The limited VD sample size constrains broader applicability.

Future Work

- **Larger Cohorts**: Increasing the number of participants, especially for VD, would bolster these findings and solidify plasma biomarkers' predictive value.
- **Longitudinal Studies**: Monitoring biomarker changes over time could clarify their role in disease progression and response to treatments.
- **Refinement**: Adding novel biomarkers or advanced modeling approaches may improve performance for the albumin index and other vascular measures.

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