

Michelle Caunca, MD, PhD¹, Sarah Ackley, PhD², Meredith N. Braskie, PhD³, Matthew Borzage, PhD⁴, Kristine Yaffe, MD^{1,5,6}

1. Department of Neurology, University of California, San Francisco, San Francisco, CA; 2. Department of Epidemiology, Brown University, Providence, RI; 3. Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Marina Del Ray, CA; 4. Fetal and Neonatal Institute, Division of Neonatology, Children's Hospital of Los Angeles, Keck School of Medicine, Los Angeles, CA; 5. Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA; 6. Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, San Francisco, CA

Background

- The Amyloid-Tau-Neurodegeneration (ATN) Framework provides diagnostic criteria for Alzheimer's disease (AD) and cites cerebrovascular disease as an important non-AD co-pathology¹.
- In the context of the ATN Framework, co-pathologies like subclinical cerebrovascular disease (sCVD) inform the etiology of dementia and also aid in evaluation of candidacy for disease-modifying therapies.
- However, the relationship of cSVD to markers of AD pathology and neurodegeneration are not yet fully understood, though cSVD is a commonly co-occurs with AD pathology².
- cSVD may improve prediction of dementia in addition to AD biomarkers, and data-driven approaches to characterize patients' biomarker status may improve prediction of dementia compared to the ATN Framework as written.
- We evaluated how sCVD may improve model prediction for dementia with biomarker profiles defined a priori versus data-driven approaches.

Methods

Study Sample

- We used data from the Health and Aging Brain-Health Disparities Study (HABS-HD), a racially/ethnically diverse, community-based cohort.
- Participants included in this analysis had complete data for AD biomarkers, MRI-based neuroimaging markers of cSVD, and adjudicated dementia data (using neuropsychological testing and Clinical Dementia Rating [CDR] scales).

Variables

- ATN indicators included amyloid-PET standardized uptake value (SUVR), plasma pTau-181, plasma neurofilament light (NFL) and MRI-derived AD-signature cortical thickness (CT).
- MRI-derived white matter hyperintensity volume (WMHV) was our indicator of sCVD.
- Covariates included age, race/ethnicity, sex, education, and APOE ε4 carrier status.
- All-cause dementia was our main outcome of interest and was defined via consensus diagnosis as: CDR sum of boxes score 2.5+ and cognitive test score at or below two standard deviations below the mean in two or more cognitive domains as measured by neuropsychological testing.

Analysis

- First, we conducted a k-means cluster analysis to group participants into biomarker categories via data-driven approach. The solution with the lowest total sum of squares was deemed the best fit.
- Second, we compared 3 logistic regression models with biomarkers listed above vs. cluster-analysis-derived groups:
 - ATN biomarkers only
 - ATN biomarkers + sCVD via MRI,
 - Clusters derived from k-mean cluster analysis of biomarkers listed above.
- All models were adjusted for age, race/ethnicity, sex, education, and APOE ε4 carrier status.
- We compared model fit using likelihood ratio tests.

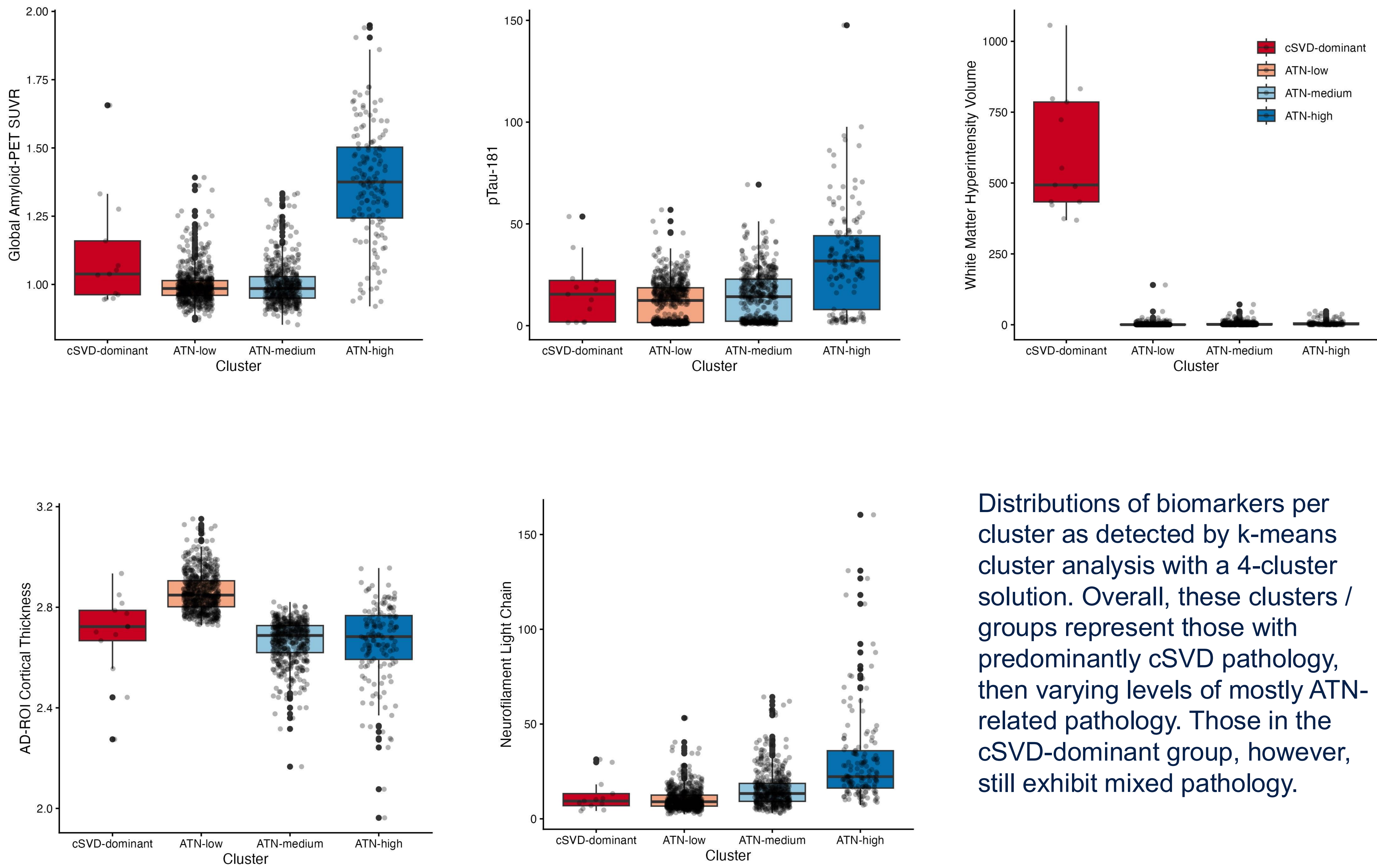
Incorporating Cerebrovascular Disease Into The ATN Framework: Comparison Of A Priori And Data-Driven Approaches In The HABS-HD Cohort

Descriptive Statistics

	cSVD-dominant N = 13 ¹	ATN-high N = 148 ¹	ATN-medium N = 497 ¹	ATN-low N = 648 ¹	p-value ²
Age (years)	63 (9), 60 (56, 67)	72 (8), 72 (67, 77)	66 (9), 66 (59, 72)	61 (7), 60 (55, 65)	<0.001
Race/Ethnicity					
White	0 (0%)	57 (39%)	144 (29%)	166 (26%)	
Black	13 (100%)	61 (41%)	229 (46%)	286 (44%)	
Hispanic	0 (0%)	30 (20%)	124 (25%)	196 (30%)	
Women	8 (62%)	87 (59%)	312 (63%)	445 (69%)	0.053
Did Not Complete College	10 (77%)	88 (60%)	294 (60%)	348 (55%)	
MMSE	27 (3), 27 (25, 29)	26 (5), 27 (23, 29)	27 (3), 28 (27, 29)	28 (2), 29 (27, 29)	<0.001
Cognitive Status					
Cognitively Unimpaired	5 (38%)	70 (47%)	338 (68%)	482 (74%)	
MCI	5 (38%)	41 (28%)	129 (26%)	150 (23%)	
Dementia	3 (23%)	37 (25%)	28 (5.7%)	15 (2.3%)	
APOE ε4 Positive	7 (54%)	80 (54%)	153 (32%)	198 (31%)	<0.001
Global Amyloid SUVR	1 (0), 1 (1, 1)	1 (0), 1 (1, 2)	1 (0), 1 (1, 1)	1 (0), 1 (1, 1)	<0.001
pTau-181 (pg/mL)	17 (16), 15 (2, 22)	32 (25), 32 (8, 44)	14 (12), 14 (2, 23)	12 (10), 12 (2, 19)	<0.001
AD meta-ROI CT (mm)	3 (0), 3 (3, 3)	3 (0), 3 (3, 3)	3 (0), 3 (3, 3)	3 (0), 3 (3, 3)	<0.001
NFL (pg/mL)	12 (9), 9 (7, 13)	32 (26), 22 (16, 36)	16 (9), 13 (9, 19)	10 (5), 9 (7, 13)	<0.001
WMHV (cm³)	597 (218), 493 (434, 786)	6 (9), 3 (1, 6)	3 (6), 1 (0, 4)	2 (6), 0 (0, 1)	<0.001

¹Mean (SD), Median (Q1, Q3); n (%)
²Kruskal-Wallis rank sum test; Fisher's exact test; Pearson's Chi-squared test

Biomarker Distribution by Cluster



Model Comparisons

	Model 1: ATN	Model 2: ATN+cSVD	Model 3: Clusters
Global Amyloid SUVR	1.80 (1.46, 2.23)	1.79 (1.46, 2.22)	
pTau181	1.03 (0.83, 1.27)	1.03 (0.83, 1.27)	
AD meta-ROI CT	0.46 (0.35, 0.60)	0.47 (0.35, 0.61)	
NFL	1.09 (0.89, 1.31)	1.10 (0.89, 1.31)	
WMHV		1.08 (0.91, 1.27)	
Cluster			
ATN-low			—
cSVD-dominant			7.73 (1.52, 30.9)
ATN-high			8.10 (3.95, 17.2)
ATN-medium			1.73 (0.89, 3.48)

Odds ratios with 95% confidence intervals shown here. Adjusted for age, race/ethnicity, sex, education, and APOE ε4 allele status.

Summary of Results

- Cluster analysis suggest that neurodegenerative and vascular pathologies often co-occur and both strongly predict dementia.
- A 4-cluster solution had best model fit (i.e. lowest total sum of squares) and improved models for predicting dementia (LRT cluster vs. ATN only p<0.001; cluster vs. ATN + sCVD p<0.001) .
- The sCVD-dominant (OR [95% CI]: 7.73 [1.52, 30.9]) and ATN-high clusters (8.10 [3.95, 17.2]) were associated with greater odds of dementia compared to the ATN-low cluster, though estimates were unstable.

Conclusions

- Cluster analysis suggest that neurodegenerative and vascular pathologies do not cluster together and both strongly predict dementia.
- Cluster analysis-derived biomarker profiles predicted dementia better than a priori-defined ATN only or ATN + sCVD profiles.
- Future work will externally validate these models in an independent sample.

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