

Estimating Alzheimer's Disease Pathology Using Composite Plasma Biomarker Probability Scores In COMPASS-ND



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Plasma Probability Scores (PPS)

Plasma probability scores (PPS) were developed to combine measures plasma A β 42/40, p-tau-181, NfL, GFAP to indicate the probability that a person has AD pathology. Two PPS were developed:

- Reference-curve PPS (RC-PPS):** Cut-offs derived from age-specific normative percentiles.
 - Used in *non-dementia stages* to indicate deviations from normative plasma levels that may be suggestive of the presence of underlying AD pathology.
- AD neuropathologic change PPS (ADNC-PPS):** Cut-offs derived from neuropathology NIA-AA ABC score.
 - Used in those *clinically diagnosed with dementia* to indicate the likelihood a participant has significant ADNC sufficient to contribute to cognitive impairment.

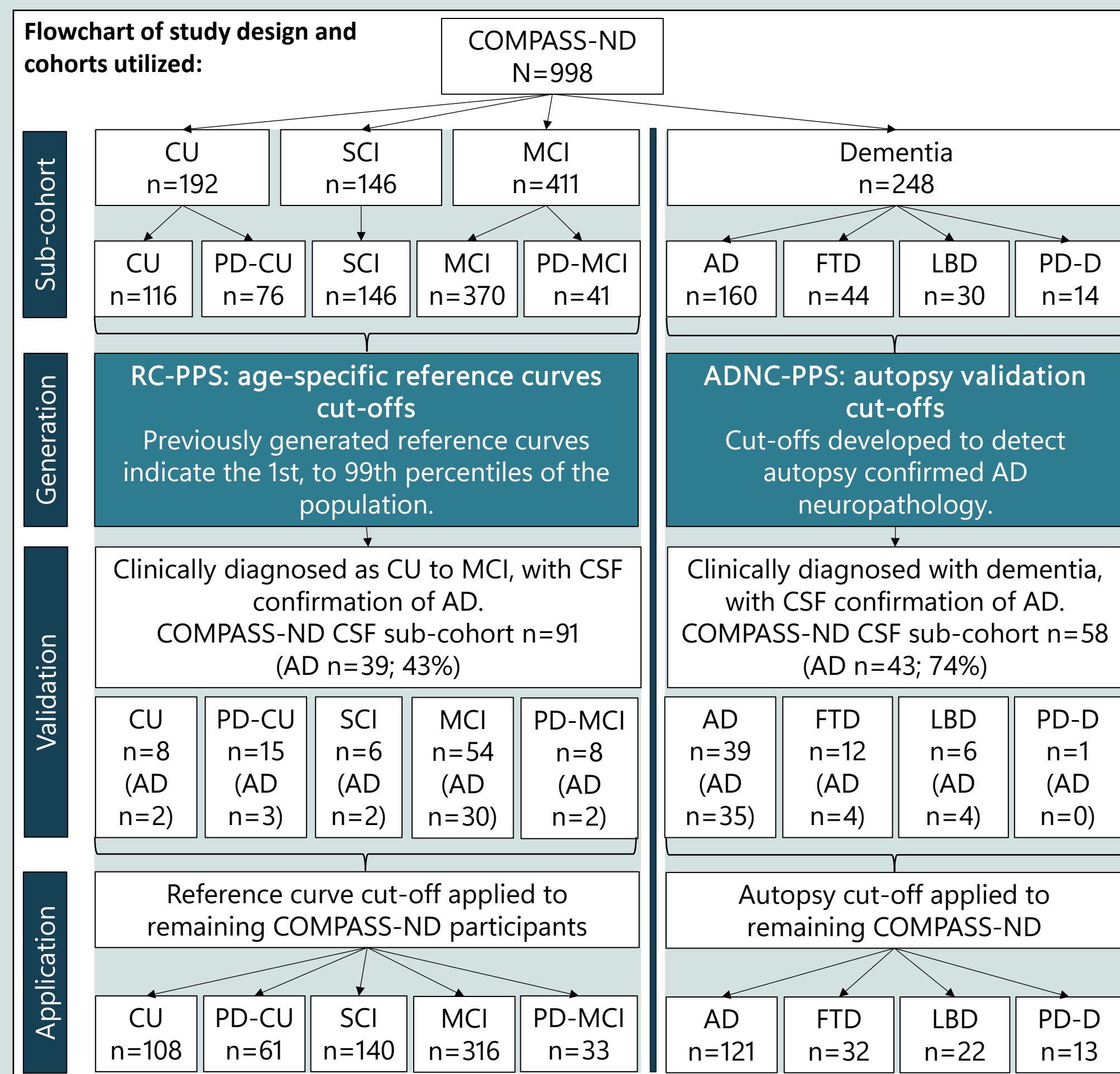
Cohorts

COMPASS-ND¹: National multicenter observational cohort recruiting participants ranging from cognitively unimpaired, MCI, to multiple types of dementia. Utilized in this study to validate PPS against CSF and apply PPS across spectrum of cognitive impairment.

CHMS²: Epidemiological sample of Canadians age 3-79. Population based normative cohort utilized to drive reference curves used in RC-PPS.

CARD³: UBC dementia clinic. Participants clinically diagnosed with dementia and had neuropathology workup used to derive ADNC-PPS cut-offs.

Study Design



Plasma analyzed using Quanterix neurology 4-plex E and p-tau-181 V2.0 assays on the HD-X platform.

Cut-offs determine using ROC analysis. RC-PPS derived cut-offs at 85% sensitivity and specificity. ADNC-PPS derived cut-offs using Youden's index.

The RC-PPS and ADNC-PPS combine plasma A β 42/40, p-tau-181, and GFAP to stratify AD pathology probability with excellent specificity and good sensitivity.

Generation and Validation of Plasma Probability Scores

Reference Curve PPS

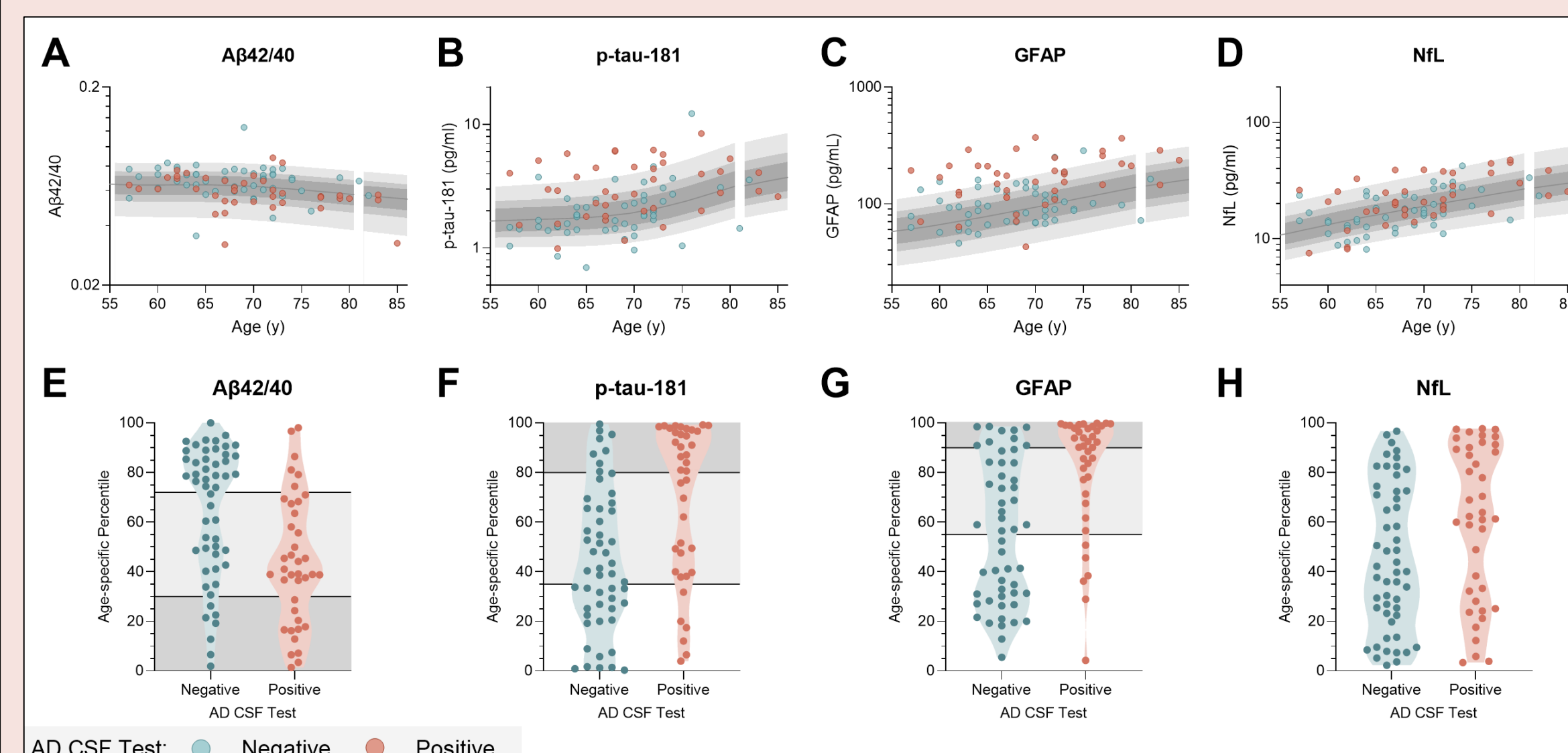


Figure 1. Deriving RC-PPS from normative reference curves. (A–D) Age-specific reference curves (CHMS, n=2,500, ages 3–79; extrapolated for ≥ 80) with COMPASS-ND CSF subgroup overlaid. (E–H) Conversion of biomarker levels to age-specific percentiles; cut-offs set at 85% sensitivity/specificity. Light grey = score of 1, dark grey = score of 2 (range 0–6). (I–L) Percentile cut-offs: A β 42/40 (72nd/30th), p-tau181 (35th/80th), GFAP (55th/90th). NfL not included in final score.

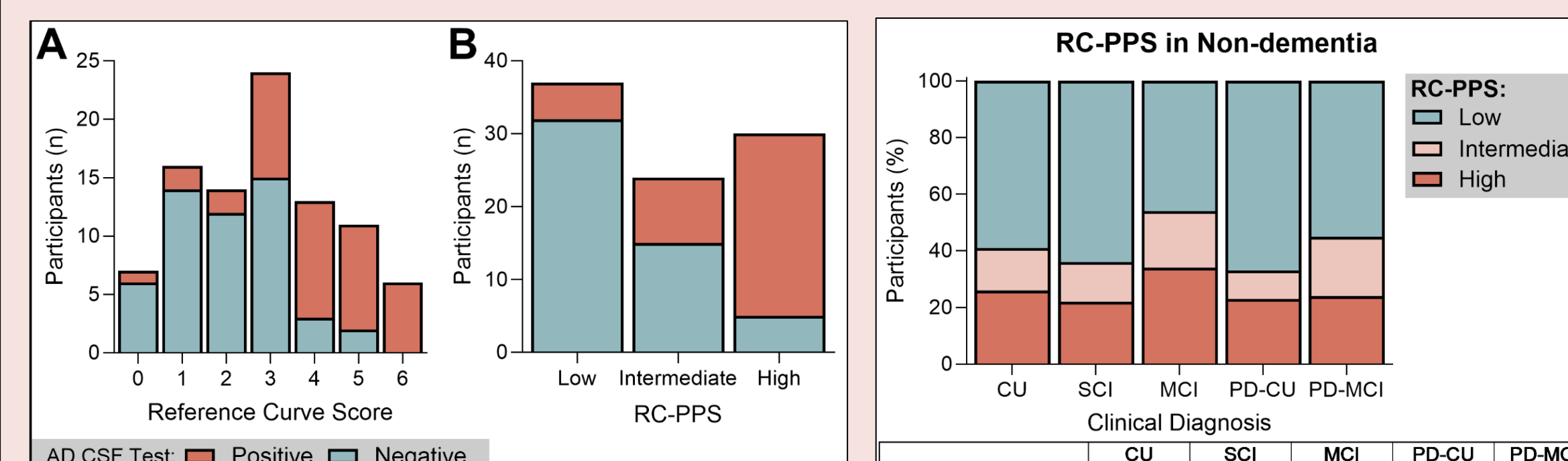


Figure 2. RC-PPS classification in COMPASS-ND (non-dementia). (A) Scoring: A β 42/40 scored 1 (<72nd percentile)/2 (<35th); p-tau181 scored 1 (>35th)/2 (>80th); GFAP scored 1 (>55th)/2 (>90th). (B) RC-PPS categories: low (0–2), intermediate (3), high (4–6).

RC-PPS	Low Cut-off		CSF +		CSF -		High Cut-off		CSF +		CSF -	
	Inter/High	Low	34	20	5	32	High	Low/Inter	25	5	14	47
Sensitivity, %			87 (73-94)		Sensitivity, %		64 (48-77)					
Specificity, %			62 (48-74)		Specificity, %		90 (79-96)					

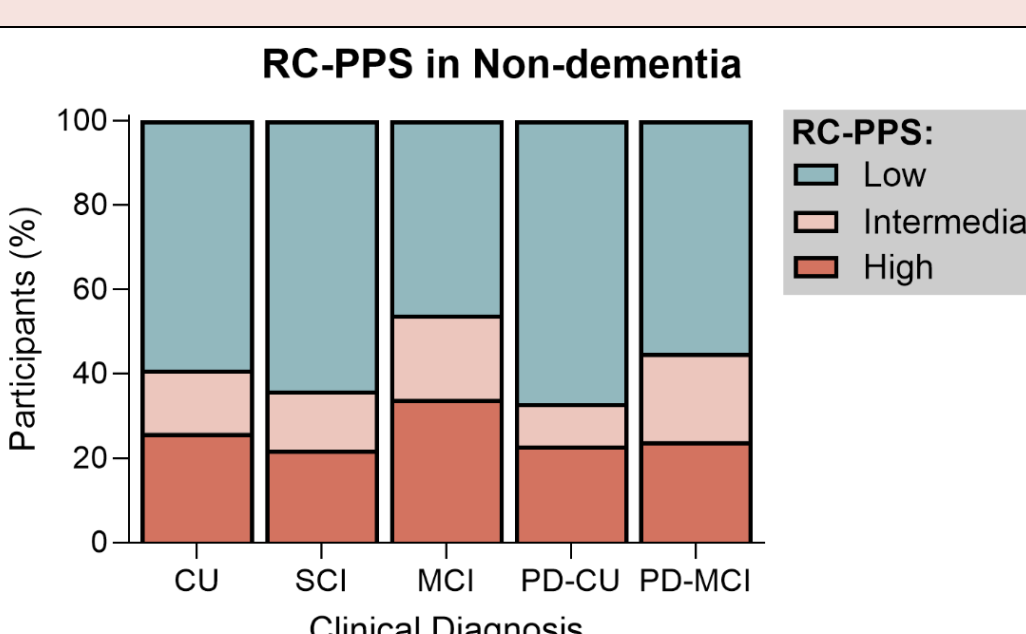


Figure 3. Estimated AD pathology prevalence by RC-PPS.

Table 1. Sensitivity/specificity for RC-PPS. Low cut-off: low vs. intermediate/high AD likelihood. High cut-off: low/intermediate vs. high. RC-PPS categories: low (0–1), intermediate (2), high (3–5).



AD Neuropathologic Change PPS

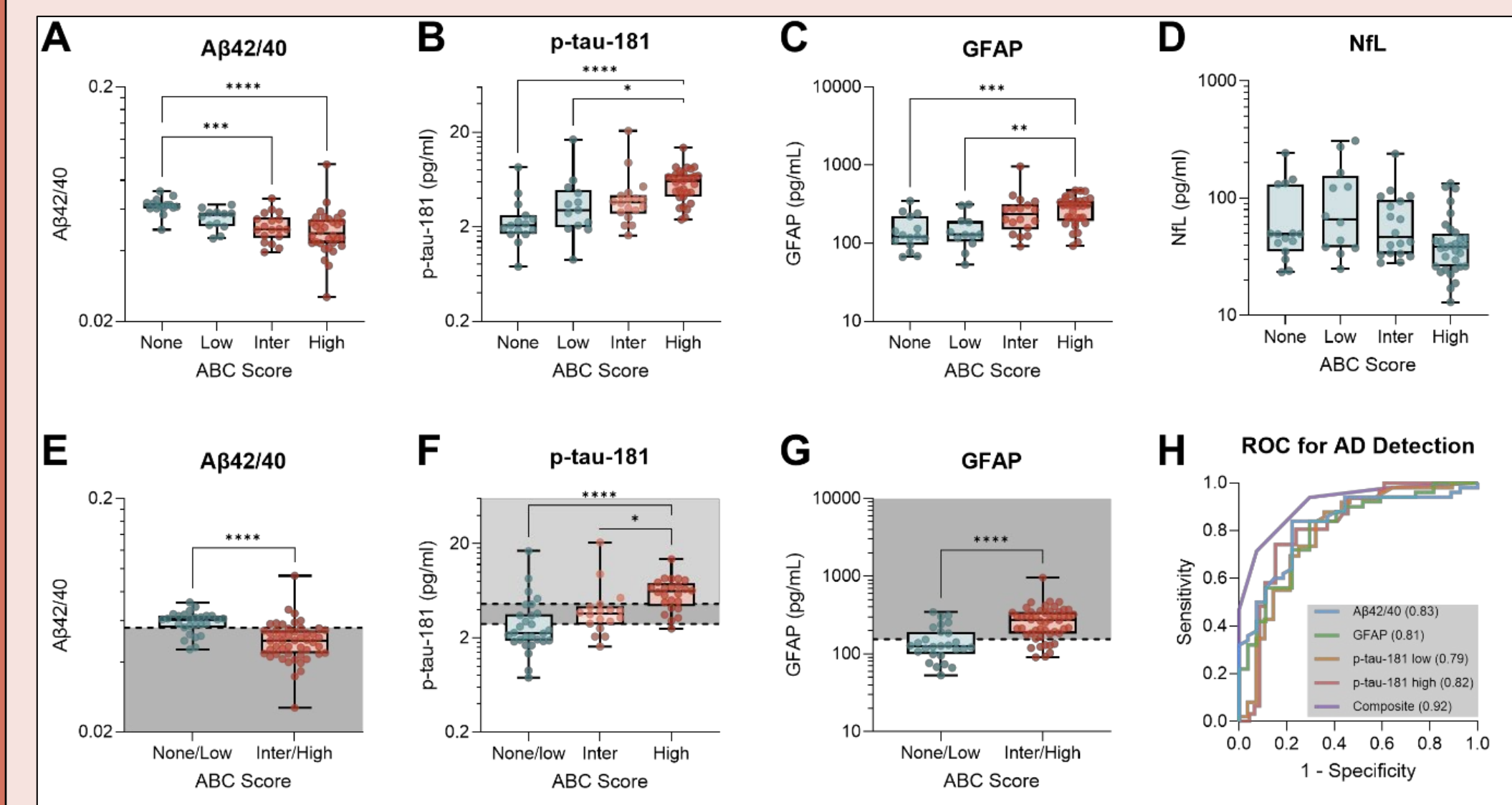


Figure 4. Cut-off development for autopsy-confirmed AD pathology. (A–D) Plasma biomarkers across ABC neuropathology scores (n=78). (E–G) Cut-offs by Youden's index (dashed lines); light/dark grey = score 1/2 (range 0–4). Mann-Whitney/Kruskal-Wallis with Dunn's correction, *p<0.05, **p<0.01, ***p<0.001. (H) AUROC for biomarker discrimination of ABC groups.

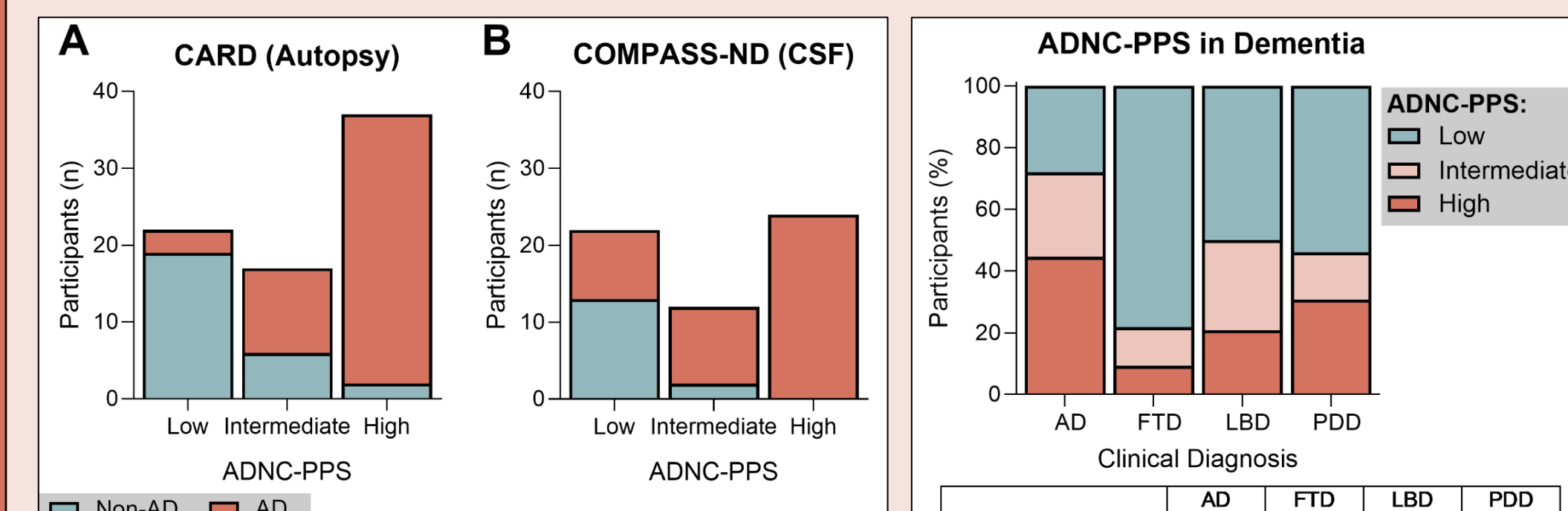


Figure 5. ADNC-PPS validation in dementia cohorts. (A) CARD, autopsy-confirmed (n=78). (B) COMPASS-ND, CSF-confirmed (n=58). ADNC-PPS categories: low (0–1), intermediate (2), high (3–4).

ADNC PPS	Low Cut-off		CSF +		CSF -		High Cut-off		CSF +		CSF -	
	Inter/High	Low	34	2	9	13	High	Low/Inter	24	0	19	15
Sensitivity, %			79 (65-89)		Sensitivity, %		56 (41-70)					
Specificity, %			87 (62-96)		Specificity, %		100 (80-100)					

Table 2. Sensitivity/specificity for ADNC-PPS. Low cut-off: low vs. intermediate/high AD likelihood. High cut-off: low/intermediate vs. high. ADNC-PPS categories: low (0–1), intermediate (2), high (3–4).

