



Frank's Sign Radiomics for Differentiating CADASIL from Sporadic Small Vessel Disease

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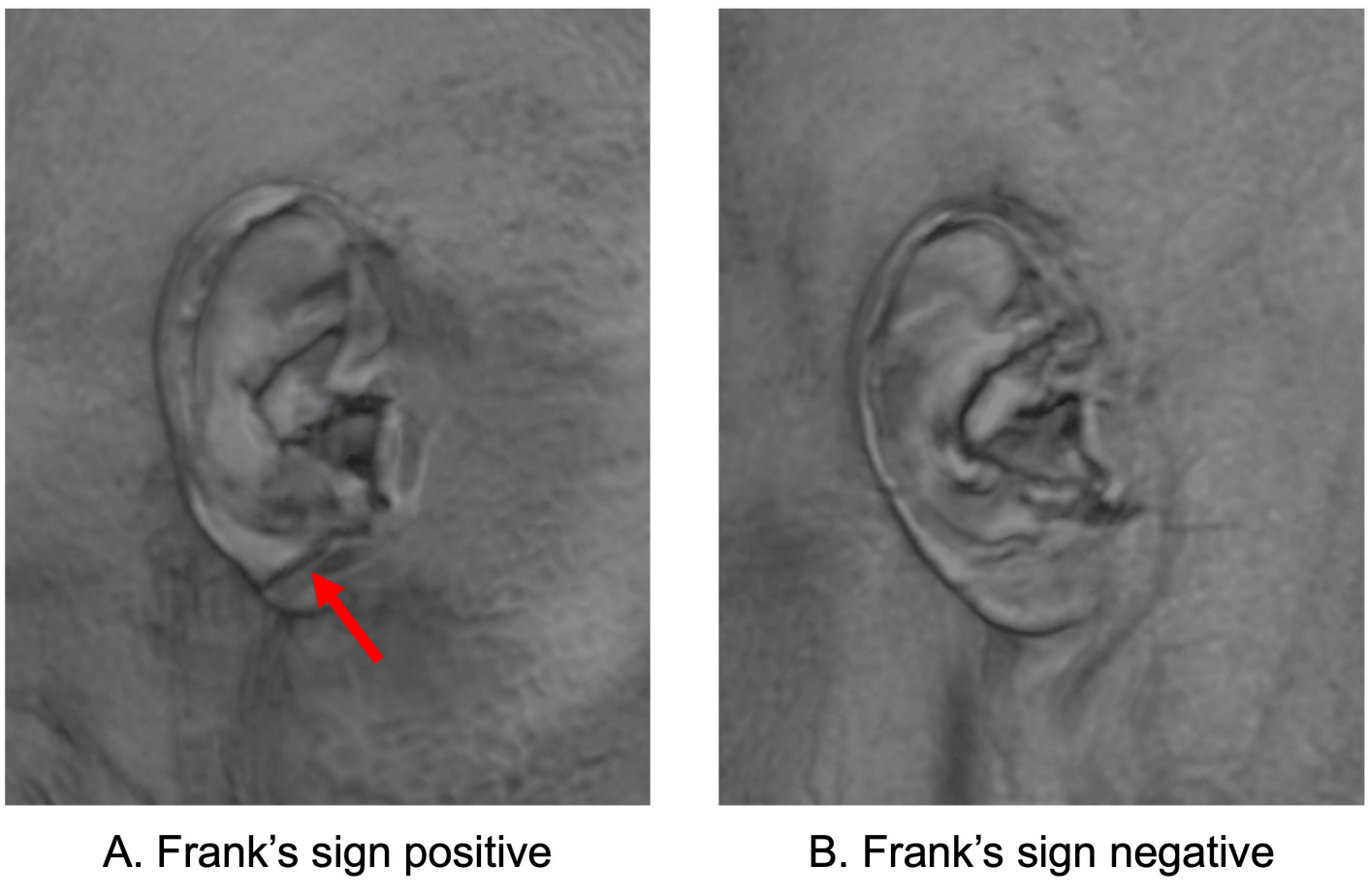
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INTRODUCTION

- CADASIL is the most common monogenic cerebral small vessel disease (SVD), caused by *NOTCH3* mutations leading to progressive arteriolar degeneration, lacunar infarcts, and vascular dementia
- Core diagnostic challenge:** White matter hyperintensity (WMH) and lacunar infarcts overlap broadly with hypertensive sporadic SVD; NOTCH3 mutations found in 12.5% of patients clinically diagnosed as lacunar stroke
- Frank's sign (FS, diagonal earlobe crease) reflects systemic vascular and connective tissue aging; prevalence 65% in general adults, 79% in ischemic stroke
- Automated U-Net segmentation of FS from routine T1 MRI
- Radiomics features capture sub-voxel microstructural heterogeneity invisible to the naked eye
- Objective:** Does quantitative radiomic texture of Frank's sign, beyond its binary detection, provide incremental discriminative value for CADASIL, and is this value CADASIL-specific?



STUDY DESIGN & COHORT

- Mean $\pm$ SD or n (%). ¹p-value for FS compares CADASIL² vs Sporadic SVD only (NC served as healthy reference).
- Age/Sex matched: CADASIL and NC are 1:1 matched by age and sex.
- HTN/HL/WMH: ANOVA or Kruskal-Wallis; categorical: chi-square.
- FS+ primary analysis subgroup: CADASIL n=36, Sporadic SVD n=53. Scanned on 3.0T Philips Achieva (JNUH) or Ingenia (SNUBH).

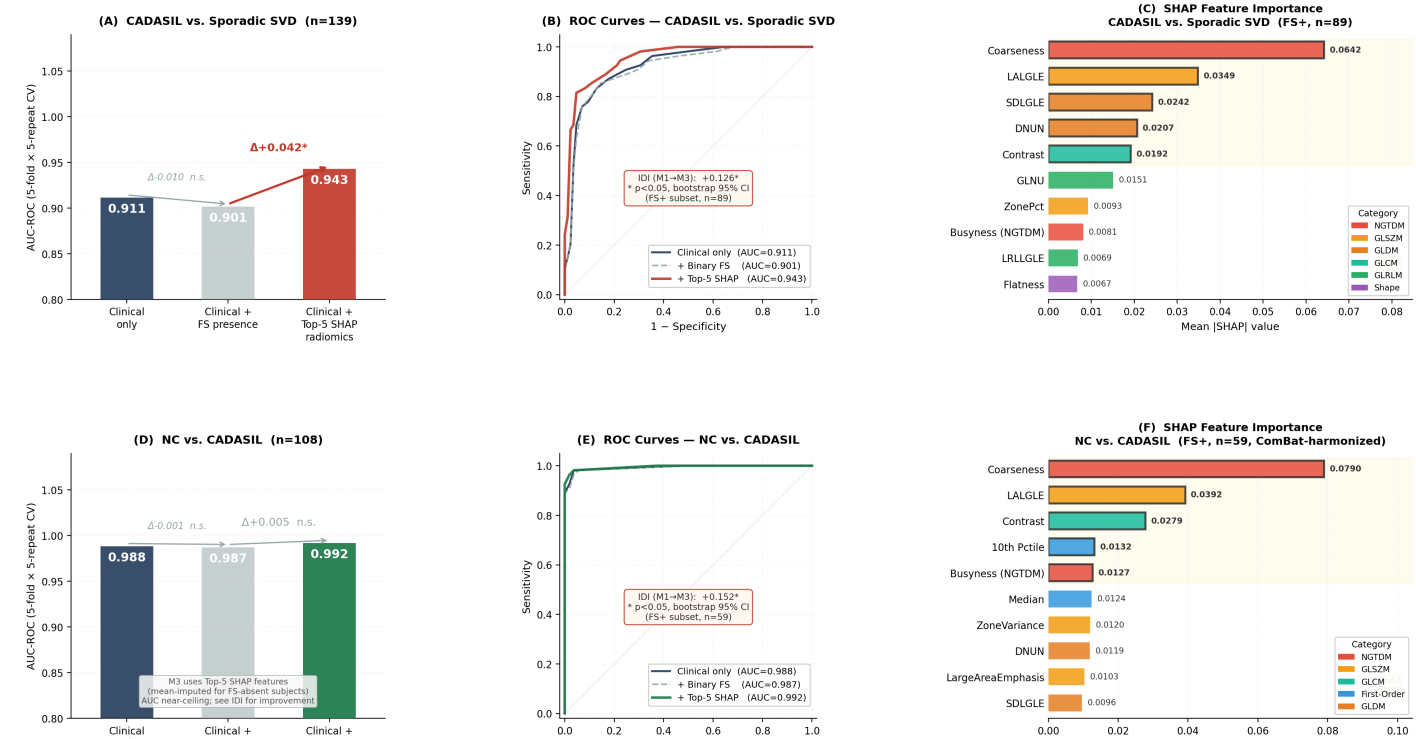
Variable	CADASIL (n = 54)	Sporadic SVD (n = 85)	NC (n = 54)	p-value
Age, years	69.1 $\pm$ 7.5	70.4 $\pm$ 6.8	70.3 $\pm$ 6.6	0.553
Female sex	26 (48%)	46 (54%)	26 (48%)	0.712
Hypertension	37 (69%)	61 (72%)	26 (48%)	0.013
Diabetes mellitus	7 (13%)	23 (27%)	10 (19%)	0.122
Hyperlipidemia	8 (15%)	52 (61%)	20 (37%)	<0.001
WMH volume, mL	54.2 $\pm$ 24.2	22.8 $\pm$ 17.8	7.4 $\pm$ 7.8	<0.001
Frank's sign (FS+)	36 (67%)	53 (62%)	23 (43%)	0.737 ¹
Site (JNUH / SNUBH)	54 / 0	0 / 85	0 / 54	n/a

METHODS

- Deep learning U-Net³: automated Frank's sign segmentation from T1-weighted MRI
- PyRadiomics⁴: 107 features — Shape (14), First-Order (18), GLCM (24), GLRLM (16), GLSZM (16), GLDM (14), NGTDM (5)
- neuroCombat harmonization (site as batch variable; age, sex as covariates) applied to all 107 features prior to category decomposition and SHAP analyses — removes scanner acquisition differences while preserving disease-related signal
- Incremental model comparison (RepeatedStratifiedKFold, 5-fold $\times$ 5-repeat): M1 = Clinical; M2 = M1 + binary FS; M3 = M1 + top-5 SHAP features (mean-imputed for FS-absent subjects)
- SHAP TreeExplainer on harmonized features: top-5 features selected a priori; incremental value by IDI & NRI (500-iteration bootstrap 95% CI)
- Validation: Propensity-score matched (PSM) cohort — 1:1 matching on age, sex, WMH, HTN, DM

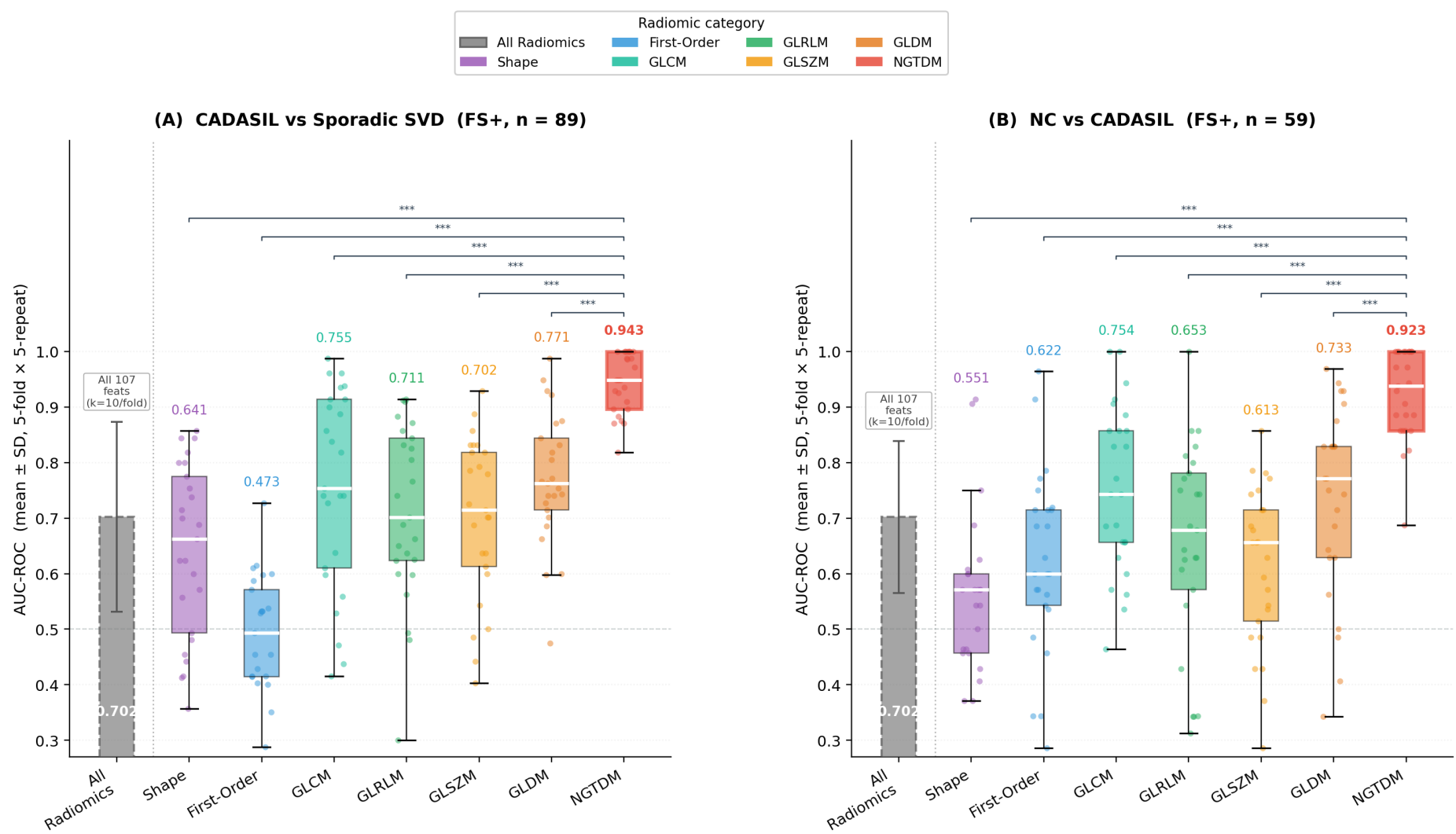
RESULT I: FS RADIOMICS, NOT BINARY FS PROVIDES INCREMENTAL VALUE

- Adding binary FS presence to clinical model (CADASIL vs. Sporadic, n=139): AUC 0.917 $\rightarrow$ 0.908 (Δ =0.009, n.s.) — FS presence alone does not discriminate
- Adding top-5 SHAP-selected FS texture radiomics: AUC 0.917 $\rightarrow$ 0.968 (Δ =0.051*); IDI +0.126*, NRI +1.027* (FS+ subset, n=89). CADASIL-specificity confirmed: negative control NC vs. Sporadic shows reversed IDI (−0.083*)
- Top-5 SHAP features: Coarsenessmax (NGTDM, |SHAP|=0.064), LALGLEmax (GLSZM), SDLGLEmax (GLDM), DNUNmax (GLDM), Contrastmax (GLCM) — spanning 4 radiomic sub-categories



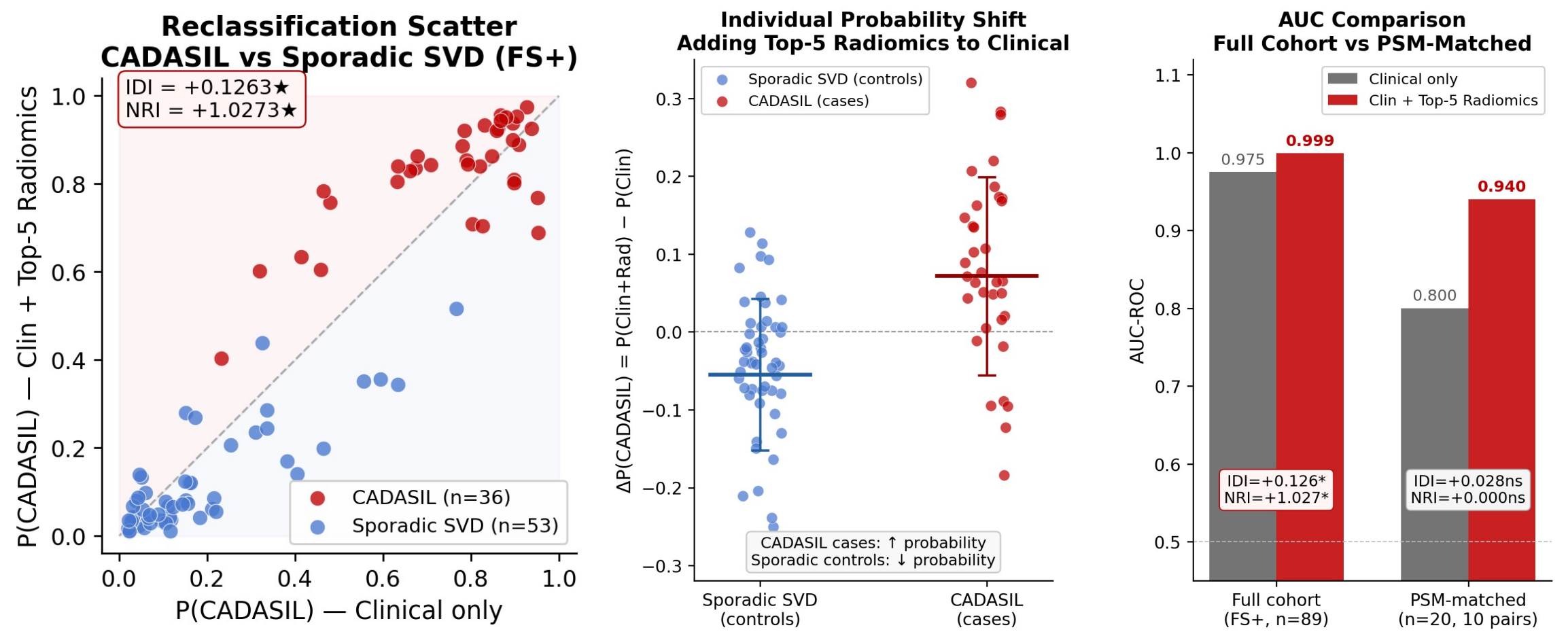
RESULT II: NGTDM TEXTURE IS THE DOMINANT RADIOMIC CATEGORY [FS+ subgroup: CADASIL n=36 / Sporadic n=53 / NC n = 23]

- All 107 radiomic features harmonized via neuroCombat (site as batch variable; age, sex as covariates) prior to category-level training and SHAP attribution — isolates category-specific discriminative signal from scanner acquisition differences
- 7 radiomic categories compared (Friedman test): significant inter-category heterogeneity (χ^2 =84.9, p<0.001); NGTDM outperformed all 6 categories (pFDR<0.001 all pairwise): AUC 0.943 $\pm$ 0.053 vs. next-best GLDM 0.771
- All 107 radiomics combined (AUC 0.702) is outperformed by NGTDM alone (AUC 0.943) — NGTDM carries concentrated, CADASIL-specific signal
- Univariate NGTDM directionality (non-harmonized): Busyness (rank-biserial r=−0.60, pFDR<0.001) and Contrast (r=−0.57, pFDR<0.001) significantly elevated in CADASIL; Coarseness dominant by SHAP but not significant univariately



VALIDATION: PROPENSITY-SCORE MATCHED COHORT [FS+ subgroup: CADASIL n=36 / Sporadic n=53]

- In the FS+ cohort (n=89), NRI = +1.027 confirms robust individual-level reclassification by FS radiomics beyond clinical features
- FS+ subgroup only (n=20): 10 CADASIL / 10 Sporadic SVD pairs — 1:1 matched on age, sex, WMH, HTN, DM to control for clinical confounders
- AUC improves from 0.800 to 0.940 in the PSM-matched cohort with Top-5 FS radiomics added to clinical features, demonstrating discriminative gain even after balancing clinical confounders



CONCLUSIONS

- FS radiomics provides significant incremental discriminative value over clinical features for CADASIL identification (IDI +0.126* vs. Sporadic SVD; IDI +0.152* vs. NC).
- NGTDM texture features dominate reflecting greater spatial intensity heterogeneity in CADASIL earlobe tissue, consistent with NOTCH3-mediated vascular microstructural changes.
- The radiomic signal is CADASIL-specific: near-zero in the same-scanner negative control and confirmed in a propensity-score matched cohort.
- FS is an underutilized incidental finding on routine brain MRI with potential for non-invasive CADASIL screening.

KEY MESSAGE

FS may harbor a CADASIL-specific radiomic phenotype dominated by NGTDM texture heterogeneity. Adding SHAP-selected features to clinical variables yields significant incremental value, confirmed in a propensity-score matched cohort.

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