

ATNIVS Biomarker Heterogeneity In Real-world Patients Receiving Lecanemab

P4-07

Biomarkers: Neuroimaging

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Conclusion:

- We identified substantial heterogeneity in ATNIVS biomarker profiles among patients receiving lecanemab in a real-world setting.
- These results are important for understanding heterogeneity in future analyses using real-world data.

Background:

- In clinical practice, amyloid- β (A β) positivity serves as the primary biomarker requirement before initiating anti-A β antibody therapies.
- However, recent revised criteria also highlight the importance of other biomarkers (ATNIVS) to understand heterogeneity in AD [1].

Objective:

- To evaluate the ATNIVS biomarker heterogeneity in real-world patients receiving anti-A β antibody therapy.

Methods:

- We reviewed patients who attended our specialty clinic [2] between December 2023 and October 2024.
- MRI scans were assessed using the Fazekas score.
- Amyloid PET scans used ¹⁸F-flutemetamol and were quantified [3].
- Some participated in a tau PET study (¹⁸F-MK6240) and were assessed for tau PET-based Braak staging [4]
- Remaining plasma samples in our TMIG biobank were analyzed for plasma neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP) on the Simoa platform.
- Remaining CSF samples were tested for previously reported α -synuclein seed amplification assay (α -syn SAA) [5].

Results:

- During the period, 200 attended and 147 proceeded to screening, including PET or CSF biomarker testing.
- Lecanemab was started in 93 of 108 A+ patients; mean age 74.2 years, 73.1% female.
- While all tested started on lecanemab were positive on amyloid PET, 21% had only regional positivity (**Figure 1**).
- While all tested had CSF A β 42/40 values below the single cut-off 0.067 in Japan, three (8.6%) had values close to the cutoff (0.059-0.067). T1 and T2 biomarkers also widely varied from normal to fully abnormal (**Figure 2**).
- Other N, I, V, S biomarkers also varied from normal to abnormal (**Figure 3**).
- Some associations were indicated, including higher Fazekas scores in the amyloid PET regional-positive group and higher plasma NfL in the CSF A β 42/40 0.059-0.067 group (**Table**).

Table

Table			Amyloid PET (n = 53)			CSF Aβ42/40 (n = 35)			
A	Aβ proteinopathy		A+region (n = 11)	A+wide (n = 42)	p value	0.059–0.067 (n = 3)	< 0.059 (n = 32)	p value	
	Baseline	Age	79.2 ± 5.1	73.3 ± 8.9	* 0.040	76.7 ± 7.4	73.9 ± 7.5	0.55	
		Female	90.9%	78.6%	0.67	0%	68.8%	* 0.044	
		MCI	81.8%	54.8%	0.34	66.7%	59.4%	1	
		MMSE	25.5 ± 2.2	24.5 ± 2.1	0.17	23.3 ± 0.58	24.7 ± 1.9	0.26	
		CDR 0.5	81.8%	81.0%	1	100%	96.9%	1	
		CSR-SB	2.68 ± 1.38	3.32 ± 1.19	0.13	2.17 ± 0.76	2.86 ± 1.42	0.42	
T1	phosphorylated and secreted AD tau AD tau proteinopathy	CSF pTau181	n/a	n/a		67.1 ± 24.5	98.0 ± 36.5	0.16	
T2		Tau PET Braak	1 [0.5-1.5]	4 [3.5-4.5]	0.20	1	5 [5-6]	0.21	
N		neurodegeneration	plasma NFL	23.4 ± 7.3	29.2 ± 20.7	0.40	30.8 ± 2.1	20.8 ± 6.6	* 0.015
I		inflammation	plasma GFAP	290 ± 148	348 ± 125	0.24	264 ± 139	312 ± 123	0.54
V	vascular brain injury	Fazekas DWM	1 [1-2]	1 [1-1]	+ 0.067	2 [1.5-2]	1 [1-1]	0.13	
		Fazekas PV	2 [1-2.5]	1 [1-1]	* 0.022	2 [1.5-2.5]	1 [1-2]	0.19	
S	α-synuclein	CSF αsyn SAA	n/a	n/a		0%	31.8%	1	

Figure 1

Age	Sex	Clinical stage	MMSE	CDR	CDR-SB	CL	Positive Regions	Frontal	Temporal	PCC/Precuneus	Parietal	Striatum
82	F	MCI	24	0.5	2	3.1	1	0	1	0	0	0
75	F	MCI	28	0.5	1	20.8	2	1	1	0	0	0
79	F	dementia	23	1	4.5	7.8	3	1	1	1	0	0
75	F	MCI	24	0.5	3	24.1	3	1	1	1	0	0
80	F	MCI	26	1	5	35.4	3	1	0	0	1	1
81	F	MCI	25	0.5	1.5	54.2	3	1	0	1	1	0
73	F	dementia	23	0.5	4.5	26.4	4	1	1	1	0	1
87	M	MCI	26	0.5	1.5	32.3	4	1	1	1	1	0
87	F	MCI	25	0.5	2	39.2	4	1	1	1	1	0
80	F	MCI	27	0.5	2.5	40.4	4	1	1	1	0	1
72	F	MCI	30	0.5	2	60.6	4	1	0	1	1	1

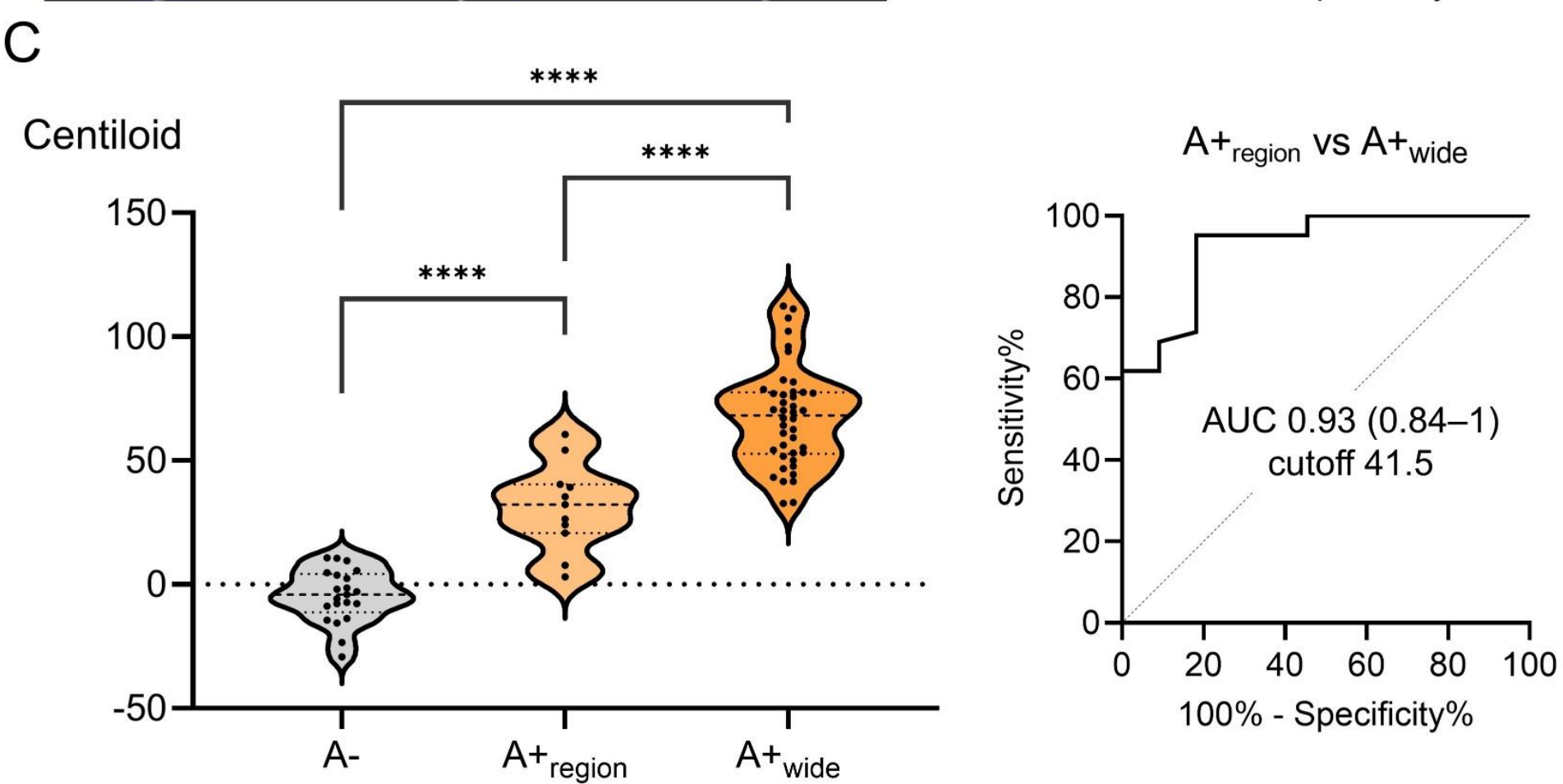
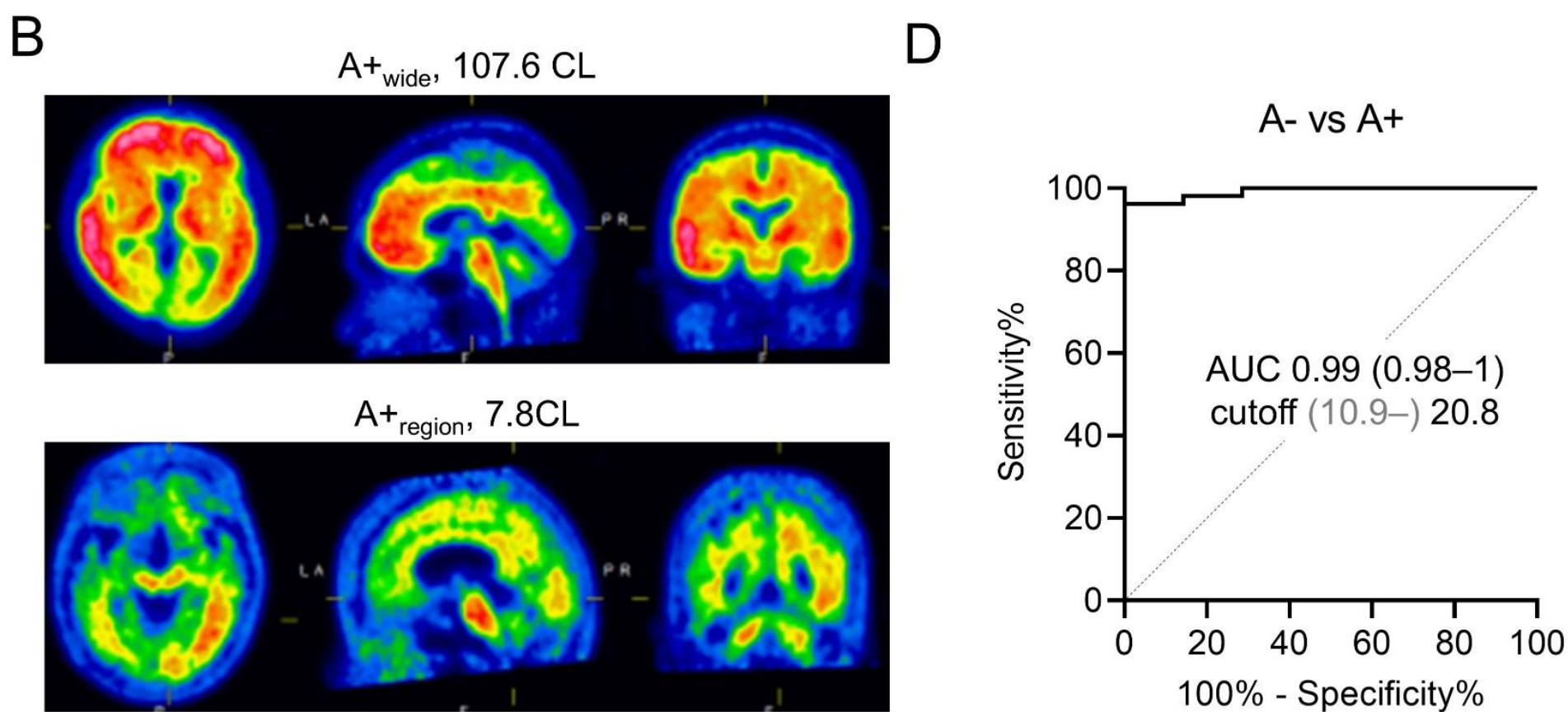


Figure 2

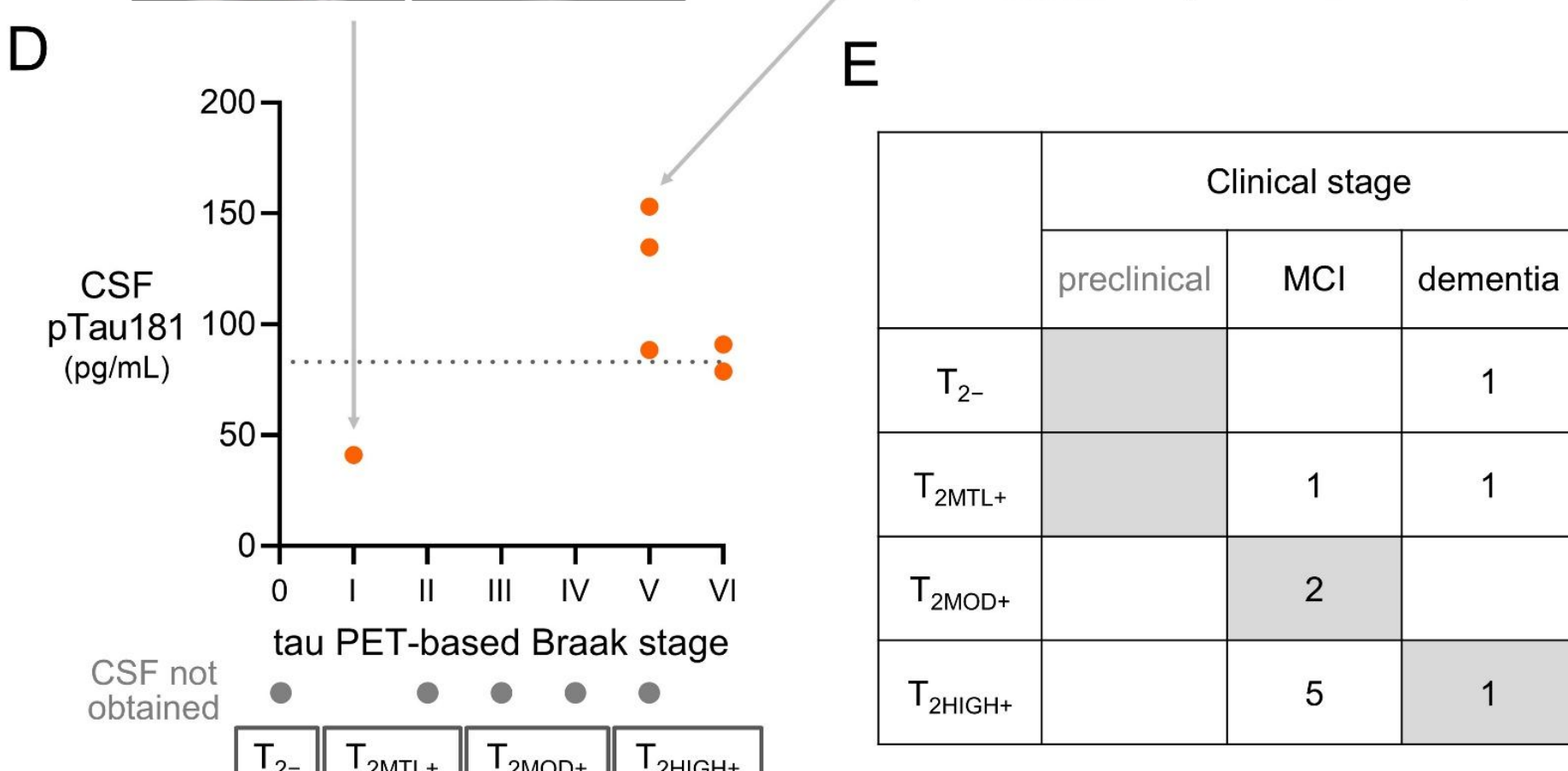
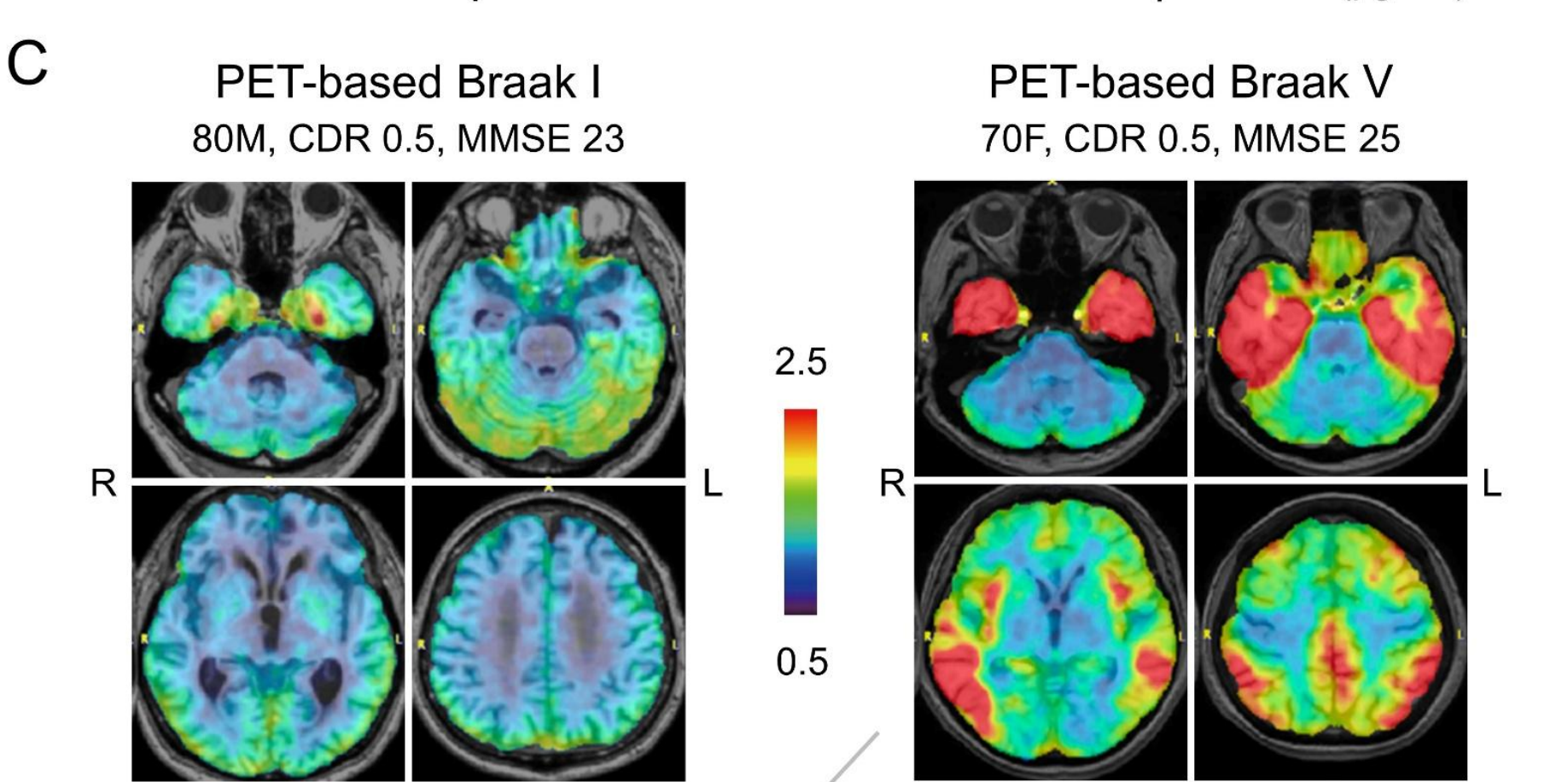
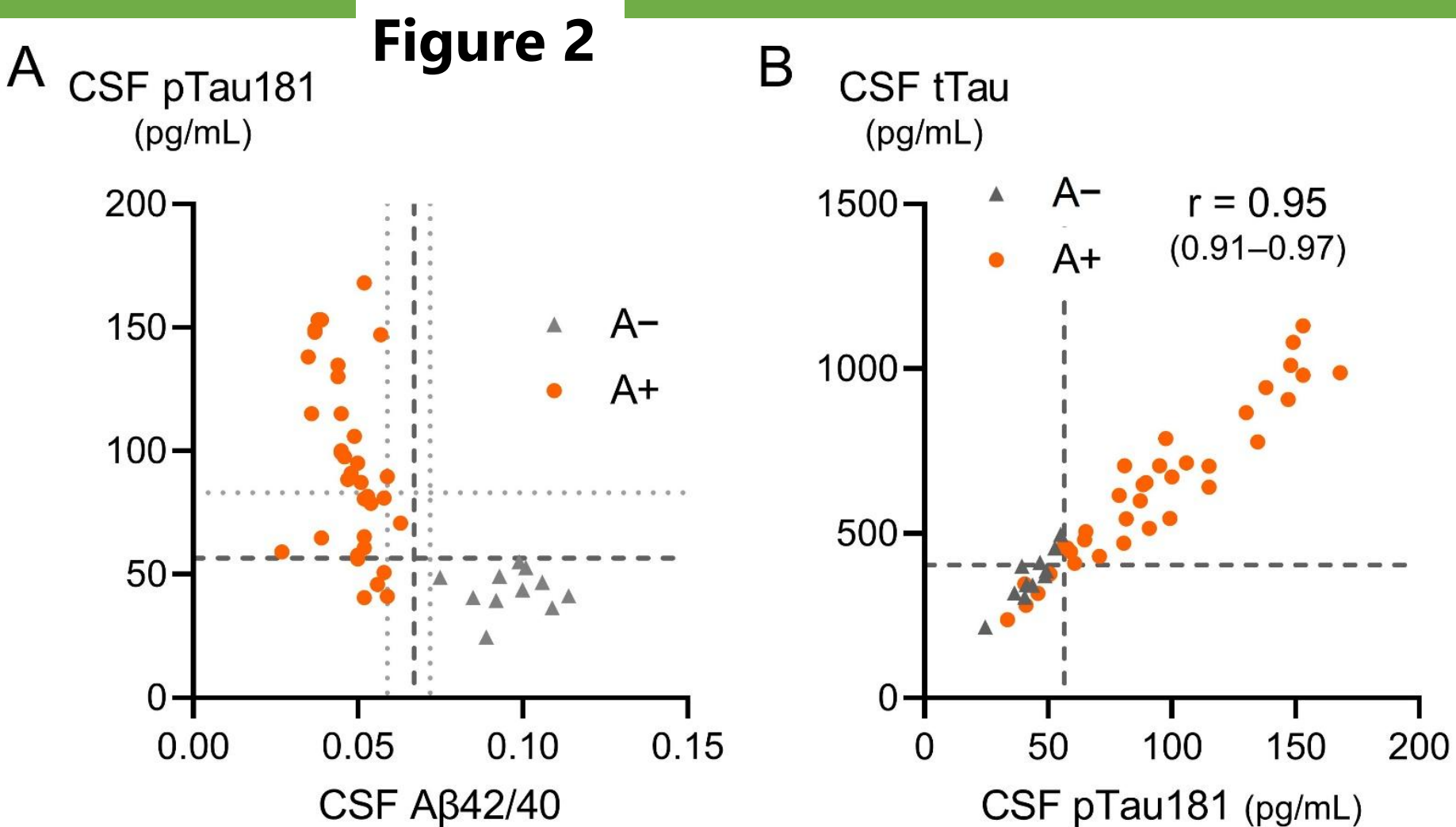
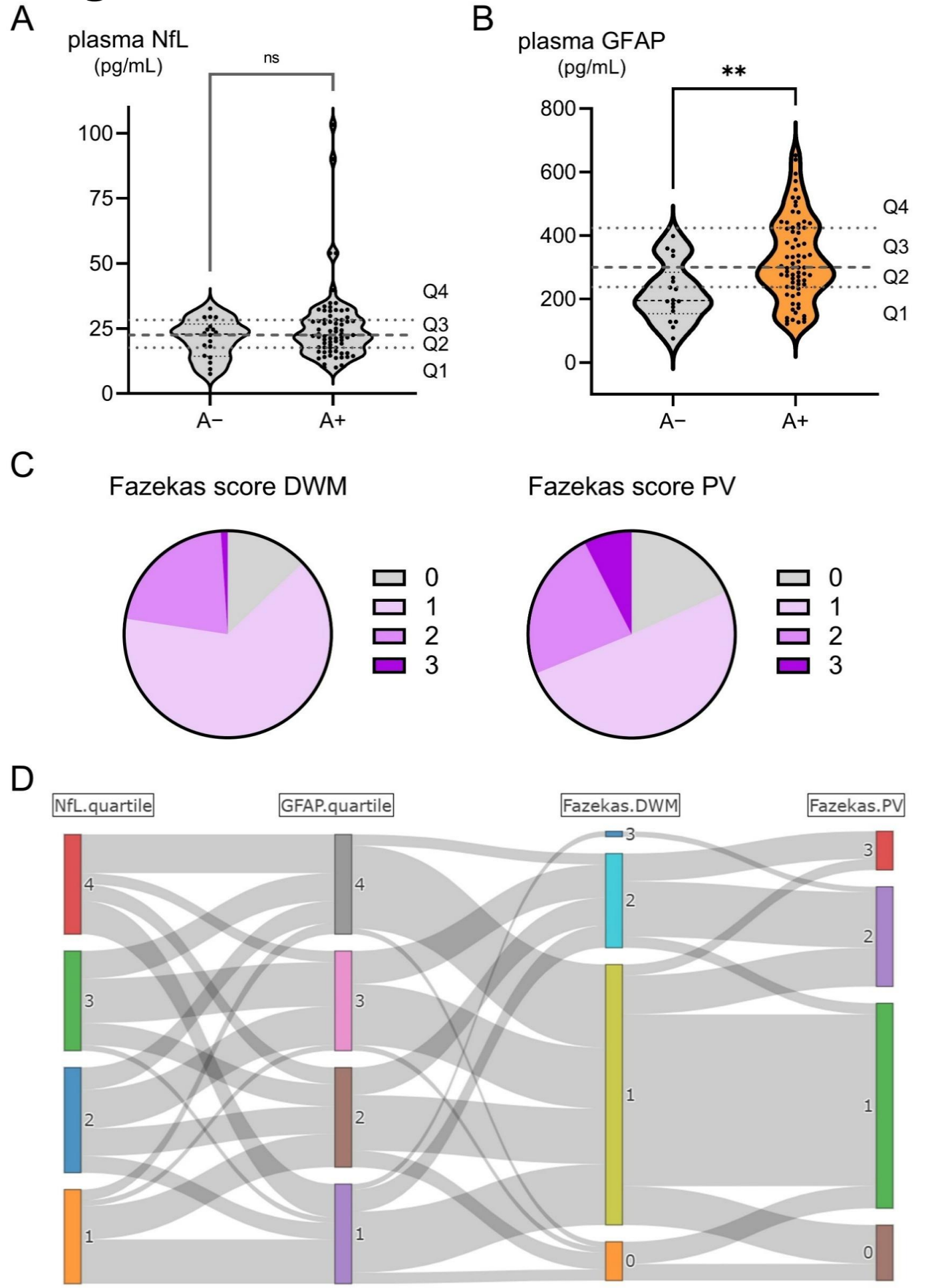


Figure 3



Discussions:

- Core 1 (A, T1)
- Regional amyloid positivity was observed in 21%, slightly higher than a previous report in a MCI research cohort [6].
 - CSF A β 42/40 was below but close to the cut-off in 8.5%.
 - CSF p-tau181 varied from normal to fully abnormal.
- Core 2 (T2)
- Tau PET distribution also varied widely, ranging from normal (no) to fully abnormal (PET-based Braak 5-6).
 - Mismatches between tau stage and clinical stage were observed, suggesting reserve/resilience/co-pathologies [1].
- NIV
- Fazekas score measuring white matter hyperintensities (V) ranged from normal (0) to fully abnormal (3). Plasma NfL and GFAP varied, leading to various combinations.
- S (α -syn)
- CSF α -syn SAA was positive in 25-33%, which was within the reported range in previous research cohorts [7,8]
- Association between A and others
- Amyloid PET regionally positive group was significantly older and had higher Fazekas scores.
 - Three with CSF A β 42/40 close to the cut-off were all men and had higher plasma NfL.
 - These patient groups may have different clinical characteristics, including vascular and other co-pathologies.

Full article available in JPAD 2026



Reference

- Jack CR Jr, et al. *Alzheimers Dement*. 2024
- Ihara R, Kurihara M, et al. *DADM* 2026
- Imabayashi E, et al. *Ann Nucl Med*. 2022
- Pascoal TA, et al. *Brain*. 2020
- Kurihara M, et al. *NPJ PD* 2024
- Farrar G, *EJNMMI*. 2019
- Pichet Binette A, et al. *Alzheimers Dement*. 2024
- Levin J, et al. *Alzheimers Dement*. 2024

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