

Data-Driven Feature Map Associating Baseline Florbetapir-PET Uptake Patterns to ARIA-E Incidence

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OBJECTIVE

- We aimed to identify spatial imaging patterns that maximally predict time-to-event outcomes such as amyloid related imaging abnormalities – edema and/or effusion (ARIA-E).
- We developed data-driven feature maps using partial least squares regression combined with Cox proportional hazard modeling to link baseline florbetapir-positron emission tomography (PET) with ARIA-E incidence.

CONCLUSION

- Analysis of three trials of donanemab with florbetapir-PET suggests that the data-driven score outperformed traditional whole-brain and regional amyloid PET measures in terms of association with ARIA-E.
- The data-driven score also provided 4-fold greater likelihood ratio χ^2 than previously reported occipital standardized uptake value ratio (SUVR) and significant hazard elevations across multiple intensity levels.
- Future research should validate these findings across additional datasets, tracers, and therapies.



BACKGROUND

ARIA-E

- ARIA-E events are a key risk with amyloid-targeting immunotherapies for Alzheimer’s disease (AD).¹
- ARIA-E is a common side effect that does not usually cause any symptoms, but serious symptoms can occur.¹
- Cases of ARIA-E may present as brain edema or sulcal effusions on magnetic resonance imaging.

Predicting risk

- Risk factors for developing ARIA-E include positive APOE-ε4 carrier status, superficial siderosis, and prior multiple cerebral microhemorrhages.^{1,2}
- In a recent analysis of the amyloid-targeting therapy donanemab, elevated amyloid burden at baseline was also independently associated with ARIA-E.³
- Specifically, we previously reported that occipital amyloid level was significantly associated with ARIA-E risk in donanemab-treated participants with early symptomatic AD.⁴
- However, predefined anatomical regions may not optimally capture voxel-level patterns predictive of ARIA-E.

RESULTS

Cox proportional hazard models

- In validation, whole-brain amyloid level did not significantly improve the reference model ($\chi^2=1.3985$, $p=0.50$).
- Regional amyloid (occipital SUVR) showed borderline improvement ($\chi^2=5.1413$, $p=0.08$), with a significant hazard ratio only for tercile 3 (hazard ratio=1.5111, $p=0.02$; **Figure 2**).
- The ARIA-E score demonstrated substantial improvement ($\chi^2=20.5236$, $p<0.0001$), with significant hazard ratios for tercile 2 (hazard ratio=1.5518, $p=0.03$) and tercile 3 (hazard ratio=2.3413, $p<0.0001$).
- ARIA-E score achieved the lowest Akaike information criterion (2398.87 vs 2414.25 and 2417.99; **Table 1**).

References

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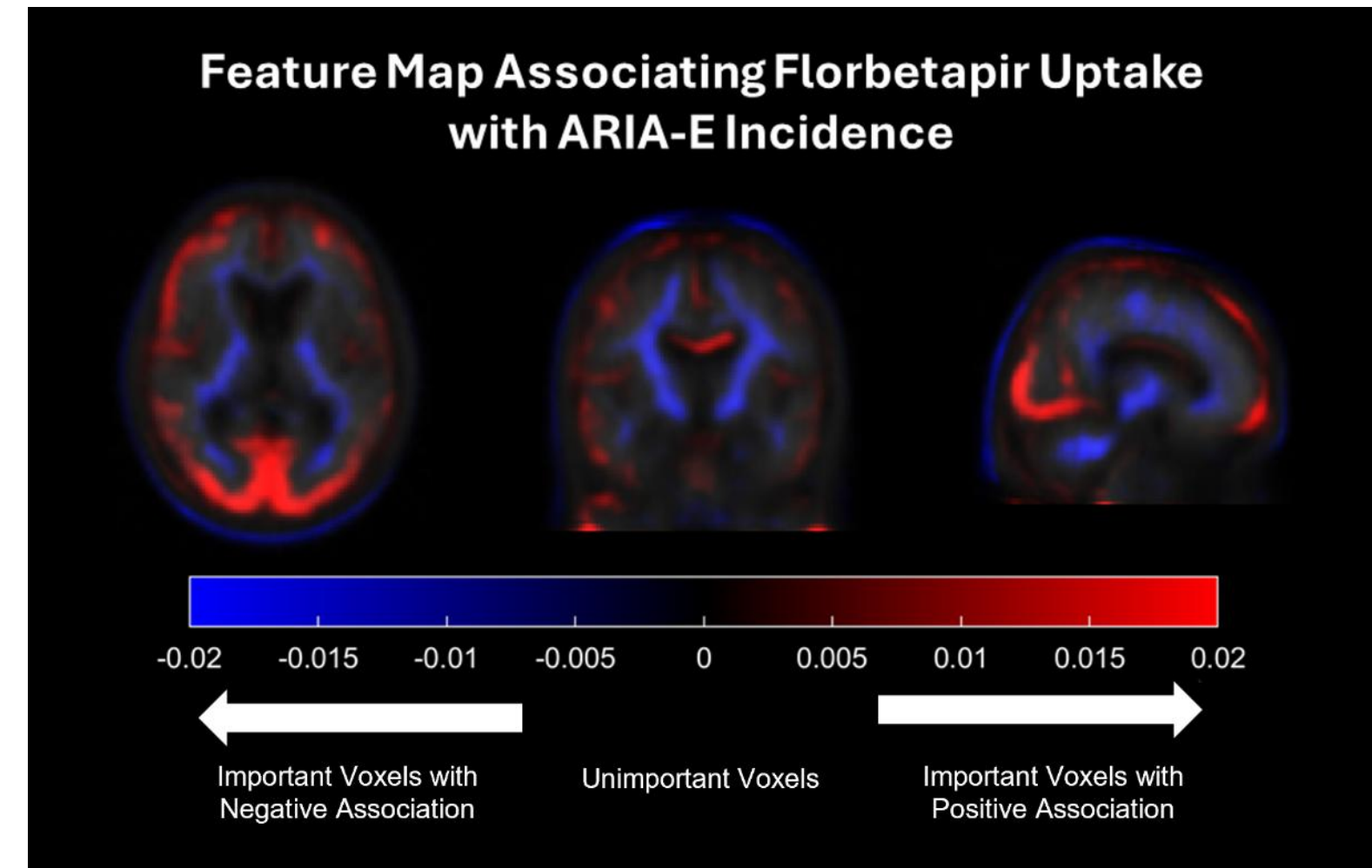
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METHODS

- Data included baseline florbetapir images from donanemab-treated participants with early symptomatic AD from TRAILBLAZER-ALZ (NCT03367403), TRAILBLAZER-ALZ 2 (NCT04437511), and TRAILBLAZER-ALZ 4 (NCT05108922).
 - Participants were divided into a development cohort (TRAILBLAZER-ALZ, TRAILBLAZER-ALZ 2 open-label addendum, TRAILBLAZER-ALZ 4; N=1,229) and validation cohort (TRAILBLAZER-ALZ 2; N=800).
- Partial least squares regression-Cox was applied to the development cohort.⁵
- Five-fold cross-validation was used to select the optimal number of feature maps. The surviving maps 1) passed a cross-validation number of components test, and 2) conveyed significantly more information when added to the model. They were then weighted by their importance in projection.
- For the validation cohort, each selected feature map was used to create a weighted SUVR from each florbetapir scan referenced to whole cerebellum. Since they are designed to capture ARIA-E risk, these weighted SUVRs are referred to as “ARIA-E Risk SUVRs.”
- Reference Cox proportional hazard models included the following established ARIA-E risk factors: APOE-ε4 status, microhemorrhage count, and superficial siderosis.
- Three Cox proportional hazard models evaluated imaging variables (composite amyloid level measure [Centiloids], occipital amyloid SUVR, and ARIA-E scores) added to the reference model.
- Significance was tested with likelihood ratio tests and hazard ratios by terciles.

KEY RESULT

One feature image showed high positive predictive weights



- One feature image passed cross-validation (**Figure 1**), showing high positive predictive weights in occipital cortex and pial boundaries.
- High negative predictive weights were seen in white matter and extracerebral regions.

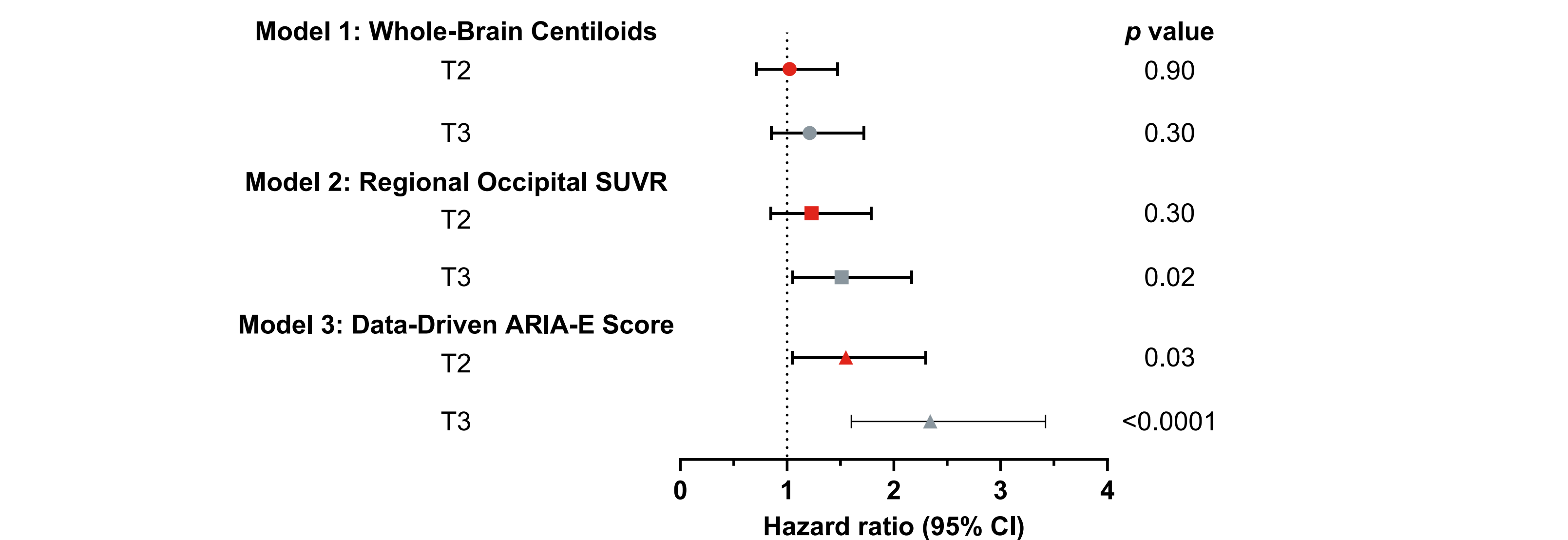
Figure 1. Final feature map used to generate the ARIA-E score. Red areas are positively associated with ARIA-E incidence; blue areas are negatively associated.

Table 1: Results from independent Cox proportional hazard models.

Amyloid Measurement	AIC	Likelihood Ratio Test		Hazard Ratio (Reference: T1)		
		χ^2	p value	Tercile	Estimate (95% CI)	p value
Model 1: Whole-Brain Centiloids	2417.99	1.3985	0.50	T2	1.0238 (0.7121, 1.4721)	0.90
				T3	1.2117 (0.8531, 1.7210)	0.30
Model 2: Regional Occipital SUVR	2414.25	5.1413	0.08	T2	1.2285 (0.8450, 1.7859)	0.30
				T3	1.5111 (1.0536, 2.1672)	0.02
Model 3: Data-Driven ARIA-E Score	2398.87	20.5236	<0.0001	T2	1.5518 (1.0477, 2.2984)	0.03
				T3	2.3413 (1.6021, 3.4217)	<0.0001

Likelihood ratio test results are against the reference model; hazard ratios for terciles 2 and 3 are referenced to tercile 1. ARIA-E, amyloid related imaging abnormalities – edema and/or effusion; AIC, Akaike information criterion; CI, confidence interval; SUVR, standardized uptake value ratio; T, terciles.

Figure 2: Forest plot of Cox proportional hazard ratios.



Hazard ratios for terciles 2 and 3 are referenced to tercile 1. ARIA-E, amyloid related imaging abnormalities – edema and/or effusion; CI, confidence interval; SUVR, standardized uptake value ratio; T, terciles.