

RESEARCH ARTICLE

Residualized occipital amyloid burden and plasma biomarker profiles in relation to ARIA-E during anti-amyloid treatment

Federica Agosta^{1,2,3,4} | Giordano Cecchetti^{1,2} | Alma Ghirelli^{1,2,3} |
 Edoardo G. Spinelli^{1,2,3} | Giulia Rugarli^{1,2,3} | Stefano Pisano^{1,2} | Federico Coraglia^{1,2,3} |
 Ana Maria Samanes Gajate⁵ | Paolo Vezzulli⁶ | Sonia Calloni⁶ | Elisa Canu^{1,2} |
 Veronica Castelnovo^{1,2} | Anna Gilioli^{1,2} | Chiara Tripodi^{1,2,3} | Fabiola Freri^{1,2} |
 Alessandra Bianchi^{1,2} | Andrea Panzacchi⁵ | Gino Pepe⁵ | Andrea Falini^{3,6} |
 Arturo Chiti^{3,5} | Massimo Filippi^{1,2,3,4,7} 

¹Center for Alzheimer's and Related Diseases (CARD), Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

²Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy

³Vita-Salute San Raffaele University, Milan, Italy

⁴Neurotech Hub, Vita-Salute San Raffaele University, Milan, Italy

⁵Nuclear Medicine Service, IRCCS San Raffaele Scientific Institute, Milan, Italy

⁶Neuroradiology Service, IRCCS San Raffaele Scientific Institute, Milan, Italy

⁷Neurorehabilitation Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

Correspondence

Massimo Filippi, CARD and Neurology Unit, IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Via Olgettina, 60, 20132 Milan, Italy.
 Email: filippi.massimo@hsr.it

Abstract

INTRODUCTION: Amyloid-related imaging abnormalities with edema (ARIA-E) represent the main safety concern of anti-amyloid monoclonal antibodies. Whether regional amyloid topology refines ARIA-E risk in real-world practice remains unclear.

METHODS: We analyzed 31 treatment courses in early Alzheimer's disease under European Medicines Agency labeling. Residualized occipital amyloid burden was defined as observed occipital standardized uptake value ratio (SUVR) minus occipital SUVR predicted from global composite SUVR in an expanded baseline positron emission tomography derivation sample ($n = 53$). Associations with ARIA-E and baseline plasma biomarkers were assessed.

RESULTS: ARIA-E occurred only in the elevated occipital amyloid group: 4/13 treatment courses, versus 0/18 low or comparable courses (Fisher exact $p = 0.055$). All ARIA-E events involved posterior regions. The elevated pattern showed higher baseline glial fibrillary acidic protein (GFAP), phosphorylated tau (p-tau)181, and p-tau217 levels, whereas amyloid beta 42/40 did not differ between groups. A GFAP + p-tau217 model showed exploratory discrimination of the elevated phenotype (area under the curve: 0.76).

DISCUSSION: Disproportionate occipital amyloid burden may identify a biologically vulnerable subgroup requiring validation in larger cohorts.

KEYWORDS

Alzheimer's disease, amyloid positron emission tomography, amyloid-related imaging abnormality, amyloid-related imaging abnormalities with edema, anti-amyloid therapy, plasma biomarkers

Federica Agosta and Giordano Cecchetti contributed equally to this study and should be considered co-first authors.

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Highlights

- Residualized occipital amyloid burden was explored as a candidate amyloid-related imaging abnormalities with edema (ARIA-E) risk marker.
- ARIA-E occurred in 4/13 elevated-pattern courses and in 0/18 low/comparable courses.
- Global Centiloid burden did not discriminate ARIA-E occurrence in this exploratory cohort.
- Elevated baseline glial fibrillary acidic protein (GFAP) and phosphorylated tau (p-tau) levels characterized the elevated occipital amyloid pattern.
- GFAP + p-tau217 provided exploratory, non-validated discrimination of the elevated pattern.

1 | BACKGROUND

Lecanemab and donanemab have been approved by the European Medicines Agency (EMA) for early symptomatic Alzheimer's disease (AD) with confirmed amyloid pathology.^{1,2} Phase 3 trials showed substantial amyloid removal and slowing of cognitive decline, but amyloid-related imaging abnormalities (ARIAs), particularly ARIA with edema (ARIA-E), remain the principal safety concern and require structured magnetic resonance imaging (MRI) surveillance.^{3–7}

In current practice, ARIA risk stratification relies primarily on apolipoprotein E (APOE) ϵ 4 genotype and baseline MRI markers, including microbleed burden and superficial siderosis.^{5–7} Pre-treatment identification of patients at increased ARIA-E risk could enable more tailored surveillance strategies and support shared decision making. In a large post hoc analysis of the TRAILBLAZER-ALZ 2 trial ($n = 2087$), elevated occipital amyloid burden at amyloid positron emission tomography (PET), defined as occipital standardized uptake value ratio (SUVR) exceeding the value expected for a given global amyloid load, was associated with increased ARIA-E risk.⁸ This regional pattern is biologically plausible given the preferential distribution of cerebral amyloid angiopathy (CAA) in posterior cortical vessels,⁹ where rapid vascular amyloid mobilization during immunotherapy may transiently affect blood–brain barrier integrity.^{10,11} However, whether this observation applies to routine European practice, for which APOE ϵ 4 homozygotes are excluded from treatment per label indication, remains unknown.^{1,2}

Plasma biomarkers may provide complementary information on amyloid-associated biological activity. Glial fibrillary acidic protein (GFAP) reflects astrocytic activation,¹² whereas phosphorylated tau (p-tau)217 and p-tau181 are closely associated with amyloid positivity and amyloid burden in AD.^{13–17} Whether these biomarkers relate to residualized occipital amyloid burden on regional PET in real-world anti-amyloid treatment cohorts remains unknown.^{18–22}

Here, we pursued two aims. First, we evaluated whether ARIA-E events clustered in patients with an elevated residualized occipital amyloid pattern at baseline in a real-world cohort treated with

lecanemab or donanemab (Aim 1). Second, we investigated whether baseline plasma biomarkers reflecting astroglial activation, amyloid-related p-tau biology, and plasma amyloid status were associated with the occipital amyloid pattern and could provide exploratory discrimination of patients with elevated residualized occipital amyloid burden (Aim 2).

2 | METHODS

2.1 | Study design and participants

This was a retrospective observational study conducted at the Center for Alzheimer's and Related Diseases (CARD—IRCCS San Raffaele Scientific Institute, Milan, Italy), a tertiary referral memory clinic that implemented a structured multidisciplinary pathway for amyloid-targeting therapies beginning in September 2024.

Patient selection followed a standardized biologically anchored workflow, described elsewhere,²³ including APOE genotyping, brain MRI for vascular eligibility and ARIA risk assessment, and baseline amyloid PET to quantify global and regional amyloid burden before treatment exposure. Baseline cerebral microbleeds were assessed on both gradient-recalled echo (GRE) and susceptibility-weighted imaging (SWI) sequences. For treatment eligibility, microbleed count on GRE was considered the reference sequence in accordance with EMA labeling.^{1,2}

We included consecutive patients who initiated treatment with lecanemab or donanemab between September 2024 and February 2026 under the Italian named-patient program, in accordance with EMA indications and appropriate use recommendations.^{5,7} APOE ϵ 4 homozygotes were not treated and were therefore not represented.

The unit of analysis was the treatment course.

The PET derivation sample comprised 53 baseline scans with regional amyloid quantification. The primary ARIA analytical cohort included courses with at least four infusions, ensuring standardized early MRI surveillance and meaningful exposure. Thirty-one courses

RESEARCH IN CONTEXT

1. **Systematic review:** We reviewed the literature using PubMed focusing on regional amyloid positron emission tomography distribution, cerebral amyloid angiopathy, amyloid-related imaging abnormality (ARIA) pathophysiology, and plasma biomarkers in anti-amyloid trials. Post hoc analyses of donanemab trials suggested that elevated occipital amyloid burden may be associated with ARIA with edema (ARIA-E) risk. Recent frameworks (e.g., treatment-related amyloid clearance [TRAC]) emphasize global Centiloid monitoring but acknowledge regional heterogeneity. Plasma glial fibrillary acidic protein (GFAP) and phosphorylated tau (p-tau) species have emerged as sensitive markers of amyloid- and tau-related biology.
2. **Interpretation:** In this exploratory real-world cohort, ARIA-E events clustered among treatment courses with elevated residualized occipital amyloid burden, despite comparable global amyloid load. The elevated occipital pattern was accompanied by higher baseline GFAP, p-tau181, and p-tau217 levels, whereas amyloid beta 42/40 showed no clear association. These findings suggest that regional amyloid topology and plasma biomarkers may provide complementary information for ARIA-E risk characterization.
3. **Future directions:** Larger multicenter cohorts are needed to validate whether residualized occipital amyloid burden provides information beyond established ARIA risk factors, including apolipoprotein E genotype and baseline hemorrhagic magnetic resonance imaging markers.

met this criterion. All initiated courses were reviewed to confirm that no ARIA-E cases were excluded because of discontinuation before the fourth infusion. One patient contributed two eligible treatment courses after switching from lecanemab to donanemab after limited amyloid reduction at the 6-month PET scan. For this second course, baseline PET was redefined as the 6-month PET acquired after lecanemab exposure and before donanemab initiation, ensuring that regional amyloid quantification preceded the monoclonal antibody exposure analyzed.

2.2 | Ethics

The study was conducted within routine clinical care. According to Italian regulations and institutional policy for observational studies based exclusively on standard-care data, formal ethics committee approval was not required. All participants provided written informed consent for treatment initiation and for the use of anonymized clinical data

for research purposes, in accordance with the Ministerial Decree of February 11, 1997, and the Declaration of Helsinki.

2.3 | ARIA ascertainment and MRI monitoring

ARIA monitoring was performed using serial brain MRI on 1.5 Tesla scanners according to the EMA-mandated schedule for each agent.^{1,2}

ARIA-E was defined as new vasogenic edema and/or sulcal effusion identified on fluid-attenuated inversion recovery. ARIA with microhemorrhage or superficial siderosis (ARIA-H) was defined as new or increased cerebral microhemorrhages and/or superficial siderosis detected on GRE and/or SWI. Severity was graded as mild, moderate, or severe according to EMA label definitions.^{1,2}

All MRI scans were reviewed by experienced neuroradiologists; suspected ARIA cases were discussed within a multidisciplinary team.

2.4 | Amyloid PET acquisition and quantification

Amyloid PET was acquired at baseline prior to treatment initiation and repeated at 6 months in patients completing follow-up. In the event of monoclonal antibody switch, the 6-month PET preceding the second agent was considered the baseline PET for the subsequent treatment course.

Imaging was performed on PET/computed tomography or PET/magnetic resonance systems (GE Healthcare) using either [¹⁸F]florbetaben or [¹⁸F]flutemetamol according to tracer-specific acquisition protocols. For each patient, the same tracer and scanner were used at baseline and follow-up.

Global amyloid burden was quantified in Centiloids using the validated tracer-specific calibration models implemented in the Combinostics cNeuro cPET platform (Combinostics Oy).^{24,25} Amyloid PET negativity was defined as Centiloid < 25.^{3,4,26}

Regional and composite SUVRs were calculated using the whole cerebellum as reference region.^{27,28} The composite SUVR included prefrontal, anterior cingulate, parietal, lateral temporal, and precuneus/posterior cingulate cortices. The occipital cortex was not included in the composite SUVR and was extracted separately for residualized occipital amyloid analysis. An illustrative region of interest overlay is provided in Figure S1 in supporting information.

2.5 | Occipital amyloid pattern

To characterize occipital amyloid burden beyond total cortical burden, we derived a residualized occipital amyloid metric based on Kennedy et al.⁸ The occipital-versus-global regression model was fitted in the full PET derivation sample ($n = 53$) to improve stability.

A linear regression model was fitted with baseline occipital SUVR as the dependent variable and global composite SUVR as the independent variable. An interaction term between composite SUVR and PET tracer ([¹⁸F]florbetaben vs. [¹⁸F]flutemetamol) was tested to evaluate

tracer-specific scaling effects. As no statistically significant interaction was observed, a single model was used across tracers. The residual, calculated as observed minus predicted occipital SUVR, represented occipital amyloid enrichment beyond that expected for a given global amyloid burden.

Tertile boundaries were derived from residuals in the $n = 53$ derivation sample and applied to classify the 31 treatment courses into low, comparable, and elevated occipital amyloid patterns. Because cutoffs were defined in the derivation sample and applied to the analytical cohort, group sizes were not expected to be equal. Secondary analyses modeled the occipital residual as a continuous variable.

2.6 | Plasma biomarker collection and assays

Plasma samples were collected at pre-treatment screening and processed according to standardized institutional procedures,²⁹ including timely centrifugation and storage at -80°C before batch analysis. GFAP, p-tau217, p-tau181, and amyloid beta ($\text{A}\beta$)42/40 were measured on the fully automated Lumipulse G600II platform (Fujirebio) using commercially available assays in the same laboratory.

2.7 | Statistical analysis

Continuous variables are reported as median (interquartile range) and categorical variables as counts (%). Group comparisons used Wilcoxon rank-sum or Fisher exact tests.

For Aim 1, the association between occipital amyloid pattern and ARIA-E was assessed using a Fisher exact test on a 3×2 table. The derivation model was summarized using R^2 and model coefficients. Sensitivity analyses retained occipital residual as a continuous predictor of ARIA-E. Given the small number of ARIA-E events, logistic regression used Firth penalized likelihood; an exploratory adjusted model included age, APOE $\epsilon 4$ carrier status, and monoclonal antibody. Non-parametric sensitivity analyses included Spearman correlation and Wilcoxon rank-sum testing. Diagnostic performance was summarized descriptively with Wilson 95% confidence intervals. Given that one individual contributed two treatment courses, we performed a sensitivity analysis excluding the subject to assess whether the ARIA-E distribution across occipital amyloid patterns was driven by this observation.

For Aim 2a, baseline plasma values were log10-transformed. Comparisons between elevated and low + comparable occipital pattern groups used Wilcoxon rank-sum tests, with rank-biserial correlation as effect size. Benjamini-Hochberg adjusted p values across the four biomarkers were reported when appropriate. Spearman correlations were computed between continuous occipital residual and each biomarker. Adjusted linear models accounted for age, APOE $\epsilon 4$ carrier status, monoclonal antibody, and PET-plasma interval.

For Aim 2b, discrimination of the elevated pattern was evaluated using receiver operating characteristic (ROC) analysis with DeLong 95% confidence intervals. Multivariable logistic regression

was restricted to two predictors. The primary combined model included GFAP and p-tau217. Performance was quantified using apparent area under the curve (AUC) and leave-one-out cross-validated AUC. Classification metrics were reported at the Youden-optimal threshold and interpreted descriptively.

All analyses were conducted in R (version 4.4.0). Statistical tests were two-sided with $\alpha = 0.05$.

3 | RESULTS

3.1 | Cohort characteristics and ARIA incidence

Of 53 baseline PET scans with available regional amyloid PET quantification, 31 treatment courses met the prespecified inclusion criterion of ≥ 4 infusions and constituted the primary ARIA analytical cohort (Table 1). These corresponded to 30 patients; one patient switched from lecanemab to donanemab after the 6-month amyloid PET showed limited amyloid reduction under lecanemab. Twenty-two courses involved donanemab and nine lecanemab.

Median age at treatment initiation was 68.9 years (interquartile range [IQR] 59.8–72.8), 54.8% were female, and APOE $\epsilon 4$ heterozygosity was present in 35.5%; no $\epsilon 4$ homozygotes were treated. Median baseline amyloid burden was 95.8 Centiloids (IQR 82.4–106.8).

ARIA occurred in 6/31 courses (19.4%). ARIA-E was observed in 4/31 (12.9%), all in the donanemab group, with median onset 16.9 weeks after first infusion. All ARIA-E events involved the occipital lobe, either alone or with parietal and/or temporal involvement. ARIA-H without edema occurred in two additional cases. Two of four ARIA-E cases were mildly symptomatic, one was asymptomatic, and isolated ARIA-H cases were asymptomatic.

Baseline microbleeds detected on SWI were more frequent among ARIA cases (66.7% vs. 20.0%, $p = 0.043$). A similar numerical trend was observed on GRE, without statistical significance. Global Centiloid burden did not differ between ARIA and no-ARIA groups ($p = 0.9$).

3.2 | Occipital amyloid pattern and ARIA-E

In the full baseline PET derivation sample ($n = 53$), the interaction between global composite SUVR and PET tracer was not statistically significant ($F = 3.20$, $p = 0.080$). A single occipital-versus-global regression model was therefore used across tracers. The final model showed a positive association between global composite and occipital SUVR ($R^2 = 0.562$, $\beta_{\text{global}} = 0.730$, intercept = 0.188; Figure S2 in supporting information).

Tertile cutoffs derived from the $n = 53$ derivation sample were then applied to the $n = 31$ ARIA analytical cohort, yielding low ($n = 6$), comparable ($n = 12$), and elevated ($n = 13$) occipital amyloid patterns. Global composite SUVR was comparable between low + comparable and elevated groups (median 1.6 [IQR 1.5–1.7] vs. 1.6 [1.5–1.7], $p = 0.764$), whereas occipital SUVR and occipital residual were higher in the elevated group (both $p < 0.001$; Table 2). Representative baseline

TABLE 1 Baseline clinical, imaging, and plasma characteristics according to ARIA status.

Variable	Overall N = 31	No ARIA N = 25	Any ARIA N = 6	p
Demographics				
Age, years, median (IQR)	68.9 (59.8, 72.8)	68.0 (59.0, 72.7)	70.4 (63.4, 73.6)	0.3
Sex, female, n (%)	17 (55%)	12 (48%)	5 (83%)	0.2
Treatment				
Donanemab, n (%)	22 (71%)	17 (68%)	5 (83%)	0.6
Lecanemab, n (%)	9 (29%)	8 (32%)	1 (17%)	0.6
Treatment duration, weeks, median (IQR)	28.0 (24.0, 34.0)	28.0 (24.0, 34.0)	24.0 (20.0, 28.0)	0.2
Genetics				
APOE ε4 carrier, n (%)	11 (35%)	10 (40%)	1 (17%)	0.4
Renal function				
eGFR, mL/min/1.73 m ² , median (IQR)	84.3 (74.8, 93.6)	87.2 (76.9, 94.3)	76.8 (70.2, 80.5)	0.040
Cognitive scores at baseline				
MMSE, median (IQR)	25.0 (20.0, 27.0)	25.0 (20.0, 27.0)	26.5 (25.0, 27.0)	0.4
CDR-SB, median (IQR)	3.5 (2.0, 4.5)	3.5 (1.5, 4.5)	2.8 (2.5, 4.0)	>0.9
Baseline amyloid PET				
Centiloids, median (IQR)	95.8 (82.4, 106.8)	96.9 (82.4, 104.8)	94.7 (93.6, 109.2)	0.9
Baseline MRI				
Fazekas score, n (%)				0.8
0	14 (45%)	12 (48%)	2 (33%)	
1	10 (32%)	8 (32%)	2 (33%)	
2	7 (23%)	5 (20%)	2 (33%)	
Any microbleed on GRE, n (%)	4 (13%)	2 (8.0%)	2 (33%)	0.2
Any microbleed on SWI, n (%)	9 (29%)	5 (20%)	4 (67%)	0.043
Vascular risk factors				
Hypertension, n (%)	11 (35%)	8 (32%)	3 (50%)	0.6
Antiplatelet use, n (%)	8 (26%)	5 (20%)	3 (50%)	0.2
Plasma biomarkers at baseline				
GFAP, pg/mL, median (IQR)	100.3 (74.1, 124.3)	98.2 (71.1, 112.7)	122.4 (90.8, 125.5)	0.2
p-tau181, pg/mL, median (IQR)	2.1 (1.7, 3.2)	2.0 (1.7, 2.9)	3.4 (2.4, 4.1)	0.034
p-tau217, pg/mL, median (IQR)	0.8 (0.5, 1.4)	0.7 (0.5, 1.4)	1.2 (1.0, 1.3)	0.085
Aβ42/40 ratio, median (IQR)	0.069 (0.066, 0.074)	0.069 (0.066, 0.074)	0.079 (0.067, 0.085)	0.12

Note: Data are presented as median (interquartile range) for continuous variables and n (%) for categorical variables. Group comparisons were performed using Wilcoxon rank-sum tests for continuous variables and Fisher exact test for categorical variables.

Abbreviations: Aβ, amyloid beta; APOE, apolipoprotein E; ARIA, amyloid-related imaging abnormality; CDR-SB, Clinical Dementia Rating Sum of Boxes; eGFR, estimated glomerular filtration rate; GFAP, glial fibrillary acidic protein; GRE, gradient-recalled echo; IQR, interquartile range; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; PET, positron emission tomography; p-tau, phosphorylated tau; SWI, susceptibility-weighted imaging.

amyloid PET images across the residualized occipital SUVR gradient are shown in Figure 1, including the four treatment courses that subsequently developed ARIA-E.

ARIA-E occurred only in the elevated occipital amyloid group: 4/13 treatment courses (30.8%) versus 0/18 low or comparable courses (Fisher exact $p = 0.055$; Figure 2). Specifically, ARIA-E occurred in 0/6 low, 0/12 comparable, and 4/13 elevated cases. Isolated ARIA-H without edema occurred in one comparable and one elevated case.

Continuous residualized occipital SUVR values are shown in Figure S3 in supporting information, with ARIA-E cases located in the upper residual range. After excluding both courses from the switched patient, who was elevated without ARIA-E in both courses, ARIA-E remained confined to the elevated group (4/11 vs. 0/18; Fisher exact $p = 0.014$).

Sensitivity analyses retaining occipital residual as a continuous predictor were directionally consistent. Firth penalized logistic regression showed a nominal association in the unadjusted model ($p = 0.041$), but

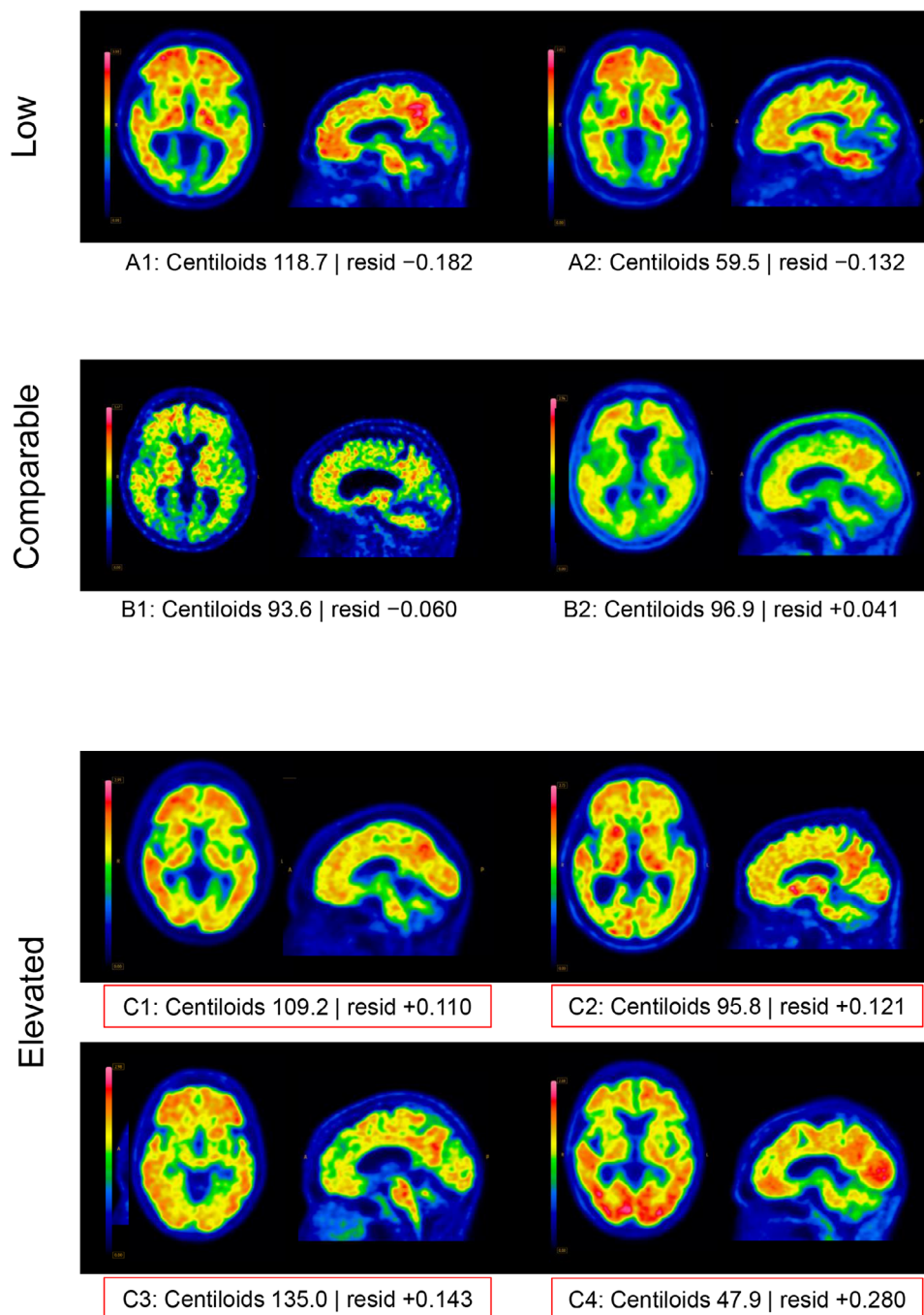


FIGURE 1 Representative baseline amyloid PET images across the residualized occipital amyloid gradient. Representative baseline amyloid PET images illustrating low, comparable, and elevated residualized occipital amyloid patterns. Eight treatment courses are shown: two examples with low occipital residuals (A1–A2), two with comparable residuals (B1–B2), and the four elevated cases that subsequently developed ARIA-E (C1–C4). For each panel, global amyloid burden is reported in Centiloids and regional occipital enrichment is reported as residualized occipital SUVR. Red outlines indicate treatment courses that subsequently developed ARIA-E. PET tracers were as follows: A1, flutemetamol; A2, flutemetamol; B1, flutemetamol; B2, florbetaben; C1, flutemetamol; C2, flutemetamol; C3, flutemetamol; C4, florbetaben. Occipital amyloid pattern was defined using residualized occipital SUVR derived from the occipital-versus-global SUVR regression model in the baseline PET derivation sample. Images are displayed for visual illustration of the quantitative residualized phenotype and were not used for visual classification. ARIA-E, amyloid-related imaging abnormality with edema/effusion; PET, positron emission tomography; resid, residualized occipital SUVR; SUVR, standardized uptake value ratio.

TABLE 2 Baseline clinical, imaging, and plasma characteristics according to occipital amyloid pattern.

Variable	Low + comparable N = 18	Elevated N = 13	p
Demographics			
Age, years, median (IQR)	69.2 (60.2, 71.4)	68.0 (61.3, 72.8)	0.857
Sex, female, n (%)	8 (44%)	9 (69%)	0.275
Genetics			
APOE ϵ 4 carrier, n (%)	9 (50%)	2 (15%)	0.066
Renal function			
eGFR, mL/min/1.73 m ² , median (IQR)	86.6 (81.1, 93.2)	78.5 (69.6, 94.3)	0.307
Baseline amyloid PET			
Centiloids, median (IQR)	95.5 (80.3, 103.2)	95.8 (92.8, 109.2)	0.400
Global SUVR, median (IQR)	1.6 (1.5, 1.7)	1.6 (1.5, 1.7)	0.764
Occipital SUVR, median (IQR)	1.3 (1.2, 1.4)	1.5 (1.4, 1.6)	<0.001
Occipital residual, median (IQR)	−0.081 (−0.138, −0.031)	0.138 (0.090, 0.204)	<0.001
Baseline MRI			
Fazekas score, median (IQR)	1.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.291
Any microbleed on GRE, n (%)	2 (11%)	2 (15%)	>0.9
Any microbleed on SWI, n (%)	5 (28%)	4 (31%)	>0.9
ARIA			
ARIA-E, n (%)	0 (0%)	4 (31%)	0.023
Any ARIA, n (%)	1 (6%)	5 (38%)	0.059
Plasma biomarkers at baseline			
GFAP, pg/mL, median (IQR)	90.8 (68.1, 106.4)	120.5 (100.3, 130.5)	0.024
p-tau181, pg/mL, median (IQR)	1.9 (1.6, 2.2)	2.9 (2.1, 3.6)	0.031
p-tau217, pg/mL, median (IQR)	0.6 (0.4, 1.2)	1.2 (0.8, 1.4)	0.036
A β 42/40 ratio, median (IQR)	0.070 (0.066, 0.074)	0.068 (0.063, 0.085)	0.327

Note: Data are presented as median (interquartile range) or n (%). Continuous variables were compared using Wilcoxon rank-sum tests; categorical variables using Fisher exact test. Occipital amyloid pattern was defined as tertiles of residuals from linear regression of occipital SUVR on global composite SUVR at baseline (n = 53 derivation sample; no tracer correction applied, as the tracer $\times$ composite SUVR interaction was not significant, $F = 3.20$, $p = 0.080$).

Abbreviations: A β , amyloid beta; APOE, apolipoprotein E; ARIA, amyloid-related imaging abnormality; ARIA-E, amyloid-related imaging abnormality with edema/effusion; eGFR, estimated glomerular filtration rate (CKD-EPI 2021); GFAP, glial fibrillary acidic protein; GRE, gradient-recalled echo; IQR, interquartile range; PET, positron emission tomography; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio; SWI, susceptibility-weighted imaging.

not after adjustment for age, APOE ϵ 4 carrier status, and monoclonal antibody ($p = 0.152$). Non-parametric analyses were concordant, with higher residualized occipital SUVR values in ARIA-E cases (Spearman $\rho = 0.398$, $p = 0.027$; Wilcoxon $p = 0.032$; Table S1 in supporting information). The continuous occipital residual yielded an exploratory AUC of 0.843 for ARIA-E.

The elevated occipital pattern showed 100.0% sensitivity (95% confidence interval [CI]: 51.0–100.0), 66.7% specificity (95% CI: 47.8–81.4), 30.8% positive predictive value (95% CI: 12.7–57.6), 100.0% negative predictive value (95% CI: 82.4–100.0), and 71.0% accuracy (95% CI: 53.4–83.9) for ARIA-E (Table S2 in supporting information).

APOE genotypes were ϵ 3/ ϵ 3 in 19/31 courses (61.3%), ϵ 3/ ϵ 4 in 11/31 (35.5%), and ϵ 2/ ϵ 3 in 1/31 (3.2%). APOE ϵ 4 heterozygosity was numerically less frequent in the elevated than in the low + comparable group (2/13 [15.4%] vs. 9/18 [50.0%], $p = 0.066$; Table 2). All four ARIA-E

cases carried the ϵ 3/ ϵ 3 genotype; no APOE ϵ 4 carrier developed ARIA-E (Fisher exact $p = 0.269$; Table S3 in supporting information).

3.3 | Baseline plasma biomarkers and occipital amyloid pattern

In unadjusted comparisons, baseline GFAP, p-tau217, and p-tau181 were higher in the elevated group than in the low + comparable group (Figure 3A–D, Table 2), whereas A β 42/40 did not differ.

Adjusted linear models were broadly consistent. After accounting for age, APOE ϵ 4 carrier status, monoclonal antibody, and PET plasma interval, the elevated pattern was associated with higher log10-transformed p-tau181 ($\beta = 0.223$, $p = 0.007$) and p-tau217 ($\beta = 0.276$, $p = 0.008$), while GFAP showed a nominal association ($\beta = 0.226$,

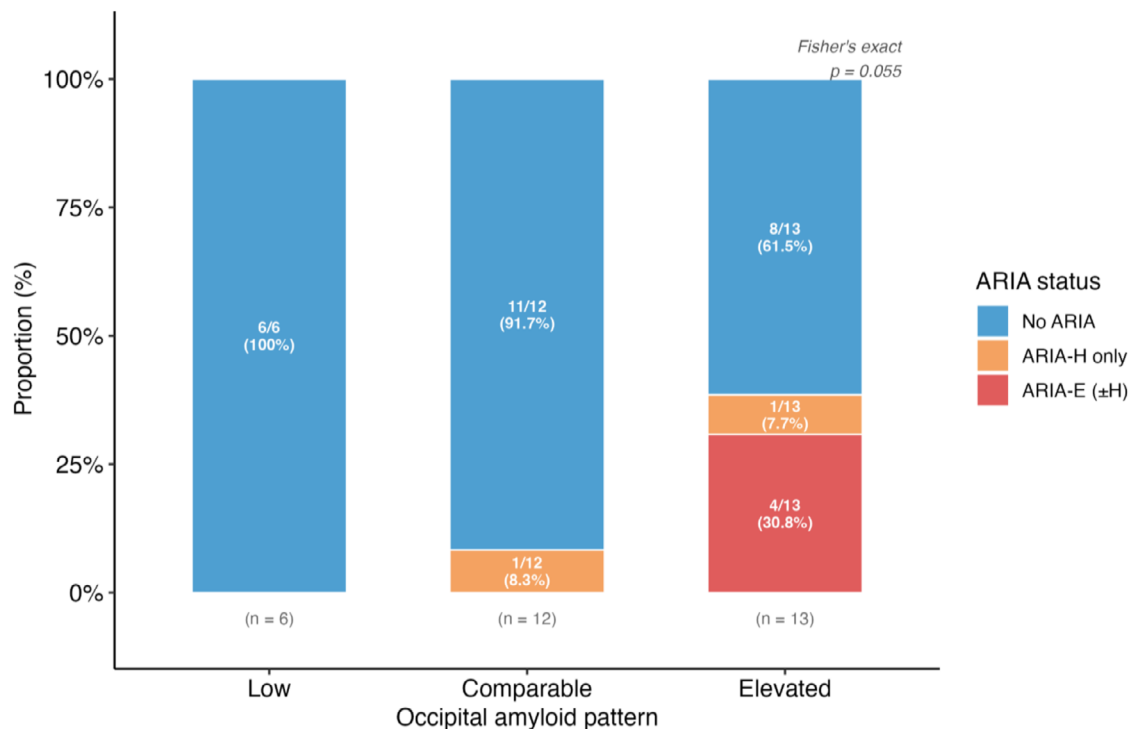


FIGURE 2 Distribution of ARIA according to baseline occipital amyloid pattern. Proportion of treatment courses with no ARIA, ARIA-H only, and ARIA-E ($\pm$ H) stratified by baseline occipital amyloid pattern (low, comparable, elevated; $n = 31$ treatment courses). Occipital amyloid pattern was defined using tertiles of residualized occipital SUVR derived from a linear regression model of occipital SUVR on global composite SUVR in the baseline PET derivation sample ($n = 53$) and then applied to the ARIA analytical cohort. ARIA-E was observed only in the elevated group, occurring in 4/13 treatment courses (30.8%), compared to 0/18 low or comparable courses. Isolated ARIA-H events occurred in one comparable and one elevated course. The p value refers to a Fisher exact test comparing ARIA-E occurrence (yes/no) across the three occipital pattern groups. ARIA, amyloid-related imaging abnormality; ARIA-E, amyloid-related imaging abnormality with edema/effusion; ARIA-H, amyloid-related imaging abnormality with microhemorrhage or superficial siderosis; PET, positron emission tomography; SUVR, standardized uptake value ratio.

$p = 0.027$). A β 42/40 was not associated with the elevated pattern ($\beta = 0.042$, $p = 0.154$).

As a continuous measure, occipital residual correlated with p-tau181 ($\rho = 0.461$, $p_{\text{adj}} = 0.036$) and p-tau217 ($\rho = 0.422$, $p_{\text{adj}} = 0.036$), while GFAP showed a weaker positive association ($\rho = 0.352$, $p_{\text{adj}} = 0.070$). A β 42/40 was not associated with continuous occipital residual ($\rho = 0.208$, $p_{\text{adj}} = 0.262$; Figure 3E–H).

3.4 | Plasma biomarkers as classifiers of elevated occipital pattern

At univariate ROC analysis, GFAP showed the highest exploratory discrimination for the elevated occipital pattern (AUC = 0.744, 95% CI: 0.560–0.927), followed by p-tau181 (AUC = 0.733, 95% CI: 0.548–0.918), p-tau217 (AUC = 0.726, 95% CI: 0.542–0.911), and A β 42/40 (AUC = 0.607, 95% CI: 0.385–0.829; Figure 4).

The prespecified GFAP + p-tau217 model achieved an apparent AUC of 0.761 (95% CI: 0.583–0.938), while leave-one-out cross-validation yielded an AUC of 0.679 (95% CI: 0.471–0.888; Figure 4). At the Youden-optimal threshold, the combined model showed 84.6% sensitivity (95% CI: 57.8–95.7), 72.2% specificity (95% CI: 49.1–87.5),

68.8% positive predictive value (95% CI: 44.4–85.8), 86.7% negative predictive value (95% CI: 62.1–96.3), and 77.4% accuracy (95% CI: 60.2–88.6). These estimates were interpreted descriptively.

4 | DISCUSSION

Anti-amyloid monoclonal antibodies have shifted early symptomatic AD care toward biologically targeted intervention, with ARIA-E as the principal safety concern.^{3,4} Because current risk stratification relies mainly on APOE ϵ 4 genotype and baseline hemorrhagic markers,^{5,7} our data suggest that regional amyloid topology may provide complementary risk information, although the small number of events precludes prediction.

In this EMA-labeled cohort, ARIA-E events clustered in patients with disproportionate occipital amyloid deposition. ARIA-E was observed only in the elevated occipital pattern group, whereas no events occurred in the low or comparable groups. However, this association was borderline at conventional statistical thresholds and based on only four ARIA-E events; therefore, it should be interpreted as hypothesis generating rather than as a validated risk-stratification model. Importantly, a sensitivity analysis excluding the only patient who contributed

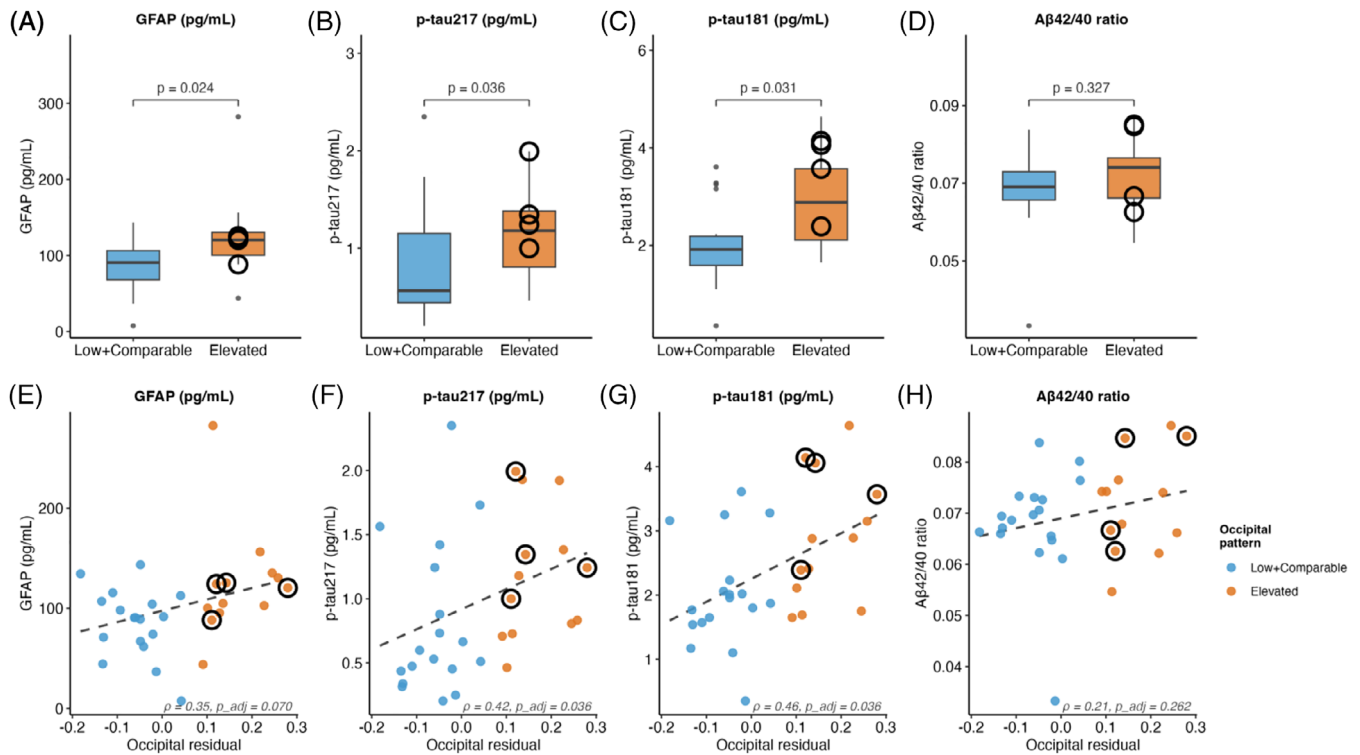


FIGURE 3 Baseline plasma biomarkers according to occipital amyloid pattern. A–D, Baseline plasma concentrations of GFAP, p-tau217, p-tau181, and Aβ42/40 stratified by binary occipital amyloid pattern (elevated vs. low + comparable). Group comparisons were performed using Wilcoxon rank-sum tests; nominal p values are shown. E–H, Association between continuous occipital residual and baseline plasma biomarkers. Spearman correlation coefficients (ρ) and Benjamini–Hochberg adjusted p values across the four displayed biomarkers are reported. Dashed lines represent linear fit for visualization purposes. Black circles indicate treatment courses that developed ARIA-E. Aβ, amyloid beta; ARIA-E, amyloid-related imaging abnormality with edema/effusion; GFAP, glial fibrillary acidic protein; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio.

two treatment courses showed that the ARIA-E enrichment in the elevated group was not driven by patient-level overrepresentation.

Global Centiloid values did not differ between ARIA and non-ARIA groups, suggesting that spatial amyloid distribution may capture information not reflected by total amyloid load alone. This distinction is relevant because global Centiloid metrics are derived from cortical composite regions that may not fully capture posterior regional heterogeneity, including occipital amyloid burden.^{24,26} In our cohort, all ARIA-E events involved the occipital lobe, either alone or with adjacent posterior regions, providing anatomical concordance with the baseline PET pattern. These findings are consistent with post hoc observations from donanemab trials, in which elevated occipital burden was associated with ARIA-E risk after adjustment for APOE ε4 status.^{3,8} Our data extend this concept to a real-world European setting, but with important differences, including routine clinical implementation, mixed anti-amyloid antibody exposure, and exclusion of APOE ε4 homozygotes under EMA labeling.

Posterior involvement is biologically plausible given the posterior predominance of CAA^{9,30} and occipital amyloid enrichment may distinguish vascular from more parenchymal-dominant amyloid patterns.⁹ However, we lacked direct measures of CAA, vascular amyloid, neuroinflammation, or blood–brain barrier permeability.^{11,30,31} Thus, dis-

proportionate occipital uptake should be interpreted as regional amyloid topology, not direct evidence of CAA or vascular dysfunction.

The APOE findings further underscore the need for caution. APOE ε4 heterozygosity was numerically less frequent in the elevated group, and all ARIA-E events occurred in APOE ε3/ε3 carriers. Although this may appear counterintuitive given the established role of APOE ε4 in ARIA risk, previous amyloid PET subtype work has similarly reported lower APOE ε4 prevalence in an occipital-predominant amyloid accumulation subtype.³² This should not be interpreted as evidence against the established role of APOE ε4 in ARIA risk, but likely reflects the small number of events, the absence of APOE ε4 homozygotes, and sampling variability. Larger cohorts with full APOE genotype representation will be required to determine whether occipital amyloid disproportion provides information independent of, or interacting with, APOE genotype.

The divergence between ARIA-E and baseline hemorrhagic MRI markers also requires caution. SWI-detected microbleeds were more frequent among ARIA cases overall, while GRE findings showed a similar numerical trend without reaching statistical significance. However, the elevated occipital pattern was not simply a surrogate for higher baseline global amyloid load, and isolated ARIA-H events occurred across different occipital patterns. These observations are compati-

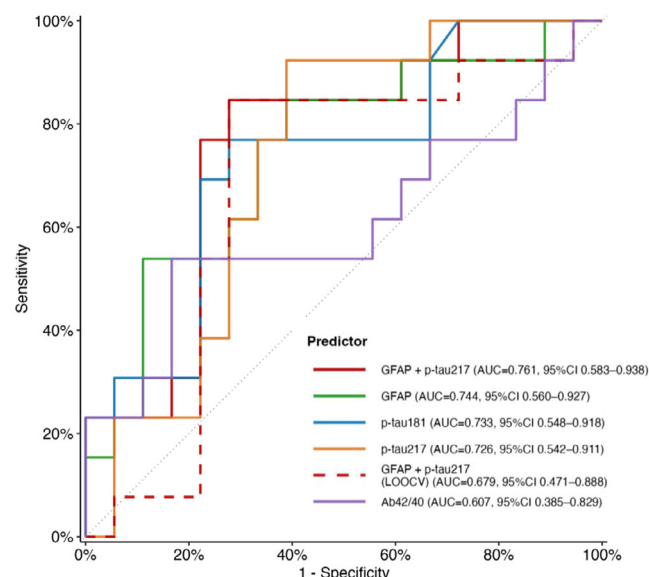


FIGURE 4 ROC curves of plasma biomarkers for discrimination of the elevated occipital amyloid pattern. ROC curves for baseline plasma biomarkers discriminating the elevated occipital amyloid pattern. Curves are shown for GFAP, p-tau217, p-tau181, A β 42/40, the combined GFAP + p-tau217 model, and the LOOCV GFAP + p-tau217 model. AUC values with 95% confidence intervals (DeLong method) are reported in the legend. The diagonal dotted line represents chance-level discrimination. These analyses were exploratory and were not intended to define validated clinical thresholds. A β , amyloid beta; AUC, area under the curve; GFAP, glial fibrillary acidic protein; LOOCV, leave-one-out cross-validation; p-tau, phosphorylated tau; ROC, receiver operating characteristic.

ble with partially distinct mechanisms underlying vasogenic ARIA-E and isolated hemorrhagic ARIA-H, although the sample size does not allow formal mechanistic separation. ARIA-E has been conceptualized as a vascular-inflammatory response to antibody-mediated amyloid mobilization, sharing some features with CAA-related inflammatory syndromes.^{8,31,33,34} Within this framework, regional amyloid topology may help identify territories more susceptible to vasogenic response during treatment, but this remains speculative.

Integration of plasma biomarkers provided an additional exploratory layer. Patients with an elevated occipital pattern exhibited higher baseline GFAP, p-tau217, and p-tau181 in unadjusted analyses, whereas A β 42/40 did not differ between groups. In adjusted and continuous analyses, the most consistent associations were observed for p-tau181 and p-tau217, while GFAP showed a weaker but directionally concordant pattern. GFAP reflects astrocytic activation and is closely linked to amyloid positivity and amyloid burden.^{12,35} P-tau species, particularly p-tau217, are strongly associated with AD pathophysiology and amyloid-related downstream tau biology.^{14,17,29} Therefore, the plasma profile observed here should be interpreted as a marker of amyloid-associated astroglial and p-tau biological activity, not as direct evidence of neuroinflammation, CAA, or blood-brain barrier dysfunction. The absence of a clear A β 42/40 difference suggests that

occipital amyloid disproportion is unlikely to be captured by a simple plasma amyloid ratio alone.

Renal function represents a potential confounder when interpreting plasma biomarker concentrations. In our cohort, estimated glomerular filtration rate (eGFR) was lower in treatment courses with any ARIA than in those without ARIAs. However, eGFR did not differ significantly between the elevated occipital pattern group and the low + comparable group, which was the primary comparison for the plasma biomarker analyses. This reduces the likelihood that the observed associations between elevated occipital amyloid pattern and higher GFAP/p-tau levels were driven primarily by renal function imbalance.

ROC analyses suggested that plasma biomarkers may provide exploratory discrimination of the elevated occipital pattern, with GFAP and p-tau species showing modest-to-moderate AUC values. The combined GFAP + p-tau217 model improved apparent discrimination only modestly, and leave-one-out cross-validation showed reduced performance with wide confidence intervals. These findings should not be interpreted as defining a clinically deployable plasma classifier. Rather, they suggest that plasma biomarkers may provide complementary biological information to regional PET topology and help prioritize future validation studies.³⁶

Several limitations must be acknowledged. This was a single-center retrospective study with a modest sample size and only four ARIA-E events, limiting statistical power and increasing uncertainty around all effect estimates. ARIA monitoring was performed on 1.5T MRI scanners as part of routine clinical care; therefore, subtle microhemorrhages or superficial siderosis may have been underestimated compared to optimized 3T protocols. The residualized occipital model was derived from an expanded baseline PET derivation sample, but not from an independent external validation cohort. The use of two amyloid PET tracers may introduce residual scaling variability, although no significant tracer interaction was observed. All ARIA-E events occurred in donanemab-treated courses, so our data cannot determine whether occipital amyloid disproportion is treatment agnostic or preferentially identifies vulnerability under a more rapidly amyloid-clearing agent. Treatment exposure was heterogeneous, and some patients had not reached later surveillance timepoints. Finally, direct measures of vascular amyloid, neuroinflammation, blood-brain barrier permeability, and longitudinal plasma biomarker dynamics were unavailable.

In summary, in this real-world European cohort treated with anti-amyloid monoclonal antibodies, ARIA-E events clustered in patients with disproportionate occipital amyloid burden despite comparable global amyloid load. This pattern was accompanied by higher plasma GFAP and p-tau biomarker levels, while A β 42/40 showed no clear association. These findings support further evaluation of regional PET topology and plasma biomarkers as complementary components of ARIA-E risk characterization, but require validation in larger multicenter cohorts before informing clinical surveillance strategies.

AUTHOR CONTRIBUTIONS

Federica Agosta, Giordano Cecchetti, and Massimo Filippi conceived the study and defined its conceptual framework. Federica Agosta, Giordano Cecchetti, and Massimo Filippi drafted the initial version

of the manuscript. Alma Ghirelli, Edoardo G. Spinelli, Giulia Rugarli, Stefano Pisano, Federico Coraglia, Ana Maria Samanes Gajate, Paolo Vezzulli, Sonia Calloni, Elisa Canu, Veronica Castelnovo, Anna Gilioli, Chiara Tripodi, Fabiola Freri, Alessandra Bianchi, Andrea Panzacchi, Gino Pepe, Andrea Falini, and Arturo Chiti contributed to data acquisition, clinical management, imaging analyses, and/or critical revision of the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

F. Agosta is associate editor of *NeuroImage: Clinical* and the *European Journal of Neurology*; has received speaker honoraria from Biogen Idec, Bristol Myers Squibb, Eisai, Eli Lilly, GE Healthcare, Neuraxpharm, and Roche; and receives or has received research supports from the Italian Ministry of Health, the Italian Ministry of University and Research, AriSLA (Fondazione Italiana di Ricerca per la SLA), the European Research Council (ERC), the EU Joint Programme–Neurodegenerative Disease Research (JPND), and Foundation Research on Alzheimer Disease (France). G. Cecchetti has received speaker honoraria from Neopharmed Gentili and Eli Lilly. A. Ghirelli received speaker honoraria from Eli Lilly. E.G. Spinelli received speaker honoraria from Eli Lilly. G. Rugarli has nothing to disclose. S. Pisano has nothing to disclose. F. Coraglia has nothing to disclose. A.M. Samanes Gajate has nothing to disclose. P. Vezzulli has nothing to disclose. S. Calloni has nothing to disclose. E. Canu has nothing to disclose. V. Castelnovo has nothing to disclose. A. Gilioli has nothing to disclose. C. Tripodi has nothing to disclose. F. Freri has nothing to disclose. A. Bianchi has nothing to disclose. A. Panzacchi has nothing to disclose. G. Pepe has nothing to disclose. A. Falini has nothing to disclose. A. Chiti reports consulting or advisory role for Blue Earth Diagnostics, Telix Pharmaceuticals, InnovaRadi Therapeutic, and General Electric Healthcare; and speaker's bureaus for Bracco Diagnostics, General Electric Healthcare, Novartis, Telix Pharmaceuticals, and United Imaging; he is editor in chief of *The EANM Journal*. M. Filippi is editor-in-chief of the *Journal of Neurology*; associate editor of *Human Brain Mapping*, *Neurological Sciences*, and *Radiology*; received compensation for consulting services from Almirall, Biogen, Bristol-Myers Squibb, Eli Lilly, Merck, Novartis, Roche, Sanofi; reports speaking activities from Amgen, Bayer, Biogen, Bristol-Myers Squibb, Celgene, Chiesi Italia SpA, Eisai, Eli Lilly, Fujirebio, Genzyme, Janssen, Merck, Neopharmed Gentili, Neuraxpharm, Novartis, Novo Nordisk, Roche, Sanofi, Takeda; participates on advisory boards for Alexion, Biogen, Bristol-Myers Squibb, Eli Lilly, GE Healthcare Ltd, Merck, Neuraxpharm, Novartis, Roche, Sandoz, Sanofi, Takeda; provides scientific direction of educational events for Biogen, Merck, Roche, Celgene, Bristol-Myers Squibb, Lilly, Novartis, Sanofi-Genzyme; and receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, the Italian Ministry of Health, the

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CONSENT STATEMENT

All participants provided written informed consent prior to inclusion. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

ORCID

Massimo Filippi  <https://orcid.org/0000-0002-5485-0479>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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