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ORIGINAL RESEARCH

Cerebrospinal Fluid Biomarkers Profiling in Cerebral Amyloid Angiopathy and Relationship With Disease Phenotypes

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BACKGROUND: Cerebral amyloid angiopathy (CAA) is a heterogeneous small vessel disease that can occur independently or alongside Alzheimer disease (AD). CAA is diagnosed using the Boston Criteria 2.0, integrating clinical and neuroimaging features, whereas the Cerebrospinal Fluid (CSF) role in clinical practice remains under investigation. This study explores whether CSF biomarkers can identify distinct disease phenotypes, supporting hemorrhagic risk stratification.

METHODS: We enrolled probable patients with CAA retrospectively (Boston Criteria 2.0) from 2 institutions, collecting clinical, neuroimaging, and follow-up data alongside core CSF biomarkers (Aβ40 [amyloid β 1–40], Aβ42 [amyloid β 1–42], p-Tau181 [phosphorylated Tau], total-Tau). Patients with CAA were stratified applying the Amyloid Tau Neurodegeneration (ATN) research framework, according to the presence of CSF amyloidosis (A^+CAA versus A^-CAA) and tauopathy (A^+T^+CAA versus A^+T^-CAA), and using unsupervised clustering, which defined CAA subgroups based on CSF biomarker levels only. Kaplan-Meier and Cox regression analyses assessed the predictive value of CSF-based subgroups for symptomatic hemorrhages during follow-up.

RESULTS: Seventy-one probable CAA patients (aged 71.77±8.45 years, 66% men, median follow-up 1.15 years [0.50–2.44]) were enrolled. A^+CAA showed a higher prevalence of cortical superficial siderosis than A^-CAA (67% versus 25%, P=0.016). A^+T^-CAA had a greater hemorrhagic risk than A^+T^+CAA during follow-up (29 versus 7 events per 100 patient-years, P=0.010; log-rank test: P=0.013). Unsupervised clustering identified 2 subgroups, which we defined as pure CAA and CAA-ADA, with pure CAA presenting more symptomatic hemorrhages during follow-up (22 versus 0 events per 100 patient-years, P=0.017; log-rank test, P=0.011).

CONCLUSIONS: CSF-based profiling effectively stratifies CAA phenotypes, offering a promising prognostic tool alongside neuroimaging markers. Further validation is needed to confirm its role in identifying patients with CAA with different natural histories.

Key Words: AT(N) framework ■ cerebral amyloid angiopathy ■ CSF biomarkers ■ phenotype

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CLINICAL PERSPECTIVE

What Is New?

- Cerebral amyloid angiopathy (CAA) is a highly heterogeneous age-related small vessel disease, and given its variability, phenotypic stratification is crucial in clinical practice.
- In this study, Cerebrospinal Fluid biomarker profiling offered meaningful phenotypic and prognostic insights in patients with CAA. A CAA-like Cerebrospinal Fluid pattern without evidence of comorbid tauopathy (pure CAA) was associated with a higher hemorrhagic risk profile compared with an Alzheimer disease-like pattern (CAA-AD).

What Are the Clinical Implications?

- Core Cerebrospinal Fluid biomarkers may serve as a readily available single-test tool for the initial evaluation of CAA, simultaneously supporting diagnosis and discerning biologically defined patient subgroups with different clinical trajectories.

Nonstandard Abbreviations and Acronyms

AT(N)	Amyloid Tau Neurodegeneration research framework
CAA	cerebral amyloid angiopathy
CMB	cerebral microbleed
cSS	cortical superficial siderosis
ICH	intracerebral hemorrhage
pTau	phosphorylated Tau
TFNE	transient focal neurological episode

Cerebral amyloid angiopathy (CAA) is a common age-related small-vessel disease that is characterized by the accumulation of β-amyloid in small and medium-sized cerebral and leptomeningeal arteries and capillaries. This deposition induces both hemorrhagic and nonhemorrhagic microangiopathic damage and, in advanced stages, cognitive decline and spontaneous intracerebral hemorrhage (ICH).[1] CAA can occur as an independent entity but is neuropathologically detected in the context of Alzheimer disease (AD) in at least 50% of patients,[2,3] representing a biological continuum.[4] However, the significance of the coexistence of these two pathologies in relation to CAA hemorrhagic manifestations has yet to be fully clarified.

Current diagnostic criteria (Boston Criteria 2.0) are based on a combination of pathological, clinical, and neuroimaging parameters, which include lobar ICH, cortical superficial siderosis (cSS), convexity subarachnoid hemorrhage (cSAH), strictly lobar cerebral microbleeds (CMBs), and nonhemorrhagic markers, such as white matter hyperintensity in a multispot pattern and enlarged perivascular spaces in the centrum semiovale (CSO-EPVS).[5] The latest criteria showed excellent diagnostic accuracy for CAA with hemorrhagic manifestations,[5] but appear to have reduced reliability in asymptomatic subjects and patients presenting with cognitive complaints.[6] In this context, a biological support for the diagnosis would be advantageous, particularly in challenging cases, and the novel pathophysiological framework provides a rationale for biomarkers application.[7] Despite the growing evidence about the existence of a specific Cerebrospinal Fluid (CSF) biomarker profile in CAA,[8,9] characterized by reduced Aβ42 (amyloid β 1–42) and Aβ40 (amyloid β 1–40) levels and a relatively preserved level of total-Tau and phosphorylated tau (pTau) compared with AD and healthy controls, these molecular signatures have not yet been incorporated into diagnostic criteria. This is in contrast with other related diseases, such as AD, for which a biological marker is now considered essential for an accurate diagnosis.[10]

The clinical manifestations and natural history of patients with CAA are typically heterogeneous,[1] and the prediction of the individual clinical evolution from a baseline evaluation, particularly on the risk of developing an ICH,[11] is currently challenging. The management of patients in this complex scenario would be greatly improved by clear stratification of CAA phenotypes.[11] Neuroimaging markers play a pivotal role in this aim, with both cSS and previous ICH having been demonstrated to confer a markedly elevated risk of hemorrhagic events.[12,13] In AD, misfolded protein levels in the CSF have been proposed to provide not only diagnostic information, but also prognostic value, and to be able to identify subjects with more active neurodegeneration.[14,15] Conversely, CAA data on biological biomarker patterns that correspond to a more aggressive disease course are scarce.[16,17]

The potential for CSF profiles to serve as an intriguing diagnostic and prognostic tool in these subjects is yet to be fully explored. The aim of this study was to ascertain whether CSF core AD biomarkers can offer insights for the classification of CAA phenotypes, particularly for the identification of a high-risk subgroup with a proclivity for hemorrhagic events.

METHODS

The anonymized data and code that support the findings of this study will be made available from the corresponding author (M. Pardini) upon reasonable request.

Ethical Approval and Patient Consent

All procedures contributing to this work comply with the ethical standards of the relevant national and

institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Patients were enrolled, and written informed consent was obtained from all participants as part of an observational protocol approved by the ethics committee (NCT04204642). The article was prepared with reference to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Study Participants and Inclusion/ Exclusion Criteria

Consecutive patients with a diagnosis of probable CAA in accordance with the Boston Criteria 2.0 that were in effect at the time of diagnosis (modified Boston Criteria 1.5 up to May 2022 and Boston Criteria 2.0 from June 2022[5,18]) were enrolled retrospectively in 2 Italian research hospitals: the IRCCS Ospedale Policlinico San Martino (Genoa) and the IRCCS C. Mondino Foundation (Pavia), between January 2019 and September 2024. Clinical charts were reviewed, and all patients with CAA fulfilling the following inclusion criteria were included: (1) patients who retrospectively met the criteria for probable CAA according to Boston Criteria 2.0[5]; (2) patients accepted during diagnostic workup to perform lumbar puncture, which was performed within 6 months from baseline magnetic resonance imaging (MRI) (from diagnosis); (3) age between 50 and 85 years; (4) in cases of hemorrhagic presentation, neuroimaging excluded secondary causes of hemorrhage. Exclusion criteria were: (1) patients with history of CAA-related inflammation,[19,20] (2) presence of radiological evidence of deep hemorrhages (micro- or macrobleeding), (3) motion artifacts or missing sequences in MRI protocol, (4) contraindications to perform lumbar puncture. CSF analysis was offered to all probable patients with CAA during this period as part of the initial diagnostic workup, based on clinical indication (eg, cognitive decline, exclusion of differential diagnoses, or to support diagnosis).

We collected demographics and medical and drug history of enrolled patients with CAA. Clinical presentations were divided into the following categories, according to the Boston Criteria 2.0: hemorrhagic presentation (ICH or cSAH), transient focal neurological episodes (TFNE) or cognitive presentation (mild cognitive impairment, MCI, or dementia). Global cognitive performance was evaluated using the Mini-Mental State Examination (MMSE). We also collected the occurrence of clinically symptomatic lobar ICH or cSAH during follow-up, which was defined as an acute neurological syndrome associated with neuroimaging evidence of a corresponding ICH (at least 10 mm in diameter) or cSAH.[21] Follow-up was performed by a comprehensive systematic chart review of all available information (including discharge summaries and follow-up outpatient evaluations). Outcome events were assessed using all clinical and radiologic information available, blinded to the CSF findings.

MRI Acquisition and Analysis

Baseline MRI scans (1.5T or 3T) were first evaluated for diagnostic purposes by 2 expert neuroradiologists (L.M.F. and L.R.), who verified the inclusion criteria for enrolment. Hemorrhagic and nonhemorrhagic features were evaluated according to updated STandards of Reporting Vascular changes on nEuroimaging (STRIVE) criteria.[22] Blood-sensitive sequences used to evaluate hemorrhagic features were T2 gradient echo sequences or susceptibility-weighted imaging. Hemorrhagic lesions were visually classified as follows: number of CMBs (according to Microbleed anatomical Rating Scale, MARS, classification, hemorrhagic lesions <10 mm in diameter),[23] were assessed as low (<3 CMBs), mild (between 4 and 10 CMBs), or high burden (>10 CMBs). Lobar ICH (hemorrhagic lesion ≥10 mm) was identified and assessed as present or absent. cSS was classified as present or absent and then scored according to the cSS multifocality score (from 0, absent to 4, disseminated bihemispheric cSS).[24] White matter hyperintensities were scored according to the Fazekas scale on T2 or fluid-attenuated inversion recovery-weighted sequences,[25] whereas CSO-EPVS were detected on T2-weighted sequences and assessed as low (<20) or high (>20) burden. Then, the composite small vessel disease CAA score (CAA-SVD score - range from 0 to 6) was calculated, as previously described.[25] Hippocampal and parietal atrophy was scored according to the Scheltens and Koedam scale on 3-dimensional T1-weighted and T2-fluid-attenuated inversion recovery sequences.[26]

Two independent raters (M.C.R. and L.G., a neurologist with expertise in neuroimaging and a neuroradiologist, respectively) rated the MRI images, blinded to CSF biomarker profile and clinical data. In cases of disagreement, the images were collectively reexamined to achieve a final consensus.

CSF Collection and Analysis

Following standard operating procedures, CSF samples (6–8 mL) were obtained via lumbar puncture at the L3-L4 or L4-L5 interspace in the early morning.[27] The CSF was collected using sterile polypropylene tubes, then centrifuged at 4000*g* for 10 minutes at 4 °C. To ensure the long-term stability of proteins, the resulting aliquots were stored in polypropylene tubes at −80 °C until analysis. We used the same assay in the 2 centers, the Lumipulse G600 II fully automated chemiluminescent enzyme immunoassay system (Fujirebio Europe, Gent, Belgium) to measure core AD-related CSF biomarkers (Aβ42, Aβ40, p-Tau181, and total-Tau)

in individuals with CAA and AD. Assay cartridge datasheet cutoffs were also verified in our centers: 600 pg/mL for Aβ42; 0.069 pg/mL for Aβ42/40 ratio, 404 pg/mL for total-Tau; 56.5 pg/mL for pTau.[28] Intratest reproducibility had an average coefficient of variation <10%, and intertest reproducibility averaged <15% for all assays.

Statistical Analysis

First, clinical, radiological, and biomarker values of patients with CAA were compared between centers. We identified CAA subgroups based on the Amyloid Tau Neurodegeneration research framework (AT[N]),[29] using previously specified a priori cutoffs, to explore any clinical, radiological, and outcome differences between AT(N)-based subgroups. To this aim, we divided probable CAA subjects into those with evidence of reduced Aβ42 levels, indicating biological evidence of β-amyloidosis (amyloid-positive probable CAA [A^+CAA]) and those without (amyloid-negative probable CAA [A^-CAA]). We then further classified patients with CAA based on pTau levels, dividing the A^+CAA group into T^+ and T^- subjects (ie, A^+T^+CAA and A^+T^-CAA, respectively) and the A^-CAA group into T^+ and T^- subjects (ie, A^-T^+CAA and A^-T^-CAA, respectively). We used Aβ42 levels as the primary stratification method for patients with CAA, because this approach has been previously reported in studies on this population.[16] Furthermore, Aβ40 levels are known to be decreased in patients with CAA,[9] potentially impacting the accuracy of the Aβ42/40 ratio as a measure of β-amyloidosis. However, we also performed an explorative analysis of changes in AT(N) classification in patients with CAA by using the Aβ42/40 ratio rather than Aβ42, given its superior accuracy in detecting cerebral amyloidosis in AD.[30] This analysis was conducted to verify the consistency of the results obtained with Aβ42-based classification.

Subsequently, we performed an unsupervised clustering (ie, a clustering on unlabeled data) using the K-means method on the levels of core CSF biomarkers (Aβ42, Aβ40, and p-Tau181), to identify CSF-based CAA subgroups in a data-driven manner. K-means was selected for its computational efficiency, interpretability, and suitability for detecting compact, nonoverlapping clusters, aligning with our goal of delineating clear patient profiles based on CSF patterns. Total-Tau levels were excluded as a clustering variable because they can be influenced by acute insults, such as recent hemorrhagic events,[31] which could introduce bias in cluster collocations. Missing Aβ40 values were imputed through linear regression using Aβ42 and p-Tau181 as predictors (see Figure S1). Before performing unsupervised clustering, a Z score normalization was performed on CSF biomarker values to ensure comparability across variables and to prevent any single biomarker from disproportionately influencing the clustering results. The Elbow method and Silhouette score were used to determine the ideal number of clusters for the automated clustering. The clustering result was validated by repeating the K-means with the leave-1-out technique, and the adjusted rand index was computed to measure the similarity among the leave-1-out clustering, allowing for assessing and validating the stability of the clusters that were later analyzed.

Descriptive statistics were expressed as mean±SD or median and interquartile range, as appropriate. The distribution of continuous variables was assessed using histograms and the Shapiro-Wilk test. Patients' data (clinical, radiological, CSF values, and annualized symptomatic hemorrhagic events during follow-up) were compared between subgroups based on the AT(N) framework and between unsupervised clusters, using a Kruskal–Wallis test for pairwise comparisons for continuous variables or using χ^2 tests for categorical variables. All statistical analyses were corrected for multiple comparisons using the false discovery rate (FDR) correction method.

We used the CSF-based CAA subgroup, according to the AT(N) framework and unsupervised clustering, as univariate predictors of ICH risk using Kaplan-Meier plots with significance testing by the log-rank test. Survival time was calculated from baseline evaluation until the occurrence of symptomatic hemorrhages at follow-up or the last known date without the outcome event of interest. We included in the main analysis only the subset of patients with at least 6 months of follow-up. However, the results of the entire cohort have also been provided. For individuals who experienced multiple lobar ICHs during follow-up, the data were censored at the time of the first ICH. Data were also censored at the time of death from causes other than documented symptomatic ICH. Cox regression analysis was performed to calculate the univariate and multivariate hazard ratio (HR) for symptomatic hemorrhages in different CSF-based subgroups, including in the multivariate models the known predictors of recurrent lobar ICH. Other covariates demonstrating a univariable association with the outcome in Cox regression analysis (P<0.1) were also considered for inclusion, and we included age in all the multivariate models, considering it a potential confounder. We constructed a directed acyclic graph to illustrate the hypothesized relationships between variables and hemorrhagic risk, guiding covariate selection in the multivariable models (Figure S2). Collinearity among covariates was assessed before model implementation, and model performance was evaluated with the concordance index and the likelihood ratio test. The proportional hazards assumption was assessed using Schoenfeld residuals. Robust standard errors were used in Cox regression to account for potential model

misspecification and small-sample bias. Survival analysis and hemorrhagic rates during follow-up stratified by CSF profile were also evaluated in a subgroup of CAA known to be at high hemorrhagic risk (previous lobar ICH, TFNE, or presence of cSS), to explore CSF values in this specific CAA subpopulation.

Statistical analysis was performed using Jamovi (version 2.3; https://www.jamovi.org), R (version 4.1.1; http://www.r-project.org/), and Python (version 3.12.2). The threshold for statistical significance was set to $P \leq 0.05$.

RESULTS

Probable CAA Population

Seventy-one probable patients with CAA were enrolled in the study, and a flowchart of patient selection is provided in Figure 1. The clinical and radiological features of the cohort at baseline are reported in Table 1. Aβ40 levels and MMSE scores were available in 63 out of 71 and 64 out of 71 patients, respectively. To note, in 5 patients, lumbar puncture was performed <1 month after a hemorrhagic event. The most prevalent initial presentation in our CAA cohort was cognitive impairment (58%; n=41), followed by hemorrhagic onset (27%; n=19) and TFNE (7%; n=5). The remaining patients (8%; n=6) had different clinical presentations (ischemic stroke, n=4; parkinsonism, n=2) in the presence of concomitant cognitive impairment and were thus included according to Boston Criteria 2.0. Thirty-three patients with CAA (47%) had >10 lobar CMBs, and 41 (58%) had cSS, of which 30 (42%) were disseminated. Fifty-six patients (79%) had at least 6 months of follow-up. During a median follow-up time of 1.15 years (interquartile range, 0.50–2.44 years), 12 patients (17%) presented at least 1 symptomatic hemorrhagic event. The results of the comparison of patients with CAA between centers and more information about the cohort are reported in Data S1.

As a reference for CSF biomarkers and to confirm the CAA-associated CSF pattern of our population, we have provided in Data S2 a group of age-matched patients with MCI or dementia due to AD[32,33] without hemorrhagic radiologic features. Patients with CAA showed lower levels of Aβ42, Aβ40, pTau, and total-Tau, but similar Aβ42/40 ratio, compared with AD (see Table S1 and Figure S3).

CAA Subgroups Classification Based on A Priori CSF Cutoffs

Characteristics of probable CAA classified according to CSF profile are shown in Table 2, and the

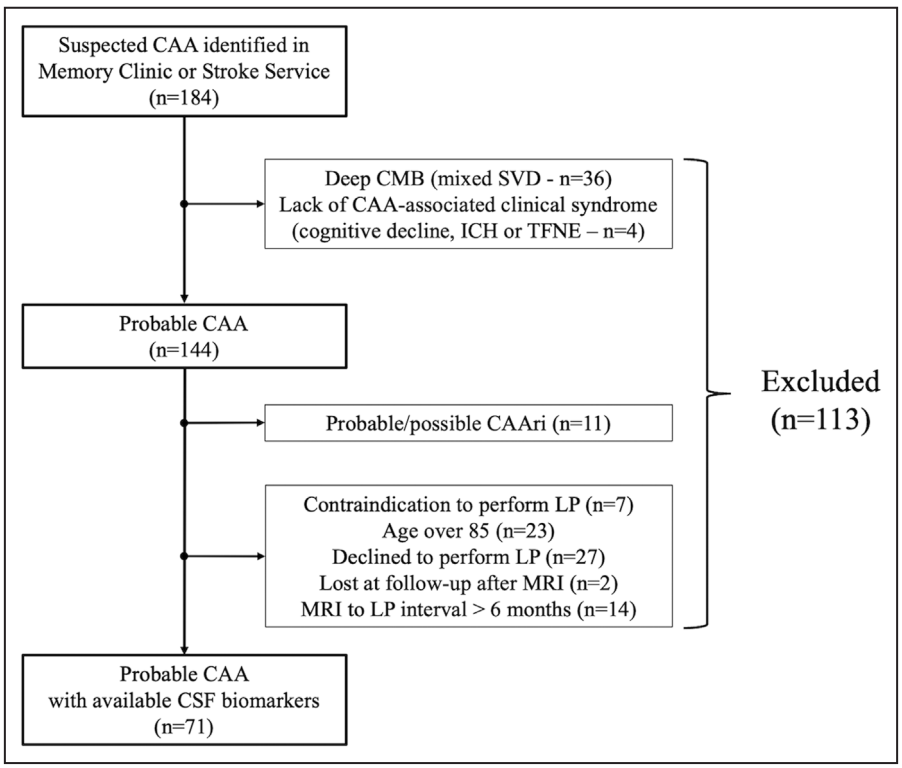

Figure 1. Flowchart of patient selection.
CAA indicates cerebral amyloid angiopathy; CAAri, CAA-related inflammation; CMB, cerebral microbleed; CSF, Cerebrospinal Fluid; ICH, intracerebral hemorrhage; LP, lumbar puncture; MRI, magnetic resonance imaging; SVD, small vessel disease; and TFNE, transient focal neurological episode.

Table 1. Demographic, Clinical, MRI, and CSF Data of Our CAA Cohort

	Probable CAA (n=71)
Sex, men, n (%)	47 (66)
Age at MRI, y	73.5 (66.0–78.0)
Age at onset, y	72.0 (64.8–75.7)
MMSE at MRI	26.0 (22.0–28.0)
Aβ42	372 (320–554)
Aβ40	8018 (6522-10990)
Aβ42/40 ratio	0.05 (0.04–0.06)
t-Tau	460 (313–787)
pTau	61 (38–105)
Cardiovascular risk factors, n (%)	
Hypertension	49 (69)
Dyslipidemia	43 (61)
Smoking	13 (18)
Chronic kidney disease	0 (0)
Diabetes	8 (11)
Atrial fibrillation	3 (4)
Anticoagulation	6 (9)
Antiplatelets	20 (28)
Cognitive onset	41 (58)
ICH onset	19 (27)
TFNE onset	5 (7)
Neuroimaging features	
3T MRI, n (%)	39 (55)
Fazekas scale, DWM	2 (2–3)
CSO-EPVS>20, n (%)	29 (41)
Lobar CMB burden, n (%)	
Low (0–3)	17 (24)
Mild (4–10)	21 (30)
High (>10)	33 (47)
cSS, n (%)	41 (58)
cSS multifocality score	1 (0–2)
CAA-SVD score	3 (2.5–4)
Lobar ICH, n (%)	22 (31)
Scheltens scale	1 (1–2)
Koedam scale	1 (0–1.5)
Follow-up, y	1.90 (1.00–3.00)
Annualized symptomatic hemorrhages during follow-up	0.13±0.34

Values are expressed as mean±SD or median (interquartile range), as appropriate, and CSF protein levels in picograms per milliliter. Fazekas scale ranges from 0 to 3. CMBs are expressed as <3, between 3 and 10, and >10. Multifocality score for cSS ranges from 0 to 4. The CAA-SVD score ranges from 0 to 6. Outcome measures and follow-up are referred to the subset of patients who have >6 months of follow-up. Aβ40 indicates amyloid β 1–40; Aβ42, amyloid β 1–42; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; CSF, Cerebrospinal Fluid; CSO-EPVS, Enlarged Perivascular Space of the centrum semiovale; cSS, cortical superficial siderosis; DWM, deep white matter; ICH, intracerebral hemorrhage; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; pTau, phosphorylated Tau; SVD, small vessel disease; TFNE, transient focal neurological episode; and t-Tau, total-Tau.

proportion of AT(N)-based subgroups are shown in Figure 2. Fifty-five probable patients with CAA (77.5%) presented a decreased CSF Aβ42 level using the AD standard cutoff (A^+CAA), whereas 16 patients with CAA (22.5%) had normal Aβ42 levels (A^-CAA). Based on the p-Tau181 cutoff, 35 patients of the A^+CAA group (49.3% of the entire cohort) were further subcategorized as A^+T^+CAA, whereas the remaining 20 patients (28.2%) were subcategorized as A^+T^-CAA. Of the 16 patients in the A^-CAA group, 7 (9.8%) were A^-T^+CAA, and 9 (12.7%) were A^-T^-CAA. Subgroup classification applying the Aβ42/40 ratio instead of Aβ42 alone is shown in Figure 2 and further explored in Data S3. Of note, 5 patients changed their classification from A^-CAA to A^+CAA (mainly A^-T^+CAA), increasing the percentage of patients classified as A^+ from 77.5% to 84.1%.

When comparing A^+CAA with A^-CAA, we found no significant differences in baseline age and MMSE score, nor in the distribution of clinical presentations. Focusing on neuroimaging features, A^+CAA had a higher prevalence of cSS (67% versus 25%; $P^{[uncorrected]}$=0.003; $P^{[FDR\text{-}adjusted]}$=0.016), a higher cSS multifocality score ($P^{[uncorrected]}$=0.001; $P^{[FDR\text{-}adjusted]}$=0.009), and CAA-SVD score ($P^{[uncorrected]}$=0.011; $P^{[FDR\text{-}adjusted]}$=0.041). In regard to hemorrhagic outcome, in the subset of patients with at least 6 months of follow-up, we observed the reporting of new symptomatic hemorrhagic events at follow-up only in the A^+CAA group (n=47) and none in the A^-CAA group (n=9; 0.16±0.37 events per year, which correspond to 16 events per 100 patient-years versus 0.00±0.00 events per year; $P^{[uncorrected]}$=0.133).

Comparing A^+T^+CAA and A^+T^-CAA, we observed a higher nonsignificant proportion of patients with A^+T^+CAA with a cognitive presentation (69% versus 43%; $P^{[uncorrected]}$=0.063) and a numerically higher hemorrhagic presentation in patients with A^+T^-CAA (17% versus 40%; $P^{[uncorrected]}$=0.070). There were no significant differences between these subgroups from a neuroimaging viewpoint, although there was a higher proportion of 3T-MRI in patients with A^+T^+CAA ($P^{[uncorrected]}$=0.053). In regard to outcome measures, patients with A^+T^-CAA (n=19) had a greater number of hemorrhagic events during follow-up than patients with A^+T^+CAA (n=28) (A^+T^-CAA: 0.29±0.41 events per year, or 29 events per 100 patient-years; A^+T^+CAA: 0.07±0.31 events per year, or 7 events per 100 patient-years; $P^{[uncorrected]}$=0.005; $P^{[FDR\text{-}adjusted]}$=0.010).

In a subgroup analysis, considering only the subset of CAA at known high hemorrhagic risk (previous lobar ICH, TFNE, or presence of cSS, n=33), patients with A^+T^-CAA were confirmed to have higher hemorrhagic rates during follow-up than patients with A^+T^+CAA, although nonsignificant after FDR correction (A^+T^-CAA, n=16: 0.35±0.43 events per year, or 35 events per 100 patient-years; A^+T^+CAA, n=17: 0.11±0.40 events per year, or 11 events per 100 patient-years; $P^{[uncorrected]}$=0.022; $P^{[FDR\text{-}adjusted]}$=0.113).

Table 2. Clinical and Radiological Characteristics, CSF Biomarker, and Hemorrhagic Outcome in the AT(N)-Based Subgroups

	A^+ CAA (n=55)	A^- CAA (n=16)	*P* value	A^+T^+ CAA (n=35)	A^+T^- CAA (n=20)	*P* value
Sex, men, n (%)	33 (60)	14 (88)	0.041	21 (60)	12 (60)	1.000
Age at MRI, y	73.0 (66.5–78.0)	74.5 (65.8–76.3)	0.967	74.0 (70.3–78.0)	72.0 (63.5–80.0)	0.502
Age at onset, y	72.0 (64.5–75.5)	71.0 (64.5–76.0)	0.962	72.0 (65.3–74.8)	72.0 (62.5–78.3)	0.714
MMSE at MRI	25.0 (22.0–28.0)	26.0 (24.3–27.8)	0.596	25.0 (22.0–28.0)	27.0 (22.0–29.0)	0.284
Aβ42	355 (312–434)	705 (648–916)	<0.001	351 (315–460)	362 (316–403)	0.714
Aβ40	7541 (6275–9409)	10990 (8421–13659)	0.013	8454 (6702–10708)	6460 (5583–7856)	0.044
Aβ42/40 ratio	0.05 (0.04–0.05)	0.09 (0.06–0.10)	<0.001	0.04 (0.04–0.05)	0.05 (0.05–0.06)	<0.001
t-Tau	449 (308–811)	493 (367–691)	0.828	728 (472–846)	259 (212–324)	<0.001
pTau	64 (39–110)	48 (40–70)	0.224	102 (65–124)	36 (28–42)	<0.001
Cardiovascular risk factors, n (%)						
Hypertension	36 (66)	13 (81)	0.218	21 (60)	15 (75)	0.229
Dyslipidemia	30 (55)	13 (81)	0.054	22 (63)	8 (40)	0.121
Smoking	8 (15)	5 (31)	0.128	4 (11)	4 (20)	0.234
Chronic kidney disease	0 (0)	0 (0)	1.000	0 (0)	0 (0)	1.000
Diabetes	6 (11)	2 (13)	0.859	4 (11)	2 (10)	0.885
Atrial fibrillation	2 (4)	1 (6)	0.647	1 (3)	1 (5)	0.699
Anticoagulation	4 (7)	2 (13)	0.508	3 (9)	1 (5)	0.891
Antiplatelets	15 (27)	5 (31)	0.756	13 (37)	2 (10)	0.025
Cognitive onset	33 (60)	8 (50)	0.476	24 (69)	9 (45)	0.063
ICH onset	15 (27)	4 (25)	0.857	6 (17)	8 (40)	0.070
TFNE onset	4 (7)	1 (6)	0.888	1 (3)	3 (15)	0.101
Neuroimaging features						
3T MRI, n (%)	32 (58)	7 (44)	0.307	24 (69)	8 (40)	0.053
Fazekas scale, DWM	2 (2–3)	2 (2–3)	0.788	2 (2–3)	2 (2–3)	0.786
CSO-EPVS>20, n (%)	24 (44)	5 (31)	0.366	15 (43)	10 (50)	0.551
Lobar CMB burden, n (%)						
Low (0–3)	13 (24)	4 (25)	0.969	9 (26)	4 (20)	0.616
Mild (4–10)	16 (29)	5 (31)		11 (31)	5 (25)	
High (>10)	26 (47)	7 (44)		15 (43)	11 (55)	
cSS, n (%)	37 (67)	4 (25)	0.016	22 (63)	15 (75)	0.319
cSS multifocality score	2 (0–3)	0 (0–0.25)	0.009	1.5 (0–2)	1.5 (0.75–3)	0.233
CAA-SVD score	4 (3–5)	3 (2–3)	0.041	4 (3–4)	4 (3–5)	0.224
Lobar ICH, n (%)	18 (33)	4 (25)	0.556	10 (29)	8 (40)	0.301
Scheltens scale	1 (1–2)	1 (0.75–2)	0.768	1.5 (1–2)	1 (0.75–2)	0.108
Koedam scale	1 (0–2)	1 (0–1)	0.630	1 (0–2)	1 (0–1)	0.718
Follow-up, y	2.0 (1.0–3.0)	1.5 (1.0–2.3)	0.455	2.00 (0.76–2.6)	2.00 (1.16–3.00)	0.322
Annualized symptomatic hemorrhages during follow-up	0.16±0.37	0.00±0.00	0.133	0.07±0.31	0.29±0.41	0.010

Values are expressed as median (interquartile) and CSF protein levels in picograms per milliliter. Fazekas scale ranges from 0 to 3. CMBs are expressed as <3, between 3 and 10, and >10. Multifocality scores for cSS range from 0 to 4. The CAA-SVD score ranges from 0 to 6. Outcome measures and follow-up are referred to the subset of patients who have >6 months of follow-up. For comparisons between groups, categorical variables were compared using the χ^2 test and continuous variables using the Kruskal-Wallis test. *P* values were corrected for multiple comparisons using the false discovery rate correction. Aβ40, amyloid β 1–40; Aβ42, amyloid β 1–42; AT(N), amyloid Tau neurodegeneration research framework; A+CAA, Amyloid-positive CAA; A-CAA, Amyloid-negative CAA; A+T+CAA, Amyloid-positive Tau-positive CAA; A+T-, Amyloid-positive Tau-negative CAA; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; CSF, Cerebrospinal Fluid; CSO-EPVS, enlarged perivascular space of the centrum semiovale; cSS, cortical superficial siderosis; DWM, deep white matter; ICH, intracerebral hemorrhage; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; pTau, phosphorylated Tau; SVD, small vessel disease; TFNE, transient focal neurological episode; and t-Tau, total Tau.

Similar results on clinical, radiological features, and hemorrhagic outcome were observed by comparing patients with A^+ versus A^-CAA classified using the Aβ42/40 ratio, patients with T^+ versus T^-CAA (ie, without considering A status), and patients with A^+T^+ versus A^+T^-CAA classified using the Aβ42/40 ratio.

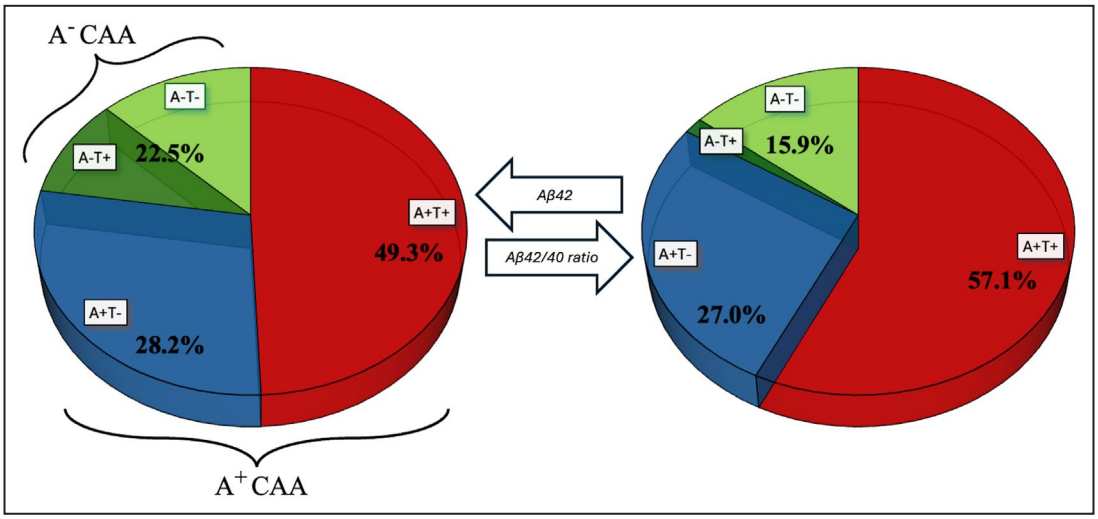

Figure 2. Proportions of AT(N)-based subgroups in our CAA cohort.
(Left) Proportions using Aβ42 levels as a reference to classify patients as amyloid-positive (A^+) status. (Right) Changes of classification applying the Aβ42/Aβ40 ratio. A indicates amyloidosis; Aβ40 indicates amyloid β 1–40; Aβ42, amyloid β 1–42; AT(N), amyloid Tau neurodegeneration research framework; CAA, cerebral amyloid angiopathy; and T, tauopathy.

Unsupervised Clustering of CAA Patients

Outlier patients on CSF protein values (n=3) were excluded from the clustering computation (2 A^-CAA and 1 A^+T^+CAA). The Elbow method and Silhouette score, combined with leave-1-out validation, revealed the presence of 2 stable clusters (a 3-cluster configuration was identified but excluded due to instability). Only 9 patients were found to be close to the decision boundary of the unsupervised clustering, whereas most of the cohort was clearly separated into the 2 clusters (Table 3).

Compared with Cluster 2 (n=28), Cluster 1 (n=40) had lower levels of Aβ40 (mean 6761±1550 versus 11 257±2252 pg/mL, $P^{[FDR\text{-}adjusted]}<0.001$), Aβ42 (mean 371.5±152.0 versus 593.8±276.8 pg/mL, $P^{[FDR\text{-}adjusted]}<0.001$), pTau (mean 51.9±24.1 versus 104.8±51.1 pg/mL, $P^{[FDR\text{-}adjusted]}<0.001$), and total-Tau (421±243 versus 739±307pg/mL, $P^{[FDR\text{-}adjusted]}<0.001$), with similar levels of Aβ42/40 ($P^{[FDR\text{-}adjusted]}=0.225$). Cluster 1 was thus labeled as pure CAA given the CSF pattern (low Aβ40, low pTau, and low total-Tau), whereas Cluster 2 was labeled as CAA-AD (Figure 3). Aβ40 proved to have the highest statistical significance in separating the patients into 2 clusters.

When comparing the 2 clusters, no significant differences in baseline MMSE and age were found. Pure CAA subjects had more frequent hemorrhagic presentations (38% versus 7%; $P^{[uncorrected]}=0.014$; $P^{[FDR\text{-}adjusted]}=0.048$), a greater prevalence of cSS (75% versus 32%; $P^{[uncorrected]}=0.001$; $P^{[FDR\text{-}adjusted]}=0.013$), a higher cSS multifocality score ($P^{[uncorrected]}=0.006$; $P^{[FDR\text{-}adjusted]}=0.016$), and a higher but nonsignificant CAA-SVD score ($P^{[uncorrected]}=0.030$; $P^{[FDR\text{-}adjusted]}=0.055$) compared with CAA-AD. Most of the high hemorrhagic risk CAA (n=26; 78.8%) were classified as pure CAA. In the subset of patients with at least 6 months of follow-up, we observed more frequent symptomatic hemorrhagic events per year during follow-up in the pure CAA group (n=32) compared with the CAA-AD group (n=22), with 0.23±0.43 events per year, corresponding to 22 events per 100 patient-years in the former group, versus 0 events in the latter ($P^{[uncorrected]}=0.004$; $P^{[FDR\text{-}adjusted]}=0.015$). Moreover, pure CAA that developed ICH during follow-up (n=10) presented even lower levels of pTau, although not statistically significant (mean 43.5±23.9 versus 55.0±23.6 pg/mL; $P^{[uncorrected]}=0.091$) compared with the other pure CAA.

ICH Risk Across CAA Subgroups: Survival Analysis

In Kaplan-Meier analysis (Figure 4), the AT(N)-based classification of CAA (i.e., A^-CAA, A^+T^+CAA, and A^+T-CAA) was a predictor of time until symptomatic ICH during follow-up ($P=0.013$, by the log-rank test; $P=0.063$ when including patients with <6 months of follow-up). The risk of symptomatic hemorrhage at 24 months was 26.3% (95% CI, 3.6%–43.7%) for patients with A^+T^-CAA and 4.8% (95% CI, 0.0%–13.4%) for patients with A^+T^+CAA.

In univariate analysis, classifying patients as A^+T^-CAA was a predictor of reduced time until symptomatic hemorrhages compared with A^+T^+CAA (HR, 5.04 [95% CI, 1.03–24.50]; $P=0.045$), and it remained an

Table 3. Clinical and Radiological Features, CSF Biomarkers, and Hemorrhagic Outcome of Data-Driven CSF-Based Clusters of Patients With CAA

	Cluster 1 (pure CAA), n=40	Cluster 2 (CAA-AD), n=28	*P* value
Sex, men, n (%)	26 (65)	18 (64)	1.000
Age at MRI, y	73.5 (65.8–78.0)	73.5 (66.8–76.0)	0.962
Age at onset, y	72.0 (62.5–76.0)	71.0 (65.0–74.0)	0.975
MMSE at MRI	26.0 (22.0–28.5)	26.0 (23.5–28.0)	0.944
Aβ42	344 (299–417)	513 (370–650)	<0.001
Aβ40	6701 (6202–7777)	11 086 (9116–11 086)	<0.001
Aβ42/40 ratio	0.051 (0.045–0.059)	0.043 (0.037–0.050)	0.225
t-Tau	349 (260–530)	769 (541–926)	<0.001
pTau	45 (36–64)	110 (68–135)	<0.001
Cardiovascular risk factors, n (%)			
Hypertension	27 (68)	19 (68)	1.000
Dyslipidemia	21 (53)	20 (71)	0.562
Smoking	8 (20)	4 (14)	0.873
Chronic kidney disease	0 (0)	0 (0)	1.000
Diabetes	6 (15)	1 (4)	0.637
Atrial fibrillation	1 (3)	2 (7)	0.960
Anticoagulation	1 (3)	2 (7)	0.960
Antiplatelets	9 (23)	11 (39)	0.430
Cognitive onset	19 (48)	21 (75)	0.164
ICH onset	15 (38)	2 (7)	0.048
TFNE onset	3 (8)	2 (7)	1.000
Neuroimaging features			
3T MRI, n (%)	22 (55)	15 (54)	1.00
Fazekas scale, DWM	2 (2–3)	2 (2–3)	0.877
CSO-EPVS>20, n (%)	16 (40)	11 (40)	0.966
Lobar CMB burden, n (%)			
Low (0–3)	10 (25)	6 (21)	0.950
Mild (4–10)	11 (28)	9 (32)	
High (>10)	19 (48)	13 (46)	
cSS, n (%)	30 (75)	9 (32)	0.013
cSS multifocality score	2 (0.75–3.25)	0 (0–1.25)	0.016
CAA-SVD score	4 (3–5)	3 (2–4)	0.055
Lobar ICH, n (%)	16 (40)	4 (14)	0.164
Scheltens scale	1 (1–2)	1 (1–2)	0.958
Koedam scale	1 (0–1)	1 (0–2)	0.912
Follow-up, y (interquartile range)	1.9 (1.0–3.0)	1.5 (1.0–2.3)	0.716
Annualized symptomatic hemorrhages during follow-up	0.23±0.43	0.00±0.00	0.015

Values are expressed as median (IQR) and CSF protein levels in pg/mL. Fazekas scale in deep white matter range from 0 to 3. CMB are expressed as <3, between 3 and 10 and >10. Multifocality scores for cSS range from 0 to 4. Outcome measures and follow-up are referred to the subset of patients who had >6 months of follow-up. For comparisons between groups, categorical variables were compared using the χ^2 test and continuous variables using the Kruskal–Wallis test. *P* values were corrected for multiple comparisons using the false discovery rate correction. Aβ40 indicates amyloid β 1–40; Aβ42, amyloid β 1–42; AD, Alzheimer disease; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; CSO-EPVS, enlarged perivascular space of the centrum semiovale; cSS, cortical superficial siderosis; DWM, deep white matter; ICH, intracerebral hemorrhage; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; pTau, phosphorylated Tau; SVD, small vessel disease; TFNE, transient focal neurological episode; and t-Tau, total-Tau.

independent predictor after including the presence of disseminated cSS in the multivariate model (HR, 5.46 [95% CI, 1.22–24.38]; *P*=0.026), but not including the presence of a previous lobar ICH in the model (Table 4). The HR in A^+CAA was not calculated due to the lack of hemorrhagic events in the A^-CAA group. In the subset of CAA at high hemorrhagic risk, it was classified as A^+T^-CAA predict time until symptomatic

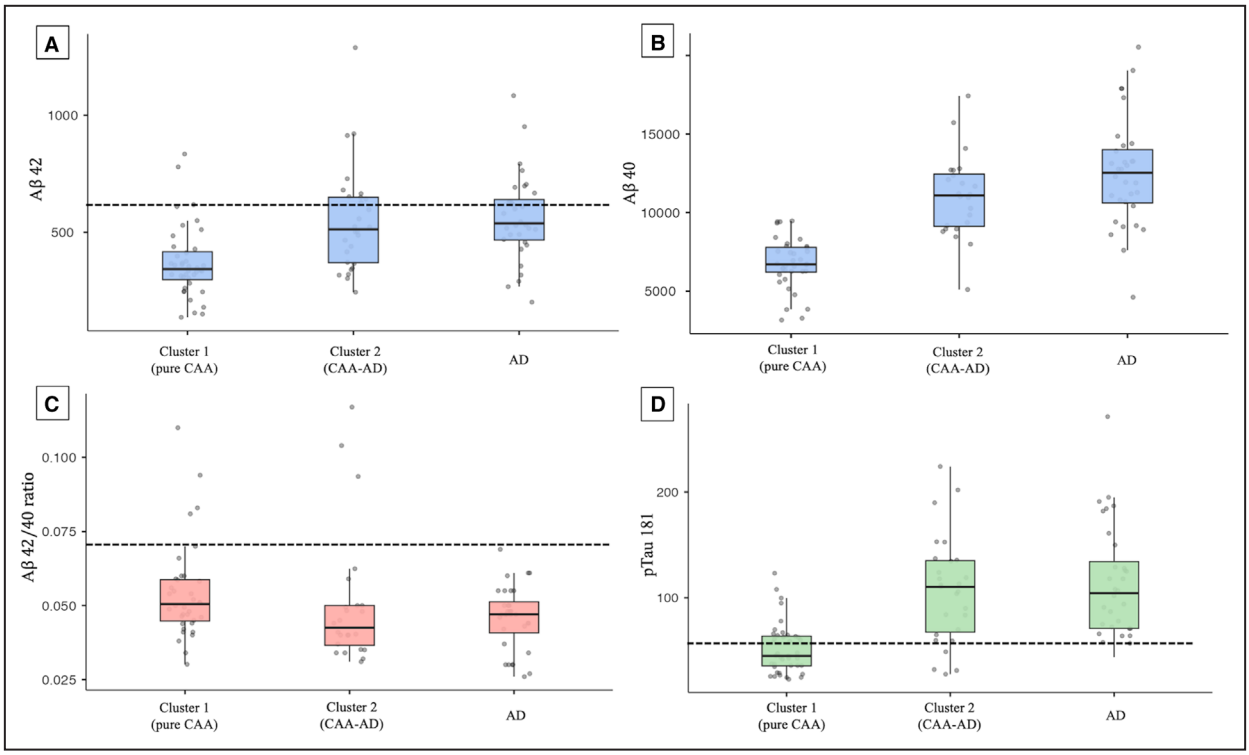

Figure 3. CSF biomarker levels in data-driven CAA clusters.
Box plot illustrating CSF biomarkers in different data-driven CSF-based clusters of probable CAA compared with an AD reference cohort. **A**, CSF level of Aβ42; **B**, CSF level of Aβ40. **C**, CSF level of Aβ42/Aβ40 ratio. **D**, CSF level of p-Tau181. The dotted lines represent the standard cut-offs used at our centers. Aβ40 indicates amyloid β 1–40; Aβ42, amyloid β 1–42; AD, Alzheimer disease; CAA, cerebral amyloid angiopathy; CSF, Cerebrospinal Fluid; and p-Tau181, phosphorylated Tau 181.

ICH with borderline significance both in the univariate analysis (*P*=0.040, by the log-rank test; HR, 4.44 [95% CI, 0.96–20.59]; *P*=0.057) and in a multivariate analysis including a previous lobar ICH (HR, 4.01 [95% CI, 0.92–17.44]; *P*=0.064), but it was an independent predictor in the multivariate model including disseminated cSS (HR, 5.03 [95% CI, 1.10–23.01]; *P*=0.037).

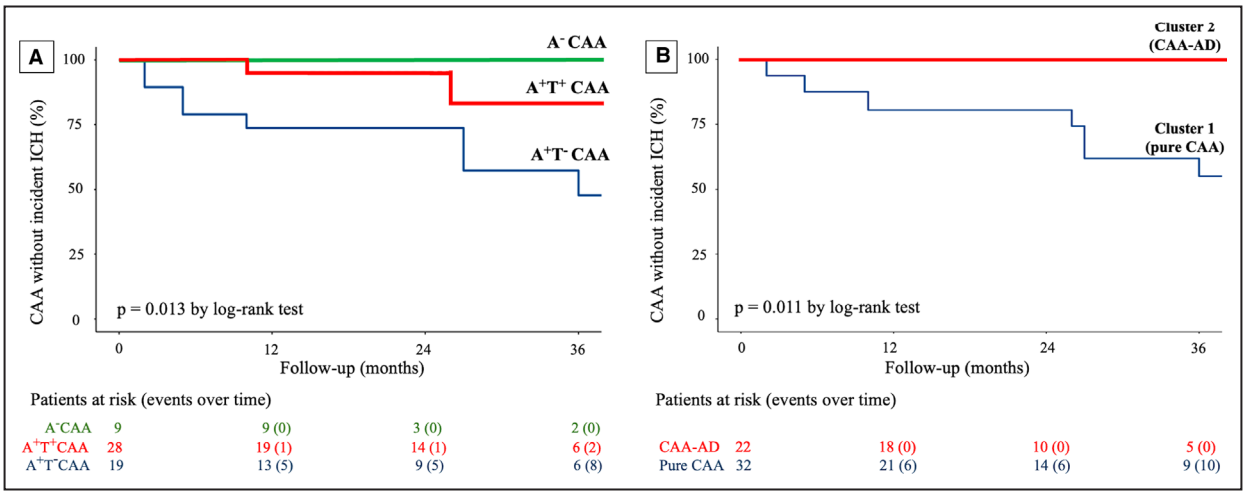

Figure 4. Survival analysis of CSF-based CAA subgroup.
Kaplan-Meier curves on (**A**) AT(N)-based CAA subgroup and (**B**) data-driven clusters on CSF protein levels. Testing of significance is by the log-rank test. A indicates amyloid; AD, Alzheimer disease; AT(N), amyloid Tau neurodegeneration research framework; CAA, cerebral amyloid angiopathy; CSF, Cerebrospinal Fluid; ICH, intracerebral hemorrhage; and T, tauopathy.

Table 4. Cox Regression Analyses of Clinical, Radiological, and CSF-Based Predictors of Symptomatic Hemorrhage During Follow-Up in Patients With CAA

Variable	HR (95% CI)	*P* value
Univariate analysis		
Age (for each year of increase)	0.97 (0.90–1.03)	0.323
Sex	0.98 (0.27–3.55)	0.981
Hypertension (yes vs no)	0.78 (0.20–3.08)	0.723
High WMH burden (Fazekas>2)	1.42 (0.42–4.72)	0.697
High CMB burden (>10)	0.78 (0.24–2.56)	0.686
High Scheltens scale (>1)	0.83 (0.25–2.82)	0.770
High Koedam scale (>1)	0.67 (0.13–3.32)	0.621
High CSO-EPVS burden (>20)	2.64 (0.73–9.56)	0.138
cSS (yes vs no)	/	/
Disseminated cSS (vs no or focal cSS)	4.59 (1.29–16.40)	0.019
Lobar ICH (yes vs no)	12.80 (2.97–54.80)	<0.001
AT(N)-based CAA group (A^+ vs A^-)	/	/
AT(N)-based CAA group (A^+T^- vs A^+T^+)	5.04 (1.03–24.50)	0.045
Data-driven clusters (pure CAA vs CAA-AD)	/	/
Multivariate analysis		
Model 1 (C index=0.818; likelihood ratio test=9.5; *P*=0.023)		
Age (for each y of increase)	1.00 (0.93–1.06)	0.907
Disseminated cSS (vs no or focal cSS)	3.86 (1.14–13.03)	0.029
AT(N)-based CAA group (A^+T^- vs A^+T^+)	5.46 (1.22–24.38)	0.026
Model 2 (C index=0.858; likelihood ratio test=16.5; *P*=0.001)		
Age (for each y of increase)	1.01 (0.95–1.08)	0.644
Lobar ICH (yes vs no)	10.98 (2.58–46.65)	0.001
AT(N)-based CAA group (A^+T^- vs A^+T^+)	4.04 (0.91–17.73)	0.064

HR for cSS (yes vs no), A^+CAA (vs A^-CAA), and data-driven CSF clusters were not calculated due to the absence of events in CAA without cSS, in the A^-CAA and the CAA-AD group. In the univariate analysis, HR refers to the entire CAA cohort with at least 6 months of follow-up (n=56). Multivariate models were restricted to A^+CAA (n=47) to explore the predictive value of an A^+T^- CSF profile compared with A^+T^+. MTA and PCA scales were divided into high and low atrophy by a median split. A indicates amyloidosis; AD, Alzheimer disease; AT(N), amyloid Tau neurodegeneration research framework; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; CSF, Cerebrospinal Fluid; CSO-EPVS, enlarged perivascular space of the centrum semiovale; cSS, cortical superficial siderosis; HR, hazard ratio; ICH, intracerebral hemorrhage; T, tauopathy, and WMH, white matter hyperintensity.

Considering unsupervised subgroups, we did not observe any hemorrhagic events in the CAA-AD group, whereas the risk of symptomatic hemorrhage at 24 months of follow-up was 19.5% (95% CI, 4.1%–32.4%) for patients with pure CAA. Kaplan-Meier analysis (Figure 4) confirmed that being classified in the pure CAA cluster was a predictor of time until symptomatic ICH compared with CAA-AD cluster (*P*=0.011, by the log-rank test). HR was not calculated due to the lack of hemorrhagic events in the CAA-AD group. Similar results were obtained including patients with <6 months of follow-up *P*=0.030, by the log-rank test).

DISCUSSION

This was a retrospective multicentric study conducted in a cohort of probable patients with CAA with available AD-related CSF biomarkers, with the aim of identifying distinct biological CAA phenotypes in a clinical setting. In our cohort, probable CAA without evidence of tauopathy (A^+T^-CAA, according to the AT(N) framework[29]) exhibited a higher hemorrhagic risk over time compared with probable CAA with an AD-like CSF profile (A^+T^+CAA). The hemorrhagic risk was 5 times higher in A^+T^-CAA compared with A^+T^+CAA, corresponding to an absolute 24-month risk of 26.3% versus 4.8%. An independent unsupervised analysis of the same data set further enhanced the separation of CAA into 2 groups. Briefly, patients with CAA with low Aβ40 and pTau, which we named pure CAA (ie, without an AD-like CSF biomarker pattern), had an ≈10% annual risk of developing a symptomatic hemorrhagic event, whereas patients with an AD-like CSF profile (CAA-AD) did not develop any events. This finding indicates that a CAA-like CSF profile at baseline may serve as a valuable tool for identifying patients with CAA with a greater risk of developing macrohemorrhages.

Although the Boston Criteria 2.0 remains the cornerstone for in vivo CAA identification,[5] there is an increasing demand in clinical practice for a biological support to diagnosis. From a diagnostic perspective, amyloid markers in CAA are an area of great interest,[34,35] yet standardization remains an unmet need. Recent meta-analyses have highlighted that the CSF profile of patients with CAA can differ from healthy controls and AD subjects,[8,9] even if this is highlighted only at the group level. We confirmed this CAA-related CSF pattern in our cohort, with CAA exhibiting similar biological evidence of β-amyloidosis (low Aβ42 and Aβ42/40 ratio), but with lower levels of Aβ40 and pTau compared with AD. Although we chose to use Aβ42 as the reference for A status classification of patients with CAA, as done in previous studies,[16] the use of the Aβ42/40 ratio in our data set was associated with a higher percentage of CAA subjects classified as A^+ (77.5% versus 84.1%). The neuropathological reliability of the Aβ42/40 ratio, as opposed to Aβ42, has not been well explored in CAA. However, the good concordance observed in our cohort between average Boston Criteria 2.0 specificity and the proportion of A^+CAA cases suggests that further investigation is warranted to substantiate the CSF capacity to depict in vivo CAA neuropathology. In this regard, the higher sensitivity of unsupervised clusters to identify CAA with a more hemorrhagic profile could indicate that the current AD cutoffs may not be fully

appropriate to classify patients with CAA. Therefore, a specific validation process for CAA is required to optimize them.

Despite a biological continuum between CAA and AD, and similar mean Aβ42 (or Aβ42/40 ratio), we did not find evidence of CSF β-amyloidosis (A^-CAA) in 22.5% and 15.9%, considering Aβ42 and Aβ42/40 ratio, respectively. Although this may be related to the use of existing non-CAA-specific cutoffs, the implications of diagnosing a probable CAA in the absence of biological evidence of amyloidosis have yet to be fully delineated. Furthermore, the presence of false-positive cases applying the Boston Criteria is acknowledged.[36] Patients with A^-CAA, even if relatively underrepresented, appeared to be a subgroup with extremely low prevalence of cSS, a radiological marker highly specific for CAA,[37,38] lower global CAA-burden (CAA-SVD score), and without symptomatic hemorrhages during follow-up, another typical feature of CAA. A neuropathological investigation of this subgroup could yield significant insights, providing evidence to perform CSF examination to support or rule out CAA diagnosis in clinically relevant situations (ie, probable CAA in a patient with an indication for anticoagulation).

CAA frequently gives rise to challenging clinical decision-making scenarios, particularly in patients with concomitant hemorrhagic and ischemic risk or indications to antithrombotic therapy.[39] In this context, the assessment of hemorrhagic risk represents a fundamental aspect of the management of patients with CAA[40] and currently is primarily based on clinical presentation[41] and radiological evaluation, with cSS, TFNE, and previous lobar ICH representing the most reliable predictors of hemorrhagic recurrence.[12] Emerging evidence suggests a potential role for fluid biomarkers in predicting (re)bleeding, with published correlations with neurofilament light chain and neuroinflammatory markers, such as YKL-40.[42,43] Our observations suggest that the CSF biomarkers pattern, applying AT(N) system categories[29] or data-driven clustering, may aid in hemorrhagic risk stratification, emerging in some models as an independent predictor beyond known hemorrhagic risk markers and showing an effect size comparable with disseminated cSS (A^+T^-CAA versus A^+T^+CAA HR, 5.04 versus disseminated cSS HR, 4.59). This can lead to potential practical implications, such as avoiding anticoagulation when unnecessary in patients with a high-risk CSF profile. Although CSF biomarkers are increasingly accessible in clinical settings due to the growing demand in memory clinics, further investigations should explore whether plasma biomarkers can provide similar information with less invasiveness.[44] Given the current pathophysiological framework of CAA,[7] which considers CSF changes to occur early in the disease history, the identification of a hemorrhagic CSF (or plasma) pattern lays the groundwork for exploring biomarkers during the presymptomatic stage of the disease, in an attempt to predict the individual patient's trajectory.

These data contribute to clarifying the biological basis of different clinical profiles observed in patients with β-amyloidosis and the established continuum between CAA and AD. Previously published data highlighted that Aβ42 levels are negatively associated with a prohemorrhagic CAA profile.[45] Aβ40 levels emerged as a major driver of our CSF-based unsupervised clustering. Aβ40 has been previously regarded as an indicator of brain Aβ production.[30] However, as demonstrated in a recent meta-analysis[9] and by our findings, low Aβ40 in the context of reduced level of Aβ42 can be considered a hallmark of significant amyloid vascular involvement. Our findings corroborate in vivo and extend previous neuropathological evidence indicating a reduced frequency of neurofibrillary tangles in CAA subjects who present with acute ICH compared with those with other presentations (42% versus 87%).[46] Although these data provide pathological evidence of an increased high-risk profile in CAA subjects without evident CSF tauopathy, further molecular studies are required to elucidate the influence between vascular amyloid deposition and Tau pathology, as well as the role of Aβ40 levels as a marker of hemorrhagic tendency.

A subgroup of patients in our cohort had a short follow-up period and was therefore excluded from the main outcome analysis, considering a minimum follow-up of at least 6 months to enhance the solidity of observations. Two subjects with hemorrhagic onset, 1 belonging to the CAA-AD and the other to the pure CAA cluster (both A^+T^+CAA), subsequently experienced a fatal hemorrhage while hospitalized (<2 weeks from the index event), potentially introducing a survivor bias in the results. Although their inclusion did not substantially modify the results of the survival analysis, we decided to exclude them from the main outcome analysis due to our focus on long-term prognosis and the potential differences in the pathophysiological mechanisms underlying early hemorrhagic recurrence, the so-called ICH cluster.[47] Nevertheless, these cases underline the unmet need for short-term hemorrhagic risk indicators, such as neuroinflammatory markers,[42] which could also represent a potential mechanism to target impending events.[48]

This study has some limitations that are inherent to its retrospective and clinical nature. First, there is heterogeneity in the MRI protocols, both in terms of the magnetic field strength and the sequences used, which hampers uniform interpretation, particularly on hemorrhagic features.[37,49] However, all key sequences necessary to assess radiological features were included. Second, the sample size in each clinical and CSF-based subgroup was relatively small. In particular,

hemorrhagic and TFNE presentations are underrepresented in our cohort, and the high prevalence of CAA with cognitive onset may have influenced the proportion of CSF profiles, which probably do not accurately reflect a naturalistic cohort. The inclusion of more patients with hemorrhagic presentation and without evidence of β-amyloidosis is warranted to validate the results in this specific CAA subgroup. Despite this, the CSF profile of our cohort was confirmed to be distinct from an AD cohort, as reported in meta-analyses,[9] and the use of 2 independent analytical approaches enhances confidence in the results. Third, the absence of a systematic neuropsychological evaluation and apolipoprotein E (APOE) genotyping in our cohort precluded further characterization of our CAA population and a more detailed investigation of the clinical and cognitive overlap between CAA and AD. Fourth, we relied on the Boston Criteria 2.0 for diagnosis, without neuropathological confirmation, as discussed previously. Fifth, although CSF analysis was systematically proposed during the study period, selection bias was intrinsic in specific clinical situations (eg, patients with severe ICH and poor short-term prognosis, who rarely undergo MRI scanning). Finally, the study design precludes the formulation of conclusions on the diagnostic accuracy of the Aβ42/40 ratio in comparison with Aβ42 alone; nevertheless, this was not the principal focus of our investigation.

Our findings suggest that CAA with low CSF levels of Aβ40 and pTau (that we named pure CAA) can be identified as a subgroup at high risk for hemorrhagic events. Consequently, CSF biomarkers could represent a valuable and readily available tool for the initial assessment of CAA, allowing clinicians to support diagnosis and discern CSF-based patient subgroups with different clinical trajectories. The identification of biological CAA subgroups could enrich the current pathophysiological framework[7] and aid in the characterization of disease phenotypes,[50] incorporating the CAA-AD continuum as part of this concept. Further investigation is required to substantiate these findings, but if confirmed in other cohorts, it would become useful in clinical settings, supporting hemorrhagic risk stratification. Finally, the CAA-like CSF pattern could also be a driver for future disease-modifying therapies, including those that selectively reduce hemorrhage risk,[51,52] as well as for the management of AD antiamyloid immunotherapies,[53] which have a higher probability of leading to amyloid-related imaging abnormalities in patients with comorbid CAA.

CONCLUSIONS

CSF biomarkers may effectively assist in the characterization of CAA, offering a promising tool beyond neuroimaging markers. If confirmed in independent cohorts, CSF profiling could represent a biological window to CAA phenotypes, potentially aiding in hemorrhagic risk stratification.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Data S1
Table S1
Figures S1–S3

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