Stroke

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Clinical, Neuroimaging, and Genetic Markers in Cerebral Amyloid Angiopathy-Related Inflammation: A Systematic Review and Meta-Analysis

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BACKGROUND: There are limited data regarding the prevalence of distinct clinical, neuroimaging and genetic markers among patients diagnosed with cerebral amyloid angiopathy–related inflammation (CAA-ri). We sought to determine the prevalence of clinical, radiological, genetic and cerebrospinal fluid biomarker findings in patients with CAA-ri.

METHODS: A systematic review and meta-analysis of published studies including patients with CAA-ri was conducted to determine the prevalence of clinical, neuroimaging, genetic and cerebrospinal fluid biomarker findings. Subgroup analyses were performed based on (1) prospective or retrospective study design and (2) CAA-ri diagnosis with or without available biopsy. We pooled the prevalence rates using random-effects models and assessed the heterogeneity using Cochran-Q and I^2-statistics.

RESULTS: We identified 4 prospective and 17 retrospective cohort studies comprising 378 patients with CAA-ri (mean age, 71.5 years; women, 52%). The pooled prevalence rates were as follows: cognitive decline at presentation 70% ([95% CI, 54%–84%]; I^2=82%), focal neurological deficits 55% ([95% CI, 40%–70%]; I^2=82%), encephalopathy 54% ([95% CI, 39%–68%]; I^2=43%), seizures 37% ([95% CI, 27%–49%]; I^2=65%), headache 31% ([95% CI, 22%–42%]; I^2=58%), T2/fluid-attenuated inversion recovery-hyperintense white matter lesions 98% ([95% CI, 93%–100%]; I^2=44%), lobar cerebral microbleeds 96% ([95% CI, 92%–99%]; I^2=25%), gadolinium enhancing lesions 54% ([95% CI, 42%–66%]; I^2=62%), cortical superficial siderosis 51% ([95% CI, 34%–68%]; I^2=77%) and lobar macrohemorrhage 40% ([95% CI, 11%–73%]; I^2=88%). The prevalence rate of the ApoE (Apolipoprotein E) ε4/ε4 genotype was 34% ([95% CI, 17%–53%]; I^2=76%). Subgroup analyses demonstrated no differences in these prevalence rates based on study design and diagnostic strategy.

CONCLUSIONS: Cognitive decline was the most common clinical feature. Hyperintense T2/fluid-attenuated inversion recovery white matter lesions and lobar cerebral microbleeds were by far the most prevalent neuroimaging findings. Thirty-four percent of patients with CAA-ri have homozygous ApoE ε4/ε4 genotype and scarce data exist regarding the cerebrospinal fluid biomarkers and its significance in these patients.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cerebral amyloid angiopathy–related inflammation ■ classification ■ prevalence

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Nonstandard Abbreviations and Acronyms

Aβ	amyloid-β
ApoE	apolipoprotein E
CAA	cerebral amyloid angiopathy
CAA-ri	cerebral amyloid angiopathy–related inflammation
CMB	cerebral microbleed
CSF	cerebrospinal fluid
cSS	cortical superficial siderosis
FLAIR	fluid-attenuated inversion recovery

Cerebral amyloid angiopathy–related inflammation (CAA-ri) is a distinct, however, rare subset of CAA and is characterized by deposition of Aβ (amyloid-β) in the media and adventitia of cortical and leptomeningeal vessels and a perivascular nondestructive accumulation of inflammatory cells.[1–3]

CAA-ri presents with various clinical manifestations such as mild cognitive impairment or rapidly progressive cognitive decline, focal neurological deficits, encephalopathy, headache, and seizures.[4] Common neuroimaging characteristics in patients with CAA-ri include cerebral microbleeds (CMBs), unifocal or multifocal, cortical or subcortical, asymmetric T2/fluid-attenuated inversion recovery (FLAIR) hyperintense white matter lesions, lesions with gadolinium-enhancement, cortical superficial siderosis (cSS), spontaneous lobar intracerebral hemorrhage, and cortical infarcts.[5–7]

CAA-ri is an increasingly recognised entity, since the recent diagnostic criteria in collaboration with the greater availability of the high resolution magnetic resonance imaging availability allow a reliable noninvasive diagnosis of probable/possible CAA-ri, avoiding the risk of brain biopsy.[8,9]

The diagnosis remains however a clinical challenge, since the early suspicion-recognition and the prompt immunosuppressive therapy initiation could mitigate the symptoms and imaging abnormalities and could also improve the prognosis of CAA-ri.

Scarce data exist regarding the prevalence of distinct clinical, neuroimaging, and genetic markers among patients diagnosed with CAA-ri. In view of the former considerations, we conducted a systematic review and meta-analysis of available studies, to correlate the clinical burden of various clinical features and neuroimaging findings among patients with CAA-ri and to assess their prevalence rates. Furthermore, we sought to evaluate the prevalence rates of genetic and cerebrospinal fluid biomarker findings.

METHODS

Data Availability Statement

The datasets used and analyzed during the current study are included in this article and its Supplemental Material. More detailed datasets are available from the corresponding author on reasonable request.

Standard Protocol Approvals, Registrations, and Patient Consents

Our study adheres to the AHA Journals' implementation of the transparency and Openess Promotion (TOP) Guidelines. The pre-specified protocol of the systematic review and meta-analysis has been registered in the International Prospective Register of Ongoing Systematic Reviews PROSPERO (CRD42022304425). The meta-analysis is reported according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[10] and was written according to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) proposal.[11] This study did not require an ethical board approval or written informed consent by the patients according to the study design (systematic review and meta-analysis).

Data Sources and Database Searches

A systematic literature search was conducted to identify eligible studies reporting on patients with CAA-ri. The literature search was performed independently by 3 reviewers (A.T., L.P., and C.Z.). We searched MEDLINE and Scopus, using search strings that included the following terms: "Cerebral Amyloid Angiopathy-related inflammation" and "CAA-ri"; the complete search algorithm used in MEDLINE and Scopus is described in the Supplemental Methods. The details on database search are included in the Methods section of the Supplemental Material. No language or other restrictions were applied. Our systematic literature search was conducted up to May 5, 2022 for each electronic database. Additional manual search included conference abstracts and bibliographies of candidate studies and recent systematic reviews for a comprehensive literature search.

Study Selection

We included full-text, published studies involving: (1) hospital-based patient cohorts diagnosed with CAA-ri based on autopsy/biopsy or the diagnostic criteria for CAA-ri[8,9]; (2) available data on the prevalence of clinical features including seizures, cognitive decline, headache, encephalopathy, or focal neurological signs at presentation and available data on neuroimaging markers such as cSS, cortical/subcortical microhemorrhages, lobar hemorrhages, asymmetric white matter hyperintensities, and gadolinium-enhancing lesions; (3) available data on ApoE (Apolipoprotein E) genotype and levels of cerebrospinal fluid biomarkers such as tau, p-tau, Aβ40 and Aβ42; (4) available data on therapy and outcomes; (5) adult patients (≥18 years old). We excluded studies that did not report the prevalence of CAA-ri related clinical features, neuroimaging markers or laboratory findings, studies with overlapping data and studies reporting on <5 patients. Editorials, commentaries, and narrative reviews were also excluded.

The definitions of the main clinical features described in the included studies are the following: Cognitive decline is defined as acute or subacute cognitive impairment and can vary from very mild cognitive disturbances (in combination with headache) to rapidly progressive cognitive decline or Alzheimer

disease dementia.[4] Focal neurological deficits include motor weakness, sensitivity or visual disturbances, aphasia, etw.[5] Encephalopathy is described in patients with confusion and impairment of consciousness.[5]

Data Extraction

Three authors (A.T., L.P., and C.Z.) independently reviewed the retrieved articles as summarized in the Supplemental Methods section of Supplemental Material and any disagreements were resolved after discussion with the senior author (G.T.). The following information was extracted: name of the study, first author and year of the publication, study design and data collection interval, mean age, sex distribution, total number of study participants, and clinical, radiological, laboratory and genetic findings.

Primary Analyses

An aggregate data meta-analysis was performed with the inclusion of all the eligible cohort studies. We primarily assessed the prevalence rates of clinical features, neuroimaging markers and laboratory, genetic findings as available from the included studies among patients with CAA-ri diagnosis. Additionally, we sought to assess the prevalence rates of patients who received steroid treatment, patients who received steroids plus other immunosuppressive treatment, and of patients with an overall favorable functional outcome. We defined the abovementioned outcomes as defined in the included studies.

Additional Analyses

Subgroup analyses were conducted to assess the prevalence rates based on (1) prospective and retrospective study design and (2) CAA-ri diagnosis with or without available biopsy. Metaregression analyses were additionally conducted to evaluate the potential association of (1) age and (2) female sex with the prevalence of various clinical and radiological subtypes.

Study Quality and Assessment of Publication Bias

Eligible studies were subjected to quality control and bias assessment employing the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool for the observational studies.[12] The ROBINS-I tool assesses confounding, selection of participants, classification of intervention, deviations from intended intervention, missing data, measurement of outcomes, and selection of the reported result. Quality control and bias identification were performed independently by 2 authors (A.T. and L.P.) and any disagreements were resolved by a tie-breaking evaluator (G.T.).

The publication bias across individual studies was evaluated graphically using funnel plots,[13] whereas funnel plot asymmetry was assessed using Egger's linear regression test, and the threshold of the statistical significance was set on $P<0.10$.[14]

Statistical Approach

All statistical analyses were conducted using the OpenMetaAnalyst and the R–software version 3.5.0 (packages: meta and metafor).[15,16] We calculated the prevalence rates and their corresponding 95% CIs to measure the effect size. Before pooling the prevalence estimates from each study and prior to the synthesis of proportions we implemented the variance-stabilizing double arcsine transformation. For the qualitative interpretation of the heterogeneity, I^2>50% and I^2>75% indicated substantial and considerable heterogeneity, respectively.[17] A random-effects model (DerSimonian Laird)[18] was used to calculate the pooled prevalence rates in both the overall and subgroup analyses.

In addition, we used a random-effects model (methods of moments) to perform meta-regression analyses, which were conducted when ≥10 studies were available to assess the association of (1) age and (2) the female-sex with the prevalence of various clinical and radiological findings.

RESULTS

Study Selection and Study Characteristics

We screened 147 titles and abstracts from which 26 eligible studies were retained for fulltext evaluation. After careful evaluation and no disagreements among the 3 investigators, 5 studies were excluded (Table S1) resulting in selection of 21 studies that met the inclusion criteria (PRISMA; Figure 1).

We included 21 studies that recruited a total of 378 patients with CAA-ri. Our systematic review and meta-analysis involved 4 prospective studies[19–22] and 17 retrospective cohort studies.[9,23–38] Two studies had no available data regarding the number of patients diagnosed with definite, probable, or possible CAA-ri and 3 studies included patients with the diagnosis of possible CAA-ri. Overall, 81 out of 337 (24%) patients were diagnosed with definite, 29/337 (9%) with probable CAA-ri with supporting pathological evidence, 204/337 (60%) with probable, and 23/337 (7%) patients with possible CAA-ri. Only one study describes separately a group of 28 patients with the diagnosis of amyloid-β–related angiitis.[36] The mean age at diagnosis of these patients was 66 years, the most common clinical characteristics were cognitive dysfunction and headache and the most prevalent neuroimaging features were the leptomeningeal gadolinium enhancing lesions. The patient characteristics, the field strength of magnetic-resonance-imaging used in each study, and the design of the included studies are shown in Tables S2 and S3, respectively.

The studies were conducted in United States (n=7), France (n=4), Japan (n=3), Spain (n=3), Italy (n=2), Germany (n=1), China (n=1).

Study Quality and Publication Bias

The risk of bias in the included observational studies was assessed by the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool[12] and is presented in the Figures S1 and S2. The assessment of confounding

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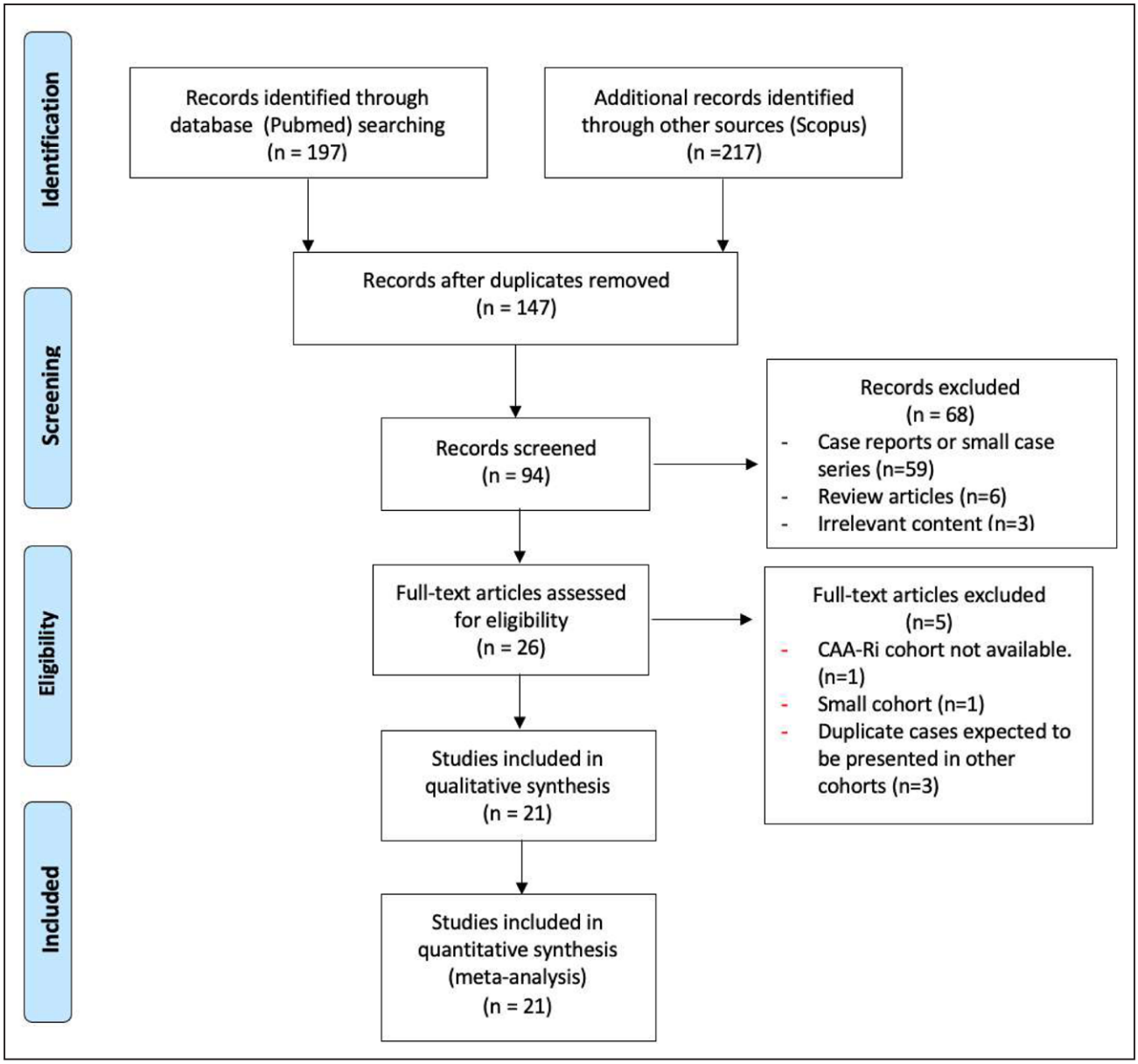

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart diagram presenting the selection of eligible studies.
CAA indicates cerebral amyloid angiopathy.

bias, bias in classification of intervention, and bias due to deviations from intended interventions was not applicable in the majority of the included studies, because these studies were not controlled. A significant selection bias was observed as well, since the study design in the majority of the studies was retrospective. However, the information and reporting biases were moderate.

We inspected funnel plot symmetry and Egger statistical test for outcomes involving ≥10 studies.[13] Funnel plot inspection revealed evidence of asymmetry in studies reporting the prevalence rates of T2/FLAIR hyperintense white matter lesions among patients with CAA-ri (P=0.06; Figure S3). No asymmetry was observed for studies reporting the prevalence rates of lobar microbleeds (P=0.84; Figure S4), Gd+ enhancing lesions (P=0.31; Figure S5), cognitive decline (P=0.63; Figure S6), focal deficits (P=0.78; Figure S7), seizures (P=0.80; Figure S8), and headache (P=0.47; Figure S9).

Overall Analysis

The mean age of the patients in the included studies was 71.5 years old (17 studies [95% CI, 70–73]; P for Cochran Q statistic=0.06; I^2=37%; Figure S10) and the prevalence of female-sex was 52% (17 studies [95% CI, 43%–61%]; P for Cochran Q statistic <0.01; I^2=51%; Figure S11).

The prevalence rates of cognitive decline, focal neurological deficits, and encephalopathy at presentation were 70% (12 studies [95% CI, 54%–84%]; *P* for Cochran Q statistic <0.01; I^2=82%; Figure 2; Table), 55% (14 studies [95% CI, 40%–70%]; *P* for Cochran Q statistic<0.01; I^2=82%; Figure S12), and 54% (6 studies [95% CI, 39%–68%]; *P* for Cochran Q statistic=0.12; I^2=43%; Figure S13), respectively. Similarly, the prevalence rates of seizures and headache were 37% (14 studies [95% CI, 27%–49%]; *P* for Cochran Q statistic <0.01; I^2=65%; Figure S14) and 31% (11 studies [95% CI, 22%–42%]; *P* for Cochran Q statistic <0.01; I^2=58%; Figure S15), respectively.

The prevalence rates of T2/FLAIR hyperintense white matter lesions and lobar microbleeds were 98% (11 studies [95% CI, 93%–100%]; *P* for Cochran Q statistic=0.06; I^2=44%; Figure 3) and 96% (13 studies [95% CI, 92%–99%]; *P* for Cochran Q statistic=0.19; I^2=25%; Figure 4) respectively with evidence of low level of heterogeneity. Similarly, the prevalence of gadolinium-enhancing lesions, cSS, lobar hemorrhages, and ischemic infarcts were 54% (13 studies [95% CI, 42%–66%]; *P* for Cochran Q statistic <0.01; I^2=62%; Figure S16), 51% (8 studies [95% CI, 34%–68%]; *P* for Cochran Q statistic<0.01; I^2=76%; Figure S17), 40% (6 studies [95% CI, 11%–73%]; *P* for Cochran Q statistic<0.01; I^2=88%; Figure S18), and 28% (4 studies [95% CI, 16%–41%]; *P* for Cochran Q statistic=0.23; I^2=30%; Figure S19) respectively. More specifically, the prevalence rate of the leptomeningeal gadolinium-enhancing lesions was 99% (12 studies [95% CI, 98%–100%]; *P* for Cochran Q statistic=0.52; I^2=0%; Figure S20), and the prevalence rate of the parenchymal gadolinium-enhancing lesions was 2% (12 studies [95% CI, 0%–10%]; *P* for Cochran Q statistic <0.01; I^2=67%; Figure S21).

The prevalence rates of the ApoE ε4/ε4 and ε2/+ allele were 34% (5 studies [95% CI, 17%–53%]; *P* for Cochran Q statistic <0.01; I^2=76%; Figure 5) and 6% (4 studies [95% CI, 0%–25%]; *P* for Cochran Q statistic<0.01; I^2=79%; Figure S22), respectively.

In addition, the mean *P*-tau, Aβ40 and Aβ42 levels in the included studies were 40.38 pg/ml (2 studies [95% CI, 32.14–48.62]; *P* for Cochran Q statistic=0.09; I^2=66%; Figure S23), 3017.13 pg/ml (2 studies [95% CI, 447.09–5587.18]; *P* for Cochran Q statistic <0.01; I^2=95%; Figure S24) and 311.21 pg/ml (2 studies [95%

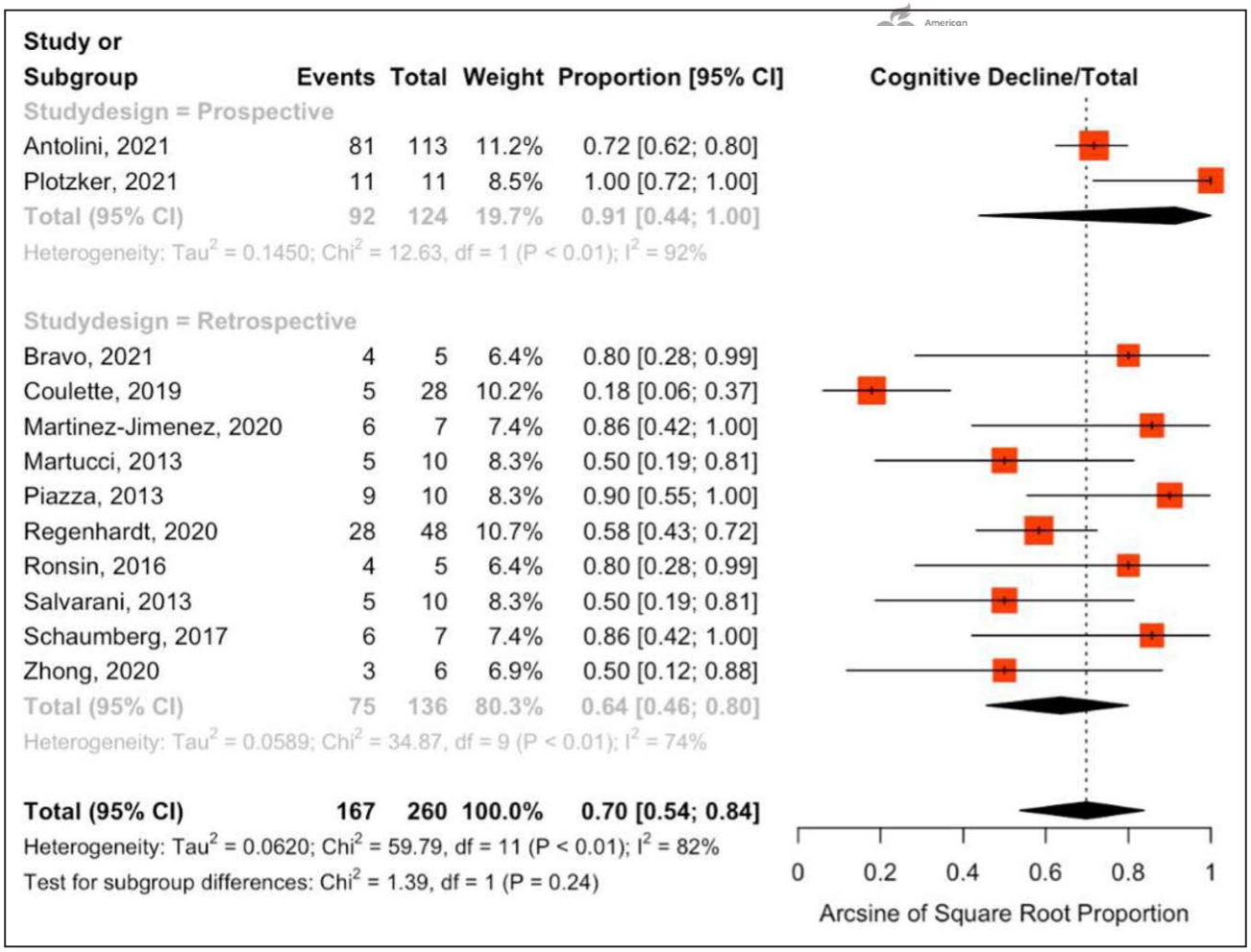

Figure 2. Forest plot presenting the pooled prevalence rates of cognitive decline at presentation among patients with cerebral amyloid angiopathy–related inflammation, based on arcsine of square root proportion.

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Table. Prevalence of Clinical Features, Neuroimaging and Genetic Markers and CSF Biomarkers Among Patients With CAA-ri

	Effect measure (95% CI)	Number of studies	I^2, *P* Value for Cochran Q
Demographics			
Female	52% (43%–61%)	17	51%, *P*<0.01
Age, y, mean	71.5 (70–73)	17	37%, *P*=0.06
Clinical features			
Cognitive decline	70% (54%–84%)	12	82%, *P*<0.01
Focal deficits	55% (40%–70%)	14	82%, *P*<0.01
Encephalopathy	54% (39%–68%)	6	43%, *P*=0.12
Seizures	37% (27%–49%)	14	65%, *P*<0.01
Headache	31% (22%–42%)	11	58%, *P*<0.01
Neuroimaging markers			
T2/FLAIR hyperintense white matter lesions	98% (93%–100%)	11	44%, *P*=0.06
Microbleeds	96% (92%–99%)	13	25%, *P*=0.19
Gd+ enhancing lesions	54% (42%–66%)	13	62%, *P*<0.01
cSS	51% (34%–68%)	8	77%, *P*<0.01
Lobar hemorrhage	40% (11%–73%)	6	88%, *P*<0.01
Ischemic infarcts	28% (16%–41%)	4	30%, *P*=0.23
Genetic findings			
ApoE ε4/ε4	34% (17%–53%)	5	76%, *P*<0.01
ApoE ε2/+	6% (0%–25%)	4	79%, *P*<0.01
CSF biomarkers			
P-tau (mean)	40.38 pg/mL (32.14–48.62)	2	65%, *P*=0.09
Aβ40 (mean)	3017.13 pg/mL (447.09–5587.18)	2	95%, *P*<0.01
Aβ42 (mean)	311.21 pg/mL (262.11–360.31)	2	0%, *P*=0.70

ApoE indicates apolipoprotein-E; CAA, cerebral amyloid angiopathy; CSF, cerebrospinal fluid; cSS, cortical superficial siderosis; and FLAIR, fluid-attenuated inversion recovery.

CI, 262.11–360.31]; *P* for Cochran Q statistic=0.70; I^2=0%; Figure S25).

Finally, the pooled prevalence rates of steroid therapy, steroid plus other immunosuppressive therapy (cyclophosphamide, azathioprine, mucophenolate mofetil, rituximab or intravenous immunoglobulin), and favorable functional outcome were 86% (15 studies [95% CI, 76%–94%]; *P* for Cochran Q statistic<0.01; I^2=74%; Figure S26), 6% (15 studies [95% CI, 2%–12%]; *P* for Cochran Q statistic<0.01; I^2=58%; Figure S27), and 88% (15 studies [95% CI, 78%–95%]; *P* for Cochran Q statistic <0.01; I^2=75%; Figure S28), respectively.

Subgroup Analyses

We assessed the studies based on their study design and evaluated the prevalence rates among patients with CAA-ri diagnosis. No significant subgroup differences were detected among prospective and retrospective studies and the prevalence rates of cognitive decline (*P*=0.24; Figure 2), focal neurological deficits (*P*=0.74; Figure S12), encephalopathy (*P*=0.05; Figure S13), seizures (*P*=0.58; Figure S14), headache (*P*=0.12; Figure S15), lobar microbleeds (*P*=0.72; Figure 4), Gd+ enhancing lesions (*P*=0.19; Figure S16), cSS (*P*=0.84; Figure S17), and ischemic infarcts (*P*=0.51; Figure S19). Radiological markers such as T2/FLAIR hyperintense white matter lesions and lobar hemorrhage were detected only in retrospective studies.

We performed additional subgroup analyses for the studies that based the diagnosis of CAA-ri only on biopsy or on the combination of clinical/radiological criteria with/without biopsy. A significant subgroup difference (*P*<0.01) was observed among the prevalence rates of seizures between the CAA-ri diagnosis with or without available biopsy (Figure S29). No other subgroup differences were observed among the clinical/radiological findings and the method of CAA-ri diagnosis. (Figures S30 through S37).

Metaregression Analyses

We additionally performed meta-regression analyses to assess the potential association of (1) age and (2) female-sex with the prevalence of various radiological and clinical markers.

A linear association was documented between age and focal deficits among patients with CAA-ri (regression coefficient, 0.0034 [95% CI, 0.00–0.068]; *P*=0.05; Figure S38). However, no other significant associations were noted between different clinical or radiological findings and demographic characteristics.

DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis involving 378 patients with CAA-ri suggesting that 70% of the patients present with cognitive decline while the vast majority (>95%) have lobar microbleeds and T2/FLAIR hyperintense white matter lesions. The pooled prevalence rates of focal neurological deficits, encephalopathy, gadolinium-enhancing lesions, and cSS appear to be high among patients with CAA-ri. Furthermore, our study documents a significant lower prevalence rate of ApoE ε4/ε4 carriers compared with higher rates previously reported in other cohorts.[26]

CAA-ri consists a disease of the elderly with an average age of 67 at diagnosis, however, without obvious gender predominance.[4,5] Patients with CAA-ri present with various clinical manifestations including cognitive decline/dementia and altered mental status sometimes in association with behavioral changes. In the largest prospective cohort of patients with CAA-ri, cognitive decline was the most common clinical manifestation, accounting

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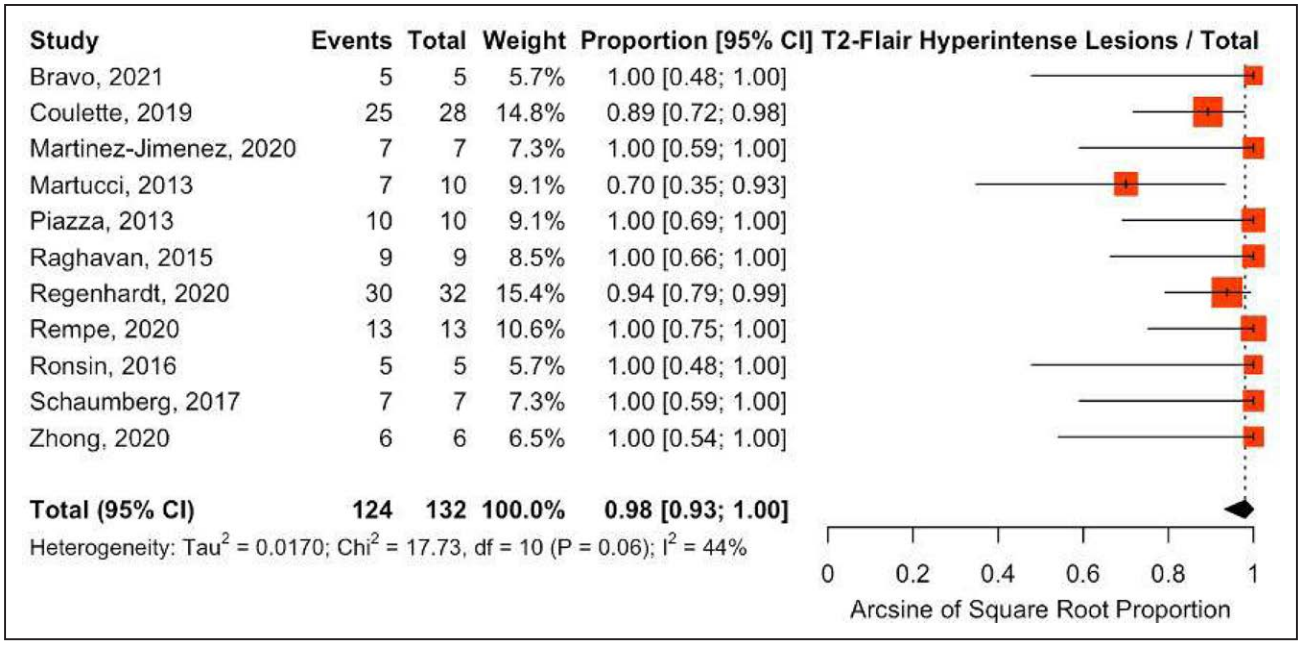

Figure 3. Forest plot presenting the pooled prevalence rates of T2/fluid-attenuated inversion recovery hyperintense white matter lesions among patients with cerebral amyloid angiopathy–related inflammation, based on arcsine of square root proportion.

for 71.7%, followed by focal neurological deficits (57.5%), seizures (34.5%), and headache (22.1%).[19] All these findings are similar to the prevalence rates of clinical manifestations among patients with CAA-ri, which were detected in the present review and meta-analysis.

Brain magnetic resonance imaging sequences such as T2*-weighted gradient echo/susceptibility-weighted imaging and FLAIR have been widely used to identify patients suspected of CAA-ri.[39] Recent studies suggest susceptibility weighted imaging as more reliable than T2*-weighted gradient echo imaging, and with greater sensitivity for detection of CMBs[40] and some cohorts have detected a colocalisation of CMBs and T2/FLAIR hyperintense white matter lesions.[27,28,30–32] Despite that the distribution of CMBs does not follow the occipital dominance regional pattern of the CAA, the incidence of multiple CMBs are much higher among patients with CAA-ri compared with those with CAA.[2,5] In the largest prospective cohort all the included patients had an abnormal susceptibility weighted imaging at presentation.[19] These data are compatible with the CMBs prevalence rate of 96%, observed in our systematic review and meta-analysis. However, there are rare case reports with typical clinical features and biopsy proven diagnosis of CAA-ri, but normal susceptibility weighted imaging at presentation, indicating probably an earlier stage of the disease.[41,42]

Another typical neuroimaging finding of CAA-ri is the presence of unifocal or multifocal, corticosubcortical or deep, mainly asymmetric white matter lesions not attributable to past intracerebral hemorrhage.[9] These lesions are detectable on T2 and FLAIR sequences and sometimes the tumefactive appearance can confuse and lead to unnecessary surgical resections in order to exclude other diagnoses such as primary CNS neoplasm, CNS vasculitis, or amyloidoma.[33,43] Leptomeningeal or intraparenchymal gadolinium enhancement in the areas of T2/FLAIR hyperintense white matter lesions is described in the literature approximately in one-third of the patients with CAA-ri, a percentage that could be explained by the nondestructive inflammatory blood vessel wall infiltration in the CAA-ri.[44,45] Remarkable is the normal conventional angiography in patients with CAA-ri in comparison to the nonspecific vasculitic abnormalities in amyloid-β–related angiitis when medium-sized arteries are involved.[8,48]

The ApoE-ε4 allele and especially the ε4/ε4 homozygosity has been established as the only confirmed risk factor for CAA-ri, since previous studies have shown a significant correlation with CAA-ri, reporting a high prevalence of ε4/ε4 (76.9%) among patients with CAA-ri.[26,31] An underlying pathogenic mechanism, which increases the Aβ deposition and has a pro-inflammatory effect is highly suspected. A recent study with the largest prospective cohort of patients with CAA-ri report a prevalence of ApoE-ε4 carriers accounting for 37.1% (22.7% heterozygotes and 14.4% homozygotes).[19] We also documented a pooled prevalence rate of ApoE ε4/ε4 homozygosity of 34%, which is much lower than what has been previously reported.

In addition, rare cases of CAA-ri with either the genotype ApoE ε2/ε2 or the ε2/ε3 have been reported.[21,46,47] Despite the fact that ε2 allele is considered as protective against Alzheimer Disease, the presence of this allele could also be a predisposing factor for CAA-ri.[49]

Furthermore, scarce data exist regarding the Alzheimer disease biomarker levels among patients with CAA-ri. There

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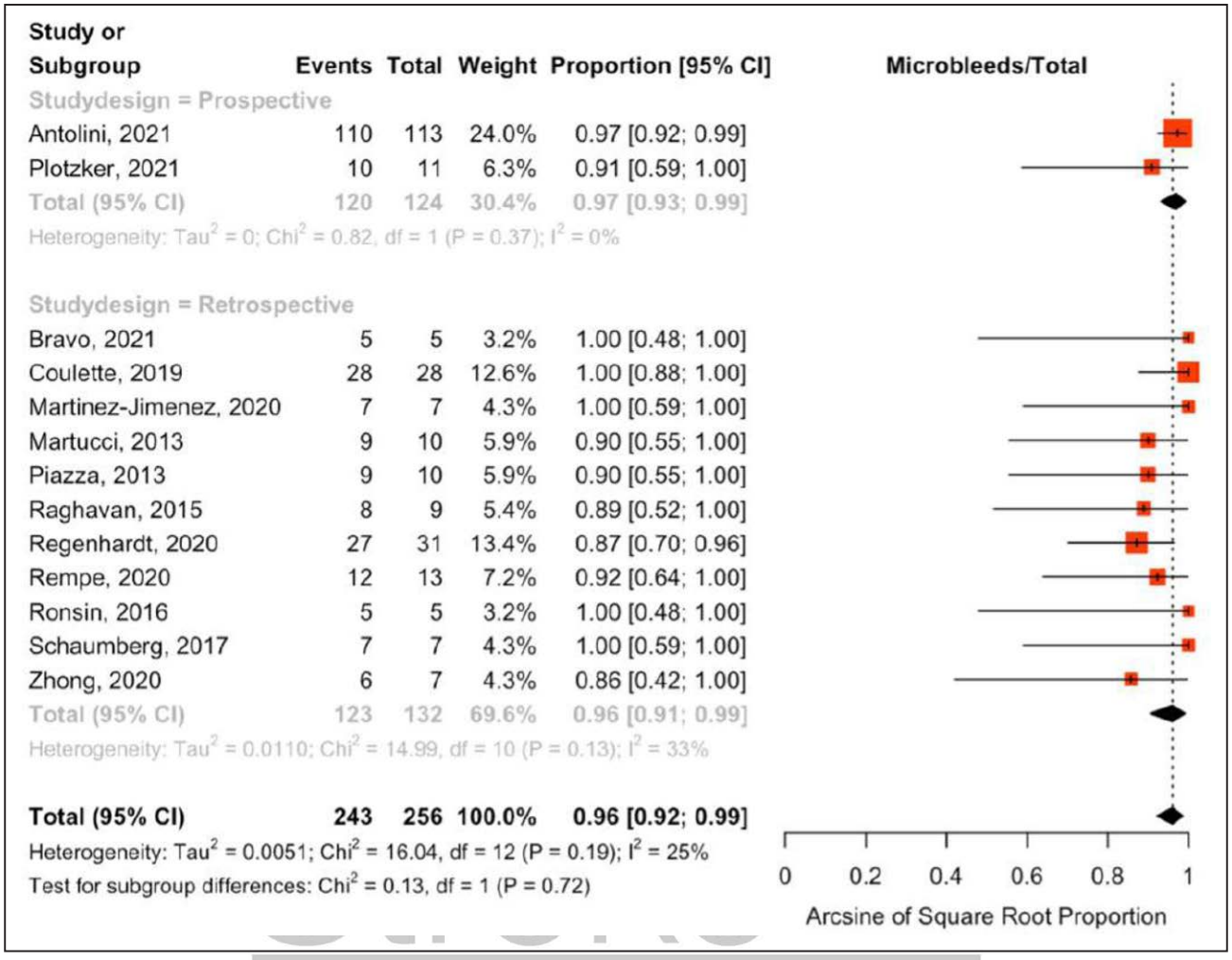

Figure 4. Forest Plot presenting the pooled prevalence rates of microbleeds among patients with cerebral amyloid angiopathy–related inflammation, based on arcsine of square root proportion.

are controversies regarding the levels of Aβ40, Aβ42, and p-tau proteins; the majority of the researchers have found relatively low levels of Aβ42 and Aβ40 in the cerebrospinal fluid and high levels of p-tau.[21,22,24,25] In the present meta-analysis, the pooled mean of p-tau, amyloid Aβ40, and Aβ42 levels were based on the findings of only 2 studies with heterogeneity. This limits substantially the validity of our observations. In the future, the significance of these decrement indices in the diagnosis and the prediction of the disease evolution should be further studied.

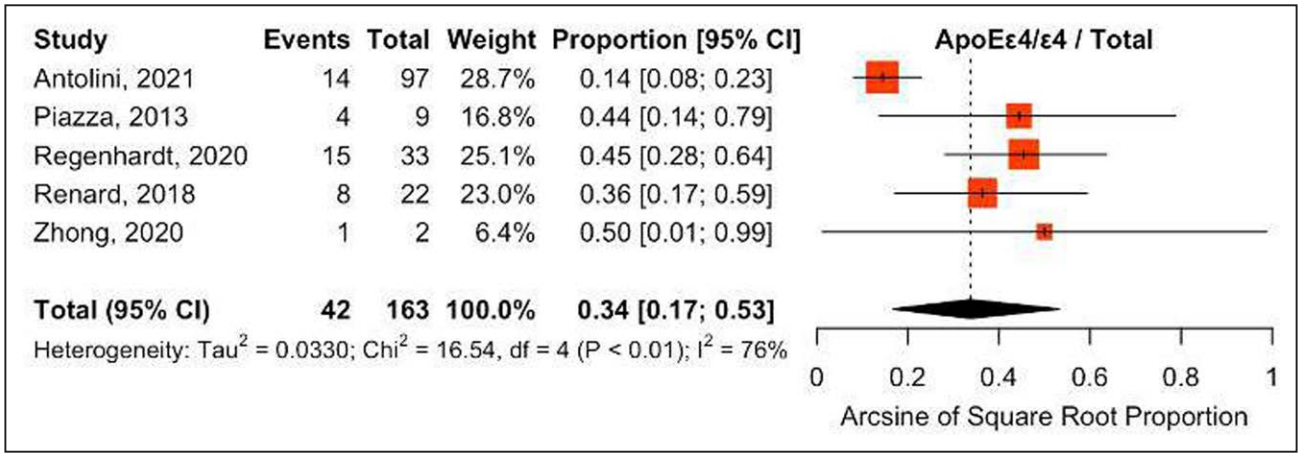

Figure 5. Forest Plot presenting the pooled prevalence rates of ApoE (apolipoprotein-E) ε4/ε4 genotype among patients with cerebral amyloid angiopathy–related inflammation, based on arcsine of square root proportion.

We also provided information regarding different therapeutic strategies and outcomes in the current meta-analysis. Our observations lend support to clinical experience, indicating that corticosteroids represent the first-line treatment in patients with CAA-ri and have been associated with clinical and radiological improvement of the primary disease episode and decreased risk of subsequent relapses.[19,20,31,32] Additional immunosuppressive therapies including cyclophosphamide, mycophenolate mofetil, azathioprine, IVIG, or rituximab have been also reported as add-on therapies in selected cases, most of them with a more severe course of the disease.[19,20,24,30–32,34] However, it should be noted that the heterogeneous and limited published data regarding treatment (regimen, dosis, duration) and outcomes prevent us from drawing robust conclusions using a meta-analytical approach.

Our study has certain limitations that warrant further consideration. First, there are limited data in the literature regarding the manifestations of CAA-ri, and this was the etiology of including cohorts with at least 5 patients in our meta-analysis. Second, the majority of the included studies were observational with a retrospective study design, which predispose to inherent biases, especially selection biases. We sought to counteract these biases and we performed further subgroup analyses to account for the moderating effect via the use of study-design classification. Although we performed subgroup and meta-regression analyses that highlight the robustness of our findings, our study is unable to exclude any residual confounding due to lack of individual study patient data. Third, limited studies relied on biopsy confirmation for diagnosis of CAA-ri, whereas the remaining studies used the proposed criteria for probable/possible diagnosis. Fourth, lack of consensus in stroke care among patients with CAA-ri, which is a combination of lack of generalizability and availability of clinical data for diagnostic workup and treatment could also act as confounders for our results. Relatively few patients have been treated with nonsteroidal agents making it impossible to compare different treatments with each other. Moreover, differences in the evaluation and record of outcomes among studies contribute to this heterogeneity. This substantial heterogeneity of the included studies likely resulted in asymmetry in funnel plots.[13] The vast majority of study findings in this meta-analysis display substantial levels of heterogeneity, which would be unexpected for many of these findings representing key manifestations/features of CAA-ri. This lends support to a cautious interpretation of our observations and may be attributed to small sample sizes of the included studies, as well as to selection bias from differences in study design, neuroimaging modalities, patient selection criteria, and differences in therapy and evaluation of the outcomes. Another explanation of the heterogeneity could be referral patterns to specialty stroke centers that are expected to have a higher prevalence of more unusual features such as patients with CAA-ri with focal neurological deficits or rapidly progressive cognitive decline.

In conclusion, the present meta-analysis documented that cognitive decline was the most common clinical feature in CAA-ri and hyperintense T2/FLAIR white matter lesions complicated with lobar cerebral microbleeds were by far the most prevalent neuroimaging findings. Thirty-four percent of patients with CAA-ri have an homozygous ApoE ε4/ε4 genotype, remarkably lower prevalence in comparison with previous cohorts. Cautious interpretation of these results should be warranted due to limited data from a small number of included studies, the majority of which were based on a retrospective study design. Although CAA-ri is a rare entity, neurologists should have a comprehensive understanding of this disease and a continuous vigilance to detect the possible or probable CAA-ri, since the early diagnosis and the prompt initiation of glucocorticoids or even immunosuppressants could improve the prognosis and the evolution.[19,31] Furthermore, future population-based studies are needed to evaluate the prevalence rates of specific clinical and neuroimaging markers as well genetic risk factors and biomarker' significance among patients with well-defined CAA-ri.

ARTICLE INFORMATION

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Supplemental Material

Supplemental Methods
Tables S1–S4
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