The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study

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Summary

Background Cerebral amyloid angiopathy (CAA) is an age-related small vessel disease, characterised pathologically by progressive deposition of amyloid β in the cerebrovascular wall. The Boston criteria are used worldwide for the in-vivo diagnosis of CAA but have not been updated since 2010, before the emergence of additional MRI markers. We report an international collaborative study aiming to update and externally validate the Boston diagnostic criteria across the full spectrum of clinical CAA presentations.

Methods In this multicentre, hospital-based, retrospective, MRI and neuropathology diagnostic accuracy study, we did a retrospective analysis of clinical, radiological, and histopathological data available to sites participating in the International CAA Association to formulate updated Boston criteria and establish their diagnostic accuracy across different populations and clinical presentations. Ten North American and European academic medical centres identified patients aged 50 years and older with potential CAA-related clinical presentations (ie, spontaneous intracerebral haemorrhage, cognitive impairment, or transient focal neurological episodes), available brain MRI, and histopathological assessment for CAA diagnosis. MRI scans were centrally rated at Massachusetts General Hospital (Boston, MA, USA) for haemorrhagic and non-haemorrhagic CAA markers, and brain tissue samples were rated by neuropathologists at the contributing sites. We derived the Boston criteria version 2.0 (v2.0) by selecting MRI features to optimise diagnostic specificity and sensitivity in a prespecified derivation cohort (Boston cases 1994–2012, n=159), then externally validated the criteria in a prespecified temporal validation cohort (Boston cases 2012–18, n=59) and a geographical validation cohort (non-Boston cases 2004–18; n=123), comparing accuracy of the new criteria to the currently used modified Boston criteria with histopathological assessment of CAA as the diagnostic standard. We also assessed performance of the v2.0 criteria in patients across all cohorts who had the diagnostic gold standard of brain autopsy.

Findings The study protocol was finalised on Jan 15, 2017, patient identification was completed on Dec 31, 2018, and imaging analyses were completed on Sept 30, 2019. Of 401 potentially eligible patients presenting to Massachusetts General Hospital, 218 were eligible to be included in the analysis; of 160 patient datasets from other centres, 123 were included. Using the derivation cohort, we derived provisional criteria for probable CAA requiring the presence of at least two strictly lobar haemorrhagic lesions (ie, intracerebral haemorrhages, cerebral microbleeds, or foci of cortical superficial siderosis) or at least one strictly lobar haemorrhagic lesion and at least one white matter characteristic (ie, severe visible perivascular spaces in centrum semiovale or white matter hyperintensities in a multispot pattern). The sensitivity and specificity of these criteria were 74·8% (95% CI 65·4–82·7) and 84·6% (71·9–93·1) in the derivation cohort, 92·5% (79·6–98·4) and 89·5% (66·9–98·7) in the temporal validation cohort, 80·2% (70·8–87·6) and 81·5% (61·9–93·7) in the geographical validation cohort, and 74·5% (65·4–82·4) and 95·0% (83·1–99·4) in all patients who had autopsy as the diagnostic standard. The area under the receiver operating characteristic curve (AUC) was 0·797 (0·732–0·861) in the derivation cohort, 0·910 (0·828–0·992) in the temporal validation cohort, 0·808 (0·724–0·893) in the geographical validation cohort, and 0·848 (0·794–0·901) in patients who had autopsy as the diagnostic standard. The v2.0 Boston criteria for probable CAA had superior accuracy to the current Boston criteria (sensitivity 64·5% [54·9–73·4]; specificity 95·0% [83·1–99·4]; AUC 0·798 [0·741–0854]; p=0·0005 for comparison of AUC) across all individuals who had autopsy as the diagnostic standard.

Interpretation The Boston criteria v2.0 incorporate emerging MRI markers of CAA to enhance sensitivity without compromising their specificity in our cohorts of patients aged 50 years and older presenting with spontaneous

intracerebral haemorrhage, cognitive impairment, or transient focal neurological episodes. Future studies will be needed to determine generalisability of the v.2.0 criteria across the full range of patients and clinical presentations.

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Introduction

Cerebral amyloid angiopathy (CAA) is an age-related small vessel disease, affecting cortical and leptomeningeal vessels and characterised pathologically by progressive deposition of amyloid β in the cerebrovascular wall. CAA is the primary cause of lobar intracerebral haemorrhage and an independent contributor to age-associated cognitive impairment. Therefore, an accurate diagnosis of CAA during life is important for both clinical care and enrolment of participants in research.

Similar to neurodegenerative disorders, the reference standard for CAA diagnosis remains histopathological analysis from brain autopsy or biopsy samples. The Boston criteria defined probable CAA (the most commonly used diagnostic category) on the basis of clinical and MRI information alone, allowing non-invasive in-vivo diagnosis.[1–5] Among the limitations of the probable CAA criteria is that they have lower sensitivity for presentations without symptomatic intracerebral haemorrhage than for intracerebral haemorrhage presentations and that they have been validated only in small numbers of patients (<100 individuals), primarily from single centres.[2,4,6,7] As first formulated in 1995 (version 1.0 or v1.0), probable CAA entailed demonstration of at least two haemorrhagic lesions restricted to lobar brain regions, including intracerebral haemorrhage and cerebral microbleeds. In the modified Boston criteria proposed in 2010 (v1.5), the presence of blood products in cortical sulci (cortical superficial siderosis) was included as an additional haemorrhagic lesion, treating any extent of cortical superficial siderosis as a single CAA-related haemorrhagic lesion. More recent observations of non-haemorrhagic, white matter markers of CAA[6,8] have raised the possibility that diagnostic sensitivity, particularly for presentations other than intracerebral haemorrhage, might be further enhanced by incorporating some of these markers.

Research in context

Evidence before this study

The clinical and imaging Boston criteria, first introduced in the 1990s and later updated to the modified Boston criteria in 2010, are widely used for the diagnosis of cerebral amyloid angiopathy (CAA). Two independent reviewers (AC and SMG) did a systematic review of diagnostic accuracy studies that used different versions of the Boston criteria against the reference standard of neuropathologically proven CAA. Studies were restricted to those listed in PubMed published between Sept 15, 1994, and Feb 23, 2022, in the English language. We used electronic search strategies combining the terms "Boston criteria" OR "cerebral amyloid angiopathy" AND "validation" OR "diagnosis". We identified four hospital-based studies and one cohort study describing the validation and performance of the Boston criteria for the diagnosis of CAA. The studies were done at single centres and had fewer than 100 individuals, and primarily included patients with intracerebral haemorrhage. The studies provided validating evidence of a good diagnostic performance for the probable CAA-related lobar intracerebral haemorrhage category. According to the 2010 version of the criteria a diagnosis of probable CAA entails demonstration of multiple (ie, two or more) haemorrhagic lesions restricted to lobar brain regions, including intracerebral haemorrhage, cerebral microbleeds, and the presence of cortical superficial siderosis. The 2010 criteria have not been validated across the spectrum of CAA clinical presentations and have not systematically incorporated more recently identified MRI features.

Added value of this study

This diagnostic accuracy study minimised some of the biases in previous studies, by using a multicentre design and included a large number of patients, and explored clinical presentations both with and without intracerebral haemorrhage. We were able to derive and validate updated criteria for probable CAA, requiring the presence of at least two strictly lobar haemorrhagic lesions (intracerebral haemorrhage, cerebral microbleeds, or a focus of cortical superficial siderosis), or at least one lobar haemorrhagic lesion and at least one white matter lesion (severe visible perivascular spaces in centrum semiovale or white matter hyperintensities in a multispot pattern). These criteria had enhanced sensitivity relative to the currently used Boston criteria without compromising their high specificity, and represent a step towards updating and improving in-vivo diagnosis of CAA within the Boston criteria framework.

Implications of all the available evidence

We have used recently recognised MRI characteristics of CAA to generate and externally validate new criteria for clinical–MRI diagnosis. The Boston criteria version 2.0 are designed to provide high diagnostic accuracy with reasonable simplicity for use in practice and research, across the clinical spectrum of CAA-related presentations and across clinical settings. Future research is required to evaluate their clinical use and further investigate their accuracy in specific patient subgroups and whether the criteria will be amenable to use of advanced imaging techniques, such as amyloid PET imaging.

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See Online for appendix

Here, we report an international collaborative study led by the International CAA Association[1,9] to update and externally validate the Boston diagnostic criteria across diverse clinical CAA presentations.[10] To this end, we systematically obtained histopathological, neuroimaging, clinical, and other available data from eligible patients with histopathologically confirmed CAA or a confirmed absence of advanced CAA (classified as CAA-negative patients according to our neuropathological definition criteria).[9] We used these data to devise and validate the Boston criteria v2.0 for CAA.[9]

Methods

Study design and participants

The protocol for this study was developed by investigators from the Massachusetts General Hospital (Boston, MA, USA) coordinating centre and University College London (London, UK) in Aug 1, 2016. An initial draft of the protocol was discussed among investigators on Sept 10, 2016, at the 5th International CAA Association Conference, and was finalised on Jan 15, 2017; it was subsequently implemented in alignment with *Standards for Reporting of Diagnostic Accuracy Studies* 2015 guidelines.[11] The full study protocol and detailed methods have been published[9] and are summarised here.

We did a multicentre, hospital-based, retrospective, diagnostic accuracy study across the International CAA Association network of patients presenting to inpatient or outpatient hospital settings in ten North American and European academic medical centres. To be eligible, participants had to have spontaneous primary intracerebral haemorrhage or other clinical syndromes associated with sporadic CAA, specifically cognitive impairment or dementia, or transient focal neurological episodes. Patients with other clinical presentations and diagnoses (including antecedent head trauma, haemorrhagic transformation of an ischaemic stroke, arteriovenous malformation, haemorrhagic tumour, or CNS vasculitis[2]) or with iatrogenic CAA[12] or hereditary CAA[13] were excluded. Patients with CAA-related inflammation were eligible for inclusion only if an MRI scan was available from a time without evidence for ongoing inflammation.[1,9] We used multiple overlapping sources of case ascertainment[9] to identify all potentially eligible patients with: (1) the above potential CAA-related clinical presentations seen in stroke, memory, or research clinics; (2) available, adequate MRI data, including at least T2-weighted, fluid-attenuated inversion recovery (FLAIR) sequences and T2*-weighted axial sequences (conventional T2*-gradient recalled-echo or more sensitive susceptibility-weighted imaging methods, on 1.5 or 3.0 Tesla MRI scanners);[9] and (3) available brain tissue (obtained by biopsy, haematoma evacuation, or autopsy, containing at least ten evaluable cortical or leptomeningeal vessels) to determine the presence or absence of CAA.

Clinical and imaging data were sent in an anonymised format to Massachusetts General Hospital for central imaging rating and statistical analysis. Ethical approval for obtaining and transferring data was obtained by the local research teams per local centre regulations. Informed consent for brain biopsy or autopsy was obtained from patients or authorised family members at the time of the procedures by the local centre; no additional consent was required for sharing of the anonymised data.

Procedures

Trained neuropathologists at each participating centre assessed routine haematoxylin–eosin staining for vessel morphology and immunohistochemical staining for the presence or absence of vascular amyloid β deposition.[9] CAA presence and severity were assessed on brain samples, with the neuropathologists masked to clinical and brain MRI findings, using the modified Vonsattel grading system and a predefined threshold as in previous studies.[9,14,15] From the assessed samples, full brain autopsy samples were required to show a Vonsattel grade of 2 and above (ie, at least one instance of replacement of whole vessel wall by amyloid β) for individuals categorised as having histopathologically confirmed CAA, whereas samples from brain biopsy or haematoma evacuation, because of the more limited tissue sampling, were required to show a Vonsattel grade of 1 and above (ie, any amyloid in a vessel wall). Controls were defined as individuals in our cohorts whose brain tissue had an absence of advanced CAA (Vonsattel grade 0 or 1 in autopsy, Vonsattel grade 0 in brain biopsy or haematoma evacuation).

Key MRI biomarkers of CAA and small vessel disease were derived from a systematic review of the relevant literature.[10] These biomarkers include characteristic haemorrhagic MRI biomarkers: lobar cerebral microbleeds, lobar intracerebral haemorrhage, cortical superficial siderosis, convexity subarachnoid haemorrhage, and the two non-haemorrhagic white matter markers[16] of severe MRI-visible perivascular spaces in the centrum semiovale (ie, more than 20 visible perivascular spaces in the centrum semiovale of one hemisphere[5]), and white matter hyperintensities in a multispot pattern (ie, more than ten small circular or ovoid T2-weighted FLAIR hyperintense lesions in the bilateral subcortical white matter[8]; figure 1). The analysis of convexity subarachnoid haemorrhage and cortical superficial siderosis explicitly allowed multiple distinct foci to be counted as independent haemorrhagic lesions. Of note, cortical superficial siderosis and acute convexity subarachnoid haemorrhage are rated as equivalent MRI markers of CAA. More detailed accounts of MRI assessment and analysis, along with classification systems and representative examples, are provided in the appendix (pp 6–10) and study protocol paper.[9] All MRI markers were rated by AC without access to clinical and pathological information, according to the Standards for Reporting Vascular Changes on Neuroimaging

(STRIVE)[17] where applicable, using validated scales and guidelines.[18] An additional trained rater (GBo) assessed a random sample of the MRI scans (n=100) to generate inter-rater agreement measures.

Statistical analysis

We split cases into prespecified cohorts: (1) a derivation cohort—individuals from the Massachusetts General Hospital presenting during 1994–2012; (2) a temporal validation cohort—individuals from the Massachusetts General Hospital presenting during 2012–18; and (3) a geographical validation cohort—individuals from centres other than Massachusetts General Hospital presenting during 2004–18. The sample size was determined by the maximum number of available cases meeting the requirements for clinical, MRI, and neuropathological data. Because of the requirement for MRI and brain pathology, the samples were considered as convenience rather than consecutive series. We compared the distributions of clinical and MRI characteristics of participants within the derivation cohort with those of the two validation cohorts using the χ^2 test (or Fisher's exact test where appropriate) for categorical variables and the Mann-Whitney U test for continuous variables, which were all non-normally distributed.

Our approach was to (1) prespecify MRI variables and appropriate cutoffs on the basis of available evidence;[9] (2) examine their associations with histopathologically confirmed CAA in the derivation cohort, quantified as odds ratios (ORs) with 95% CIs; (3) propose provisional Boston criteria v2.0 for probable and possible CAA based on classification measures (ie, sensitivity, specificity, positive and negative predictive values, area under the receiver operating characteristic curve [AUC], and 95% CIs) for different combinations of CAA MRI biomarkers within the derivation cohort; (4) validate Boston criteria v2.0 in the external validation cohorts using the same classification measures; and finally (5) combine all cohorts to perform prespecified secondary analyses. The prespecified secondary analyses were confirmation of the independent contribution of the identified MRI marker via multivariable logistic regression with histopathologically confirmed CAA as the outcome variable, determination of the performance of the v2.0 criteria in the subgroup of patients with the diagnostic gold standard of brain autopsy, comparison of the v2.0 criteria with the modified Boston criteria currently in use (v1.5),[4] and further breakdown of the whole combined cohort into subgroups of patients presenting with versus without intracerebral haemorrhage, or imaged using susceptibility-weighted imaging versus T2*-gradient recalled-echo MRI.[9] Comparison of overall diagnostic accuracy between the v2.0 criteria and the Boston criteria v1.5 currently in use was done with the STATA roccomp command for correlated samples. We did the statistical analyses using STATA 13. No data were missing from the study.

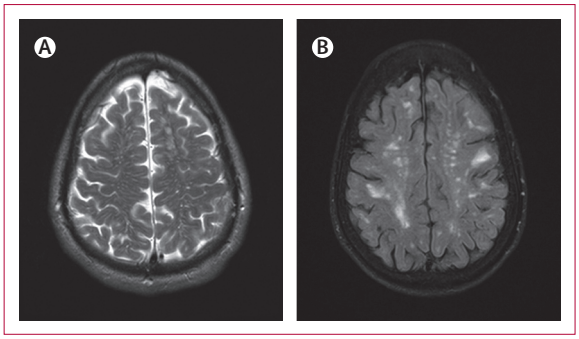

Figure 1: **Non-haemorrhagic white matter MRI markers assessed and finally included in the Boston criteria v2.0**
(A) Severe centrum semiovale perivascular spaces, identified on axial T2-weighted images,[17] are defined as more than 20 visible perivascular spaces in the centrum semiovale of one hemisphere.[6] (B) The multispot white matter hyperintensity pattern is defined as more than ten T2-weighted fluid-attenuated inversion recovery small circular or ovoid hyperintense lesions in the subcortical white matter of both hemispheres.[8]

We followed a conceptual framework fully outlined in the study protocol paper[9] of maintaining the current Boston criteria (v1.5) core categories of probable and possible CAA and maintaining a common set of criteria for intracerebral haemorrhage and other CAA presentations, to improve usability. Probable CAA is intended as a rule-in diagnostic category with the goal (for the v2.0 criteria) of using emerging haemorrhagic and non-haemorrhagic markers to enhance sensitivity (compared with the v1.5 criteria) without losing specificity. Possible CAA is intended as a rule-out diagnostic category with the goal (for the v2.0 criteria) of maximising sensitivity while maintaining reasonably high specificity. Definite CAA based on full brain autopsy, and the additional category of probable CAA with supporting pathology based on clinical scenarios of having brain tissue from biopsy or haematoma evacuation, were retained unchanged in the v2.0 criteria.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Patient identification was completed on Dec 31, 2018, and imaging analyses on Sept 30, 2019. Of 401 potentially eligible patients presenting to Massachusetts General Hospital, 183 were excluded: 43 for not presenting with intracerebral haemorrhage, cognitive impairment, or transient focal neurological episodes; 44 for not having all required MRI sequences; and 96 for inadequate pathological tissue (figure 2). Of 160 patient datasets from non-Massachusetts General Hospital centres, 37 were excluded for missing MRI sequences or pathological diagnoses. The remaining 341 participants with available MRI and neuropathology data were split into the derivation cohort (n=159), temporal validation

cohort (n=59), and geographical validation cohort (n=123; appendix pp 2–3). 24 participants with pathologically confirmed CAA had previously been reported on in previous studies, including validation studies of the Boston criteria v1.5 (11 from the derivation cohort[2,4] and 13 from the geographical validation cohort[4,6]).

Within the derivation cohort (median age 73 years), 107 (67%) individuals had pathologically verified CAA and 52 (33%) had verified non-CAA (table 1). In the univariable analysis, MRI markers strongly associated with CAA were lobar intracerebral haemorrhage (OR 4·2 [95% CI 2·0–8·7]; p<0·0001), cortical superficial siderosis (40 [5–300]; p<0·0001), lobar cerebral microbleeds (3·4 [1·7–6·6]; p<0·0001), severe perivascular spaces in the centrum semiovale (6·3 [3·0–13·5]; p<0·0001), and white matter hyperintensities in a multispot pattern (3·5 [1·6–7·6]; p=0·002). Severity of periventricular and deep white matter hyperintensities was not associated with CAA and was hence not considered further.

For all MRI markers assessed, the inter-rater κ values were more than 0·80 (ie, 0·94 [95% CI 0·85–1·00] for presence of multifocal cortical superficial siderosis, 0·86 [0·75–0·96] for severe perivascular spaces in the centrum semiovale, 0·89 [95% CI 0·80–0·98] for white matter hyperintensities in a multispot pattern), indicating excellent agreement.

We used these results to draft provisional Boston criteria v2.0 for further validation. The analyses of various combinations of markers within the derivation cohort are summarised in the appendix (pp 4–5). Of note, of the non-haemorrhagic MRI features, the addition of visible perivascular spaces in the centrum semiovale contributed most to the sensitivity and specificity, with marginal added performance from the

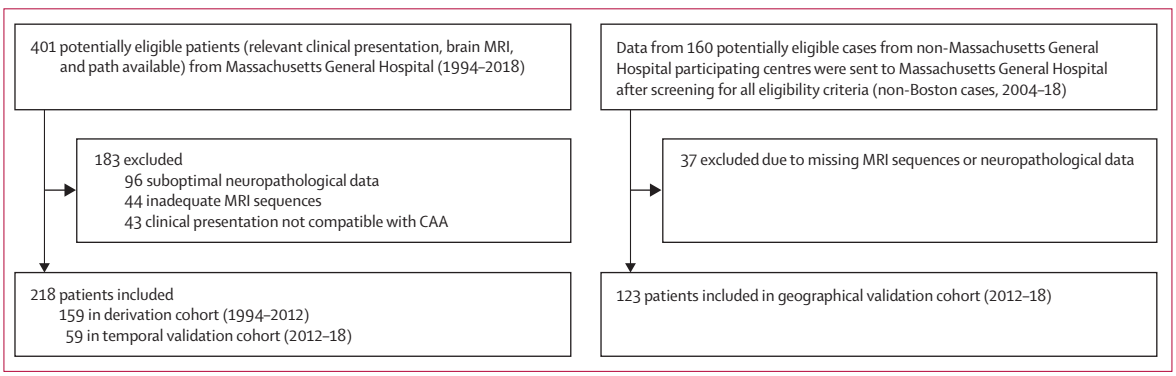

Figure 2: **Flow chart of patient selection**

	Derivation cohort (n=159)	Temporal validation cohort (n=59)	p value (*vs* derivation cohort)	Geographical validation cohort (n=123)	p value (*vs* derivation cohort)
Clinical history and presentation					
Age, years	73 (68–78)	70 (61–76)	0·0060	69 (63–77)	0·0083
Sex					
Men	74 (47%)	24 (41%)	0·44	61 (50%)	0·611
Women	85 (53%)	35 (59%)	0·44	62 (50%)	0·611
Race*					
Asian	4/148 (3%)	2/58 (3%)	..	0	..
Black	7/148 (5%)	3/58 (5%)	..	0	..
Hispanic	0	1/58 (2%)	..	0	..
White	137/148 (93%)	52/58 (90%)	..	91/91 (100%)	..
Hypertension	96 (60%)	37 (63%)	0·75	60 (49%)	0·052
Antiplatelet use at presentation	47 (30%)	19 (32%)	0·71	36 (29%)	0·96
Anticoagulant use at presentation	17 (11%)	4 (7%)	0·38	16 (13%)	0·55
ICH presentation	77 (48%)	40 (68%)	0·011	94 (76%)	<0·0005
Non-ICH presentation	82 (52%)	19 (32%)	0·011	29 (24%)	<0·0005
TFNE	9 (6%)	7 (12%)	..	9 (7%)	..
Cognitive impairment	54 (34%)	5 (8%)	..	17 (14%)	..
Other†	19 (12%)	7 (12%)	..	3 (2%)	..

(Table 1 continues on next page)

	Derivation sample (n=159)	Temporal external validation (n=59)	p value (versus derivation sample)	Geographical external validation (n=123)	p value (versus derivation sample)
(Continued from previous page)					
MRI method and findings					
3T MRI	20 (13%)	26 (44%)	<0·0001	17 (14%)	0·76
T2*-gradient recalled-echo	139 (87%)	33 (56%)	<0·0001	103 (84%)	0·38
Susceptibility-weighted imaging	20 (13%)	26 (44%)	..	20 (16%)	..
Multiple intracerebral haemorrhage	26/77 (34%)	7/40 (18%)	0·070	21/94 (22%)	0·12
Lobar intracerebral haemorrhage	68/77 (88%)	29/40 (73%)	0·0070	86/94 (91%)	0·29
Non-lobar (deep) intracerebral haemorrhage	4/77 (5%)	11/40 (28%)	0·0070	5/94 (5%)	0·29
Mixed intracerebral haemorrhage	2/77 (3%)	0	0·0070	2/94 (2%)	0·29
Cerebellar intracerebral haemorrhage	3/77 (4%)	1/40 (3%)	0·0070	0	0·29
Presence of lobar cerebral microbleeds	85 (53%)	41 (69%)	0·033	71 (58%)	0·48
Number of lobar cerebral microbleeds	1 (0–13)	3 (0–19)	0·12	2 (0–22)	0·26
Multiple lobar cerebral microbleeds (>1)	69 (43%)	37 (63%)	0·011	62 (50%)	0·24
Presence of non-lobar cerebral microbleeds	17 (11%)	10 (17%)	0·21	16 (13%)	0·55
Number of non-lobar (deep) cerebral microbleeds	0 (0–0)	0 (0–0)	0·20	0 (0–0)	0·60
Multiple non-lobar cerebral microbleeds (>1)	11 (7%)	9 (15%)	0·058	9 (7%)	0·90
Presence of cortical superficial siderosis	46 (29%)	20 (34%)	0·48	56 (46%)	0·0040
Focal cortical superficial siderosis	20 (13%)	7 (12%)	0·62	24 (20%)	0·016
Disseminated cortical superficial siderosis	26 (16%)	13 (22%)	0·62	32 (26%)	0·016
Multifocal or extensive cortical superficial siderosis	34 (21%)	16 (27%)	0·67	40 (33%)	0·015
Moderate or severe periventricular white matter hyperintensities‡	88 (55%)	45 (76%)	0·0050	67 (54%)	0·88
Moderate or severe deep white matter hyperintensities‡	78 (49%)	37 (63%)	0·073	48 (39%)	0·093
Moderate or severe total white matter hyperintensities‡	98 (62%)	49 (83%)	0·0030	71 (58%)	0·51
Multispot white matter hyperintensity pattern	53 (33%)	26 (44%)	0·14	37 (30%)	0·56
Severe visible perivascular spaces in centrum semiovale	76 (48%)	28 (47%)	0·96	58 (47%)	0·95
Severe visible perivascular spaces in basal ganglia	11 (7%)	7 (12%)	0·24	13 (11%)	0·26
Neuropathology method and findings					
Autopsy	79 (50%)	29 (49%)	0·091	42 (34%)	0·0080
Biopsy	37 (23%)	7 (12%)	0·091	48 (39%)	0·0080
Haematoma evacuation	43 (27%)	23 (39%)	0·091	33 (27%)	0·0080
Pathologically verified CAA	107 (67%)	40 (68%)	0·94	96 (78%)	0·046
MRI-neuropathology delay, years	0·2 (0·0–2·4)	0·7 (0·1–4·5)	0·057	0·4 (0·1–2·8)	0·19

Data are presented as median (IQR) for continuous variables and n (%) for categorical variables; where p values are not reported, comparisons were not done because it was not deemed informative. CAA=cerebral amyloid angiopathy. TFNE=transient focal neurological episodes. WMH=white matter hyperintensities. *Information on race is missing from 11 participants in derivation cohort, one in temporal validation cohort, 23 in geographic validation cohort (for the geographic validation cohort, only information on White *vs* non-White was available). †Other non-ICH presentations include CAA-related inflammation[19] (in the remission phase), MRI detection of ischaemic stroke, and transient non-focal neurological episodes. ‡As assessed with the Fazekas rating scale.

Table 1: **Characteristics of patients across the three study cohorts**

addition of white matter hyperintensities in a multispot pattern. On the basis of these results, we selected rule-in criteria for probable CAA (panel) as the presence of two or more strictly lobar haemorrhagic lesions (intracerebral haemorrhage, cerebral microbleeds, convexity subarachnoid haemorrhage–cortical superficial siderosis) or one lobar haemorrhagic lesion and at least one white matter lesion (severe perivascular spaces in the centrum semiovale or white matter hyperintensities in a multispot pattern). For patients presenting with symptomatic intracerebral haemorrhage, these provisional criteria yielded a sensitivity of 86·7% (95% CI 75·4–94·1%), a specificity of 70·6% (44–89·1%), and an AUC of 0·79 (0·67–0·88) for probable CAA (*vs* non-probable CAA; appendix p 4). For patients with presentations other than intracerebral haemorrhage, these values were 59·6% (44·3–73·6%), 91·4% (76·9–98·2%), and 0·75 (0·67–0·84). Possible CAA was defined as a single lobar haemorrhagic or white matter lesion (panel). Across all presentations in the derivation cohort, possible

***Panel*: Boston criteria version 2.0 for sporadic cerebral amyloid angiopathy**

1. Definite CAA

Full brain post-mortem examination demonstrating:

- Spontaneous intracerebral haemorrhage, transient focal neurological episodes, convexity subarachnoid haemorrhage, or cognitive impairment or dementia
- Severe CAA with vasculopathy
- Absence of other diagnostic lesion

2. Probable CAA with supporting pathology

Clinical data and pathological tissue (evacuated haematoma or cortical biopsy) demonstrating:

- Presentation with spontaneous intracerebral haemorrhage, transient focal neurological episodes, convexity subarachnoid haemorrhage, or cognitive impairment or dementia
- Some degree of CAA in specimen
- Absence of other diagnostic lesion

3. Probable CAA

For patients aged 50 years and older, clinical data and MRI demonstrating:

- Presentation with spontaneous intracerebral haemorrhage, transient focal neurological episodes, or cognitive impairment or dementia
- At least two of the following strictly lobar haemorrhagic lesions on T2*-weighted MRI, in any combination: intracerebral haemorrhage, cerebral microbleeds, or foci of cortical superficial siderosis or convexity subarachnoid haemorrhage

OR

- One lobar haemorrhagic lesion plus one white matter feature (severe perivascular spaces in the centrum semiovale or white matter hyperintensities in a multispot pattern)†
- Absence of any deep haemorrhagic lesions (ie, intracerebral haemorrhage or cerebral microbleeds) on T2*-weighted MRI
- Absence of other cause of haemorrhagic lesions‡
- Haemorrhagic lesion in cerebellum not counted as either lobar or deep haemorrhagic lesion

4. Possible CAA

For patients aged 50 years and older, clinical data and MRI demonstrating:

- Presentation with spontaneous intracerebral haemorrhage, transient focal neurological episodes, or cognitive impairment or dementia
- Absence of other cause of haemorrhage‡
- One strictly lobar haemorrhagic lesion on T2*-weighted MRI: intracerebral haemorrhage, cerebral microbleeds, or foci of cortical superficial siderosis or convexity subarachnoid haemorrhage

OR

- One white matter feature (severe visible perivascular spaces in the centrum semiovale or white matter hyperintensities in a multispot pattern)†
- Absence of any deep haemorrhagic lesions (ie, intracerebral haemorrhage or cerebral microbleeds) on T2*-weighted MRI
- Absence of other cause of haemorrhagic lesions‡
- Haemorrhagic lesion in cerebellum not counted as either lobar or deep haemorrhagic lesion

CAA=cerebral amyloid angiopathy. †Notable changes from the Boston criteria v1.5. ‡Other causes of haemorrhagic lesion: antecedent head trauma, haemorrhagic transformation of an ischaemic stroke, arteriovenous malformation, haemorrhagic tumour, CNS vasculitis. Other causes of cortical superficial siderosis and acute convexity subarachnoid haemorrhage should also be excluded.

plus probable CAA showed a sensitivity of 91·6% (84·6–96·1%), compared with 74·8% (65·4–82·7%) for probable CAA in the same cohort, and a specificity of 57·7% (43·2–71·3%), compared with 84·6% (71·9–93·1%) for probable CAA in the same cohort, versus no CAA diagnostic categories (table 2).

We did post-hoc analyses of two MRI markers that emerged after publication of our study protocol: lobar lacunes and superficial cerebellar microbleeds.[20,21] Inclusion of one lobar haemorrhagic lesion plus at least one lobar lacune or one superficial cerebellar microbleed did not reclassify any possible CAA cases in the derivation cohort as probable CAA and thus did not affect our calculations of sensitivity and specificity. Similarly, including at least one lobar lacune or at least one superficial cerebellar microbleed in the definition of possible CAA did not reclassify any false negative case in the derivation cohort as possible CAA. In the temporal external validation and geographical external validation cohorts, we found that the provisional (ie, prior to validation) Boston criteria v2.0 retained consistently good sensitivity and specificity for the probable CAA diagnosis (table 2): a sensitivity of 92·5% (79·6–98·4%) and specificity of 89·5% (66·9–98·7%) for the temporal validation cohort and a sensitivity of 80·2% (70·8–87·6%) and specificity of 81·5% (61·9–93·7%) for the geographical validation cohort. As expected for the diagnosis of probable plus possible CAA, sensitivity was around 90% with lower, but still acceptable, specificities (table 2). Compared with the modified Boston criteria (v1.5) currently in use, the Boston criteria v2.0 achieved higher sensitivity with comparable specificity across all three cohorts (table 2).

Given the external validation of the provisional Boston criteria v2.0, we merged all cohorts (n=341) to perform prespecified secondary analyses. In the whole cohort, each of the MRI markers remained independently associated with CAA histopathological diagnosis in multivariable logistic regression (table 3). Boston criteria v2.0 sensitivity was 79·8% (74·2–84·7%) and specificity was 84·7% (76·0–91·2%) for probable CAA, whereas sensitivity was 91·8% (87·6–94·9%) and specificity was 62·2% (51·9–71·8%) for probable plus

	Probable CAA (*vs* non-probable CAA)		Probable plus possible CAA (*vs* no CAA)	
	Boston criteria v2.0	Boston criteria v1.5	Boston criteria v2.0	Boston criteria v1.5
Derivation cohort (n=159)				
Sensitivity	74·8% (65·4–82·7)	62·6% (52·7–71·8)	91·6% (84·6–96·1)	77·6% (68·5–85·1)
Specificity	84·6% (71·9–93·1)	86·5% (74·2–94·4)	57·7% (43·2–71·3)	75% (61·1–86)
AUC	0·797 (0·732–0·861)	0·746 (0·68–0·811)	0·746 (0·674–0·819)	0·763 (0·691–0·834)
PPV	90·9% (82·9–96)	90·5% (81·5–96·1)	81·7% (73·6–88·1)	86·5% (78–92·6)
NPV	62% (49·7–73·2)	52·9% (41·8–63·9)	76·9% (60·7–88·9)	61·9% (48·8–73·9)
Temporal validation cohort (n=59)				
Sensitivity	92·5% (79·6–98·4)	87·5% (73·2–95·8)	97·5% (86·8–99·9)	95% (83·1–99·4)
Specificity	89·5% (66·9–98·7)	100% (82·4–100)	78·9% (54·4–93·9)	78·9% (54·4–93·9)
AUC	0·91 (0·828–0·992)	0·938 (0·886–0·989)	0·882 (0·785–0·98)	0·87 (0·77–0·97)
PPV	94·9% (82·7–99·4)	100% (90–100)	90·7% (77·9–97·4)	90·5% (77·4–97·3)
NPV	85% (62·1–96·8)	79·2% (57·8–92·9)	93·8% (69·8–99·8)	88·2% (63·6–98·5)
Geographical validation cohort (n=123)				
Sensitivity	80·2% (70·8–87·6)	72·9% (62·9–81·5)	89·6% (81·7–94·9)	86·5% (78–92·6)
Specificity	81·5% (61·9–93·7)	85·2% (66·3–95·8)	59·3% (38·8–77·6)	63% (42·4–80·6)
AUC	0·808 (0·724–0·893)	0·791 (0·709–0·872)	0·744 (0·645–0·844)	0·747 (0·648–0·846)
PPV	93·9% (86·3–98)	94·6% (86·7–98·5)	88·7% (80·6–94·2)	89·2% (81·1–94·7)
NPV	53·7% (37·4–69·3)	46·9% (32·5–61·7)	61·5% (40·6–79·8)	56·7% (37·4–74·5)
Whole cohort (n=341)				
Sensitivity	79·8% (74·2–84·7)	70·8% (64·6–76·4)	91·8% (87·6–94·9)	84% (78·7–88·3)
Specificity	84·7% (76·0–91·2)	88·8% (80·8–94·3)	62·2% (51·9–71·8)	72·4% (62·5–81)
AUC	0·823 (0·779–0·866)	0·798 (0·755–0·84)	0·77 (0·719–0·821)	0·782 (0·731–0·832)
PPV	92·8% (88·4–95·9)	94% (89·5–97)	85·8% (80·9–89·8)	88·3% (83·5–92·2)
NPV	62·9% (54–71·1)	55·1% (47–63)	75·3% (64·5–84·2)	64·5% (54·9–73·4)

Analyses were done for patients with probable CAA versus patients not fulfilling criteria for probable CAA, and for probable plus possible CAA versus non-CAA diagnostic categories. CAA=cerebral amyloid angiopathy. AUC=area under the receiver operating characteristic curve. PPV=positive predictive value. NPV=negative predictive value.

Table 2: **Diagnostic performance of Boston criteria v2.0 and Boston criteria v1.5**

possible CAA in the full cohort (table 2). Restricting our analysis to the subgroup of individuals with full brain autopsy (table 4), the specificity increased to 95·0% for probable CAA and to 70·0%. for probable plus possible CAA. Relative to the modified Boston criteria v1.5, Boston criteria v2.0 for probable CAA showed the same specificity (95·0% *vs* 95·0%) in the autopsy subgroup, greater sensitivity (74·5% *vs* 64·5%), and overall higher diagnostic accuracy among all presentations (AUC 0·848 [0·794–0·901] *vs* 0·798 [0·741–0·854], p=0·0005), as well as in the subgroups presenting with intracerebral haemorrhage (p=0·0047), and presentations other than intracerebral haemorrhage (p=0·040). Diagnostic accuracy appeared highest in patients with susceptibility-weighted imaging MRI (table 4).

	OR (95% CI)	p value
At least two strictly lobar cerebral microbleeds	2·42 (1·33–4·39)	0·0040
At least one focus of cortical superficial siderosis	36·53 (8·70–153·90)	<0·0001
Perivascular spaces in the centrum semiovale	3·17 (1·66–6·08)	0·0010
White matter hyperintensities in a multispot pattern	2·04 (1·06–3·91)	0·032

OR=odds ratio.

Table 3: **Multivariable logistic regression of MRI markers' association with neuropathologically defined CAA in the whole cohort**

Discussion

We have done a large, multicentre study to update and validate criteria for clinical and MRI-based diagnosis of CAA. The product of this study, the Boston criteria v2.0, are designed to provide high diagnostic accuracy with reasonable simplicity for use in practice across sporadic CAA clinical presentations, which was the same motivating approach as was used to develop previous versions of the Boston criteria, which have been used by clinicians and researchers over the past 20 years.[1]

The current study updates the definition of probable CAA to incorporate emerging CAA MRI markers. The notable changes are allowing probable CAA to be diagnosed on the basis of (1) multifocal convexity subarachnoid haemorrhage or cortical superficial siderosis, or both, without requiring accompanying parenchymal intracerebral haemorrhage or cerebral microbleeds, or (2) the presence of a CAA-related white matter lesion

	Probable *vs* non-probable CAA*	Probable and possible *vs* no CAA
All patients with brain autopsy (n=150; Boston criteria v1.5)		
Sensitivity	64·5% (54·9–73·4)	75·5% (66·3–83·2)
Specificity	95·0% (83·1–99·4)	87·5% (73·2–95·8)
AUC	0·798 (0·741–0·854)	0·815 (0·749–0·881)
PPV	97·3% (90·5–99·7)	94·3% (87·2–98·1)
NPV	49·4% (37·8–61)	56·5% (43·3–69)
All patients with brain autopsy (n=150; Boston criteria v2.0)		
Sensitivity	74·5% (65·4–82·4)	88·2% (80·6–93·6)
Specificity	95·0% (83·1–99·4)	70·0% (53·5–83·4)
AUC	0·848 (0·794–0·901)	0·791 (0·713–0·869)
PPV	97·6% (91·7–99·7)	89% (81·6–94·2)
NPV	57·6% (44·8–69·7)	68·3% (51·9–81·9)
Patients with brain autopsy who presented with intracerebral haemorrhage (n=75; Boston criteria v2.0)		
Sensitivity	90·2% (79·8–96·3)	91·8% (81·9–97·3)
Specificity	92·9% (66·1–99·8)	71·4% (41·9–91·6)
AUC	0·915 (0·836–0·995)	0·816 (0·689–0·944)
PPV	98·2% (90·4–100)	93·3% (83·8–98·2)
NPV	68·4% (43·4–87·4)	66·7% (38·4–88·2)
Patients with brain autopsy and presentations other than intracerebral haemorrhage (n=75; Boston criteria v2.0)		
Sensitivity	55·1% (40·2–69·3)	83·7% (70·3–92·7)
Specificity	96·2% (80·4–99·9)	69·2% (48·2–85·7)
AUC	0·756 (0·676–0·836)	0·765 (0·66–0·869)
PPV	96·4% (81·7–99·9)	83·7% (70·3–92·7)
NPV	53·2% (38·1–67·9)	69·2% (48·2–85·7)
Patients with brain autopsy and T2*-GRE (n=127; Boston criteria v2.0)		
Sensitivity	72·6% (62·5–81·3)	87·4% (79·–93·3)
Specificity	93·8% (79·2–99·2)	68·8% (50–83·9)
AUC	0·832 (0·77–0·894)	0·781 (0·692–0·869)
PPV	97·2% (90·1–99·7)	89·2% (81·1–94·7)
NPV	53·6% (39·7–67)	64·7% (46·5–80·3)
Patients with brain autopsy and SWI (n=23; Boston criteria v2.0)		
Sensitivity	86·7% (59·5–98·3)	93·3% (68·1–99·8)
Specificity	100% (63·1–100)	75% (34·9–96·8)
AUC	0·933 (0·844–1)	0·842 (0·668–1)
PPV	100% (75·3–100)	87·5% (61·7–98·4)
NPV	80% (44·4–97·5)	85·7% (42·1–99·6)

Prespecified subgroup analyses of the Boston criteria (v.15 and v2.0) within the whole cohort. CAA=cerebral amyloid angiopathy. GRE=gradient-recalled echo. SWI=susceptibility-weighted imaging. AUC=area under the receiver operating characteristic curve. PPV=positive predictive value. NPV=negative predictive value. *Non-probable CAA refers to patients not fulfilling criteria for probable CAA.

Table 4: **Diagnostic performance of Boston criteria v2.0 in prespecified subsets of all individuals with available autopsy**

(primarily perivascular spaces in the centrum semiovale, with some additional effect of white matter hyperintensities in a multispot pattern) together with a single haemorrhagic marker (ie, intracerebral haemorrhage, cerebral microbleeds, convexity subarachnoid haemorrhage or cortical superficial siderosis). Comparison of the v2.0 criteria with the Boston criteria v1.5[4] suggest the additional MRI features capture some true-positive patients with CAA without a substantial increase in false positives, thus enhancing sensitivity without compromising specificity and providing overall superior diagnostic accuracy. We also incorporated the additional MRI markers into an updated possible CAA category, which aims for the highest level of sensitivity. The validation results suggested some trade-off between improved sensitivity and worsened specificity relative to the v1.5 criteria and indicated that the possible CAA category is likely to include some false-positive diagnoses. The category nonetheless appears to meet the goal of a possible disease diagnosis by ruling out most non-CAA cases.

The incorporation of multifocality of cortical superficial siderosis, in addition to its presence, is one of the core updates of the Boston criteria v2.0, counting multifocal convexity subarachnoid haemorrhage or cortical superficial siderosis as at least two haemorrhagic lesions that can alone meet the definition of probable CAA. From a methodological standpoint, we attempt to distinguish between a single focus of cortical superficial siderosis (even if it extends to an adjacent gyrus) and multifocal or extensive cortical superficial siderosis that involves gyri separated by uninvolved areas or involving three or more adjacent gyri, excluding foci of cortical superficial siderosis from adjacent lobar intracerebral haemorrhage.[1,9] Of note, cortical superficial siderosis and acute convexity subarachnoid haemorrhage are rated as equivalent MRI markers of CAA, with the understanding that convexity subarachnoid haemorrhage is the acute form and cortical superficial siderosis the chronic form of the same underlying process of superficial cortical haemorrhage.[22] In cases where acute convexity subarachnoid haemorrhage is potentially connected or in close vicinity to cortical superficial siderosis, they are counted as evidence of two haemorrhagic markers of CAA as the acuity of convexity subarachnoid haemorrhage provides evidence of dissemination in time.

The other substantial update in the Boston criteria v2.0 is incorporation of the white matter markers of severe perivascular spaces in the centrum semiovale and white matter hyperintensities in a multispot pattern (figure 1). Although these white matter lesions are neither perfectly specific nor perfectly sensitive for CAA, our data suggest their presence in conjunction with a single haemorrhagic lesion identifies a subset of true-positive patients with CAA who would otherwise be diagnosed as possible rather than probable CAA. Even in the absence of a haemorrhagic lesion, these white matter lesions identify some additional true-positive patients with CAA (detected in 15 of 21 individuals with presentations other than intracerebral haemorrhage who had histopathological confirmation of CAA in the full study cohort *vs* ten of 33 individuals with presentations other than intracerebral haemorrhage who were CAA-negative based on histopathology, with a specificity of 69·7%) and were therefore

also incorporated into the v2.0 criteria for possible CAA. Their specificity for CAA before the occurrence of a haemorrhage in people who have not had a haemorrhage offers scope for early intervention to prevent worsening of CAA accumulation and haemorrhage. CAA-associated perivascular spaces in the centrum semiovale appear related to the perivascular trafficking of amyloid β peptide[23] and CAA severity in the overlying cortical vessels.[24] The mechanistic basis for white matter hyperintensities in a multispot pattern is unknown but might also reflect CAA involvement of cortical penetrating vessels. The association of white matter hyperintensities in a multispot pattern with CAA has been less widely studied than that of perivascular spaces in the centrum semiovale and might also be somewhat less robust (table 3; appendix pp 4–5). Although this marker showed independent association and good inter-rater reliability in our analysis, it will require independent replication to establish its usefulness for CAA diagnosis in practice.

The contributions of the white matter markers to the sensitivity of CAA diagnosis highlights the observation that lobar haemorrhagic lesions, although characteristic of CAA, are fairly late disease manifestations[25] and therefore less sensitive for earlier disease stages. The fairly late occurrence of haemorrhage in CAA progression probably also accounts for the lower diagnostic sensitivity for presentations other than intracerebral haemorrhage than for intracerebral haemorrhage clinical presentations, even using the v2·0 criteria (table 4).

An important MRI finding in clinical practice are haemorrhagic lesions in both lobar and non-lobar locations in a single patient. Previous studies suggest that this pattern can represent non-CAA small vessel disease in some individuals and advanced CAA in others,[26,27] highlighting the importance of devising imaging criteria that could identify the CAA subgroup. There were only 36 mixed haemorrhage cases across all three cohorts in our study, which was an insufficient number to allow criteria to be developed and validated. Therefore, we did not address this group in the current validation analysis and will instead report the details of this subgroup and potential approaches for identifying CAA in a separate publication. Other non-MRI biomarkers of CAA, such as amyloid-PET imaging and CSF amyloid β,[28,29] have not yet been validated for incorporation into diagnostic criteria but might have roles in future diagnostic schemes.

We designed the current study to avoid some of the shortcomings of previous CAA validation studies, such as small sample sizes, limited assessment for different MRI biomarkers, restriction primarily to intracerebral haemorrhage presentations, and single-centre settings.[1] In particular, the geographical external validation suggests that the Boston criteria v2.0 have similar accuracy across a range of medical centres and MRI scanners. The current sample size also allowed us to perform prespecified subgroup analyses in individuals with full brain autopsy, for whom the presence or absence of CAA can be confirmed with the highest certainty. Although brain tissue from biopsy or haematoma evacuation provides useful diagnostic information, there is still potential for sampling error and misclassification of CAA cases as non-CAA.[15] We chose to include biopsy-confirmed or evacuation-confirmed diagnoses in the derivation and validation analyses, but also to recheck the Boston criteria v2.0 performance in pooled individuals with full brain autopsies. The high specificity achieved by probable CAA in this analysis (92·9% in intracerebral haemorrhage presentations and 96·2% in other presentations without intracerebral haemorrhage; table 4) offer strong support for the accuracy of the revised criteria.

The current effort has limitations inherent to the retrospective observational study design. There is substantial selection bias due to the requirements for MRI and neuropathological tissue. The requirement for brain tissue might bias towards patients who had more severe underlying CAA leading to death (and hence autopsy), rapidly progressing clinical symptoms (leading to brain biopsy), or large intracerebral haemorrhage (leading to haematoma evacuation). The systematic differences between the pathologically verified participants in the current analysis and the broader group of potential CAA patients seen in clinical practice probably lead to overestimation of diagnostic accuracy via spectrum bias. Another limitation to the generalisability of the current Boston criteria v2.0 is that they were almost entirely derived from White participants of European ancestry, highlighting the need for further external validation in other racial and ethnic groups and geographical settings. We also note the use of different neuropathology raters at each site as well as variation in MRI methods, such as variation in T2-weighted techniques for detection of perivascular spaces and T2*-weighted techniques for detection of haemorrhagic lesions.[30] Our subgroup analysis suggests that the primary effect of susceptibility-weighted imaging is to improve diagnostic accuracy (table 4). A further methodological issue that might introduce bias is delay between MRI and neuropathological sampling (ranging from ~1 week to 2·2 years in the current study; table 1). Finally, we acknowledge the general challenges in identifying appropriate controls for this type of diagnostic accuracy study. Our approach was to apply the standard case-control method of selecting as controls individuals who would themselves have been cases if their neuropathology had been positive for CAA.

The Boston criteria v2.0 appear to be a useful basis for clinical diagnosis of CAA and research study enrolment for individuals with intracerebral haemorrhage or other presentations compatible with CAA. Future studies will be required to determine their generalisability across the full range of patients and clinical presentations, such as iatrogenic or hereditary CAA, individuals with mixed lobar and non-lobar haemorrhagic lesions, cognitively

impaired patients with the full range of neurodegenerative pathologies, and non-White populations. These criteria also require MRI with T2*-weighted sequences (for haemorrhagic lesion detection) and T2-weighted sequences (for perivascular space detection), highlighting the importance of alternative CT-based approaches, such as the Edinburgh criteria for CAA-related intracerebral haemorrhage.[31] Finally, the Boston criteria v2.0 have not been validated for use in asymptomatic individuals who do not present to medical attention, a potentially important application given the independent contribution of CAA pathology to cognitive decline among community-based older people.[32] Validation studies for each of these specific clinical scenarios are currently underway and represent further opportunities for detection of this common and clinically important small-vessel pathology.

Contributors

AC was involved in conceptualisation, data curation and verification, formal analysis, methodology, project administration, and writing of the original draft. GBo, MPF, and MP were involved in the formal analysis, and review and editing of the manuscript. J-CB, JFA, GBa, CB, FB, SB, LC, FC, BC, CC, M-BD, VD, MD, EG, JH, MH-G, HRJ, ZJ, JL, SM-R, EM-S, CM, JM, SM, J-MO, FP, LP, NR, MAR, SR, JRR, NS, JAS, SS, FS, CSc, CSm, LS, PV, AV, JMW, AW, FAW, MZ, MavB, MEG, AV, RA-SS, and EES were involved in data collection, methodology, and review and editing of the manuscript. DJW was involved in conceptualisation, data collection, methodology, and review and editing of the manuscript. SMG was involved in conceptualisation, data curation and verification, formal analysis, funding acquisition, investigation, methodology, resources, supervision, validation, and writing of the original draft. All authors had full access to the data and had final responsibility for the decision to submit for publication.

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Data sharing

Deidentified data from Massachusetts General Hospital and other participating sites can be made available after review of requests for overlap with ongoing analyses and according to site-specific policies for data access agreement. Data sharing requests should be sent to SEM at sgreenberg@mgh.harvard.edu.

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