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The Boston Criteria v2.0 for cerebral amyloid angiopathy: A multicentre MRI-neuropathology diagnostic accuracy study

A full list of authors and affiliations appears at the end of the article.

Abstract

Background: The Boston Criteria are used worldwide for *in vivo* diagnosis of cerebral amyloid angiopathy (CAA) but have not been updated since 2010, prior to emergence of additional MRI markers.

Methods: We performed a retrospective analysis of clinical, radiological, and histopathological data available to sites participating in the International CAA Association to formulate and determine the diagnostic accuracy of updated Boston Criteria across different samples and clinical presentations. Ten North American and European academic medical centres identified patients age 50 with potential CAA-related clinical presentations (spontaneous intracerebral haemorrhage, cognitive impairment, or transient focal neurological episodes), available brain MRI, and histopathologic assessment for CAA diagnosis. MRIs were centrally rated for haemorrhagic and non-haemorrhagic CAA markers and brain tissue samples rated by neuropathologists at the contributing sites for CAA. We derived Boston criteria v2.0 by selecting MRI features to optimize diagnostic specificity and sensitivity in a prespecified derivation sample (Boston cases 1994–2012, n=159), then externally validated the criteria in prespecified temporal (Boston cases 2012–2018, n=59) and geographical (non-Boston cases 2004–2018; n=123) validation samples, comparing their accuracy to the currently used modified Boston criteria.

* **Correspondence:** Andreas Charidimou, MD, PhD, Haemorrhagic Stroke Research Program, Massachusetts General Hospital Stroke Research Center, 175 Cambridge Street, Suite 300, Boston, MA, 02139 USA andreas.charidimou.09@ucl.ac.uk, +1 (617) 505-7384. Authors' contributions

Andreas Charidimou: conceptualisation, data curation and verification, formal analysis, methodology, project administration, writing – original draft

Gregoire Boulouis: formal analysis, writing – review & editing

Matthew P. Frosch: formal analysis, writing – review & editing

Marco Pasi: formal analysis, writing – review & editing

Jean-Claude Baron, Jean Francois Albucher, Gargi Banerjee, Carmen Barbato, Fabrice Bonneville, Sebastian Bradner, Lionel Calviere, François Caparros, Barbara Casolla, Charlotte Cordonnier, Marie-Bernadette Delisle, Vincent Deranecourt, Martin Dichgans, Elif Gokcal, Joechen Herms, Mar Hernandez-Guillamon, Rolf Jager, Zane Jaunmuktane, Jennifer Linn, Sergi Martinez-Ramirez, Elena Martínez-Sáez, Christian Mawrin, Joan Montaner, Solene Moulin, Jean Marc Olivot, Fabrizio Piazza, Laurent Puy, Nicolas Raposo, Mark Rodrigues, Sigrun Roeber, Jose Rafael Romero, Neshika Samarasekera, Julie A. Schneider, Stefanie Schreiber, Frank Schreiber, Corentin Schwall, Colin Smith, Levente Szalardy, Pascale Varlet, Alain Viguier, Joanna M. Wardlaw, Andrew Warren, Frank A. Wollenweber, Marialuisa Zedde, Mark A. van Buchem, M. Edip Gurol, Anand Viswanathan, Rustam Al-Shahi Salman, Eric E. Smith: data collection, methodology, writing – review & editing

David J. Werring: conceptualisation, data collection, methodology, writing – review & editing

Steven M. Greenberg: conceptualisation, data curation and verification, formal analysis, funding acquisition, investigation, methodology, resources, supervision, validation, writing – original draft

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Findings: The study protocol was finalized 15 January 2017, patient identification completed 31 December 2018, and imaging analyses completed 30 September 2019. Based on the derivation sample, we derived provisional criteria for probable CAA requiring the presence of 2 strictly lobar haemorrhagic lesions (intracerebral haemorrhages, cerebral microbleeds, or cortical superficial siderosis foci) or 1 strictly lobar haemorrhagic lesion and 1 white matter characteristic (severe visible perivascular spaces in centrum semiovale or white matter hyperintensities in a multispot pattern). Sensitivity/specificity/area under the area under receiver operating characteristic (AUC) curve (95% confidence interval) of these criteria were 74.8% (65.4–82.7)/84.6% (71.9–93.1)/0.797 (0.732–0.861 in the derivation sample, 92.5% (79.6–98.4)/89.5% (66.9–98.7)/0.91 (0.828–0.992) in the temporal validation sample, 80.2% (70.8–87.6)/81.5% (61.9–93.7)/0.808 (0.724–0.893) in the geographic validation sample, and 74.5% (65.4–82.4)/95.0% (83.1–99.4)/0.848 (0.794–0.901) in cases across all samples with autopsy as the diagnostic standard. The v2.0 criteria for probable CAA had superior accuracy to the current Boston criteria (64.5% (54.9–73.4)/95% (83.1–99.4)/0.798 (0.741–0.854), $p=0.0005$ for comparison of AUC) across all individuals with full autopsy as the diagnostic standard.

Interpretation: The Boston criteria v.2.0 incorporate emerging MRI markers of CAA to enhance sensitivity without compromising their specificity. Future use of the v.2.0 criteria will determine their generalizability across the full range of patients and clinical presentations.

Keywords

cerebral amyloid angiopathy; diagnosis; cerebral microbleeds; cortical superficial siderosis; cerebral small vessel disease; intracerebral hemorrhage

Introduction

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

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) based on clinical and MRI information alone, allowing non-invasive *in vivo* diagnosis.^{1–5} Among limitations to the probable CAA criteria is that they have lower sensitivity for non-ICH than for ICH disease presentations and have been validated only in small samples (total <100) primarily from a single centre.^{2,4,6,7} As first formulated in 1995 (“v1.0”), probable CAA entailed demonstration of multiple (i.e., 2) haemorrhagic lesions restricted to lobar brain regions, including ICH and cerebral microbleeds (CMB). In the modified Boston criteria proposed in 2010 (“v1.5”), the presence of blood products in cortical sulci (cortical superficial siderosis, cSS) was included as an additional haemorrhagic lesion, treating any extent of cSS as a single CAA-haemorrhagic lesion. More recent observations of non-haemorrhagic white matter markers of CAA^{6,8} have raised the possibility that diagnostic sensitivity, particularly

for non-ICH presentations, might be further enhanced by incorporating some of these markers.

Here, we report an international collaborative study led by the International CAA Association (ICAAA)^{1,9} to update and externally validate the Boston diagnostic criteria across the full spectrum of clinical CAA.¹⁰ To this end, we systematically obtained histopathological, neuroimaging, clinical and other available data from eligible patients with histopathologically-confirmed CAA or confirmed absence of advanced CAA.⁹ We used these data to devise and validate a “v2.0” of the Boston criteria for CAA.⁹

Methods

Study design and participants

The protocol for this study was developed by investigators from the Massachusetts General Hospital (MGH, Boston, USA) coordinating centre and University College of London (London, UK) in August 2016. An initial draft of the protocol was presented and discussed among investigators in September 2016 at the 5th ICAAA Conference, finalized in January 2017, and subsequently performed in alignment with STARD 2015 guidelines.¹¹ Patient identification was completed in December 2018, and imaging analyses in September 2019. The full study protocol and detailed methods have been published⁹ and are summarized here.

We performed a multicentre hospital-based retrospective study across the ICAAA network of patients presenting to inpatient or outpatient hospital settings with spontaneous primary ICH or other clinical syndromes associated with sporadic CAA, specifically cognitive impairment/dementia or transient focal neurological episodes (TFNE). Patients with other clinical presentations and diagnoses (including antecedent head trauma, haemorrhagic transformation of an ischemic stroke, arteriovenous malformation, haemorrhagic tumor, or central nervous system vasculitis²) or with iatrogenic¹² or hereditary¹³ CAA were excluded. CAA-related inflammation cases were eligible for inclusion only if an MRI at a time without evidence for ongoing inflammation was available.^{1,9} We used multiple overlapping sources of case ascertainment⁹ to identify all potentially eligible patients with: (a) the above potential CAA-related clinical presentations seen in stroke, memory, or research clinics; (b) available adequate MRI data, including at least T2-weighted, FLAIR and T2*-weighted axial sequences (conventional T2*-gradient recalled-echo [GRE] or more sensitive susceptibility weighted imaging [SWI] methods on 1.5 or 3.0 Tesla MRI models);⁹ and (c) available brain tissue (obtained by biopsy, hematoma evacuation, or autopsy, containing at least 10 evaluable cortical or leptomeningeal vessels) to determine the presence or absence of CAA.

Clinical (variables listed in Table 1) and imaging data were sent in anonymised format to MGH 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 patient or authorised family member at the time of the procedures by the local centre; no additional consent was required for sharing of the anonymised data.

Reference test: Definition of cases and controls

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, masked to clinical and brain MRI findings, using the modified Vonsattel grading system and predefined threshold as in previous studies.^{9,14,15} For cases categorized as histopathologically-confirmed CAA, full brain autopsy samples were required to demonstrate Vonsattel grade 2 (i.e. at least one instance of replacement of whole vessel wall by amyloid- β), whereas samples from brain biopsy or hematoma evacuation, because of the more limited tissue sampling, were required to demonstrate Vonsattel grade 1 (i.e. any amyloid in a vessel wall). Controls were defined by absence of advanced CAA as above (Vonsattel 1 in autopsy, Vonsattel=0 in brain biopsy or hematoma evacuation).

Index tests: MRI assessment and analysis

Key MRI biomarkers of CAA and small vessel disease were derived from a systematic review of the relevant literature.¹⁰ These included the characteristic haemorrhagic MRI biomarkers of lobar CMB, lobar ICH, cSS and convexity subarachnoid haemorrhage (cSAH) and the non-haemorrhagic white matter markers¹⁶ of severe MRI-visible perivascular spaces in the centrum semiovale (CSO-PVS, defined as >20 visible perivascular spaces in the centrum semiovale of one hemisphere⁵) and white matter hyperintensities-multispot pattern (WMH-MS, defined as >10 small circular or ovoid T2/FLAIR-hyperintense lesions in the bilateral subcortical white matter⁸ (Figure 1). The analysis of cSAH-cSS explicitly allowed multiple distinct foci to be counted as independent haemorrhagic lesions. More detailed accounts of MRI assessment and analysis along with classification systems and representative examples are provided in the Supplementary material and study protocol paper.⁹ All MRI markers were rated by a trained observer without knowledge of clinical and pathological information, according to STandards for ReportIng Vascular changes on nEuroimaging (STRIVE)¹⁷ where applicable and validated scales and guidelines.¹⁸ Additional trained raters (AC and GB) assessed a random sample of the MRI scans (n=100) to generate inter-rater agreement measures. For all MRI markers assessed the inter-rater kappa values were >0.8 (0.94 (95% CI: 0.85–1) for presence of multifocal cSS, 0.86 (95% CI: 0.75–0.96) for severe CSO-PVS, 0.89 (96% CI: 0.80–0.98) for WMH-MS) indicating excellent agreement.

Statistical analysis and development of Boston Criteria v2.0

We undertook prespecified sample splitting into: (a) a derivation sample – MGH, Boston cases from 1994 to 2012; (b) a temporal validation sample - MGH, Boston cases from 2012–2018; and (c) a geographical validation sample –non-MGH cases from 2004–2018. 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 convenience rather than consecutive series. We compared the distributions of clinical, and MRI characteristics of participants within the derivation vs. the two validation samples using χ^2 test (or Fisher's exact test,

where appropriate) for categorical variables and the Mann-Whitney U test for non-normally distributed continuous variables.

Our approach was to (a) prespecify MRI variables and appropriate cut-offs based on available evidence;⁹ (b) examine their associations with histopathological CAA in the derivation sample, quantified as odds ratios (ORs) with 95% confidence intervals (CIs); (c) propose provisional Boston criteria v2.0 for probable and possible CAA based on classification measures (sensitivity, specificity, positive and negative predictive values, area under the receiver-operating characteristics curve [AUC] and 95% CIs) for different combinations of CAA MRI biomarkers within the derivation sample; (d) validate Boston criteria v2.0 in the external validation samples using the same classification measures; and finally (e) combine all samples 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 histopathological CAA as 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 to the modified Boston criteria currently in use,⁴ and further breakdown into subgroups of patients presenting with vs. without ICH, and imaged using SWI vs. T2*-GRE MRI methods.⁹ Comparison of overall diagnostic accuracy between the v2.0 criteria and the current modified Boston criteria was performed by the STATA roccomp command for correlated samples. We performed statistical analyses using STATA 13. No data were missing from the study.

We followed a conceptual framework fully outlined in the study protocol paper⁹ of maintaining the current Boston Criteria core categories of probable and possible CAA and maintaining a common set of criteria for ICH and non-ICH 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 without losing specificity. The goal for the v2.0 possible CAA rule-out diagnostic category is to maximize sensitivity while maintaining reasonably high specificity. Definite CAA based on full autopsy, and the additional category of probable CAA with supporting pathology based on clinical scenarios of having limited brain tissue from biopsy or hematoma 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. All authors had full access to the data and accept responsibility for the decision to submit for publication.

Results

Of 401 potentially eligible patients presenting to MGH, 43 were excluded for not presenting with ICH, cognitive impairment or TFNE, 44 for not having all required MRI sequences, and 96 for inadequate pathologic tissue (Figure 2). Of 160 patient datasets from non-MGH centres, 37 were excluded for missing MRI sequences or pathologic diagnosis. The remaining total of 341 participants with available MRI and neuropathology data were split

per predefined design into a derivation sample (MGH, 159 Boston cases from 1994 to 2012), temporal validation sample (MGH, 59 Boston cases from 2012–2018), and geographical validation sample (123 non-Boston cases 2004–2018; Supplementary Table 1). The baseline demographic, clinical and MRI characteristics across the three samples are shown in Table 1. Twenty-four CAA cases were previously published in prior validation studies (11^{2,4} from the derivation sample, 13^{4,6} from the geographical validation sample).

Within the derivation sample (mean age: 73), 107 (67%) individuals had pathologically verified CAA, 52 (33%) verified non-CAA. In univariable analysis, MRI markers strongly associated with CAA were lobar ICH (OR 4.2, 95% CI 2–8.7; $p < 0.0001$), cSS (40, 5–300; $p < 0.0001$), lobar CMB (3.4, 1.7–6.6; $p < 0.0001$), severe CSO-PVS (6.3, 3–13.5; $p < 0.0001$) and WMH-MS (3.5, 1.6–7.6; $p = 0.002$). Periventricular and deep WMH severity was not associated with CAA and was hence not considered further.

We used these results to draft provisional Boston criteria v 2.0 for further validation. The analyses of various combinations of markers within the derivation sample are summarized in Supplementary Tables 2 and 3. Of note, of the non-haemorrhage features, the addition of CS-PVS added most sensitivity/specificity with fairly marginal added performance from WMH-MS. Based on these results, we selected rule-in criteria for probable CAA (Table 2) of presence of 2 or more strictly lobar haemorrhagic lesions (ICH, CMB, cSAH-cSS) or 1 lobar haemorrhagic lesion and at least 1 white matter lesion (severe CSO-PVS, WMH-MS). For patients presenting with symptomatic ICH, these criteria yielded sensitivity, specificity, and AUC of 86.7% (95% CI: 75.4–94.1%), 70.6% (44–89.1%), and 0.79 (95% CI: 0.67–0.91) for probable CAA (vs. non-probable CAA). For those with non-ICH presentations, these values were 59.6% (44.3–73.6%), 91.4% (76.9–98.2%), and 0.75 (95% CI: 0.67–0.84). Possible CAA was defined as a single lobar haemorrhagic or white matter lesion (Table 2). Across all ICH and non-ICH presentations in the derivation sample, possible + probable CAA showed sensitivity of 91.6% (84.6%–96.1%) (compared with 74.8% for probable CAA in the same sample) and specificity of 57.7% (43.2%–71.3%) (compared with 84.6% for probable CAA in the same sample) vs. no CAA diagnostic categories (Table 3).

We also performed post-hoc analyses of two MRI markers that emerged after publication of our study protocol: lobar lacunes and superficial cerebellar microbleeds.^{19,20} Including 1 lobar haemorrhagic lesion plus 1 lobar lacune or 1 superficial cerebellar microbleed did not reclassify any possible CAA case in the derivation cohort as probable CAA and thus did not affect the above calculations of sensitivity and specificity. Similarly, including 1 lobar lacune or 1 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 (n=59) and geographical external validation (n=123) samples we found that the provisional Boston criteria v.2.0. retained consistently good sensitivity and specificity for the probable CAA diagnosis (Table 3): sensitivity 92.5% (79.6%–98.4%) / 80.2% (70.8%–87.6%) and specificity 89.5% (66.9%–98.7%) / 81.5% (61.9%–93.7%), respectively. As expected for the diagnosis of probable + possible CAA, sensitivity was ~90% with lower, but still acceptable specificities (Table 3). Compared to the modified Boston criteria currently in use, the Boston criteria v.2.0 achieved higher sensitivity with comparable specificity across all three samples (Table 3).

Given the external validation of Boston criteria v2.0, we merged all samples (n=341) to perform prespecified secondary analyses. In the whole sample, each of the MRI markers remained independently associated with CAA histopathologic diagnosis in multivariable logistic regression (Table 4). Boston criteria v2.0 probable / probable + possible CAA in the full sample showed sensitivities of 79.8% (74.2%–84.7%) / 91.8% (87.6%–94.9%) and specificities of 84.7% (76%–91.2%) / 62.2% (51.9%–71.8%) respectively. Restricting to the subgroup of individuals with full brain autopsy (Table 5), the specificity for both diagnostic categories increased to 95.0% and 70.0% respectively. Relative to the modified Boston criteria, Boston criteria v2.0 probable CAA demonstrated 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 with ICH ($p=0.0047$), and non-ICH ($p=0.04$) presentations. Diagnostic accuracy appeared highest in patients with SWI MRI (Table 5).

Discussion

We have assembled a large multicentre sample of patients to update and validate criteria for clinical-MRI 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, the same motivating approach as previous versions 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 v2.0 to be diagnosed based on 1) multifocal cSAH-cSS alone without requiring accompanying parenchymal ICH or CMB, or 2) presence of a CAA-related white matter lesion (primarily CSO-PVS with some additional effect of WMH-MS) together with a single haemorrhagic marker (ICH, CMB, cSAH-cSS). Comparison of the v2.0 criteria to the currently used modified Boston criteria⁴ suggest the additional MRI features capture some true-positive CAA patients 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 currently used 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 of ruling out most non-CAA cases.

The incorporation of cSS multifocality as well as presence is one of the core updates of the Boston criteria v2.0, counting multifocal cSAH-cSS as 2 haemorrhagic lesions that can alone meet the definition of probable CAA. From a methodologic standpoint, we attempt to distinguish between a single focus of cSS (even if it extends to a second adjacent gyrus) and multifocal/extensive cSS that involves gyri separated by uninvolved areas or involves three or more adjacent gyri, excluding foci of cSS from adjacent lobar ICH.^{1,9} Of note, cSS and acute cSAH are rated as equivalent MRI markers of CAA, with the understanding that cSAH is the acute form and cSS the chronic form of the same underlying process of

superficial cortical haemorrhage.²¹ In cases where acute cSAH is potentially connected or in close vicinity to cSS, they are counted as evidence of two haemorrhagic markers of CAA as the acuity of cSAH 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 CSO-PVS and WMH-MS (Fig. 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-positives 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 CAA patients (detected in 15 of 21 CAA-positive no-haemorrhage individuals in the full study sample vs. 10 of 33 CAA-negative, specificity 69.7%) and were therefore incorporated into the v2.0 possible CAA criteria as well. Their specificity for CAA prior to the occurrence of a haemorrhage offers scope for early intervention to prevent worsening of CAA accumulation and haemorrhage. CAA-associated CSO-PVS appears related to the perivascular trafficking of amyloid- β peptide²² and CAA severity in the overlying cortical vessels.²³ The mechanistic basis for WMH-MS is unknown but may also reflect CAA involvement of cortical penetrating vessels. We note that the association of WMH-MS with CAA has been less widely studied than that of CSO-PVS and may also be somewhat less robust (Table 4, Supplementary Tables 2 and 3). Although this marker showed independent association and good inter-rater reliability in our analysis, it may require independent replication to determine 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, though characteristic of CAA, are relatively late disease manifestations²⁴ and therefore less sensitive for earlier disease stages. The relatively late occurrence of haemorrhage in CAA progression likely also accounts for the lower diagnostic sensitivity for non-ICH than ICH clinical presentations, even using the expanded v2.0 criteria (Table 5).

An important MRI finding encountered in practice are mixed lobar plus non-lobar locations of haemorrhagic lesions. Prior studies suggest this pattern can represent non-CAA small vessel disease in some individuals and advanced CAA in others,^{25,26} highlighting the importance of devising imaging criteria that could identify the CAA subgroup. There were only 36 mixed haemorrhage cases across all three samples in our study, however, an insufficient number to allow criteria to be developed and validated. We therefore 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 cerebrospinal fluid amyloid- β ^{27,28} have not yet been validated for incorporation into diagnostic criteria but may 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 size, limited subset of MRI biomarkers, restriction primarily to ICH presentations, and primarily single-centre settings.¹ The geographical external validation in particular suggests the v2.0 criteria have comparable accuracy across

a range of medical centres and MRI scanners. The current sample size also allowed us to perform prespecified subgroup analysis in individuals with full brain autopsy, where the presence/absence of CAA can be confirmed with highest certainty. Although brain tissue from biopsy or hematoma 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/evacuation-confirmed diagnoses in the derivation and validation analyses, but also to recheck the v2.0 criteria performance in pooled individuals with full autopsies. The high specificity achieved by probable CAA in this analysis (92.9% and 96.2% in ICH and non-ICH presentations respectively, Table 5) offer strong support for the accuracy of the revised criteria.

The current effort has limitations inherent to the retrospective observational study design that relies on clinical MRI markers and availability of neuropathologic tissue. There is substantial selection bias due to the requirements for MRI and neuropathological tissue. The requirement for brain tissue may bias towards more severe underlying CAA leading to death (and hence autopsy), rapidly progressing clinical symptoms (leading to brain biopsy), or large ICH (leading to hematoma 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 lead to likely overestimation of diagnostic accuracy via spectrum bias. Another limitation to the generalizability of the current criteria is they were almost entirely derived from white participants of European ancestry, highlighting the need for further external validation in other racial/ethnic groups and geographic 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 PVS and T2*-weighted techniques for detection of haemorrhagic lesions.²⁹ Our subgroup analysis suggests that the primary effect of SWI is to improve diagnostic accuracy (Table 5). 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 presented like the cases and would themselves have been cases if their neuropathology had been positive for CAA.

The Boston Criteria for CAA v2.0 appear to be a useful basis for clinical diagnosis and research study enrolment for individuals with ICH or non-ICH presentations. Future studies will be required determine their generalizability 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 in non-white populations. These criteria also require MRI with T2*-weighted (for haemorrhagic lesion detection) and T2-weighted (for PVS detection) sequences, highlighting the importance of alternative CT-based approaches such as the Edinburgh criteria for CAA-related ICH.³⁰ 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 elderly.³¹ Validation studies for each of these

specific clinical scenarios is currently underway and represent further opportunities for detection of this major small vessel pathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Andreas Charidimou^{*},
Gregoire Boulouis,
Matthew P. Frosch,
Jean-Claude Baron,
Marco Pasi,
Jean Francois Albucher,
Gargi Banerjee,
Carmen Barbato,
Fabrice Bonneville,
Sebastian Brandner,
Lionel Calviere,
François Caparros,
Barbara Casolla,
Charlotte Cordonnier,
Marie-Bernadette Delisle,
Vincent Deramecourt,
Martin Dichgans,
Elif Gokcal,
Jochen Herms,
Mar Hernandez-Guillamon,
Hans Rolf Jäger,
Zane Jaunmuktane,
Jennifer Linn,
Sergi Martinez-Ramirez,
Elena Martínez-Sáez,
Christian Mawrin,
Joan Montaner,
Solene Moulin,
Jean-Marc Olivot,
Fabrizio Piazza,
Laurent Puy,
Nicolas Raposo,

Mark A. Rodrigues,
 Sigrun Roeber,
 Jose Rafael Romero,
 Neshika Samarasekera,
 Julie A. Schneider,
 Stefanie Schreiber,
 Frank Schreiber,
 Corentin Schwall,
 Colin Smith,
 Levente Szalardy,
 Pascale Varlet,
 Alain Viguier,
 Joanna M. Wardlaw,
 Andrew Warren,
 Frank A. Wollenweber,
 Marialuisa Zedde,
 Mark A. van Buchem,
 M. Edip Gurol,
 Anand Viswanathan,
 Rustam Al-Shahi Salman,
 Eric E. Smith,
 David J. Werring,
 Steven M. Greenberg

Affiliations

Hemorrhagic Stroke Research Program, J. Philip Kistler Research Center, Department of Neurology, Massachusetts General Hospital, Boston, MA, USA (G Boulouis MD, A Charidimou MD, E Gokcal MD, S Martinez-Ramirez MD, M Pasi MD, A Warren BS, M E Gurol MD, A Viswanathan MD, Prof S M Greenberg MD); GHU Paris Psychiatrie et Neurosciences, Institut de Psychiatrie et Neurosciences de Paris (IPNP), INSERM UMR_S1266, Université Paris Cité, Paris, France (G Boulouis MD, Prof J C Baron ScD, C Schwall MD, P Varlet MD); C.S Kubik Laboratory of Neuropathology, Department of Pathology, Massachusetts General Hospital, Boston, MA, USA (M P Frosch MD); GHU Psychiatrie et Neurosciences, site Sainte-Anne, Paris, France (Prof J C Baron ScD, C Schwall MD, P Varlet MD); Univ. Lille, Inserm, CHU Lille, U1172-LiINCog – Lille Neuroscience & Cognition, F-59000 Lille, France (F Caparros MD, B Casolla MD, Prof C Cordonnier MD, M Pasi MD, Prof S Moulin MD, L Puy MD, Prof V Deramecourt MD); Departments of Neurology, Neuroradiology, and Pathology, Hôpital Pierre-Paul Riquet, CHU Toulouse, Toulouse NeuroImaging Centre, Université da Toulouse, INSERM UPS, France (J F Albucher MD, Prof F Bonneville MD, L Calviere MD, Prof M B Delisle MD, Prof J M Olivot MD, N Raposo MD, A Viguier MD);

Stroke Research Centre, Department of Brain Repair and Rehabilitation, University College London Queen Square Institute of Neurology and National Hospital for Neurology and Neurosurgery, London, UK (G Banerjee PhD, C Barbato MD, Prof S Brandner MD, Prof H R Jäger MD, Z Jaunmuktane FRCP, Prof D J Werring PhD); Institute for Stroke and Dementia Research, Ludwig-Maximilians University Munich, Munich, Germany (Prof M Dichgans MD, Prof F A Wollenweber MD); Munich Cluster for Systems Neurology (SyNergy) and German Center for Neurodegenerative Diseases (DZNE), Munich, Germany (Prof. M Dichgans MD); Center for Neuropathology and Prion Research, Ludwig-Maximilians University Munich, Munich, Germany (Prof J Herms MD, S Roeber MD); Neurovascular Research Laboratory, Institut de Recerca Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain (M Hernandez-Guillamon PhD, E Martínez-Sáez MD, J Montaner MD); Institute of Biomedicine of Seville, IBiS, Hospital Universitario Virgen Macarena, CSIC, University of Seville, Spain (J Montaner MD); Institute for Diagnostic and Interventional Neuroradiology, University Hospital, Dresden, Germany (Prof J Linn MD); Departments of Neuropathology, Neurosurgery, and Neurology, Otto-von-Guericke University, Magdeburg, Germany (Prof C Mawrin MD, Prof S Schreiber MD, F Schreiber MSc); CAA and AD Translational Research & Biomarkers Laboratory, School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy (Prof F Piazza PhD); Centre for Clinical Brain Sciences University of Edinburgh, Edinburgh, UK (M A Rodrigues FRCR, N Samarasekera PhD, Prof C Smith MD, Prof J M Wardlaw MD, Prof R Al-Shahi Salman PhD); UK Dementia Research Institute, University of Edinburgh, Edinburgh, UK (Prof J M Wardlaw MD, Prof R Al-Shahi Salman PhD); Department of Neurology, Boston University School of Medicine, MA and the Framingham Heart Study, MA, USA (J R Romero, MD, S Martinez-Ramirez MD); Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA (Prof J A Schneider MD); Department of Neurology, Faculty of Medicine, Albert Szent-Györgyi Clinical Center, University of Szeged, H-6725, Szeged, Semmelweis u 6, Hungary (L Szalardy MD); Helios Dr. Horst Schmidt Kliniken, Wiesbaden, Germany (Prof F A Wollenweber MD); Neurology Unit-Stroke Unit, Azienda Unità Sanitaria Locale – IRCCS di Reggio Emilia, Reggio Emilia, Italy (M Zedde MD); Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands (Prof M A van Buchem MD); and Department of Clinical Neurosciences and Hotchkiss Brain Institute, University of Calgary, Canada (Prof E E Smith MD)

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Data Sharing

Deidentified data from MGH 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 Prof Greenberg sgreenberg@mg.harvard.edu.

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Research in context

Evidence before this study

The clinical-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) performed a systematic review of diagnostic accuracy studies using different versions of the Boston criteria against the reference standard of neuropathologically proven CAA published in PubMed (from September 15 1994 to February 23 2022, English language) using comprehensive electronic search strategies combining terms “Boston criteria” OR “cerebral amyloid angiopathy” AND validation OR diagnosis. We identified 4 hospital-based studies and one population-based sample describing the validation and diagnostic performance of the Boston criteria. The studies to date were based on single-centre and relatively small samples (<100), primarily including patients with intracerebral haemorrhage. They provided validating evidence of a good diagnostic performance of the probable CAA-related lobar intracerebral haemorrhage (ICH) category. As currently formulated, probable CAA entails demonstration of multiple (i.e., 2 or more) haemorrhagic lesions restricted to lobar brain regions, including ICH, cerebral microbleeds (CMBs) and the presence of cortical superficial siderosis (cSS). The 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 test accuracy study minimized some previous biases, used a multicentre design, large patient sample and explored both ICH and non-ICH clinical presentations. We were able to derive and validate updated criteria for probable CAA requiring the presence of 2 strictly lobar haemorrhagic lesions (ICH, CMB, or cSS focus) or 1 lobar haemorrhagic lesion and 1 white matter lesion (severe degree of visible perivascular spaces in centrum semiovale or white matter hyperintensities in a multispot pattern). These criteria showed enhanced sensitivity relative to the currently used Boston criteria without comprising their high specificity and represented 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 recognized 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 spectrum of CAA-related presentations and across sites. Future research is required to evaluate their clinical use and further investigate specific patient subgroups and advanced imaging techniques.

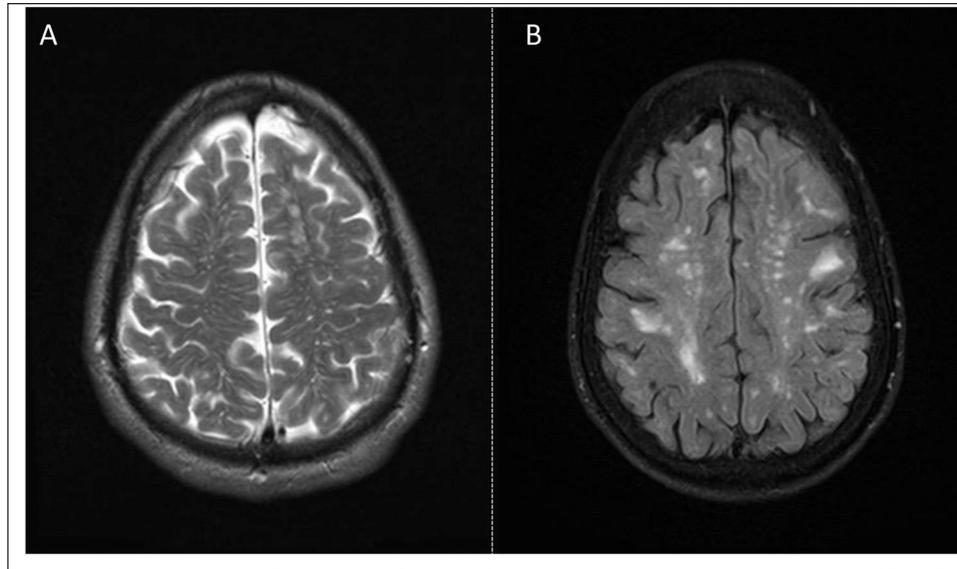


Figure 1.

Boston Criteria v2.0 white matter MRI markers.

A. Severe centrum semiovale perivascular spaces, identified on axial T2-weighted images¹⁷ are defined as greater than 20 visible perivascular spaces in the centrum semiovale of one hemisphere.⁶ B. Multispot white matter hyperintensity pattern is defined as greater than 10 T2/FLAIR small circular or ovoid hyperintense lesions in the subcortical white matter of both hemispheres.⁸

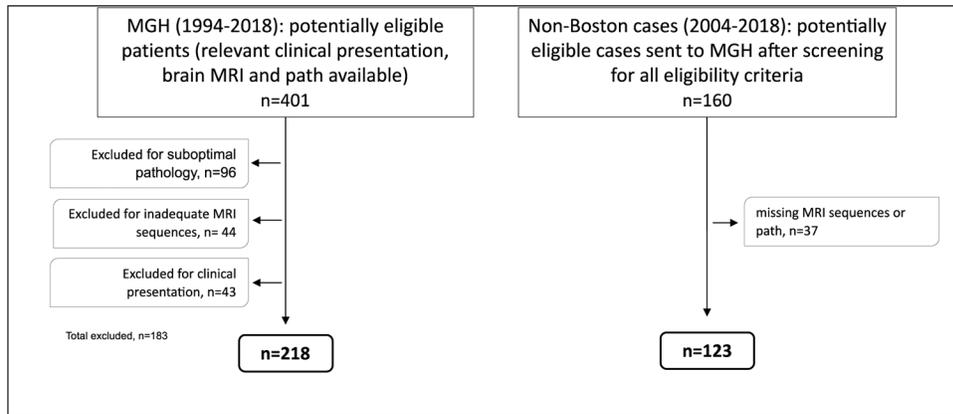


Figure 2.
Flow chart of patient selection

Table 1.

Characteristics of patients across the three study samples

	Derivation sample (n=159)	Temporal external validation (n=59)	p-value versus Derivation	Geographical external validation (n=123)	p-value versus Derivation
Clinical history and presentation					
Age, years	73 (68–78)	70 (61–76)	0.006	69 (63–77)	0.0083
Sex, men	74 (47%)	24 (41%)	0.439	61 (50%)	0.611
women	85 (53%)	35 (59%)		62 (50%)	
Race, Asian	4 (2.7%)	2 (3.5%)		-	-
Black	7 (4.7%)	3 (5.2%)		-	
Hispanic	0 (0%)	1 (1.7%)		-	
White	137 (92.6%)	52 (89.7%)		91 (100%)	
Hypertension	96 (60%)	37 (63%)	0.754	60 (49%)	0.052
Antiplatelet use at presentation	47 (30%)	19 (32%)	0.706	36 (29%)	0.958
Anticoagulant use at presentation	17 (11%)	4 (7%)	0.384	16 (13%)	0.548
ICH presentation	77 (48%)	40 (68%)	0.011	94 (76%)	<0.0005
Non-ICH presentation	82 (52%)	19 (32%)		29 (24%)	
TFNE	9	7		9	
Cognitive impairment	54	5		17	
*Other	19	7		3	
MRI method and findings					
3T MRI	20 (13%)	26 (44%)	<0.0001	17 (14%)	0.759
T2*GRE	139 (87%)	33 (56%)	<0.0001	103 (84%)	0.380
SWI	20 (13%)	26 (44%)		20 (16%)	
Multiple ICH	26 (33%)	7 (18%)	0.070	21 (23%)	0.117
Lobar ICH	68 (88%)	29 (71%)	0.007	86 (93%)	0.291
Non-lobar (deep) ICH	4 (5%)	11 (27%)		5 (5%)	
Mixed ICH	2 (3%)	0 (0%)		2 (2%)	
Cerebellar ICH	3 (4%)	1 (2%)		0 (0%)	
Lobar CMB presence	85 (54%)	41 (70%)	0.033	71 (58%)	0.475
Lobar CMB, number	1 (0–13)	3 (0–19)	0.116	2 (0–22)	0.263
Multiple (>1) lobar CMBs	69 (43%)	37 (63%)	0.011	62 (50%)	0.242
Non-lobar CMBs presence	17 (11%)	10 (17%)	0.213	16 (13%)	0.548
Non-lobar (deep) CMB, number	0 (0–0)	0 (0–0)	0.195	0 (0–0)	0.600
Multiple (>1) non-lobar CMBs	11 (7%)	9 (15%)	0.058	9 (7%)	0.897
cSS presence	46 (29%)	20 (34%)	0.478	56 (46%)	0.004
Focal cSS	20 (13%)	7 (12%)	0.623	24 (20%)	0.016
Disseminated cSS	26 (16%)	13 (22%)		32 (26%)	

	Derivation sample (n=159)	Temporal external validation (n=59)	p-value versus Derivation	Geographical external validation (n=123)	p-value versus Derivation
Multifocal/extensive cSS	34 (21%)	16 (27%)	0.669	40 (33%)	0.015
Moderate-severe periventricular WMH	88 (55%)	45 (76%)	0.005	67 (55%)	0.884
Moderate-severe deep WMH	78 (49%)	37 (63%)	0.073	48 (39%)	0.093
Moderate-severe total WMH	98 (62%)	49 (83%)	0.003	71 (58%)	0.506
Multispot WMH pattern	53 (33%)	26 (44%)	0.143	37 (30%)	0.561
Severe CSO-PVS	76 (48%)	28 (48%)	0.964	58 (47%)	0.953
Severe BG-PVS	11 (7%)	7 (12%)	0.238	13 (11%)	0.256
Neuropathology method and findings					
Autopsy	79 (50%)	29 (49%)	0.091	42 (34%)	0.008
Biopsy	37 (23%)	7 (12%)		48 (39%)	
Haematoma evacuation	43 (27%)	23 (39%)		33 (27%)	
Pathologically-verified CAA prevalence	107 (67%)	40 (68%)	0.944	96 (78%)	0.046
MRI-neuropathology delay (years)	0.2 (0.02–2.4)	0.7 (0.06–4.5)	0.057	0.4 (0.08–2.8)	0.194

Values are presented as median (interquartile range) for continuous variables and (% total) for categorical variables. Information on race missing from 11 participants in Derivation sample, 1 in Temporal external validation sample, 23 in Geographic external validation sample (for the Geographic external validation only information on White vs. non-White was available).

* Other non-ICH presentations include CAA-related inflammation³² (in the remission phase), MRI detection of ischaemic stroke, transient nonfocal neurologic episodes

Abbreviations: CAA cerebral amyloid angiopathy, ICH intracerebral haemorrhage, TFNE transient focal neurologic episodes, MRI magnetic resonance imaging, CMB cerebral microbleed, GRE gradient-recalled echo, SWI susceptibility-weighted imaging, cSS cortical superficial siderosis, WMH white matter hyperintensities, CSO-PVS visible perivascular spaces in the centrum semiovale, BG-PVS visible perivascular spaces in the basal ganglia

Table 2.

Boston criteria version 2.0 for sporadic cerebral amyloid angiopathy.

	Boston Criteria (Version 2.0)
1. Definite CAA	<u>Full post-mortem examination demonstrating:</u> <ul style="list-style-type: none"> • Presentation with spontaneous ICH, TFNEs, cSAH, or CI/Dementia • Severe CAA with vasculopathy • Absence of other diagnostic lesion
2. Probable CAA with supporting pathology	<u>Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating:</u> <ul style="list-style-type: none"> • Presentation with spontaneous ICH, TFNEs, cSAH, or CI/Dementia • Some degree of CAA in specimen • Absence of other diagnostic lesion
3. Probable CAA	<u>Clinical data and MRI demonstrating:</u> <ul style="list-style-type: none"> • Age ≥ 50 years • Presentation with spontaneous ICH, TFNEs, or CI/Dementia • 2 of the following strictly lobar haemorrhagic lesions on T2*-weighted MRI, in any combination: ICH, CMB, cSS/cSAH foci <p>OR</p> <ul style="list-style-type: none"> • 1 lobar haemorrhagic lesion + 1 white matter feature (Severe CSO-PVS or WMH-MS) • Absence of any deep haemorrhagic lesions (ICH, CMB) 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	<u>Clinical data and MRI demonstrating:</u> <ul style="list-style-type: none"> • Age ≥ 50 years • Presentation with spontaneous ICH, TFNEs, or CI/Dementia • Absence of other cause of haemorrhage* • 1 strictly lobar haemorrhagic lesion on T2*-weighted MRI: ICH, CMB, cSS/cSAH focus <p>OR</p> <ul style="list-style-type: none"> • 1 white matter feature (Severe CSO-PVS or WMH-MS) • Absence of any deep haemorrhagic lesions (ICH, CMB) on T2*-weighted MRI • Absence of other cause of haemorrhagic lesions* • Haemorrhagic lesion in cerebellum not counted as either lobar or deep haemorrhagic lesion

Notable changes from currently used criteria indicated in bold font.

* Other causes of haemorrhagic lesion: antecedent head trauma, haemorrhagic transformation of an ischemic stroke, arteriovenous malformation, haemorrhagic tumor, central nervous system vasculitis. Other causes of cSS and acute cSAH should also be

Abbreviations: CAA cerebral amyloid angiopathy, MRI magnetic resonance imaging, ICH intracerebral haemorrhage, TFNE transient focal neurologic episodes, CI cognitive impairment, CMB cerebral microbleed, cSS cortical superficial siderosis, cSAH convexity subarachnoid haemorrhage, CSO-PVS visible perivascular spaces in the centrum semiovale, WMH-MS white matter hyperintensities in a multispot pattern

Table 3.

Diagnostic performance of Boston criteria v2.0 (see Table 2) and Modified Boston criteria (v1.5) in the derivation, temporal external validation, geographical external validation samples and all samples combined. Analyses were done for probable vs. non probable CAA and probable + possible vs. non-CAA diagnostic categories.

Study Group	Probable CAA (vs. non-probable CAA)		Probable+Possible CAA (vs. no CAA)	
	Boston Criteria v2.0	Modified Criteria v1.5	Boston Criteria v2.0	Modified Criteria v1.5
Derivation sample (n=159)	Se=74.8% (65.4%–82.7%) Spe=84.6% (71.9%–93.1%) AUC: 0.797 (0.732–0.861) PPV: 90.9% (82.9%–96%) NPV: 62% (49.7%–73.2%)	Se=62.6% (52.7%–71.8%) Spe=86.5% (74.2%–94.4%) AUC: 0.746 (0.68–0.811) PPV: 90.5% (81.5%–96.1%) NPV: 52.9% (41.8%–63.9%)	Se=91.6% (84.6%–96.1%) Spe=57.7% (43.2%–71.3%) AUC: 0.746 (0.674–0.819) PPV: 81.7% (73.6%–88.1%) NPV: 76.9% (60.7%–88.9%)	Se=77.6% (68.5%–85.1%) Spe=75% (61.1%–86%) AUC: 0.763 (0.691–0.834) PPV: 86.5% (78%–92.6%) NPV: 61.9% (48.8%–73.9%)
Temporal validation (n=59)	Se=92.5% (79.6%–98.4%) Spe=89.5% (66.9%–98.7%) AUC: 0.91 (0.828–0.992) PPV: 94.9% (82.7%–99.4%) NPV: 85% (62.1%–96.8%)	Se=87.5% (73.2%–95.8%) Spe=100% (82.4%–100%) AUC: 0.938 (0.886–0.989) PPV: 100% (90%–100%) NPV: 79.2% (57.8%–92.9%)	Se=97.5% (86.8%–99.9%) Spe=78.9% (54.4%–93.9%) AUC: 0.882 (0.785–0.98) PPV: 90.7% (77.9%–97.4%) NPV: 93.8% (69.8%–99.8%)	Se=95% (83.1%–99.4%) Spe=78.9% (54.4%–93.9%) AUC: 0.87 (0.77–0.97) PPV: 90.5% (77.4%–97.3%) NPV: 88.2% (63.6%–98.5%)
Geographical validation (n=123)	Se=80.2% (70.8%–87.6%) Spe=81.5% (61.9%–93.7%) AUC: 0.808 (0.724–0.893) PPV: 93.9% (86.3%–98%) NPV: 53.7% (37.4%–69.3%)	Se=72.9% (62.9%–81.5%) Spe=85.2% (66.3%–95.8%) AUC: 0.791 (0.709–0.872) PPV: 94.6% (86.7%–98.5%) NPV: 46.9% (32.5%–61.7%)	Se=89.6% (81.7%–94.9%) Spe=59.3% (38.8%–77.6%) AUC: 0.744 (0.645–0.844) PPV: 88.7% (80.6%–94.2%) NPV: 61.5% (40.6%–79.8%)	Se=86.5% (78%–92.6%) Spe=63% (42.4%–80.6%) AUC: 0.747 (0.648–0.846) PPV: 89.2% (81.1%–94.7%) NPV: 56.7% (37.4%–74.5%)
Whole sample (n=341)	Se=79.8% (74.2%–84.7%) Spe=84.7% (76%–91.2%) AUC: 0.823 (0.779–0.866) PPV: 92.8% (88.4%–95.9%) NPV: 62.9% (54%–71.1%)	Se=70.8% (64.6%–76.4%) Spe=88.8% (80.8%–94.3%) AUC: 0.798 (0.755–0.84) PPV: 94% (89.5%–97%) NPV: 55.1% (47%–63%)	Se=91.8% (87.6%–94.9%) Spe=62.2% (51.9%–71.8%) AUC: 0.77 (0.719–0.821) PPV: 85.8% (80.9%–89.8%) NPV: 75.3% (64.5%–84.2%)	Se=84% (78.7%–88.3%) Spe=72.4% (62.5%–81%) AUC: 0.782 (0.731–0.832) PPV: 88.3% (83.5%–92.2%) NPV: 64.5% (54.9%–73.4%)

Abbreviations: CAA cerebral amyloid angiopathy. Se sensitivity, Spe specificity, AUC area under the receiver operating characteristics curve, PPV positive predictive value, NPV negative predictive value.

Table 4.

Multivariable logistic regression of MRI markers' association with CAA in the whole sample.

MRI marker	OR (95%CI)	p-value
2 strictly lobar CMB	2.42 (1.33–4.39)	0.004
1 foci of cSS	36.53 (8.7–153.9)	<0.001
Severe CSO-PVS	3.17 (1.66–6.08)	0.001
WMH-MS	2.04 (1.06–3.91)	0.032

Abbreviations: OR (95% CI) odds ratio (95% confidence interval), CMB cerebral microbleeds, cSS cortical superficial siderosis, CSO-PVS perivascular spaces in the centrum semiovale, WMH-MS white matter hyperintensities in a multispot pattern

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Table 5.

Diagnostic performance of Boston criteria v2.0 (see Table 3) in prespecified subset of all samples with available autopsy. Prespecified analyses compare v2.0 vs Modified Boston criteria v1.5, ICH vs non-ICH clinical presentations, and T2*-GRE vs SWI MRI methods.

Sample/Sub-analysis	Probable vs. non-probable CAA	Probable and possible vs. no CAA
Whole sample-Autopsies (n=150) Modified Boston criteria	Se=64.5% (54.9%–73.4%) Spe=95% (83.1%–99.4%) AUC: 0.798 (0.741–0.854) PPV: 97.3% (90.5%–99.7%) NPV: 49.4% (37.8%–61%)	Se=75.5% (66.3%–83.2%) Spe=87.5% (73.2%–95.8%) AUC: 0.815 (0.749–0.881) PPV: 94.3% (87.2%–98.1%) NPV: 56.5% (43.3%–69%)
Whole sample-Autopsies (n=150) Boston criteria v2.0	Se=74.5% (65.4%–82.4%) Spe=95% (83.1%–99.4%) AUC: 0.848 (0.794–0.901) PPV: 97.6% (91.7%–99.7%) NPV: 57.6% (44.8%–69.7%)	Se=88.2% (80.6%–93.6%) Spe=70% (53.5%–83.4%) AUC: 0.791 (0.713–0.869) PPV: 89% (81.6%–94.2%) NPV: 68.3% (51.9%–81.9%)
Whole sample-Autopsies ICH (n=75) Boston criteria v2.0	Se=90.2% (79.8%–96.3%) Spe=92.9% (66.1%–99.8%) AUC: 0.915 (0.836–0.995) PPV: 98.2% (90.4%–100%) NPV: 68.4% (43.4%–87.4%)	Se=91.8% (81.9%–97.3%) Spe=71.4% (41.9%–91.6%) AUC: 0.816 (0.689–0.944) PPV: 93.3% (83.8%–98.2%) NPV: 66.7% (38.4%–88.2%)
Whole sample-Autopsies non-ICH (n=75) Boston criteria v2.0	Se=55.1% (40.2%–69.3%) Spe=96.2% (80.4%–99.9%) AUC: 0.756 (0.676–0.836) PPV: 96.4% (81.7%–99.9%) NPV: 53.2% (38.1%–67.9%)	Se=83.7% (70.3%–92.7%) Spe=69.2% (48.2%–85.7%) AUC: 0.765 (0.66–0.869) PPV: 83.7% (70.3%–92.7%) NPV: 69.2% (48.2%–85.7%)
Whole sample-Autopsies T2*-GRE (n=127) Boston criteria v2.0	Se=72.6% (62.5%–81.3%) Spe=93.8% (79.2%–99.2%) AUC: 0.832 (0.77–0.894) PPV: 97.2% (90.1%–99.7%) NPV: 53.6% (39.7%–67%)	Se=87.4% (79%–93.3%) Spe=68.8% (50%–83.9%) AUC: 0.781 (0.692–0.869) PPV: 89.2% (81.1%–94.7%) NPV: 64.7% (46.5%–80.3%)
Whole sample-Autopsies SWI (n=23) Boston criteria v2.0	Se=86.7% (59.5%–98.3%) Spe=100% (63.1%–100%) AUC: 0.933 (0.844–1) PPV: 100% (75.3%–100%) NPV: 80% (44.4%–97.5%)	Se=93.3% (68.1%–99.8%) Spe=75% (34.9%–96.8%) AUC: 0.842 (0.668–1) PPV: 87.5% (61.7%–98.4%) NPV: 85.7% (42.1%–99.6%)

Abbreviations: CAA cerebral amyloid angiopathy, ICH intracerebral haemorrhage, MRI magnetic resonance imaging, GRE gradient-recalled echo, SWI susceptibility-weighted imaging Se sensitivity, Spe specificity, AUC area under the receiver operating characteristics curve, PPV positive predictive value, NPV negative predictive value