

1 **MRI and CT imaging biomarkers of cerebral amyloid angiopathy in lobar**
2 **intracerebral haemorrhage**

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4 Ghil Schwarz^{1,2}, Gargi Banerjee¹, Isabel C. Hostettler^{1,3}, Gareth Ambler⁴, David J. Seiffge^{1,5}, Hatice
5 Ozkan¹, Simone Browning¹, Robert Simister¹, Duncan Wilson^{1,6}, Hannah Cohen⁷, Tarek Yousry⁸,
6 Rustam Al-Shahi Salman⁹, Gregory Y.H. Lip¹⁰, Martin M. Brown¹, Keith W. Muir¹¹, Henry Houlden¹²,
7 Rolf Jäger⁸, David J. Werring¹ on behalf of the CROMIS-2 and SIGNaL investigators

8

9 ¹ *Stroke Research Centre, University College London, Institute of Neurology, London, UK*

10 ² *Department of Neurology and Stroke Unit ASST Grande Ospedale Metropolitano Niguarda, Milan,*
11 *Italy*

12 ³ *Department of Neurosurgery, Cantonal Hospital St. Gallen, St. Gallen, Switzerland*

13 ⁴ *Department of Statistical Science, University College London, Gower Street, London, UK*

14 ⁵ *Department of Neurology and Stroke Center, Inselspital, Bern, Switzerland*

15 ⁶ *New Zealand Brain Research Institute, Christchurch, New Zealand*

16 ⁷ *Haemostasis Research Unit, Department of Haematology, University College London, 51 Chenies*
17 *Mews, London, UK*

18 ⁸ *Neuroradiological Academic Unit, Department of Brain Repair and Rehabilitation, UCL Institute of*
19 *Neurology, Queen Square, London, UK and Lysholm Department of Neuroradiology, The National*
20 *Hospital for Neurology and Neurosurgery, Queen Square London*

21 ⁹ *Centre for Clinical Brain Sciences, School of Clinical Sciences, University of Edinburgh, Edinburgh,*
22 *UK*

23 ¹⁰ *Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest*
24 *Hospital, Liverpool, United Kingdom; and Department of Clinical Medicine, Aalborg University,*
25 *Aalborg, Denmark*

26 ¹¹ *Institute of Neuroscience & Psychology, University of Glasgow, Queen Elizabeth University*
27 *Hospital, Glasgow, UK*

28 ¹² *Department of Molecular Neuroscience, UCL Institute of Neurology and the National Hospital for*
29 *Neurology and Neurosurgery, Queen Square, London*

30

31 **Corresponding author:** Professor David Werring, FRCP, PhD, National Hospital of Neurology
32 and Neurosurgery, Institute of Neurology, University College London, Queen Square, WC1N
33 London, United Kingdom, Phone: +44 20 3447 5994, Fax: +44 20 7833 8613, Email:
34 d.werring@ucl.ac.uk

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59 **ABSTRACT**

60 **Background.** Cerebral amyloid angiopathy (CAA), a common cause of intracerebral haemorrhage
61 (ICH), is diagnosed using the Boston criteria including MRI biomarkers (cerebral microbleeds [CMB]
62 and cortical superficial siderosis [cSS]). The simplified Edinburgh criteria include CT biomarkers
63 (subarachnoid extension [SAE] and finger-like projections [FLP]). The underlying mechanisms and
64 diagnostic accuracy of CT compared to MRI biomarkers of CAA are unknown.

65 **Methods.** We included 140 survivors of spontaneous lobar supratentorial ICH with both acute CT
66 and MRI. We assessed associations between MRI and CT biomarkers and the diagnostic accuracy
67 of CT- compared to MRI-based criteria.

68 **Results.** FLP were more common in patients with strictly lobar CMB (44.7% vs 23.5%; $p=0.014$) and
69 SAE was more common in patients with cSS (61.3% vs 31.2%; $p=0.002$). The high probability of the
70 CAA category of the simplified Edinburgh criteria showed 87.2% (95%CI 78.3-93.4) specificity,
71 29.6% (95%CI 18.0-43.6) sensitivity, 59.3% (95%CI 38.8-77.6) positive predictive value and 66.4%
72 (95%CI 56.9-75.0), negative predictive value, 2.3 (95%CI 1.2-4.6) positive likelihood ratio and 0.8
73 (95%CI 0.7-1.0) negative likelihood ratio for probable CAA (vs non-probable CAA), defined by the
74 modified Boston criteria; the area under the receiver operating curve (AUROC) was 0.62 (95%CI
75 0.54-0.71).

76 **Conclusion.** In lobar ICH survivors, we found associations between putative biomarkers of
77 parenchymal CAA (FLP and strictly lobar CMBs) and putative biomarkers of leptomeningeal CAA
78 (SAE and cSS). CT biomarkers might help rule-in probable CAA (diagnosed using the Boston
79 criteria), but their absence is probably not useful to rule it out, suggesting an important continued
80 role for MRI in ICH survivors with suspected CAA.

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85 INTRODUCTION

86 Spontaneous lobar intracerebral haemorrhage (ICH) related to cerebral amyloid angiopathy (CAA)
87 is associated with high risks of death, poor functional outcome, dementia [1] and intracerebral
88 hemorrhage (ICH) recurrence [2], so it is important to identify in clinical practice. Histopathological
89 assessment is the reference standard to identify CAA, but cerebral tissue is rarely available, so
90 neuroimaging biomarkers are usually used to infer the presence of CAA. The modified Boston criteria
91 for CAA [3][4] are widely used MRI-based criteria. However, MRI is not always available, tolerated,
92 or possible due to contraindications, particularly during acute care.

93 More recently, the acute CT-based Edinburgh criteria have been proposed [5]; a CT-only version of
94 the criteria (the simplified Edinburgh criteria) include only subarachnoid extension (SAE) and finger-
95 like projections (FLP). The Edinburgh criteria demonstrated excellent diagnostic accuracy for
96 autopsy-proven CAA in severe ICH (fatal events), but still require external validation. Furthermore,
97 little is known about the underlying mechanisms of FLP or SAE. FLP might reflect CAA affecting
98 brain parenchymal small vessels (causing blood to dissect into abnormal brain tissue), while SAE
99 might be due to leptomeningeal arteriolar CAA (leading to acute bleeding into the subarachnoid
100 space).

101 We aimed to evaluate: (1) whether FLP are associated with CMBs (as a putative biomarker of
102 parenchymal CAA); (2) whether SAE is associated with cSS (as a putative biomarker of
103 leptomeningeal CAA); and (3) to evaluate the diagnostic accuracy and concordance of simplified
104 Edinburgh criteria compared to modified Boston criteria.

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106 METHODS

107 We retrospectively included consecutive adult patients with spontaneous (non-traumatic) ICH from:
108 an observational prospective multicenter cohort study (Clinical Relevance of Microbleeds in Stroke;
109 CROMIS-2 [ICH] - NCT02513316 [6]) and from the SIGNaL register (Stroke InvestiGation in North
110 and Central London). We included patients with ICH and both CT and MRI performed after the index
111 event. Exclusion criteria were: age < 55 years; and non-lobar, infratentorial or secondary ICH (Figure
112 1). We reported the study in accordance with STARD reporting guidelines. [7] [8] Measurement of

113 ICH volume was performed on CT scans via a semi-automated approach [9] and on MRI by manual
114 segmentation on SWI sequences. ICH location was assessed using the Cerebral Haemorrhage
115 Anatomical RaTing inStrument (CHARTS) [10].

116 All neuroimaging biomarkers were rated by a single trained rater, blinded to other clinical and
117 neuroradiological data. Observers evaluated CT for FLP and SAE as previously described [5] after
118 attending a web-based training module (www.ed.ac.uk/edinburgh-imaging/ecciting). Each patient
119 was categorized for the probability of CAA using the simplified Edinburgh criteria (with a high
120 probability defined by the presence of both FLP and SAE) [5] In the derivation study [5], no
121 participants had FLP in isolation, but given the strong association between CAA and FLP [5] we
122 classified FLP in isolation as intermediate risk of CAA. To obtain inter-rater reliability a random
123 sample of 19 CT scans (SIGNaL cohort) was rated by a blinded experienced Stroke Neurologist
124 (DJW).

125 CMBs and cSS were rated on T2*-weighted gradient-recalled echo (GRE) or susceptibility-weighted
126 imaging (SWI) using a validated rating scale [11] and per consensus criteria [12][13], respectively.
127 The typical appearance of cSS (“track-like” low signal in the subpial layers of cortex either side of
128 the sulcus) and the distance in space from the symptomatic ICH were used to distinguish cSS from
129 acute convexity subarachnoid haemorrhage (SAH). No patients with isolated convexity SAH were
130 included. Each patient was categorized using the modified Boston criteria [3]. We compared the
131 probable CAA category to all other lobar ICH (namely, non-probable CAA: including possible CAA
132 and lobar ICH not meeting the criteria for CAA [i.e. patients with no additional haemorrhagic CAA
133 markers (lobar CMBs or cortical siderosis) or ≥ 1 deep CMB]). From the CROMIS-2 cohort a random
134 10% sample (149 scans) was rated to quantify intra-rater and inter-rater reliability for CMBs. For cSS
135 presence the entire cohort of patients included in the SIGNaL cohort (42 scans, 30% of the entire
136 cohort) were rated twice for intra-rater reliability.

137 Univariate analysis was performed to evaluate association between variables and categories; the
138 strength of associations was quantified via agreement proportion and kappa (κ) values. The
139 diagnostic accuracy of a high probability of CAA (according to the simplified Edinburgh criteria) in
140 predicting probable CAA (according to the modified Boston criteria) was assessed by calculating the

141 area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, positive and
142 negative predictive values. Positive and negative likelihood ratios (LR+ and LR-) were also
143 calculated. Univariable and multivariable (adjusted for age and sex) linear regression analysis was
144 performed to assess if presence of CT (SAE or FLP) and MRI (strictly lobar CMB or cSS) biomarkers
145 of CAA were correlated with ICH volume. To test for selection bias, we compared (univariate
146 analysis) patients with and without available MRI. Inter/intra-observer variability of ratings was
147 calculated using the Cohen κ statistic. The significance level was set at $p=0.05$. Statistical analysis
148 was performed using STATA 16 (StataCorp. 2019 *Stata Statistical Software: Release 16*).

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150 **Standard Protocol Approvals, Registrations and patient consents.** Written informed consent
151 was obtained from all participants in CROMIS-2 (approved by UK National Health Service
152 Research Ethics Committee: 10/H0716/64); in case of lack of capacity written informed consent was
153 obtained from a relative or representative. For the SIGNaL cohort, data were collected as part of
154 routine clinical care and data analysis was approved as a service evaluation by the University
155 College London Hospitals NHS Trust Data Governance Review Board.

156 **Data Availability Statement.** All de-identified participant data requests should be submitted to the
157 corresponding author for consideration by the CROMIS-2 and SIGNaL Steering Committees.

158

159 **RESULTS**

160 We included 140 adult patients with spontaneous lobar supratentorial ICH. Baseline characteristics,
161 neuroimaging variables and classifications according to the Edinburgh and Boston criteria are
162 reported in [Table 1](#).

163 Associations between CT and MRI biomarkers (with agreement proportion and κ values) are
164 reported in [Table 2](#). FLP presence was associated with CMB presence (35.8% vs 20.3%; $p=0.047$),
165 strictly lobar CMBs (44.7% vs 23.5%; $p=0.014$) and total CMB count ($p=0.013$). FLP were not
166 significantly more common in patients with cSS (35% vs 27.5%; $p=0.390$) and were not associated
167 with cSS severity ($p=0.691$). SAE was more common in patients with cSS (61.3% vs 31.2%;

168 $p=0.002$), and was associated with cSS severity ($p=0.002$). SAE was not significantly associated
169 with CMB presence (37% vs 39%; $p=0.815$), strictly lobar CMB (47.4% vs 34%; $p=0.157$) or CMB
170 count ($p=0.787$).

171 Compared to patients without probable CAA, FLP were more common in patients with probable CAA
172 (40.7% vs 22.1%, $p = 0.018$). Compared to patients without probable CAA, SAE was more common
173 in patients with probable CAA (51.9% vs 29.1%, $p = 0.007$). In both cases the agreement proportion
174 was 63.6% (95%CI 55.0 – 71.5).

175 Adopting probable CAA based on the modified Boston criteria as the diagnostic reference, a high
176 probability of CAA according to the simplified Edinburgh criteria showed specificity 87.2% (95%CI
177 78.3–93.4), sensitivity 29.6% (95%CI 18.0–43.6), positive predictive value 59.3% (95%CI 38.8–
178 77.6), negative predictive value 66.4% (95%CI 56.9–75.0), LR+ 2.3 (95%CI 1.2-4.6) and LR- 0.8
179 (95%CI 0.7-1.0). The discrimination (AUROC) of the simplified Edinburgh criteria (high probability
180 vs intermediate or low probability), for probable CAA according to the Boston criteria (vs non-
181 probable) was 0.62 (95%CI 0.54-0.71) (Table 3).

182 The median ICH volume was significantly higher when FLP were present (20.4 ml vs 7.7 ml; p
183 <0.001) or SAE (16.7 vs 6.7 ml; $p < 0.001$); these differences remained significant after correcting
184 for age and gender ($p < 0.001$). We found no differences in the presence of cSS and strictly lobar
185 CMBs according to ICH volume. When we assessed the subgroup of patients with ICH volume
186 greater than the median value of our cohort (12.0 mL), the sensitivity of Edinburgh criteria increased
187 from 29.6% (95%CI 18.0–43.6) to 50.0% (95%CI 27.2 - 72.9), while specificity was slightly reduced
188 at 77.4% (95%CI 58.9 - 90.4).

189 Comparison between patients with and without available MRI (Table e1) and intra/inter-rater
190 reliability for the presence of CAA biomarkers (Table e2) are reported in Supplementary material.

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193 **DISCUSSION**

194 In this study of patients with spontaneous lobar ICH we found significant and specific associations
195 between FLPs and SAE (on CT) and CMBs and cSS (on MRI), respectively. These observations

196 provide new insights into the mechanisms and anatomical distribution of the underlying CAA
197 pathology: FLPs are likely to represent parenchymal-predominant CAA (indicated by strictly lobar
198 CMBs on MRI), while SAE might reflect leptomeningeal-predominant CAA (indicated by cSS on
199 MRI). We also found that the prevalence of CT biomarkers increased with the degree of diagnostic
200 certainty regarding CAA defined by the modified Boston criteria and with the volume of ICH. CT
201 diagnostic biomarkers for CAA could be useful in everyday clinical practice, but have only been
202 validated in patients who suffered fatal ICH [5]. Our study in ICH survivors showed that the Edinburgh
203 CT-only criteria [5] do increase the likelihood of CAA (defined by the Boston MRI-based criteria), but
204 to a modest extent (LR+ 2.3 [95%CI 1.2-4.6]; a LR+ of more than 3 is considered to be a good test
205 to rule in a disease). Nevertheless, when a diagnosis of CAA is suspected and MRI is not available
206 (i.e. very unwell or claustrophobic patients, non-MRI compatible implanted devices), the presence
207 of both SAE and FLP on CT might help to rule-in CAA but their absence is probably not useful to
208 rule it out (LR- 0.8 [95%CI 0.7-1.0]; a LR- of less than 0.33 is considered a good test to rule out a
209 disease).

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211 The original Edinburgh criteria validation study [5] found that all cases with high or intermediate
212 probability of having moderate or severe CAA were classified as probable CAA by the Boston criteria,
213 but this analysis was available for only 7 patients (with both CT and MRI available). A recent study
214 [14] found that FLP presence (on CT) was significantly more frequent in probable than in possible
215 CAA, but did not specifically examine associations between CT and MRI biomarkers. Our findings
216 are consistent with these previous observations, but also provide new evidence regarding the
217 underlying mechanisms and diagnostic accuracy of the simplified Edinburgh acute CT criteria.
218 Another recent study [15] on Dutch-type hereditary CAA patients documented that the presence of
219 FLP and SAE correlate with ICH volume with higher sensitivity of simplified Edinburgh criteria in
220 large ICH volumes. Our results are in line with this finding: when simplified Edinburgh criteria were
221 applied in patients with ICH volume greater than 12 mL (the median volume), sensitivity increased
222 with only slightly lower specificity. Further studies may be helpful to determine whether a minimum

223 ICH volume cutoff point should be considered to maximize the diagnostic accuracy of the Edinburgh
224 criteria.

225 CAA is not a uniform disease, having a complex range of clinical, imaging and neuropathological
226 subtypes [16]. An autopsy-based study described two CAA phenotypes [17]: in CAA type 1, amyloid
227 beta-protein (A-beta) is primarily found in cortical capillaries, while in CAA type 2 A-beta is primarily
228 deposited in leptomeningeal and cortical vessel, sparing cortical capillaries. These phenotypes are
229 hypothesized to be partially driven by APOE genotype: APOE e4 is associated with type 1
230 (parenchymal-predominant) CAA, while APOE e2 is associated with type 2 (leptomeningeal-
231 predominant) CAA [17]. In line with these recent histopathological observations, two recent meta-
232 analyses found that strictly lobar CMB are related to APOE e4 [18] and that cSS is most strongly
233 associated with APOE e2 genotype [19]. We found strong association between cSS and SAE
234 presence, and between CMBs (especially strictly lobar CMBs) and FLP presence. Our results
235 suggest that FLP and SAE might be related to different anatomical distributions of CAA pathology,
236 which may in part be related to underlying APOE genotype.

237 Our study has strengths. We included a consecutive sample of participants with lobar ICH. CT and
238 MRI were assessed by trained blinded experienced raters with standardized rating instruments and
239 consensus criteria with substantial or excellent intra-rater and inter-rater agreement. Moreover, MRI
240 scans were performed soon after CT; for patients included in the SIGNaL cohort the median was 2
241 days (IQR 1-3).

242 We also acknowledge limitations. The requirement of an MRI scan and of signed informed consent
243 could have created a selection bias towards non-severe, clinically stable ICH patients. The patients
244 with MRI available were significantly younger, but there was not a major difference in clinical severity.
245 We could not evaluate the accuracy of Edinburgh criteria against histopathological assessment,
246 which is the reference standard for a diagnosis of CAA. However, histopathological analysis of brain
247 tissue is rarely performed in clinical practice, while in clinical practice the diagnosis of CAA is often
248 made based on the modified Boston criteria, which show good diagnostic accuracy for
249 pathologically-proven CAA in ICH (specificity 81.2% [95% CI 61.5–92.7], sensitivity 94.7% [95% CI
250 82.7–98.5]) [3]. While our findings need to be validated against histopathological assessment, they

251 remain relevant to guide clinicians in every day clinical practice, especially where MRI is not
252 available.

253 **CONCLUSION**

254 We have shown associations between putative biomarkers of parenchymal CAA (FLP and CMB),
255 and between putative biomarkers of leptomeningeal CAA (SAE and cSS). Our findings indicate that,
256 in lobar ICH survivors where CAA is suspected, CT biomarkers suggesting a high probability of CAA
257 might help rule-in MRI-defined probable CAA. However, the absence of FLP and SAE on CT are
258 probably not useful to rule-out the presence of CAA, suggesting an important continued role for MRI
259 in the investigation of ICH survivors with suspected CAA.

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Table 1. General characteristics of the cohort

Clinical variables	N (%)
Age (median; IQR)	72.5 (65-78)
Female gender	81 (57.9)
Hypertension	82 (58.6)
Oral anticoagulant drug at index ICH	28 (20.0)
Prior ICH	14 (10.0)
Glasgow Coma Scale at admission (median; IQR)	15 (1)
ICH volume (median [IQR]) #	12.0 (4.5-20.0)
MRI-based variables and criteria	N (%)
Cerebral microbleed	
Absent	59 (42.1)
Present	81 (57.9)
1-5	37 (26.4)
6-10	14 (10.0)
11-20	14 (10.0)
>20	16 (11.4)
Lobar CMB presence	63 (45.0)
Strictly lobar CMB presence	38 (27.1)
Deep CMB presence	31 (22.1)
Brainstem CMB presence	16 (11.4)
Infratentorial CMB presence	39 (27.9)
Cortical superficial siderosis	
Absent	109 (77.9)
Present	31 (22.1)
Focal	17 (12.1)
Disseminated	14 (10.0)
Modified Boston criteria	
Non-probable CAA	86 (61.4)
Probable CAA	54 (38.6)
CT-based variables and criteria	
Finger-like projection presence	41 (29.3)
Subarachnoid extension presence	53 (37.9)
Simplified Edinburgh criteria	
Low probability of CAA	73 (52.1)
Intermediate probability of CAA	40 (28.6)
High probability of CAA	27 (19.3)

IQR, Interquartile range; ICH, intracerebral haemorrhage; CMB, cerebral microbleeds; CAA, cerebral amyloid angiopathy

Volume in mL; data available for 101 patients (72% of the entire cohort).

Table 2.

Association between FLP and MRI biomarkers

	Finger-like projections		<i>P value</i>	<i>Agreement % (95% CI)</i>	<i>κ value (95%CI)</i>
	Absent	Present			
CMB			0.047*	54.3 (45.7 – 62.7)	0.142 (0.006 – 0.277)
Absence	47 (79.7)	12 (20.3)			
Presence	52 (64.2)	29 (35.8)			
Strictly Lobar CMB			0.014*	67.9 (59.4 - 75.5)	0.207 (0.034 – 0.380)
No	78 (76.5)	24 (23.5)			
Yes	21 (55.3)	17 (44.7)			
CMB count			0.013§	-	-
0	47 (79.7)	12 (20.3)			
0-5	28 (75.7)	9 (24.3)			
6-10	5 (35.7)	9 (64.3)			
11-20	11 (78.6)	3 (21.4)			
>20	8 (50.0)	8 (50.0)			
cSS			0.390*	64.3 (55.8 – 72.2)	0.071 (-0.097 – 0.240)
Absent	79 (72.5)	30 (27.5)			
Present	20 (64.5)	11 (35.5)			
cSS severity			0.691*	-	-
Absent	79 (72.5)	30 (27.5)			
Focal	11 (64.7)	6 (35.3)			
Disseminated	9 (64.3)	5 (35.7)			

Association between SAE and MRI biomarkers

	Subarachnoid extension		<i>P value</i>	<i>Agreement % (95% CI)</i>	<i>k values (95%CI)</i>
	Absent	Present			
CMB			0.815*	47.1 (38.7 – 55.8)	-0.018 (-0.0171 – 0.135)
Absence	36 (61.0)	23 (39.0)			
Presence	51 (63.0)	29 (37.0)			
Strictly Lobar CMB			0.157*	60.7 (52.1 – 68.9)	0.116 (-0.048 – 0.280)
No	67 (65.7)	35 (34.3)			
Yes	20 (52.6)	18 (47.4)			
CMB count			0.787§	-	-
0	36 (61.0)	23 (39.0)			
0-5	23 (62.2)	14 (37.8)			
6-10	7 (50.0)	7 (50.0)			
11-20	10 (71.4)	4 (28.6)			
>20	11 (68.8)	5 (31.2)			
cSS presence			0.002*	67.1 (58.7 – 74.8)	0.240 (0.081 – 0.399)
Absent	75 (68.8)	34 (31.2)			
Present	12 (38.7)	19 (61.3)			
cSS severity			0.002*	-	-
Absent	75 (68.8)	34 (31.2)			

Focal	9 (52.9)	8 (47.1)
Disseminated	3 (21.4)	11 (78.6)

*FLP, finger-like projections; cSS, cortical superficial siderosis; CI, confidence interval CMB, cerebral microbleeds; SAE, subarachnoid extension; * χ^2 test; §Wilcoxon rank sum test*

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Table 3. Comparison between simplified Edinburgh criteria and modified Boston criteria and discrimination of simplified Edinburgh criteria for Probable CAA (per MRI-based modified Boston criteria)

Classification per simplified Edinburgh criteria and modified Boston criteria: AUC = 0.62 (95%CI 0.54-0.71)

Simplified Edinburgh criteria	Modified Boston criteria		
	Probable CAA	Non-probable CAA	
High probability of CAA	16 (59.3)	11 (40.7)	27 (100)
Intermediate probability of CAA	18 (45.0)	22 (55.0)	40 (100)
Low probability of CAA	20 (27.4)	53 (72.6)	73 (100)

Discrimination, sensitivity, specificity, PPV and NPV of high probability of CAA (vs Intermediate/low probability) for probable CAA (per MRI-based modified Boston criteria)

Simplified-Edinburgh criteria	Modified Boston criteria		TOTAL
	Probable CAA	Non-probable CAA	
High Probability of CAA	16	11	27
Intermediate/low probability of CAA	38	75	113
TOTAL	54	86	140
Sensitivity	29.6% (95%CI 18.0-43.6)		
Specificity	87.2% (95%CI 78.3-93.4)		
PPV	59.3% (95%CI 38.8-77.6)		
NPV	66.4% (95%CI 56.9-75.0)		
LR+	2.3 (95%CI 1.2-4.6)		
LR-	0.8 (95%CI 0.7-1.0)		

CAA, cerebral amyloid angiopathy; PPV, positive predictive value; NPV, negative predictive value. LR+, positive likelihood ratio; LR-, negative likelihood ratio.