Simplified Edinburgh and modified Boston criteria in relation to amyloid PET for lobar intracerebral hemorrhage

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ABSTRACT

Background: Histopathological evidence of cerebral vascular amyloid β accumulation is the gold standard to diagnose cerebral amyloid angiopathy (CAA). Neuroimaging findings obtained with CT and MRI can suggest the presence of CAA when histopathology is lacking. We explored the role of amyloid PET in patients with lobar intracerebral hemorrhage (ICH) as this may provide molecular evidence for CAA as well.
Methods: In this retrospective, monocenter analysis, we included consecutive patients with non-traumatic lobar ICH who had undergone amyloid PET. We categorized patients according to amyloid PET status and compared demographics and neuroimaging findings. We calculated sensitivity and specificity of the simplified Edinburgh criteria and amyloid PET with probable modified Boston criteria as reference standard, as well as sensitivity and specificity of the simplified Edinburgh and modified Boston criteria with amyloid PET status as molecular marker for presence or absence of CAA.
Results: We included 38 patients of whom 24 (63%) were amyloid PET positive. Amyloid PET positive patients were older at presentation (p = 0.004). We observed no difference in prevalence of subarachnoid hemorrhages, fingerlike projections or microbleeds between both groups, but cortical superficial siderosis (p = 0.003) was more frequent in the amyloid PET positive group. In 5 out of 38 patients (13%), the modified Boston criteria were not fulfilled due to young age or concomitant vitamin K antagonist use with INR > 3.0. With the modified Boston criteria as reference standard, there was no difference in sensitivity nor specificity between the simplified Edinburgh criteria and amyloid PET status. With amyloid PET status as reference standard, there was also no difference in sensitivity nor specificity between the simplified Edinburgh and modified Boston criteria.
Conclusions: Amyloid PET was positive in 63% of lobar ICH patients. Under certain circumstances, patients might not be diagnosed with probable CAA according to the modified Boston criteria and in these cases, amyloid PET may be useful. Accuracy to predict CAA based on amyloid PET status did not differ between the simplified Edinburgh and modified Boston criteria.

1. Introduction

Cerebral Amyloid Angiopathy (CAA) is characterized by deposition of amyloid β in small cortical and leptomeningeal blood vessels and is a frequent cause of lobar intracerebral hemorrhage (ICH). The distinction between ICH caused by CAA or non-CAA microangiopathy may be of

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clinical relevance since CAA is associated with a higher recurrence risk (Charidimou et al., 2017; Charidimou et al., 2019) and potentially more challenging decisions on the use of antithrombotic drugs (Banerjee et al., 2017; Kelly, 2021).

The gold standard for a diagnosis of 'definite CAA' relies on full post mortem evaluation, but histopathological examination of biopsy tissue (which is not frequently available for patients presenting with an ICH in clinical practice), can also support a probable diagnosis of CAA. Neuroimaging with Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) can reveal characteristics suggestive of CAA. The simplified Edinburgh criteria (Table 1) (Rodrigues et al., 2018; Schwarz et al., 2022; Sembill et al., 2022) and the modified Boston criteria (Table 2) (Smith and Greenberg, 2003; Linn et al., 2010; Greenberg and Charidimou, 2018) evaluate and categorize these features to make a clinical diagnosis of CAA when tissue analysis is lacking. Validation studies of these criteria against histopathological evidence revealed 88–100% specificity for ruling in "high risk CAA" and "probable CAA" (Rodrigues et al., 2018; Greenberg and Charidimou, 2018). Moreover, the "low risk CAA" group of the simplified Edinburgh criteria rules out CAA with 82–89% sensitivity (Rodrigues et al., 2018; van Etten et al., 2020).

A third imaging modality may aid in diagnosing patients with CAA: amyloid Positron Emission Tomography (PET). Amyloid PET is very well cross-validated with anatomopathological amyloid burden for various widely available PET tracers such as ^{11}C-PiB (Pittsburgh Compound B), ^{18}F-flutemetamol, ^{18}F-florbetapir and ^{18}F-florbetaben (Clark et al., 2012; Curtis et al., 2015; Sabri et al., 2015) and it has been shown to bind both parenchymal as well as vascular amyloid (Lockhart et al., 2007; Johnson et al., 2007; Greenberg et al., 2008; Ly et al., 2010; Gurol et al., 2013; Baron et al., 2014; Gurol et al., 2016; Raposo et al., 2017), two forms of amyloid that typically co-occur (Ellis et al., 1996; Jellinger, 2002; Attems et al., 2007; Charidimou et al., 2015). Therefore, whereas CT and MRI can reveal imaging characteristics associated with CAA, amyloid PET is able to directly visualize the underlying pathology itself although not specifically for CAA. We hypothesize that amyloid PET could therefore potentially replace histopathological evidence in patients with suspected CAA in whom tissue analysis is lacking.

In this retrospective study we compared imaging modalities related to CAA in patients with lobar ICH. We focused on the role of amyloid PET by comparing demographics and imaging characteristics between amyloid PET positive and amyloid PET negative patients. We investigated sensitivity and specificity of the simplified Edinburgh criteria and amyloid PET using probable CAA according to the modified Boston criteria as reference standard as well as sensitivity and specificity of the simplified Edinburgh and modified Boston criteria with amyloid PET status as molecular marker for presence or absence of CAA.

2. Methods

This retrospective, monocenter study was approved by the local University Ethics Committee (UZ Leuven / KU Leuven) and was conducted in accordance with the latest version of the Declaration of

Table 1
Simplified Edinburgh criteria

	Subarachnoid hemorrhage	Fingerlike projections
High risk	+	+
Medium risk	+–	–+
Low risk	–	–

The simplified Edinburgh criteria are based on analysis of the non-contrast CT. (Rodrigues et al., 2018) In the original study, (Rodrigues et al., 2018) no patients had fingerlike projections in isolation, but given the association between CAA and fingerlike projections, fingerlike projections in isolation were (in line with previous studies) (Schwarz et al., 2022; Sembill et al., 2022) categorized as medium risk.

Table 2
Modified Boston criteria.

	Clinical data and MRI/CT demonstrating:
Probable CAA	- Multiple hemorrhages (ICH, CMB) restricted to lobar, cortical, or cortico-subcortical regions (CBL allowed) OR single lobar, cortical, or cortico-subcortical hemorrhage and cSS (focal or disseminated) - Age ≥ 55 years - Absence of other cause of hemorrhage
Possible CAA	- Single lobar, cortical, or cortico-subcortical ICH, CMB, or cSS (focal or disseminated) - Age ≥ 55 years - Absence of other cause of hemorrhage

To classify patients according to the modified Boston criteria non-contrast CT and/or MRI are evaluated. In this table, only the categories without incorporation of histopathological data are shown. CAA = cerebral amyloid angiopathy; CBL = cerebellum; CMB = cerebral microbleed; cSS = cortical superficial siderosis; ICH = intracerebral hemorrhage.

Helsinki. Written informed consent was waived. Anonymized data that support the findings of this study could be shared upon reasonable request and after approval by the Ethics Committee.

2.1. Participants

We analyzed all patients admitted to the Leuven University Hospital (Belgium) with non-traumatic lobar ICH in whom a ^{11}C-PiB PET was performed between March 11th 2015 and December 13th 2017. Patients presenting with lobar ICH (without underlying structural abnormality on initial non-contrast CT) were scheduled to undergo brain MRI and amyloid PET as part of the routine diagnostic workup. Patients were excluded from this study if imaging revealed a possible etiology of ICH other than CAA. Demographic data was obtained through patient records. We collected age, sex, cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, obesity and smoking status), history of atrial fibrillation, history of ICH, history of dementia, National Institutes of Health Stroke Scale (NIHSS) at presentation and use of antithrombotic drugs at presentation. Cognitive testing was not routinely performed in these patients.

2.2. Structural imaging

Structural imaging (both CT and/or MRI) was acquired as part of clinical workup. Selected device and imaging parameters were therefore at the discretion of the radiologist. LM calculated ICH volume on the first non-contrast CT at presentation using the ABC/2 method (Kothari et al., 1996). An experienced neuroradiologist (PD) blinded to amyloid PET status rated all other structural neuroimaging characteristics. He determined localization of ICH, presence of fingerlike projections and presence of subarachnoid hemorrhage on the first non-contrast CT at presentation. The Fazekas grade (deep [0–3] and periventricular [0–3]), amount of deep and lobar microbleeds, presence of cortical superficial siderosis (>3 sulci = disseminated / < 4 sulci = focal / absent) and evidence of old macrohemorrhages were documented on the first MRI acquired after the index event. These data were lacking if no MRI was available within the first year after the occurrence of the lobar ICH. Based on the combination of these imaging findings and the clinical data, we classified patients according to the simplified Edinburgh criteria (Rodrigues et al., 2018; Schwarz et al., 2022; Sembill et al., 2022) into high, medium or low risk CAA, and according to the modified Boston criteria (Smith and Greenberg, 2003; Linn et al., 2010; Greenberg and Charidimou, 2018) into probable or possible CAA, or not fulfilling the criteria for CAA.

2.3. PET imaging

Amyloid PET imaging of patients was acquired 40–60 min post

injection of a median injected activity of 314 MBq (IQR: 306–327 MBq) ^{11}C-PiB. Over the time course of the study, three different PET scanners were used: Siemens Biograph HI-REZ PET/CT (n = 14), Siemens Biograph TruePoint PET/CT (n = 23) and GE Signa PET/MR (n = 1). PET acquisitions were performed in list mode, rebinned into 4 frames of 5 min and reconstructed iteratively with ordered subset expectation maximization, after correction for decay, scatter, deadtime, random and attenuation.

We preprocessed the ^{11}C-PiB PET images using PMODv3.9 (PMOD technologies, Zurich, Switzerland): we performed motion correction by rigidly realigning all frames to the first frame and we averaged the frames. Given the rather long and variable time interval between MR imaging and PET imaging (median = 56 days [IQR: 29–108 days]), we applied a PET-only quantification protocol given the potential mass effect of the lobar ICH in the acute phase. We spatially normalized the PET images non-linearly to an in-house available amyloid positive and amyloid negative template and then we calculated the normalized cross correlation to determine and adopt the most suitable template characterized by the higher normalized cross correlation. (Akamatsu et al., 2016) Similar to the studies that validated amyloid tracers against histopathology (Clark et al., 2012; Curtis et al., 2015; Sabri et al., 2015) and the way amyloid PET is assessed in clinical practice, a certified nuclear medicine physician with expertise in amyloid imaging (KVL) visually assessed amyloid status of patients. He was blinded for CT and MRI results and PET imaging was scored as amyloid positive if ≥ 1 cortical brain area showed elevated ^{11}C-PiB binding.

2.4. Statistics

We performed general statistics in RStudio (v1.1.463. RStudio, Inc., Boston, MA). Data are presented as mean ± standard deviation if normally distributed and as median (interquartile range [IQR]) if not normally distributed. We verified normality of the distributions with Shapiro-Wilk tests (α = 0.05).

We assessed differences in demographics and neuroimaging characteristics with Fisher's exact tests, Cochran-Armitage tests (=chi square test for trends), Mann-Whitney U tests and Welch's t-tests as appropriate. As this study was exploratory, a Bonferroni correction for multiple comparison was considered too strict, but significance level was set to α = 0.01 to reduce type I errors.

For comparison to literature and since the modified Boston criteria are considered the gold standard to diagnose CAA in clinical practice (if histopathology is unavailable), we calculated sensitivity and specificity of the simplified Edinburgh criteria and amyloid PET with probable modified Boston criteria as reference standard for presence or absence of CAA. However, as we were mainly interested in exploring the existing neuroimaging criteria in relation to amyloid PET, we also calculated sensitivity and specificity of the simplified Edinburgh and modified Boston criteria with amyloid PET status as molecular marker for presence or absence of CAA. For the simplified Edinburgh criteria, we calculated these parameters for both the rule-in criteria (=dichotomization in high risk vs medium/low risk) and rule-out criteria (=dichotomization in high/medium risk vs low risk), as was done in the original study (Rodrigues et al., 2018). For the modified Boston criteria, we calculated sensitivity and specificity based on the probable CAA category only, as is common in literature (Greenberg and Charidimou, 2018). To compare the sensitivity and specificity of both sets of diagnostic criteria, we used McNemar's exact test (α = 0.05). Although MRI is not mandatory for classification according to the modified Boston criteria (CT can also be used to assess neuroimaging features), it is preferable as it is more sensitive to detect various hemorrhagic manifestations (Linn et al., 2010; Schrag and Greer, 2014; Kidwell et al., 2004). Therefore, we also calculated sensitivity and specificity for only patients in whom gradient echo MRI was available. Likewise, although the age criterion and absence of other cause of hemorrhage are inherent features of the modified Boston criteria, one

could argue that comparison of diagnostic criteria in patients < 55 years or concomitant vitamin K antagonist use with INR > 3.0 is undesirable as the presence of these elements precludes CAA diagnosis according to the modified Boston criteria (structural secondary causes of lobar ICH were already excluded at the beginning). Therefore, we also calculated sensitivities and specificities for only patients ≥ 55 years with gradient echo MRI available and with INR ≤ 3.0 (Greenberg and Charidimou, 2018).

Although hematoma size is not (yet) included in the (simplified) Edinburgh criteria, a better sensitivity has been reported in hematoma ≥ 40 ml compared to volumes < 15 ml (van Etten et al., 2020). Due to our small sample size, we were not able to robustly explore the effect of ICH volume on accuracy of the (simplified) Edinburgh criteria, but we preliminary investigated the effect by dichotomizing patients based on median ICH volume in small and large ICH volumes and comparing accuracy of the simplified Edinburgh criteria in small versus large hematoma.

3. Results

3.1. Demographics

Demographic data of the full cohort are shown in Table 3. We included 38 patients (18 male / 20 female) with a lobar ICH. Median age was 71.5 years (IQR: 65–79 years). Median NIHSS was 7 (IQR: 1–14). Cognitive testing was not routinely performed, but no patient had a history of dementia. The median interval between presentation and MR imaging was 16 days (IQR: 4–60 days), the median interval between presentation and ^{11}C-PiB PET imaging was 81 days (IQR: 36–114 days).

3.2. Simplified Edinburgh and modified Boston criteria

We classified patients according to the simplified Edinburgh criteria: 11 patients (29%) fulfilled the criteria for low risk of CAA, 15 patients (39%) met the criteria of medium risk of CAA and 12 patients (32%) satisfied the criteria for high risk of CAA (Table 4). When categorized according to the modified Boston criteria, 10 patients (26%) did not meet the criteria (5 patients had ≥ 1 deep microbleed(s), 3 patients were < 55 years old and 2 patients had concomitant vitamin K antagonist use with INR > 3.0), 9 patients (24%) were categorized as possible CAA and 19 patients (50%) fulfilled the criteria for probable CAA (Table 4). 3 patients did not have MRI data available and 1 patient did not undergo

Table 3
Demographics.

	Patients (n = 38)
Median age, years (IQR)	71.5 (65–79)
Male sex, n (%)	18 (47%)
Medical history or risk factors, n (%)	
arterial hypertension	23 (61%)
hypercholesterolemia	23 (61%)
diabetes mellitus	9 (24%)
obesity	12 (32%)
former or current smoker †	15 (41%)
atrial fibrillation	4 (11%)
ICH	4 (11%)
Use of antithrombotic therapy at presentation, n (%)[§]	
no antithrombotic therapy	22 (58%)
antiplatelet therapy	9 (24%)
anticoagulant therapy	8 (21%)
Median NIHSS at presentation (IQR) [‡]	7 (1–14)
Median interval presentation – MR imaging, days (IQR) [¶]	16 (4–60)
Median interval presentation – PET imaging, days (IQR)	81 (36–114)
Median interval MR imaging – PET imaging, days (IQR) [¶]	56 (29–108)

IQR = interquartile range; NIHSS = National Institutes of Health Stroke Scale. [†] 1 missing data point. [‡] 2 missing data points. [§] The sum of the percentages is > 100 % as 1 patient used both antiplatelet and anticoagulant therapy and is counted twice. [¶] n = 35 (3 patients did not undergo MRI).

Table 4

Classification of patients according to the simplified Edinburgh and modified Boston criteria with information about amyloid PET status included.

		modified Boston		
		probable	possible	not
simplified Edinburgh	high	5 PET positive	1 PET positive	3 PET positive
		3 PET negative	0 PET negative	0 PET negative
	medium	4 PET positive	3 PET positive	2 PET positive
		2 PET negative	2 PET negative	2 PET negative
	low	3 PET positive	2 PET positive	1 PET positive
		2 PET negative	1 PET negative	2 PET negative

gradient echo MRI and therefore belonged to the possible CAA category.

3.3. Amyloid PET

Visual rating resulted in an amyloid positive read in 24 of 38 patients (63%). Table 5 shows differences in baseline characteristics and neuroimaging findings between amyloid PET negative (n = 14) and amyloid PET positive (n = 24) subjects. Amyloid PET positive patients were older compared to amyloid PET negative subjects (median 75.5 vs 66, p = 0.0040). There was no difference in cardiovascular risk factors or stroke severity between both groups.

There was no difference in ICH volume or localization of lobar ICH between amyloid PET positive and negative patients. White matter disease was more pronounced in the amyloid PET positive group, as evidenced by periventricular Fazekas grade (p = 0.0036). There was no

Table 5

Demographics and neuroimaging characteristics of amyloid PET negative and amyloid PET positive lobar ICH patients.

	PiB PET negative (n = 14)	PiB PET positive (n = 24)	p-value
DEMOGRAPHICS			
Age (years), median (IQR)	66 (60–69)	75.5 (71–82)	**0.0040**
Male sex, n (%)	7 (50%)	11 (46%)	1.0
Medical history or risk factors, n (%)			
arterial hypertension	7 (50%)	16 (67%)	0.49
hypercholesterolemia	7 (50%)	16 (67%)	0.49
diabetes mellitus	6 (43%)	3 (13%)	0.052
obesity	5 (36%)	7 (29%)	0.73
former or current smoker [†]	7 (50%)	8 (35%)	0.49
atrial fibrillation	3 (21%)	1 (4%)	0.13
ICH	1 (7%)	3 (13%)	1.0
Use of antiplatelet / anticoagulant at presentation, n (%)			
antiplatelet therapy	1 (7%)	8 (33%)	0.11
anticoagulant therapy	5 (36%)	3 (13%)	0.12
NIHSS at presentation, median (IQR) [‡]	2 (1–7)	9 (1.5–14.5)	0.27
NEUROIMAGING			
ICH volume (ml), median (IQR)	18 (6–35)	25 (17–37)	0.27
Location ICH, n (%) [§]			
frontal involvement	3 (21%)	15 (63%)	0.020
parietal involvement	6 (43%)	8 (33%)	0.73
temporal involvement	6 (43%)	3 (13%)	0.052
occipital involvement	5 (36%)	3 (13%)	0.12
Fingerlike projections, n (%)	6 (43%)	17 (71%)	0.17
Subarachnoid hemorrhage, n (%)	6 (43%)	10 (42%)	1.0
Fazekas grade – periventricular, n (%)[¶]			**0.0036**
grade 0	1 (7%)	0 (0%)	
grade 1	5 (36%)	3 (14%)	
grade 2	6 (43%)	4 (19%)	
grade 3	2 (14%)	14 (67%)	
Fazekas grade – deep, n (%)[¶]			0.017
grade 0	3 (21%)	1 (5%)	
grade 1	8 (57%)	6 (29%)	
grade 2	2 (14%)	11 (52%)	
grade 3	1 (7%)	3 (14%)	
Microbleeds, median (IQR) [¶]			
lobar	1 (0–1.75)	4.5 (0.75–11.5)	0.015
deep	0 (0–0)	0 (0–0)	1.0
Old macrohemorrhages, median (IQR) [¶]	0 (0–0.75)	0 (0–1)	0.28
Cortical superficial siderosis, n (%)[¶]			**0.0032**
no	11 (79%)	6 (30%)	
focal	2 (14%)	4 (20%)	
disseminated	1 (7%)	10 (50%)	
Simplified Edinburgh criteria, n (%)			0.31
low	5 (36%)	6 (25%)	
medium	6 (43%)	9 (38%)	
high	3 (21%)	9 (38%)	
Modified Boston criteria, n (%)			0.90
not fulfilling	4 (29%)	6 (25%)	
possible	3 (21%)	6 (25%)	
probable	7 (50%)	12 (50%)	

[†] 1 missing data point. [‡] 2 missing data points. [§] Sum exceeds 100 % as patients could have involvement of multiple lobes. [¶] n = 35 (no MRI data available for 3 patients). [¶¶] n = 34 (no gradient echo MRI data available for 1 extra patient). ICH = intracerebral hemorrhage; IQR = interquartile range; NIHSS = National Institutes of Health Stroke Scale; SD = standard deviation.

Table 6

Sensitivities and specificities of simplified Edinburgh criteria and amyloid PET with probable modified Boston criteria as reference standard for presence/absence of CAA.

		Sensitivity % (95% CI)	Specificity % (95% CI)
TOTAL COHORT (n = 38)			
simplified Edinburgh	rule-in criteria	42 (20–67)	79 (54–94)
	rule-out criteria	74 (49–91)	32 (13–57)
amyloid PET		63 (38–84)	37 (16–62)
	McNemar's exact test	*OR = 0.6 (0.09–3.1) p = 0.73*	*OR = ∞ (1.7–∞) p = 0.0078*
GRADIENT ECHO MRI AVAILABLE (n = 34)			
simplified Edinburgh	rule-in criteria	42 (20–67)	80 (52–96)
	rule-out criteria	74 (49–91)	33 (12–62)
amyloid PET		63 (38–84)	47 (21–73)
	McNemar's exact test	*OR = 0.6 (0.09–3.1) p = 0.73*	*OR = ∞ (0.9–∞) p = 0.063*
GRADIENT ECHO MRI AVAILABLE + AGE ≥ 55y + INR ≤ 3.0 (n = 29)			
simplified Edinburgh	rule-in criteria	42 (20–67)	90 (55–100)
	rule-out criteria	74 (49–91)	20 (3–56)
amyloid PET		63 (38–84)	50 (19–81)
	McNemar's exact test	*OR = 0.6 (0.09–3.1) p = 0.73*	*OR = ∞ (0.7–∞) p = 0.13*

Simplified Edinburgh criteria: rule-in criteria = dichotomization in high risk vs medium/low risk; rule-out criteria = dichotomization in high/medium risk vs low risk. The results of the McNemar's exact tests are based on the simplified Edinburgh rule-out criteria for sensitivity and based on the simplified Edinburgh rule-in criteria for specificity. CAA = cerebral amyloid angiopathy; CI = confidence interval; OR = odds ratio.

difference in deep microbleeds between both groups, but lobar microbleeds trended to be more prevalent in amyloid PET positive subjects (p = 0.015). Cortical superficial siderosis was more prevalent in the amyloid PET positive group (p = 0.0032).

3.4. Sensitivity and specificity of simplified Edinburgh and amyloid PET with probable modified Boston as reference standard

The sensitivities and specificities of the simplified Edinburgh criteria and amyloid PET with probable modified Boston criteria as reference standard are shown in Table 6. In the total sample, simplified Edinburgh rule-in specificity was better compared to amyloid PET specificity (p = 0.0078), but there was no difference in specificity when only patients with gradient echo MRI available were analyzed or when patients < 55 years or with INR > 3 were excluded (p > 0.05). Throughout the subanalyses, sensitivities remained unchanged as all excluded patients did not fulfill the criteria for probable CAA.

3.5. Sensitivity and specificity of diagnostic criteria with amyloid PET status as reference standard

The sensitivities and specificities of the simplified Edinburgh criteria and the modified Boston criteria with amyloid PET status as reference standard are shown in Table 7. There was no difference in sensitivity between the simplified Edinburgh rule-out criteria and modified Boston criteria, nor a difference in specificity between the simplified Edinburgh rule-in criteria and modified Boston criteria in any of the analyses. Interestingly, 2 out of 3 patients < 55 years and 1 out of 2 patients with INR > 3.0 were amyloid PET positive. Moreover, 3 out of 5 patients with deep microbleed(s) were amyloid PET positive.

3.6. Effect of ICH volume on accuracy of simplified Edinburgh criteria

Calculating the accuracy of the simplified Edinburgh criteria in small versus large hematoma did not show an effect of ICH volume although this analysis was clearly underpowered (Supplementary Table 1).

Table 7

Sensitivities and specificities of simplified Edinburgh and modified Boston criteria with amyloid PET status as reference standard for presence/absence of CAA.

		Sensitivity % (95% CI)	Specificity % (95% CI)
TOTAL COHORT (n = 38)			
simplified Edinburgh	rule-in criteria	38 (19–59)	79 (49–95)
	rule-out criteria	75 (53–90)	36 (13–65)
modified Boston		50 (29–71)	50 (23–77)
	McNemar's exact test	*OR = 0.3 (0.06–1.3) p = 0.15*	*OR = ∞ (0.7–∞) p = 0.13*
GRADIENT ECHO MRI AVAILABLE (n = 34)			
simplified Edinburgh	rule-in criteria	40 (19–64)	79 (49–95)
	rule-out criteria	75 (51–91)	36 (13–65)
modified Boston		60 (36–81)	50 (23–77)
	McNemar's exact test	*OR = 0.5 (0.08–2.3) p = 0.51*	*OR = ∞ (0.7–∞) p = 0.13*
GRADIENT ECHO MRI AVAILABLE + AGE ≥ 55y + INR ≤ 3.0 (n = 29)			
simplified Edinburgh	rule-in criteria	35 (14–62)	75 (43–95)
	rule-out criteria	76 (50–93)	25 (5–57)
modified Boston		71 (44–90)	42 (15–72)
	McNemar's exact test	*OR = 0.8 (0.1–4.4) p = 1.0*	*OR = ∞ (0.7–∞) p = 0.13*

Simplified Edinburgh criteria: rule-in criteria = dichotomization in high risk vs medium/low risk; rule-out criteria = dichotomization in high/medium risk vs low risk. Modified Boston criteria: based on probable CAA category. The results of the McNemar's exact tests are based on the simplified Edinburgh rule-out criteria for sensitivity and based on the simplified Edinburgh rule-in criteria for specificity. CAA = cerebral amyloid angiopathy; CI = confidence interval; OR = odds ratio.

4. Discussion

In this retrospective, monocenter study of patients with non-traumatic lobar ICH who underwent amyloid PET imaging, we found amyloid PET positivity in 63% of patients. Amyloid PET positive patients were older, as expected since it is well-known that the prevalence of amyloid pathology increases with aging (Jansen et al., 2015; Biffi and Greenberg, 2011). We demonstrated that superficial siderosis, an important element of the modified Boston criteria, was more prevalent in amyloid PET positive lobar ICH patients compared to amyloid PET negative lobar ICH patients. We detected no differences in accuracy between the simplified Edinburgh criteria and amyloid PET with modified Boston criteria as reference standard, nor between the simplified Edinburgh and modified Boston criteria with amyloid PET status as reference standard.

Different studies have already investigated the accuracy of amyloid PET in diagnosing CAA, but performance was only moderate to good with sensitivities ranging from 60% to 91% and specificities ranging from 56% to 90% (Farid et al., 2017; Charidimou et al., 2017). However, an important element to consider is that only a minority of patients in these studies had histopathological proof of CAA and that the majority of included patients were diagnosed with probable CAA based on the (modified) Boston criteria. Multiple hospital-based studies have validated the (modified) Boston criteria for probable CAA against histopathology with sensitivities ranging from 42% to 77% and specificities ranging from 88% to 100% (Greenberg and Charidimou, 2018). The moderate sensitivity might imply a false negative result in 23% to 58% of histologically proven CAA patients which in turn will affect specificity of all diagnostic tests that consider the (modified) Boston criteria as reference standard for CAA. The strength of the (modified) Boston criteria is their good specificity (88–100%) (Greenberg and Charidimou, 2018), but the specificity of a diagnostic test depends on the studied population and only few studies investigated a population of solely lobar ICH patients. The first study with only lobar ICH patients reported a specificity of 100%, but in this study only 10 patients were CAA negative and only 4 of them had undergone gradient echo MRI (Knudsen et al., 2001). A more recent study in which patients with lobar ICH were included and histopathology was available, revealed a specificity of the modified Boston criteria of 71% (Baron et al., 2022). With the continuously advancing MRI techniques and facilitated detection of (both deep and lobar) microbleeds (Nandigam et al., 2009), future studies will have to explore the sensitivity and specificity of the modified Boston criteria in lobar ICH patients.

To improve sensitivity to detect CAA in patients < 55 years (or concomitant vitamin K antagonist use with INR > 3.0), consideration of amyloid PET may be useful. The main hurdle to use amyloid PET as diagnostic tool in CAA is the inability to discriminate between vascular amyloid (as seen in CAA) and parenchymal amyloid (as seen in Alzheimer disease). Both forms of amyloid accumulate with aging and both forms of amyloid often co-exist (Jansen et al., 2015; Biffi and Greenberg, 2011), probably implying they result from a common underlying pathophysiology (Greenberg et al., 2020) . Previous research suggests that amyloid tracer binding in Alzheimer disease is relatively more prominent in the frontal lobes and amyloid tracer binding in CAA relatively more prominent in the occipital lobes (Johnson et al., 2007; Ly et al., 2010; Jang et al., 2019), but these studies show a substantial overlap between occipital/whole cortex and frontal/whole cortex ratios in patients with CAA and Alzheimer disease and differences in regional relative amyloid tracer binding have not yet been investigated in large cohorts. It is therefore unlikely that current amyloid tracers, which bind to both vascular and parenchymal amyloid, will be able to robustly differentiate between amyloid pathology in the context of CAA and amyloid pathology in the context of Alzheimer disease as the spatial resolution of PET is limited. The lack of specificity of the current amyloid tracers to bind to only one form of pathological amyloid likely contributes to the thus far limited accuracy of amyloid PET in diagnosing CAA. Especially in the elderly, incipient Alzheimer disease may cause false positive results as it is known that amyloid PET can be positive in cognitively unimpaired elderly (about 30% in subjects ≥ 75 years) (Jansen et al., 2015). This is less of a concern in young individuals, as amyloid positivity in young healthy subjects is much lower (< 10% below 50 years) (Jansen et al., 2015) . The different forms of amyloid deposition can be present in variable degrees, leading to a variety of clinical manifestations. Therefore, results of a study that showed that vascular amyloid did not significantly contribute to amyloid PET signal in a population of healthy elderly and patients with dementia, cannot be generalized to patients with lobar ICH as none of the included patients had lobar ICH (McCarter et al., 2021). Other studies have shown that vascular amyloid contributes to amyloid PET signal (Lockhart et al., 2007; Johnson et al., 2007; Greenberg et al., 2008; Ly et al., 2010) and amyloid PET might therefore aid to diagnose CAA under certain circumstances. We acknowledge that our study cannot proof the validity of amyloid PET as in vivo marker of CAA, and that future studies validating the use of amyloid PET against histopathology in patients with lobar ICH are needed. The current diagnostic criteria are unable to diagnose CAA in patients < 55 years old (8% of lobar ICH patients in our study), concomitant vitamin K antagonist use with INR > 3.0 (5%), or any deep microbleed (13%). Exploring the role of amyloid PET in these patients can be of interest as 6/10 patients not fulfilling the modified Boston criteria based on these characteristics were amyloid PET positive (suggestive, but of course not conclusive for CAA). Interestingly, although still preclinical, research is ongoing to develop a vascular amyloid only tracer which will be of great value to further dissect the presence of either one or two components of amyloid pathology in patients suffering a non-fatal ICH (Abrahamson et al., 2021; Zhang et al., 2021).

With amyloid PET status as reference standard, the rule-out sensitivity of the simplified Edinburgh criteria in our study was somewhat lower compared to previous studies that used histopathology (or genetic diagnosis of Dutch-type hereditary CAA) as reference standard (75–76% vs 82–100%) (Baron et al., 2022; Rodrigues et al., 2018; van Etten et al., 2020). Our rule-in specificity was lower than the original study (75–79% vs 100%) (Rodrigues et al., 2018), but slightly higher compared to the rule-in specificity in another study that investigated the accuracy of the simplified Edinburgh criteria compared to histopathologically proven CAA (75–79% vs 67%) (Baron et al., 2022). Importantly, patients in the original study validating the Edinburgh criteria died from their ICH whereas other studies (including ours) investigated stroke survivors. ICH volume is a known predictor of worse outcome (Pinho et al., 2019) and different studies have shown that fingerlike projections and subarachnoid hemorrhage are associated with larger ICH volumes (van Etten et al., 2020; Renard et al., 2019; Ornello et al., 2021), possibly contributing to differences in accuracy over studies. Unfortunately, our sample size was too small to robustly explore the role of ICH volume on accuracy of the simplified Edinburgh criteria and preliminary results showed no effect of ICH volume.

Apart from the small sample size, our study has some more limitations. First, the lack of histopathological evidence is a limitation as we could not correlate amyloid PET findings to a tissue diagnosis of CAA. Second, as patients were admitted in the context of ICH (and not in a memory clinic), formal premorbid cognitive assessment was unknown, implying that pre-existing dementia could not be ruled out. Third, this retrospective analysis may be subject to selection bias, since only those lobar ICH patients who underwent amyloid PET were included in this analysis. This resulted in exclusion of patients who died soon after the index event or who were too disabled or unwilling to undergo PET scan. This could have led to a selection bias opposite to selection bias in studies with histopathological evidence, and this may explain the higher amyloid positivity in one study exploring patients with lobar ICH where presence of CAA was determined histopathologically (presence of CAA: 74%), compared to our study (amyloid PET positivity: 63%) (Knudsen et al., 2001). Fourth, scanners and acquisition protocols were not standardized because neuroimaging was acquired as part of the diagnostic

workup, potentially influencing the detection rate of cerebral micro-bleeds and therefore the modified Boston categorization. Last, amyloid PET imaging is not routinely available in many places limiting the translational value of our findings to clinical practice.

5. Conclusion

In our cohort of lobar ICH patients, amyloid PET was positive in 63% of patients. We highlight that the current clinical criteria cannot diagnose probable CAA under certain circumstances and we suggest consideration of amyloid PET in such cases. With amyloid PET status as reference standard, there was no difference in accuracy between the simplified Edinburgh and modified Boston criteria.

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CRediT authorship contribution statement

Laura Michiels: Methodology, Software, Investigation, Data curation, Formal analysis, Writing – original draft. **Laurens Dobbels:** Investigation, Data curation, Writing – review & editing. **Jelle Demeestere:** Investigation, Resources, Writing – review & editing. **Philippe Demaerel:** Investigation, Resources, Data curation, Writing – review & editing. **Koen Van Laere:** Methodology, Investigation, Resources, Data curation, Writing – review & editing. **Robin Lemmens:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – original draft, Supervision.

Declaration of Competing Interest

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Appendix A. Supplementary data

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