Comparison of Boston criteria v2.0/v1.5 for cerebral amyloid angiopathy to predict recurrent intracerebral hemorrhage

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Short title: Boston criteria and risk of ICH recurrence

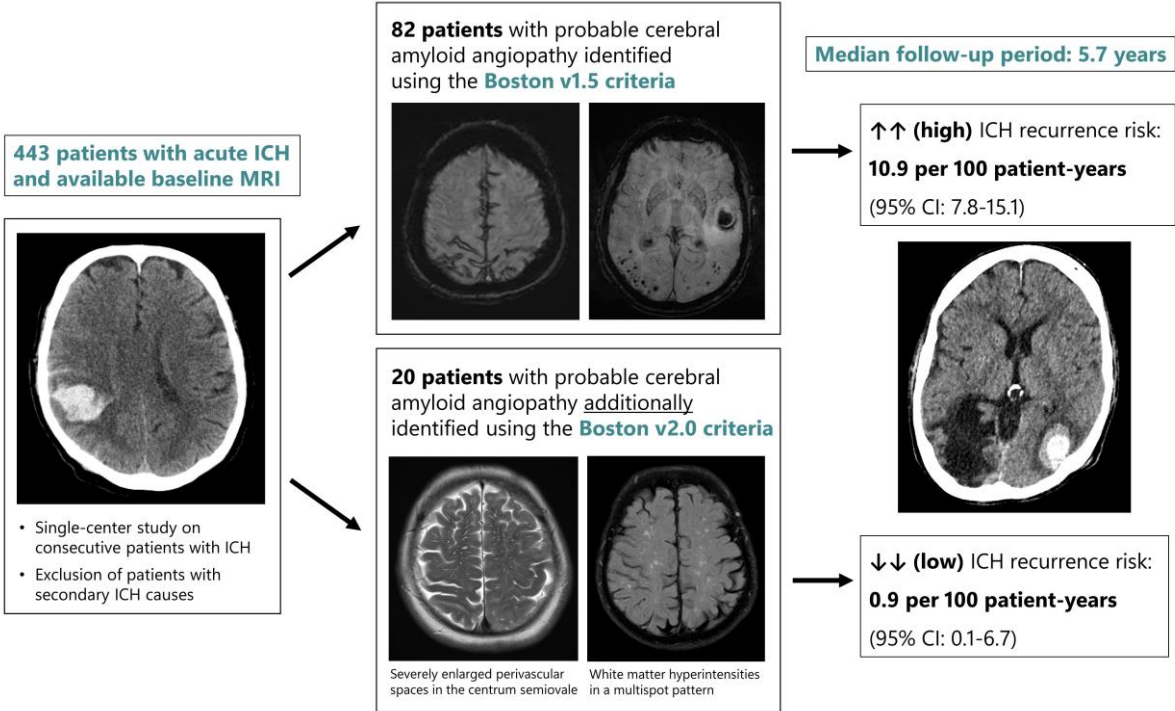Word count: 2000

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Abstract

Background: Intracerebral hemorrhage (ICH) caused by cerebral amyloid angiopathy (CAA) has a high recurrence risk. The Boston criteria, while not designed to predict recurrence, are commonly used for in-vivo diagnosis of CAA and have recently been revised to the version 2.0 (v2.0), introducing non-hemorrhagic white matter features. We investigated whether the new v2.0 criteria change ICH recurrence risk in patients with probable CAA.

Methods: We assessed ICH recurrence risk in consecutive patients with ICH and available brain MRI. Patients with macrovascular or structural causes were excluded. Recurrent ICH was determined using electronic health records and confirmed by neuroimaging. We compared ICH recurrence risk for Boston criteria v2.0 versus v1.5 for probable CAA using survival analysis.

Results: 59 of 443 patients (13.3%) had recurrent ICH over a median follow-up of 5.7 years (2682 patient-years). 37/102 patients (36.3%) with probable CAA according to the Boston criteria v2.0 had recurrent ICH compared to 36/82 patients (43.9%) according to the v1.5 criteria. Patients with probable CAA according to the Boston v1.5 criteria had a higher ICH recurrence rate (10.9 per 100 person-years; 95%-CI, 7.8-15.1) compared to those diagnosed by the v2.0 criteria (8.5 per 100 person-years; 95%-CI, 6.1-11.7). The 20 patients defined as probable CAA only by the v2.0 criteria had a very low recurrence rate (0.9 per 100 person-years; 95%-CI, 0.1-6.7), lower than those diagnosed using the v1.5 criteria (p<0.001).

Conclusions: Our findings suggest a wide spectrum of ICH recurrence risk in patients with probable CAA. Patients with ICH diagnosed with CAA based only on the non-hemorrhagic white matter markers introduced in the Boston v2.0 criteria had a much lower risk of recurrence than those diagnosed with the previous Boston criteria v1.5, comparable to that of patients with ICH not fulfilling any probable CAA criteria.

Comparison of Boston criteria v2.0/v1.5 for cerebral amyloid angiopathy to predict recurrent intracerebral hemorrhage

443 patients with acute ICH and available baseline MRI

- Single-center study on consecutive patients with ICH
- Exclusion of patients with secondary ICH causes

82 patients with probable cerebral amyloid angiopathy identified using the Boston v1.5 criteria

20 patients with probable cerebral amyloid angiopathy additionally identified using the Boston v2.0 criteria

Severely enlarged perivascular spaces in the centrum semiovale | White matter hyperintensities in a multispot pattern

Median follow-up period: 5.7 years

↑↑ (high) ICH recurrence risk: **10.9 per 100 patient-years** (95% CI: 7.8-15.1)

↓↓ (low) ICH recurrence risk: **0.9 per 100 patient-years** (95% CI: 0.1-6.7)

Non-standard Abbreviations and Acronyms

CAA: Cerebral amyloid angiopathy

ICH: Intracerebral hemorrhage

Introduction

Cerebral amyloid angiopathy (CAA) is a common cause of lobar intracerebral hemorrhage (ICH), accounting for about one-third of all spontaneous ICH in older people.[1] The Boston diagnostic criteria, first proposed in 1995, allow accurate in-vivo diagnosis of CAA using brain imaging with CT and especially MRI.[2]

Recently, version 2.0 (v2.0) Boston criteria were developed and validated against neuropathology.[3] In comparison with the v1.5 criteria, published in 2010[4], major changes were the inclusion of non-hemorrhagic white matter markers on MRI (severely enlarged perivascular spaces in the centrum semiovale and the white matter hyperintensities multispot pattern) and a reduction of the minimal age limit from 55 to 50 years.[3] These changes increased the sensitivity for CAA, with only slightly decreased specificity.[3]

Assessment of recurrence risk in patients with ICH is important to inform prognosis with relevance for secondary prevention. CAA according to the Boston criteria v1.5 is associated with high risk of ICH recurrence (7.4% per year for CAA vs. 1.1% in non-CAA patients)[5], but it is unknown how this risk might be affected when using the new v2.0 criteria. We compared the risk of recurrent ICH in patients diagnosed using the v2.0 versus v1.5 Boston criteria in a cohort study utilizing MRI for ICH classification over a long follow-up period.

Methods

Datasets generated during this study are available from the corresponding author upon reasonable request.

We retrospectively assessed 562 consecutive patients admitted to the University Hospital of Graz who survived a nontraumatic ICH and had available baseline structural MRI and CT- or MR-angiography over a 14-year-period. 119 patients were excluded due to secondary causes (e.g., macrovascular or structural, **figure 1**). MRI included at least a T2-fluid-attenuated inversion recovery, T2 and blood-sensitive sequence (susceptibility-weighted imaging or T2*) and was rated by a neurovascular specialist (SFH). Inter-rater reliability for probable CAA according to the Boston v2.0 and v1.5 criteria was assessed in 30 randomly selected cases between the primary rater and a senior neurovascular specialist with neuroradiological expertise (TG). Assessment of recurrent ICH was performed via electronic patient health records and confirmed by neuroimaging. More detailed information is provided in the **data supplement**.

Statistical analysis was performed using STATA, version 16 (StataCorp LLC, College Station, USA). Risk to first recurrent ICH was assessed with survival analysis, using Cox regression and Kaplan-Meier-Curves. This manuscript follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

The study was approved by the ethics committee of the Medical University of Graz (approval number: 32-265ex19/20). The need for individual informed consent was waived.

Results

We included 443 patients (mean age 67±13 years, 41% female). Probable CAA was diagnosed in 102 patients (23%) using the Boston v2.0 criteria and 82 patients (18.5%) using the Boston v1.5 criteria **(table S1)**. The inter-rater reliability for both assessments was kappa=1.0, indicating perfect agreement. Over a median follow-up of 5.7 years (IQR 7.2, 2681 person-

years), 59 patients had a recurrent ICH. 37 of 102 patients (36.3%) with probable CAA according to the Boston v2.0 criteria had recurrent ICH compared to 36 of 82 patients (43.9%) according to the v1.5 criteria. The one-, three- and five-year recurrence risks were higher in patients fulfilling the Boston v1.5 vs. v2.0 criteria (one-year-risks 21% [95%-CI, 14-31%] vs. 17% [95%-CI, 11-26%], three-year-risks 31% [95%-CI, 22-43%] vs. 25% [95%-CI, 18-35%], five-year-risks 48% [95%-CI, 36-61%] vs. 41% [95%-CI, 31-53%], **table 1**). The ICH recurrence rate was 10.9 per 100 person-years (95%-CI, 7.8-15.1) in patients with probable CAA according to the v1.5 criteria and 8.5 per 100 person-years (95%-CI, 6.1-11.7) for the v2.0 criteria, a non-significant difference.

Of 20 patients defined as probable CAA in the v2.0 criteria but not the v1.5 criteria, 17 were reclassified due to the new non-hemorrhagic white matter features (14 with severely enlarged perivascular spaces in the centrum semiovale, 3 with white matter hyperintensity multispot pattern), one due to the lower age limit, and two because of both age and white matter features. Of these 20 patients, only one had a recurrent ICH (a patient not diagnosed using Boston criteria v1.5 due to being 52 years old). The ICH recurrence rate was lower in these 20 patients compared to those fulfilling both the v1.5 and v2.0 criteria (p<0.001), but similar compared to the 341 patients with ICH that did not have probable CAA according to either the Boston v1.5 or v2.0 criteria (**table 1**). **Figure 2** shows Kaplan-Meier-Curves according to the Boston v1.5/2.0 criteria.

No significant differences were found regarding risks of ischemic stroke or other vascular events during follow-up (Boston v1.5 criteria: ischemic stroke in 9.8% and non-cerebral vascular events in 6.1%; Boston v2.0 criteria: ischemic stroke in 7.8% and non-cerebral vascular events in 7.8%).

Discussion

Our main novel finding is that while patients defined as probable CAA according to the Boston v1.5 criteria (which require at least two lobar hemorrhagic features) have a high risk for recurrent ICH, those additionally classified as probable CAA by the v2.0 criteria due to non-hemorrhagic white matter features appear to have a much lower recurrence risk. Thus, while the white matter features introduced by the Boston v2.0 criteria identify cases with underlying CAA pathology with greater sensitivity, especially in non-ICH presentations, specificity of the criteria was somewhat reduced in patients who presented with ICH.[3] Our data indicate that the resulting reclassifications diminish the attributable risk for ICH recurrence. However, this is not a limitation in the v2.0 criteria per se, as they were primarily designed to identify CAA, not to predict ICH recurrence risk. The lower recurrence risk might also be explained by less severely advanced CAA in patients identified by the v2.0 criteria, reflected by the lower age of those patients.

There is limited evidence regarding associations of recurrent ICH risk with the two novel non-hemorrhagic MRI features introduced by the Boston v2.0 criteria and the assessment of these markers may be less reliable. One previous study found a higher risk with anticoagulant-related ICH in patients with enlarged basal ganglia perivascular spaces but not in those with enlarged perivascular spaces in the centrum semiovale.[6] However, this study of ischemic stroke/TIA cohorts included only four recurrent lobar ICH and features of CAA were rare.

Our findings highlight the importance of individual neuroimaging markers of CAA for assessment of ICH recurrence risk (particularly cortical superficial siderosis[7]) rather than using the diagnosis of probable CAA alone. Indeed, our findings suggest a wide spectrum of bleeding risk in CAA, with the lowest risk in patients identified only using non-hemorrhagic MRI markers.

Core strengths of our study are the inclusion of a large cohort of consecutive ICH patients who had brain MRI and the long follow-up period to assess for ICH recurrence as well as ischemic stroke. The main limitation is the single-center design, which makes selection bias possible, although it is unlikely that this would substantially affect our main findings. The small number of recurrent ICH events reduces the statistical precision of our estimates. Although the electronic health records used for assessment of recurrence are comprehensive, we cannot exclude missing individual events. However, the recurrence rate in our study is slightly higher than in previous cohorts, making missing recurrent events less likely.[5] We also lacked pathological confirmation of presence or absence of CAA. Larger, multi-center studies would thus be useful to confirm our findings.

Supplemental Material:

Supplemental Methods
Table S1

References

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Table 1: Recurrence risk of intracerebral hemorrhage according to Boston v2.0 and v1.5 criteria

|	Number	Person-years	1-year risk (95%-CI) n=423	3-year risk (95%-CI) n=343	5-year risk (95%-CI) n=283	Cumulative incidence rate per 100 person-years (95%-CI)
Any intracerebral hemorrhage	443	2681	5% (3%-8%)	8% (6%-11%)	13% (10%-17%)	2.2 (1.7-2.8)
Probable CAA according to Boston v2.0 criteria	102 (23.0%)	438	17% (11%-26%)	25% (18%-35%)	41% (31%-53%)	8.5 (6.1-11.7)
Probable CAA according to Boston v1.5 criteria	82 (18.5%)	331	21% (14%-31%)	31% (22%-43%)	48% (36%-61%)	10.9 (7.8-15.1)
Probable CAA according to Boston v2.0, but not v1.5 criteria	20 (4.5%)	106	0% (0%-8%)	0% (0%-11%)	8% (0%-43%)	0.9 (0.1-6.7)
Patients without probable CAA according to both Boston criteria versions	341 (77.0%)	2244	1% (0%-4%)	3% (2%-6%)	5% (3%-8%)	1.0 (0.6-1.5)

Figure 1: Study flowchart.
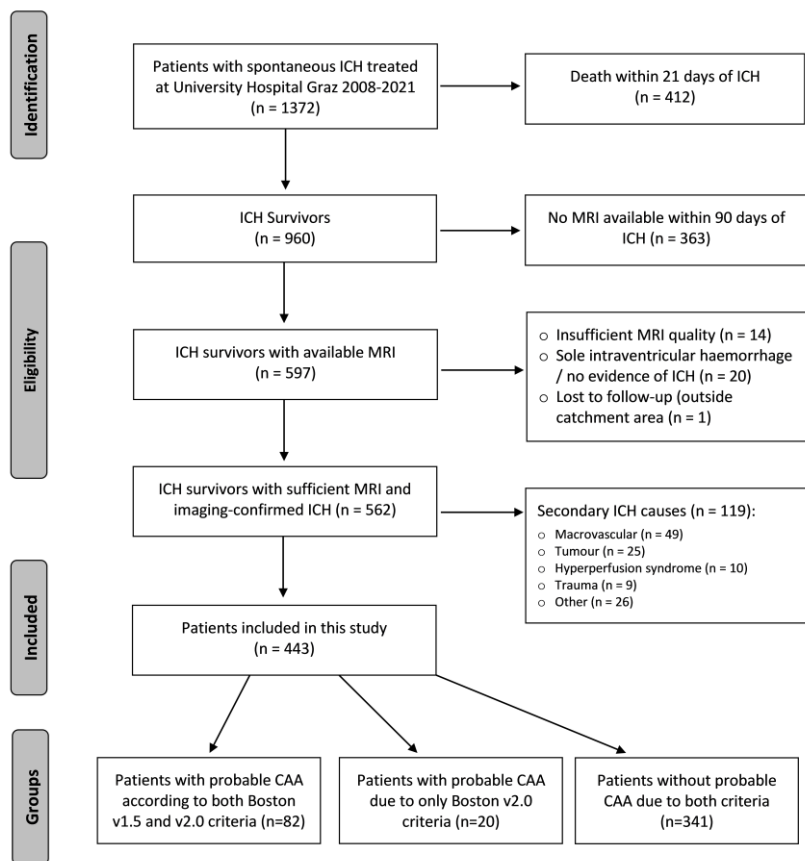
Figure 2: Kaplan-Meier curves for intracerebral hemorrhage recurrence risk according to Boston v1.5 and v2.0 criteria.