



Radiological versus CSF-integrated Classification of Cerebral Amyloid Angiopathy: Toward an In Vivo Biological Definition

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INTRODUCTION: The Boston Criteria represent the gold standard for diagnosing Cerebral Amyloid Angiopathy (CAA), but their application is precluded in mixed small vessel disease (SVD), where hemorrhagic deep perforator arteriopathy (DPA) markers coexist with lobar involvement. Moreover, biological biomarkers are not included in the current diagnostic framework. **The aims of this study were (i)** to determine which cerebrospinal fluid (CSF) biomarker (A β 42, A β 40, A β 42/40 ratio) is the **best candidate to support CAA diagnosis**; (ii) to define a **data-driven cut-off**; (iii) to explore if a **biomarker-integrated classification** significantly improves the identification of CAA.

RESULTS

We enrolled 121 patients (age: 72 [66-77] years old; 35% female – n=74 [60%] probable CAA; n=47 [40%] mixed SVD).

The A β 42/40 ratio showed a **bimodal distribution** and **consistent associations with all CAA-specific radiological features** (not evident with A β 40, less evident with A β 42). GMM identified a data-driven cut-off for A β 42/40 ratio more reliable than for A β 42 alone (**Figure 1**).

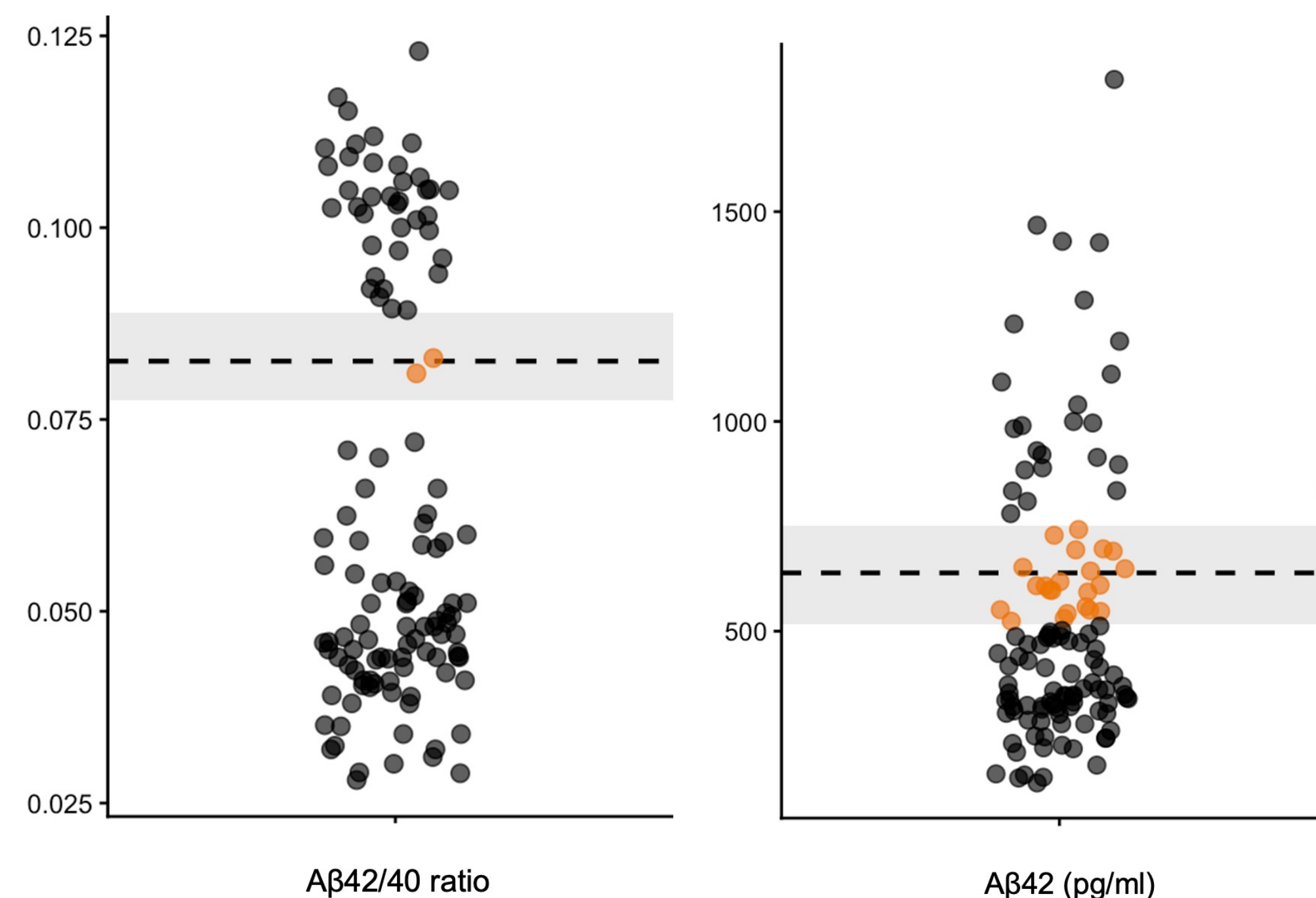


Figure 1: on the left, the distribution of A β 42/40 ratio in a suspected CAA cohort, with the dragged lines representing the data-driven cut-off (with 95%CI). On the right, the A β 42 alone, which showed a greater number of patients in a diagnostic grey zone

The **biomarkers-integrated reclassification**, particularly using the data-driven cut-off identified by GMM, **significantly improved the distinction between subgroups regarding CAA- and DPA-related MRI features (Figure 2)**

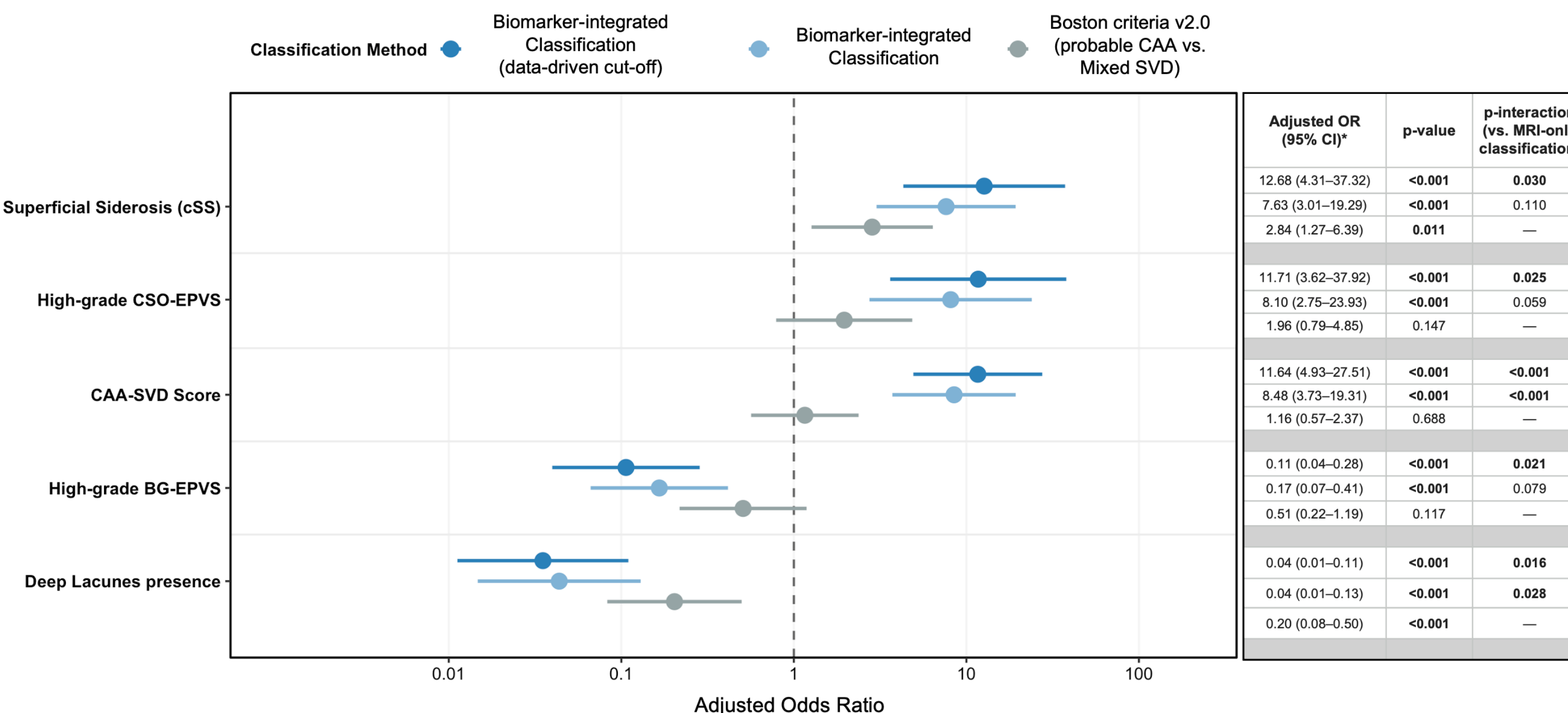


Figure 2: Comparison of the association between MRI-visible manifestations of CAA and different classification methods.

METHODS

We analyzed data from a retrospective multicenter cohort of patients with **suspected CAA, defined according to the “probable CAA” category (Boston criteria v2.0) but without considering the deep bleeding criterion**, and available CSF biomarkers.

We evaluated the **biomarker distribution and association with MRI-visible SVD features**. We employed a **Gaussian Mixture Model (GMM)** to identify a data-driven threshold for amyloid positivity (A⁺).

Then, we compared subgroups using different frameworks, namely the current **MRI-based classification** (probable CAA vs. mixed SVD) and a **biomarker-integrated classification** (A⁺ vs. A⁻), using both AD-related and data-driven derived cut-offs.

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CONCLUSION: A **CSF biomarker-integrated classification** showed a possible additive performance in the detection of the likely predominant SVD (CAA vs. DPA) compared to the radiological-only classification. These findings are cohort-specific and would benefit from further validation but these data support a potential future transition toward an **integrated bio-radiological framework**, which may refine in vivo CAA diagnosis.