Edinburgh Research Explorer

The Boston criteria version 2.0 for cerebral amyloid angiopathy

Supplementary material contents

Supplementary material

Supplementary Table 1. Characteristics of patients in the geographical external validation constituent medical centers

Centres	Univ of Milano-Bicocca, IRCCS Reggio Emilia (n=15)	Univ of Edinburgh (n=17)	Sainte-Anne Hospital (n=8)	Univ Hospital Munich (n=11)	Vall d'Hebron (n=6)	Univ Lille (n=16)	German Center Magdeburg (n=3)	Univ College London (n=28)	Toulouse Hospital (n=19)
Age, years	68 (63-77)	81 (77-85)	62 (60-71)	70 (66-73)	75 (72-82)	69 (65-82)	75 (62-83)	68 (61-75)	65 (58-67)
Sex, men	7 (47%)	9 (53%)	5 (63%)	5 (46%)	3 (50%)	5 (31%)	1 (33%)	15 (54%)	11 (58%)
Race	15 White	17 White	8 White	11 White	6 White	16 unknown	3 White	12 White 3 "other ethnic background" (treat as unknown) Others unknown	19 White
Hypertension	5 (33%)	11 (65%)	3 (38%)	3 (28%)	6 (100%)	8 (50%)	2 (67%)	19 (68%)	3 (165)
ICH presentation	12 (80%)	15 (88%)	7 (88%)	10 (91%)	2 (33%)	11 (69%)	3 (100%)	18 (64%)	16 (84%)
T2*GRE MRI	14 (93%)	17 (100%)	8 (100%)	10 (91%)	6 (100%)	16 (100%)	3 (100%)	10 (36%)	19 (100%)
SWI MRI	1 (7%)	0	0	1 (9%)	0	0	0	18 (64%)	0
Autopsy	1 (7%)	17 (100%)	1 (13%)	0	5 (83%)	16 (100%)	0	0	2 (11%)
Biopsy	14 (93%)	0	0	5 (46%)	0	0	0	19 (68%)	3 (16%)
Haematoma evacuation	0	0	7 (88%)	6 (55%)	1 (17%)	0	3 (100%)	9 (32%)	14 (74%)

Values are presented as median (interquartile range) for continuous variables and (% total) for categorical variables.
See authors affiliations for full hospital listings.
Abbreviations: ICH intracerebral hemorrhage, GRE gradient-recalled echo, SWI susceptibility-weighted imaging

Supplementary Table 2 Criteria performance for probable CAA diagnosis (vs possible + non-CAA) according to MRI diagnostic markers combination in the derivation cohort

A. ICH clinical presentations (n=77)

+number strictly lobar ICH	+number strictly lobar CMB	+number cSS foci	+ severe CSO-PVS (y/n)	+ WMH-MS (y/n)	Sum	Sensitivity	Specificity	AUC (95% CI)
X	X	X				76.7%	76.5%	0.78 (0.65-0.88)
X	X	X	X			85%	70.6%	0.78 (0.66-0.90)
X	X	X		X	2 or more	86.7%	76.5%	0.82 (0.70-0.93)
X	X	X	X	X		86.7%	70.6%	0.79 (0.67-0.88)

B. Non-ICH clinical presentation (n=82)

+number strictly lobar CMB	+ cSS foci y/n	+ cSS foci number	+ severe CSO-PVS (y/n)	+ WMH-MS (y/n)	Sum	Sensitivity	Specificity	AUC (95% CI)
X	X					44.7%	91.4%	0.68 (0.60-0.77)
X		X				48.9%	94.3%	0.72 (0.63-0.80)
X		X	X		2 or more	59.6%	91.4%	0.76 (0.67-0.84)
X		X		X		53.2%	91.4%	0.72 (0.64-0.81)
X		X	X	X		59.6%	91.4%	0.75 (0.67-0.84)

Abbreviations: ICH intracerebral hemorrhage, CMB cerebral microbleeds, cSS cortical superficial siderosis, CSO-PVS perivascular spaces in the centrum semiovale, WMH-MS white matter hyperintensities in a multisport pattern, y/n yes (lesion present)/no (lesion absent), AUC area under the receiver operating characteristics curve

Supplementary Table 3 Criteria performance for any CAA diagnosis (probable + possible vs non-CAA) according to MRI diagnostic markers combination in the derivation cohort

A. ICH clinical presentations (n=77)

+ strictly lobar ICH	+ strictly lobar CMB	+ cSS foci	+ severe CSO-PVS (y/n)	+ WMH-MS (y/n)	Sum	Sensitivity	Specificity	AUC (95% CI)
X	(X)	(X)	(X)	(X)	1 or more	96.7%	41.2%	0.69 (0.57-0.81)

B. Non-ICH clinical presentation (n=82)

+ strictly lobar CMB	+ cSS foci	+ severe CSO-PVS (y/n)	+ multispot WMH (y/n)	Sum	Sensitivity	Specificity	AUC (95% CI)
X	X				58.7%	91.4%	0.75 (0.67-0.84)
X	X	X		1 or more	80.4%	80%	0.80 (0.71-0.89)
X	X		X		69.6%	71.4%	0.71 (0.60-0.81)
X	X	X	X		84.8%	65.7%	0.75 (0.66-0.85)

Abbreviations: ICH intracerebral hemorrhage, CMB cerebral microbleeds, cSS cortical superficial siderosis, CSO-PVS perivascular spaces in the centrum semiovale, WMH-MS white matter hyperintensities in a multisport pattern, y/n yes (lesion present)/no (lesion absent), AUC area under the receiver operating characteristics curve

For Supplementary Table 3A, presence of one strictly lobar ICH is itself sufficient for a diagnosis of possible CAA.

Supplementary Methods:
Please access the published study protocol paper for further details:
https://discovery.ucl.ac.uk/id/eprint/10085528/3/Werring_Advancing%20diagnostic%20criteria%20for%20sporadic%20cerebral%20amyloid%20angiopathy_AAM.pdf

or

https://journals.sagepub.com/doi/abs/10.1177/1747493019855888

MRI assessment and analysis

Key MRI biomarkers of CAA and small vessel disease were derived from a systematic review of the relevant literature.[1] These included characteristic hemorrhagic MRI biomarkers of CAA[2] (cerebral microbleeds-CMBs, ICH, cortical superficial siderosis-cSS, as well as non-hemorrhagic (white matter) markers[2] (white matter hyperintensities-WMH, posterior predominant WMH, WMH spots and MRI-visible perivascular spaces in the centrum semiovale-CSO-EPVS[3-5]. All MRI markers will be rated by a trained observer blinded to clinical and pathological information, according to STandards for ReportIng Vascular changes on nEuroimaging (STRIVE)[6] where applicable and validated scales and guidelines. Additional trained raters will assess a random sample of the MRI scans (n=100) to generate inter-rater agreement measures.

CMBs presence and number will be evaluated on axial T2*-weighted images using current consensus criteria[7] and categorized according to a simplified version of the previously validated Microbleeds Anatomic Rating Scale (MARS).[8] For purposes of statistical analyses, the number of lobar CMBs will be taken into account as a continuous variable as well as categories using cut-points (0, 1, 2–4, ≥5 or 5-10 and ≥10).[9] Non-lobar (i.e. deep CMBs) will also be categorized accordingly. ICH will be defined and categorized as lobar or non-lobar according to the simplified The Cerebral Hemorrhage Anatomical RaTing inStrument (CHARTS) definitions.[10]

cSS will be defined as per recent consensus recommendations[11] (curvilinear hypointensities following the cortical surface, distinct from the vessels), and assessed on axial blood-sensitive sequences according to a validated scale: absent, focal (restricted to ≤3 sulci) or disseminated (affecting 4 or more sulci).[12,13] cSS will also be rated for multifocality (i.e. taking into account cSS presence at spatially separate foci in each hemisphere) using another developed and validated protocol as: (a) 0 – none; (b) 1 -1 sulcus or up to 3 immediately adjacent sulci with cSS; or (c) 2 - 2 or more non-adjacent sulci or more than 3 adjacent sulci with cSS. Based on the total score:

0–no cSS, 1 –unifocal cSS, while ≥2 multifocal cSS.[14] Acute convexity subarachnoid hemorrhage (cSAH) will also be defined and assessed in line with recent consensus recommendations,[11] as linear hypointensity in the subarachnoid space affecting one or more cortical sulci on T2*-GRE/SWI sequences with corresponding hyperintensity in the subarachnoid space on T1-weighted or FLAIR images.[7,13] cSS and acute cSAH are rated as equivalent MRI marker of CAA. They are both superficial cortical hemorrhages that follow the curvilinear shape of the surrounding cerebral gyri – cSAH is the acute form, while cSS is the chronic form, of essentially the same underlying process.[15] In cases where acute cSAH is potentially connected (or in close vicinity) to cSS, they are counted as evidence of two hemorrhagic markers of CAA (e.g. similar to having 2 independent sulci of cSS or 2 lobar CMBs), since the acuity if cSAH provides evidence of dissemination in time (it's a new CAA-related superficial cortical hemorrhage event) compared to the chronic nature of cSS. This is the same rationale for counting single vs. two cSS sulci within the focal cSS category and also using the cSS multifocality scale: to potentially distinguishing cSS related to individual bleeding events originating from one focus or multiple different bleeding foci.

Periventricular and deep WMH will be classified using the 0-3 Fazekas scale on axially oriented FLAIR images.[16] In patients with ICH, the unaffected hemisphere will be scored. In patients with bilateral ICH or significant edema, an estimation will be made, using the non-involved white matter areas. The antero-posterior ratio of WMH lesions' distribution will be computed using a validated approach on FLAIR,[17] using multiplanar reformatting as necessary to provide axial orientation. In this method, WMH in the frontal lobe are evaluated around the frontal horn of the lateral ventricle and WMH in the occipital lobe are evaluated around the occipital horn of the lateral ventricle. For the frontal and occipital lobes, visual scales are separately used to rate WMH surrounding the ventricles (≤5 mm from ventricle), within juxtacortical white matter (≤5 mm from the cortex) and within the deep white matter (defined as the region between juxtacortical and ventricular areas). Periventricular WMH are graded as 0 (absent), 1 (caps or pencil-thin periventricular lining), 2 (smooth halo or thick lining), and in deep or in juxtacortical white matter as 0 (absent), 1 (punctate or nodular foci), 2 (confluent areas). The overall severity is then calculated separately for the frontal and occipital lobes by adding the scores for these three areas (range 0–6), and then the frontal-occipital (FO) gradient calculated as the WMH score in the frontal lobe minus that in the occipital lobe, ranging −6 to 6 (>0 implies frontal dominance

and <0 implies occipital dominance). As previously shown, using this method, a lower score reflects more posteriorly distributed WMH lesions.[17]

Multiple subcortical spots WMH refers to a pattern which appears in the subcortical white matter and corresponds to more than 10 small spots (circular or ovoid) of WMH on FLAIR images.[18] This pattern in the subcortical white matter refers to small circles or spots of WMH (the total number of spots must be higher than 10 to meet this pattern requirement; this cutoff, though arbitrary, was prespecified based on its possible clinical usefulness as an easily identified pattern, see Supplementary Figure 1 below).[18] When evaluating MRI scans for the presence of multiple subcortical WMH spots pattern, the following aspects should be taken into account:

-Assessment should be made on FLAIR images, covering the whole brain. All the slices, and both hemispheres, should be evaluated.

-Foci should only be counted if restricted to subcortical areas and isolated, that is, not confluent or continuous to periventricular foci.

-WMH foci related to acute or chronic infarcts, lacunes, PVS, or ICH should not be counted.

-There are no established size limits for subcortical WMH foci, but they should be visible without requiring extensive windowing.

-More than 10 subcortical WMH foci are required to establish the pattern.

-Cases with large confluent periventricular WMH foci can be challenging. In this context, raters should carefully assess subcortical areas in the high convexity and temporal regions for small, isolated spots.

- Small round or ovoid spots in the subcortical areas in the high convexity and temporal regions should be counted if they appear isolated from each other, i.e. separated by normal parenchyma. For small, isolated spots that are often adjacent to each other giving the impression of confluence, they rater might try windowing the image/changing magnification to identify if spots in close proximity are in fact separate foci. When this is not possible or is still unclear that area of small confluent spots should be counted as a single lesion. When there is question re confluence of certain spots, the rater might first try to assess whether the pattern of 10 or more spots is fulfilled based on the presence of less ambiguous and isolated lesions as defined above. In this case, individual decisions regarding ambiguous confluence lesions will likely not influence the identification for the pattern since the number criterion is already fulfilled.

-When 10 or 11 foci are identified, that is, when the number of foci is within or extending slightly beyond the threshold, the overall pattern, rather than the raw number, should be considered.

MRI-visible PVS will be rated on axial T2-weighted MR images, in the basal ganglia (BG) and CSO, using a validated 4-point visual rating scale (0=no PVS, 1=<10 PVS, 2=11-20 PVS, 3=21-40 PVS and 4=>40 PVS).[5,19-22] The numbers refer to PVS on one side of the brain: after reviewing all relevant slices for the anatomical area being assessed, the count for the slice and side with the highest number of PVS is recorded. The assessment of PVS may be influenced by the presence of confluent WMH; in such cases estimation is made for the PVS rating category, using the non-involved white matter region, and cortical gray matter according to the rating scale used. In cases of large lobar or deep ICH, PVS are assessed in the contralateral hemisphere, an estimation of the closest category ipsilateral to the lesion is made, and the highest severity is recorded. We pre-specified a dichotomised classification of PVS degree as high (score >2) or low (score ≤2). This definition is in line with the PVS burden used in previous studies and found to relate with different vascular risk factors and imaging markers of small vessel disease,[21,22] in particular the association between CSO-EPVS and CAA.[5,22,23] For a visual guide on PVS rating, please see:

https://www.ed.ac.uk/files/imports/fileManager/epvs-rating-scale-user-guide.pdf
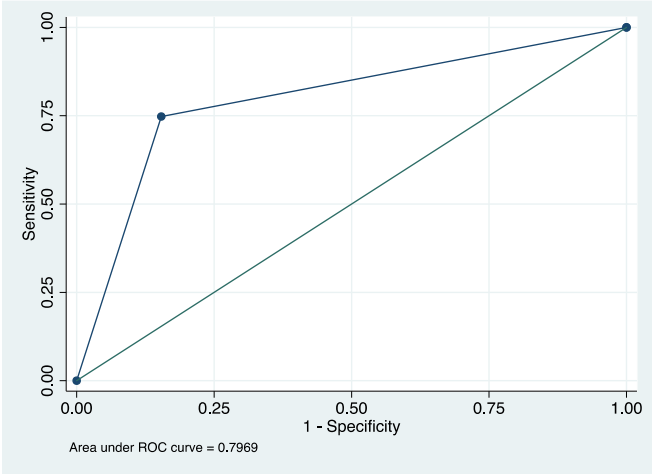
Supplementary Figure 1. Boston Criteria v2.0 multispot white matter hyperintensity pattern examples, defined as greater than 10 T2/FLAIR small circular or ovoid hyperintense lesions in the subcortical white matter of both hemispheres. Yellow arrows points to WM spots that should fulfill the definitions and should be counted for the pattern. Each arrow represent a lesion that should be counted as one.
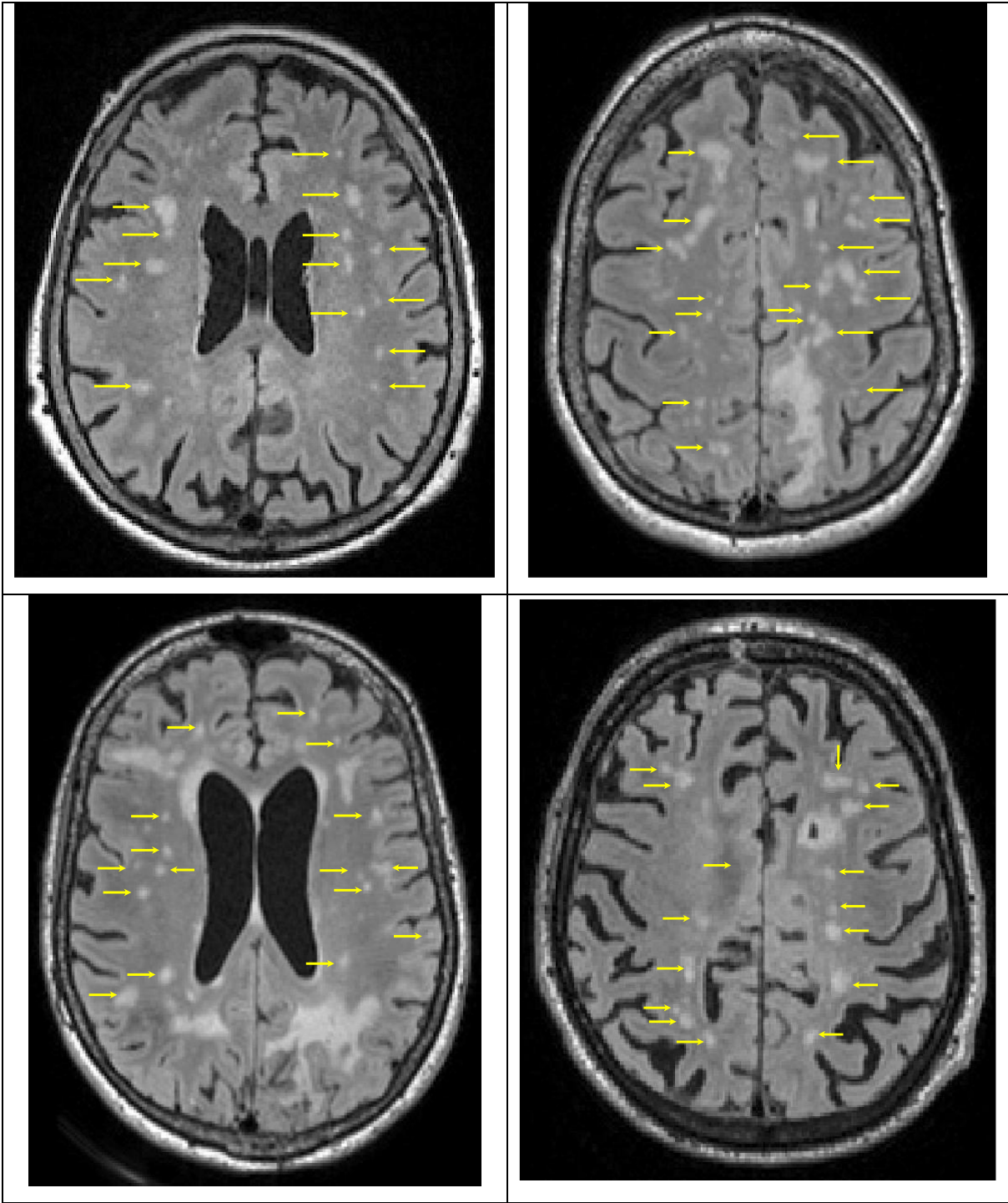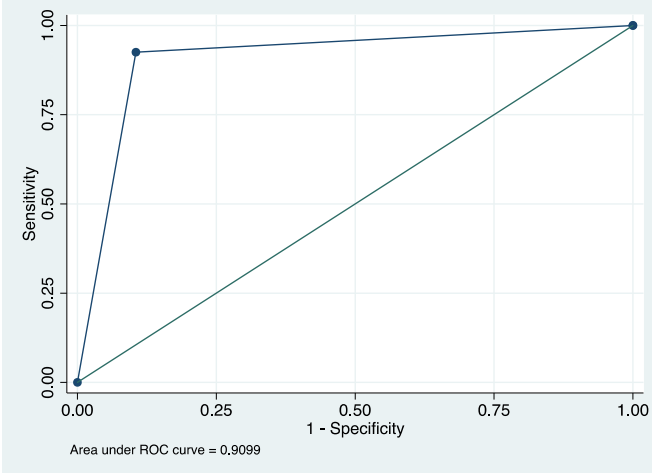
Supplementary Figure 2. ROC curves for diagnostic accuracy of Boston criteria v2.0 (probable vs. non probable CAA) across the derivation cohort, validation cohorts and the final whole sample analyses.
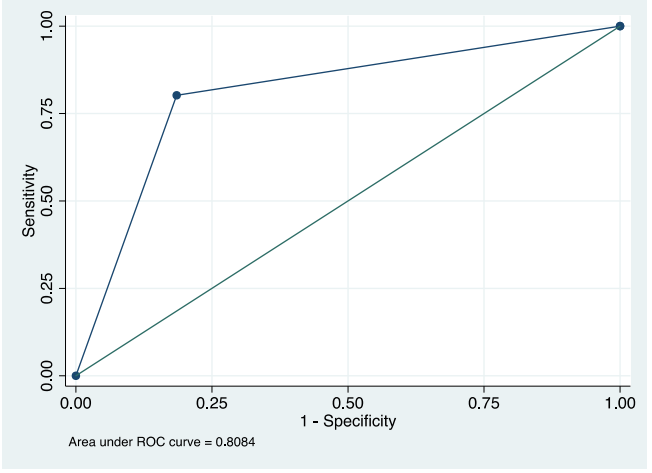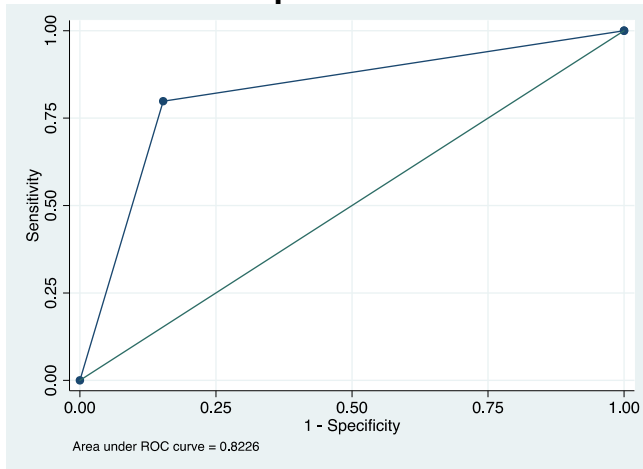
A. Derivation cohort

Area under ROC curve = 0.7969

B. Temporal external validation

Area under ROC curve = 0.9099

C. Geographical external validation

Area under ROC curve = 0.8084

D. Whole sample

Area under ROC curve = 0.8226

E. Whole sample – autopsies

Area under ROC curve = 0.8477

C. Whole sample – autopsies, ICH

Area under ROC curve = 0.9151
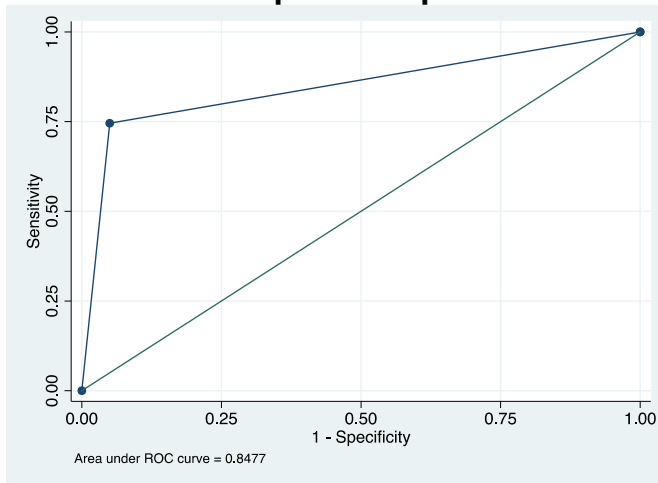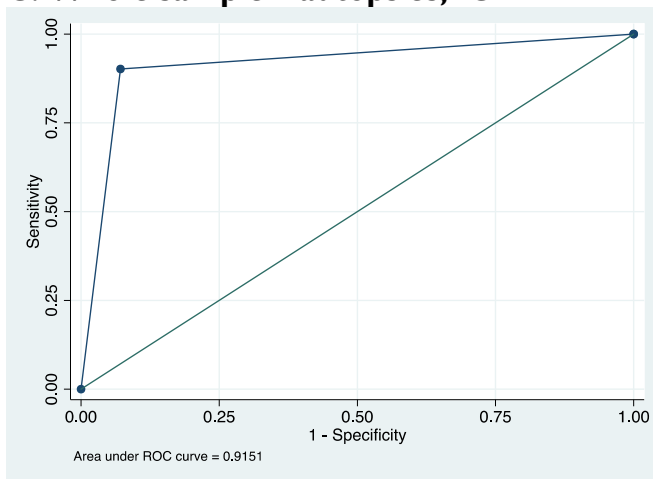
D. Whole sample – autopsies, non-ICH

Area under ROC curve = 0.7563
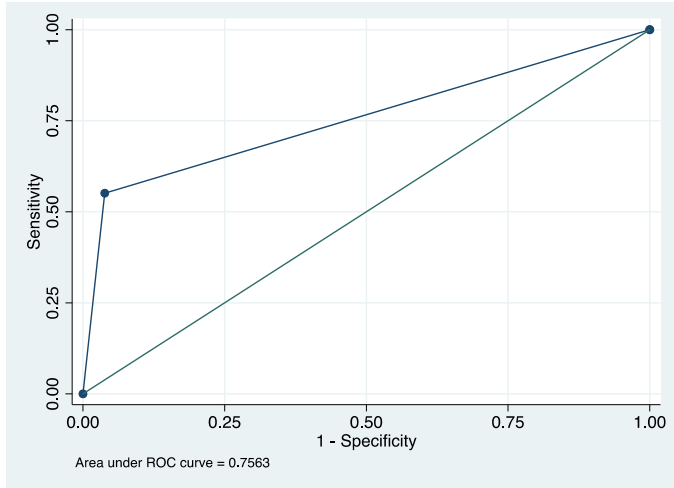
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